Kettering hyperthermia form of artificial hyperpyrexia

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THE KETTERING HYPERThERM
A Form of Artificial Hyperpyrexia

Senior Thesis
University of Nebraska
College of Medicine

John H. Weare
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"Those diseases which medicines do not cure, iron cures; those which iron cannot cure, fire cures; and those which fire cannot cure are not to be reckoned wholly incurable." (18) This Hippocratic aphorism might be taken as the theory in which workers in fever therapy believe. At the time of Hippocrates, fever was regarded as a defensive mechanism against disease. Then Claude Bernard, Virchow, and others supposedly demonstrated harmful physiological and pathological reactions to fever. This initiated the era of antipyresis by medical and physical means. W.H. Welch, in 1888, and others during the past forty years have propounded the idea of the beneficial effect of fever in the body defense against disease. The recent developments in fever therapy is a testimonial to the general acceptance of their views.

There have been several methods of producing hyperpyrexia of which most wide spread interest has been shown in the Kettering Hypertherm fever cabinet. This seems to be the most satisfactory type at the present time. This apparatus was conceived and perfected at the Miami Valley Hospital and at the Research Laboratories of the Frigidaire Division of the General Motors Corporation, Dayton, Ohio, by Dr. Walter M. Simpson, with the collaboration of Mr. Charles F. Kettering, director of the Research
Laboratories of the General Motors Corporation. These units have been placed in different medical centers in the United States for the purpose of research. Fifty-five of these units have been loaned to twenty medical research centers. (57) There are three cabinets in the Fever Therapy Unit of the University of Nebraska at the Lutheran Hospital in Omaha, Nebraska.

In this paper I will discuss this method of treatment and give a brief summary of some of the clinical results obtained by different workers over the country.
HISTORY

Study of the history of artificial fever convinces one that this therapy originated in antiquity. Like many other therapeutic measures the knowledge of its beneficial action was empirical and enshrouded with magical formulas and superstitions. The general layman has always been certain of the curative value of external heat. Many remember the hot baths followed by sweats given by our parents in an attempt to overcome bad colds and such upper respiratory infections. Such knowledge has been handed down from generation to generation. Sweat baths were frequently prescribed by the general practitioner of the middle of the nineteenth century and rests on a perfectly logical basis of common sense and experience. The voluntary knowing production of artificial fever by means of physical agents and of its scientific evaluation in curing disease, is a product of the last seven or eight years of research. In other words, previously, artificial fever has been used without realizing just what they were doing or the physiological effects produced. It is, therefore, lately that we have become aware of the value of artificial fever produced by physical means. Hence, this cannot be classed as a new discovery, but rather a crystallization of long established knowledge.

The Greeks were probably the first to convert their
natural thermal springs into baths. Several of these, administered by priest-physicians, were recommended for their curative virtue. The ancient Egyptians, Chinese and Jews advocated hot bathing, and even aboriginal tribes such as the American Indians, the Negroes of tropical Africa, and the Japanese used hot water and steam baths in the treatment of acute and chronic infections. The Romans built luxurious baths with elaborate heating plants, some of which occupied many acres of territory, and were the meeting place and social center of Rome. Such baths were later established in all the principal cities of the empire, and continued to flourish in less ostentatious buildings during the dark ages.

The advent of syphilis made these baths more unhygienic and dangerous. The communal bath of medieval Europe was not only a place of social but venereal pleasures, and as a consequence, of venereal infections. The spread of syphilis, which public opinion regretfully associated with these institutions, caused the bath house to fall into disrepute, and in the period that followed, personal hygiene was neglected. Nevertheless, the knowledge of the empirical value of hot bathing persisted, especially in Finland and Russia, where many a peasant cottage had a steam room closely adjoining the main domicile.

The Japanese were the first modern people to use
intensely hot baths solely for therapeutic purposes. This was because of a natural occurrence of hot springs in conjunction with the volcanic formations of the islands. The baths are given in large communal tanks about four feet deep, at a temperature between 113 and 128 degrees F. As the water flows into these reservoirs, it is unbearably hot, and the bathers stir it with large wooden paddles, thereby cooling it somewhat. They then immerse themselves to the neck and pour the hot water over their heads. After about six minutes of this refined torture, they bob out almost parboiled with the body temperature ranging between 103 and 105 degrees F. Since this temperature continues for some time after the patient has left the bath, and since these hardy people take about five baths a day, it is clear that quite a decided, persistent, elevation of temperature results. These thermal springs are renowned for their curative effects on all forms of syphilis, arthritis, rheumatism, acute genital-urinary infections, and respiratory, digestive, nervous, and ocular diseases. The curative effect of these springs have heretofore been attributed to their high mineral content. They have been very popular throughout the entire empire since the sixteenth century, and enjoyed local renown for
several centuries before this time. (1) In

In 1848, Koster studied the influence of Malaria on mental diseases and he considered building an insane asylum in a place that was constantly exposed to intermittent fever.

In 1853, Kostl reported a great improvement in a case of dementia paralytica after the patient had had Small Pox.

Schloger in 1857 reported six psychotic patients out of eleven cured after having typhoid fever.

Nasse in 1864 noted the good influence of malaria on mental disease and mentioned the especially striking result in dementia paralytica. In 1864 and 1874 Rosenblum, in Russia, made use of relapsing fever and malaria in the different psychoses, syphilitic and nonsyphilitic.

In 1883, Philips (2) 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 respiration and pulse rate. This extremely important observation was buried and forgotten in the pages of the Columbia Medical Journal, and had to be rediscovered several times before its importance was appreciated.

In 1883 Fehrleisen reported the cure of Lupus
by the injection of a pure culture of Streptococcus from a case of erysipelas.

Preparations of sulphur were made for subcutaneous injections by the French as early as 1907. Strangely enough, in view of the recent use of injections of sulphur to produce fever, they claimed that it reduced fever in cases of bronchopneumonia and pulmonary tuberculosis. (3)

In 1917 Wagner Von Jäuregg innoculated patients with malaria. Two of four patients showed marked improvement, the treatment being used for dementia paralytica.

Weichbrodt and Johnel in 1919, used hot water for the purpose of raising the temperature in syphilitic rabbits. (4)

In 1921, Meye-Bisch and Basch used sulphur in oil injections in the treatment of arthritis.

In 1926, Kunde, Hall and Gerty used combined typhoid vaccine in general paresis.

In 1927, Schamberg and Tseng used hot water to raise temperature for treatment of syphilis in the humans.

Walenski in 1928, caused induced pyrexia by hot air. King et al first applied diathermy to a paretic in October 1928. Rosonaff independently, revived the

In 1929 Mehrten's and Pouppirt treated central nervous system syphilis by means of hot air. In September 1929, Neymann and Osborne (5) and in March, 1930 King and Cocke (6) reported their experiences with artificial fever production with diathermy.

In 1931 Simpson (7) began to investigate the influence of an ultra high frequency field on Neurosyphilis, gonococcal infections, arthritis, and vascular diseases of the extremities. In 1933 Simpson discarded the short radio waves and perfected the idea of air-conditioned cabinets through experimentations with the small hot air blowers employed in the radiotherm apparatus for the evaporation of moisture from the patients and for the maintenance of the temperature. He found that the temperature of the patient could be carried and maintained consistently by airconditioning alone without resorting to radio waves.

It seems that this first form of artificially induced fever is the best and it will be concerning this Kettering hypertherm that I will devote this paper.
APPARATUS

Before the development of the Kettering Hypertherm, we already had several different forms of producing heat artificially such as hot baths, cabinets heated with carbon-filament electric lamps, electric blankets, diathermy and radiotherapy. The clinical results obtained with any of these methods were essentially similar, when the fever could be maintained at a sufficiently high level for a sufficient length of time. The recognition of the fact that some of these methods possessed inherent dangers, prompted Simpson and Kendell (13) to attempt to develop a relatively safe and simple method for fever induction and maintenance.

The apparatus now used for fever induction and maintenance is an air-conditioned cabinet developed at the Miami Valley Hospital and at the Research Laboratories of the Frigidaire Division of the General Motors Corporation, Dayton, with the collaboration of Mr. Charles F. Kettering and Mr. Edwin C. Sittler. The name "Kettering hypertherm" has been applied to the apparatus. In the present stage of its development, the Kettering hypertherm consists of an insulated cabinet about 7½ feet long, 3½ feet wide and 3¼ feet high that is resting on four metal legs which hold it about 2 3/4 feet from the floor. The patient lies nude in this cabinet with his head extending
outside the cabinet. Sponge-rubber insulation is utilized in the neck region to permit the patient to shift his position. The patient lies on a comfortable air mattress, supported by a box-like bed, which is rolled in and out of the cabinet at will. In the rear of the cabinet is a small insulated fire-proof compartment in which the air-conditioning apparatus is contained. The dry-bulb air temperature is controlled by a thermostat. The wet-bulb temperature, which governs the percentage of relative humidity is controlled by a humidistat or by a wet-bulb thermostat. The air velocity within the cabinet is controlled by blowers of fixed speed. Dry-bulb and wet-bulb temperatures within the cabinet are shown on large dials, equipped with warning pilot lights, on the top of the front end of the cabinet where they may be constantly observed by the nurse-technician. The temperature-humidity factors may be controlled by the turning of a single knob. The average set of air conditions to which the patient's body is subjected is dry bulb air temperature of 140 degrees to 150 degrees F., relative humidity of 35-40 percent, and air velocity of 425 cubic feet per minute. The elevation of the rectal temperature to 105 degrees F. is usually accomplished in forty minutes to one hour. The air is constantly conditioned by continuous passage through the air-conditioning compartment. The safety and comfort of the
patient are greatly enhanced by the accurate control of the relative humidity.

The mechanism of fever induction with the Kettering hypertherm depends primarily upon heat transfer by conduction from the circulated heated air and the heated air-mattress. This factor, combined with prevention of the normal rate of heat loss from the body by radiation and evaporation as discussed before, is responsible for the elevation of the body temperature and its maintenance at any desired level. (13)

Small sliding doors in the sides of the cabinet give access by which the patient's protective covering of blankets can be rearranged, his skin temperature noted, his rectal temperature taken, and his general condition easily inspected at all times.

The patient is put in the cabinet when it is heated to a temperature of about 120 degrees F. The front vertical plane is lowered and the treatment begins. A fan is used to circulate cold air over the patient's head which is often packed with ice. The patient is constantly watched by a specially trained nurse-technician. Blood pressure, pulse, temperature, respirations are checked throughout the treatment. The patient is encouraged to take large amounts of fluids in the form of 0.6% sodium chloride solution to replace the fluid and chloride loss, from the
If at any time the temperature of the patient gets out of control, or he has some untoward reaction he is quickly removed from the cabinet and the condition treated. These will be discussed more in detail later.

The simplification of the apparatus, the removal of hazards inherent in certain other physical modalities, and the supplying of two to four liters of sodium chloride solution (0.6 per cent) by mouth during the treatment have changed this form of therapy from one requiring hospitalization to one in which the patient is usually able to return to his work the day following his treatment, unless the extent of his disability is such as to make hospitalization desirable.

The advantages of the Kettering hypertherm may be briefly summarized:

1. The temperature is raised and maintained by circulating, heated, humidified air.
2. The cabinet has a known controlled temperature, known air velocity, and controlled humidity.
3. The mechanism of operations is simple and easily controlled.
4. The patient's body is uniformly heated.
5. The height of the temperature can be controlled at will.
6. Does not require electrodes, condensor plates, or other electrical appliances.
7. There is no danger from electric burns.
8. There are no confining jackets.
9. Patients can be easily and quickly observed at all times.
10. Patient can be quickly removed from the cabinet in case of an emergency.
11. Must have trained attendants.
12. Nursing care simpler than with other methods.
13. Temperature can be rapidly raised.
14. No toxic substance dangerous to patient's health are introduced into the patient's body.
15. Low percentage of mortalities.
16. High constant temperature more easily and accurately maintained.
17. Clinical results better with this type of hypertherm.
Our modern ideas as to the origin of animal heat dates back to the time of Lavoisier (1774-77). To the older physiologists animal heat was a most difficult problem. The animal's body produces heat continually and maintains a temperature higher, as a rule, than that of the surrounding air. Since oxygen and the nature of ordinary combustion were unknown, they naturally explained this heat formation by reference to causes which science of the day had shown to be capable of producing heat, such as friction and fermentation. Haller (1757) taught that the body heat arises mainly from friction of the circulating blood and the movements of the heart and blood vessels. Lavoisier first gave to the physiologists the conception that the heat produced in the body is due to combustion or oxidation, and that therein lies the significance of our respiratory intake of oxygen. He believed that this oxidation took place in the lungs. After a long and interesting controversy, it was also shown satisfactorily that the oxidation of the body does not occur in the lungs alone, but all over this entire body. The oxygen is transported to the cells and there does its work of effecting oxidations and giving rise to heat. This heat is equalized more or less over the whole body. Chiefly by the circulation of the blood, which absorbs heat from the warmer
organs and distributes it to the cooler ones. The body temperature is maintained at a nearly constant level by an intricate adjustment of physiological reflexes which together constitute the heat-regulating mechanism. Such in brief, is the general theory of our times regarding heat production in the body.

With respect to the regulation of the body temperature, fundamental differences exist among animals. In the so-called cold-blooded or poikilothermic animals the temperature of the body depends on the temperature of the surrounding medium. It rises in warm weather and falls in the cold. In the so-called warm-blooded or homothermic animals the body temperature is maintained at a fairly constant level. (9)

Although it is customary to fix 37 degrees C. (98.6 degrees F.) as the normal temperature of man it should be remembered that considerable variations occur both in different parts of the body and during different times of the day. The rectal temperature is usually about 0.6 degrees C. (1.0 F.) higher than the mouth temperature and this difference is increased when the mouth has been cooled by taking cold food or liquid, by talking, or by breathing with the mouth open.

The temperature of the body is determined by the relation which exists between the amount of heat pro-
duced and the amount of heat eliminated. The heat produced depends upon the basal body metabolism and upon excesses above this resulting from muscular activity, the ingestion of food. Heat is lost mainly through conduction and radiation from the skin and through evaporation of water from the skin and respiratory tract. Under the usual prevailing conditions in a temperate climate from two to three times as much heat is lost by conduction and radiation as by evaporation; and since during rest the losses by evaporation are about equally divided between the skin and the lungs, it is evident that the skin is the main organ through which heat is lost from the human body.

The delicate adjustment which exists in the body between heat production and heat elimination is under the constant control of the central nervous system. The principle centers for heat regulation lie in or near the basal ganglia, but they have not been identified with any definite anatomical structures. These centers influence both the production and the dissipation of heat, and they in turn are influenced by afferent stimuli from the skin and mucous membranes as well as by the temperature of the blood which circulates through them.

We have seen that heat elimination is ordinarily accomplished mainly through radiation, conduction and
evaporation. The amount of heat lost by conduction and radiation is determined in part by the temperature of the skin, and this in turn by the rate at which the blood circulates through the cutaneous vessels. The circulation in the periphery of the body is very sensitive to changes which affect heat regulation. When exposed to room temperature sufficiently high to cause moderate feelings of warmth the blood flows through the arm usually increases to about twice the normal. It is evident, however, that if the external temperature is higher than that of the body, heat losses by radiation becomes the sole method of heat elimination. Since the rate of evaporation depends mainly upon the humidity of the air, the latter plays an important part in the physiological effect of warm climate. From the physiological standpoint the wet bulb thermometer gives far better indications of effective heat than does the ordinary dry bulb thermometer. When the humidity is low, evaporation takes place at a more rapid rate and far higher temperatures can be borne. Movement of air also assists evaporation from the skin and excessive heat is better borne when the air is in motion.

We have seen that in man the regulation against overheating is effected mainly by a dilatation of the cutaneous blood vessels and by an increase in the perspiration. These reactions are under control of the cen-
tral nervous system and they do not take place in an
extremity which has been separated from its central
nervous control. The nervous center seem to be guided
in this regulation against overheating by two factors:
(1) the temperature of the blood coming to them and
(2) reflexes from the warm skin. (9)

If the temperature of the nervous centers be raised
either by warming the carotid blood going to the brain or
by the direct application of heat through small tubes in-
troduced into the region of the corpora striata, the
various physiological changes that characterize the reg-
ulation against overheating take place. Apparently in man
also the temperature of the blood is an important factor
in setting in operation the mechanism for increasing
it heat lossed. Thus, Stern showed that when a person
is immersed in a moderately warm bath, sweating does not
occur at first, but appears when the body temperature has
been raised for 0.2 to 1.4 degrees F. (10)

Our conception of fever is based upon the reaction
seen in infectious diseases. This reaction consists in
part of an alteration in the body temperature together
with changes in the mechanisms which control this tem-
perature. The reaction consists also of various other
body responses such as the formation of antibodies. The
term fever is applied particularly to the reaction which
has to do with the elevation of body temperature, and in this broader sense may be due to many causes other than infections. That due to the parenteral introduction of foreign proteins or to the unusual destruction of protein substances within the body is most closely related to infectious fever. On the other hand, certain forms of hyperthermia are distinctly different from infectious fever. This is true of the rise of body temperature induced by exposure to moist heat where the normal regulation of the body heat is broken down by external conditions. This is caused by a lack of thermic regulation, whereas, in true fever, heat regulation is present but perverted. The former type is, of course, the condition produced in the Kettering Hypertherm.

The findings and observations of Aldrich in 1928 explain the physiology underlying the principle of the Kettering hypertherm. He did his work surveying the ventilation problems in the school buildings of New York City. He studied the amount of heat a person lost by radiation and the relations to the total loss of heat changes in air, motion and humidity has. His findings may be briefly summarized: (1) Increase in room temperature produces a progressive lowering of radiation loss; (2) Increasing the air motion decreases radiation loss; (3) Normal fluctuations in humidity indoors produce neg-
ligible effect on radiation loss.

Therefore the purpose of the Kettering hypertherm is to distort this normal ratio and set up a combination of conditions that will discourage heat loss from the body. This is accomplished by dropping the relative humidity from 80% (12) to between 35 to 45%, by increasing the temperature from 64 degrees F. to 145 to 150 degrees F., and by increasing the air velocity to 450 cubic feet per minute. Under these conditions heat loss from the body is greatly diminished so when external heat is applied the patient's temperature will rise. The temperature is maintained at the desired level by adjusting the humidity and the heating unit.

The following list of physiological effects to hyperthermia have been noted by different investigators.

**Bacteriolysis.**

*Gonococci:* Are usually destroyed at a temperature of 106 to 107 degrees for 5 to 23 hours (13).

*Streptococci:* No data.

*Spirochaeta pallida:* The thermal death is at about 103 to 106 degrees F. in about three to five hours. (22)

*Staphylococci:* Survives over 100 hours exposure to heat at 107 degrees F. (22)

**Blood Flow.**

*Pulse rate:* Increased up to from 130 to 150 beats per
minute. (23)(24)(25)

Circulation Rate: Increased. (23)(24)(26)

Cardiac output: Increased minute volume output. (24)

Blood pressure: Initial rise, subsequent fall. (27)(28)

Blood Volumes: No change, or slight concentration. (27)(28)

Viscosity: No change if intake is encouraged. (27)(29)

Nail-bed Capillaries: Increased in number and size. (29)

Blood Cellular Elements.

Erythrocyte count: Generally no change (29)

Erythrocyte, sedimentation rate: Little or no change. (30)

Increased. (29)(31)(32)

Leukocyte Count: Initial fall, subsequent rise to

15,000 per cubic millimeter. (24)(33)

Leukocytes: Increased rate of phagocytosis. (33)

Blood Chemistry.

Non-nitrogenous elements (urea, uric acid, creatinine);

No change (34) or slight increase (blood concentration). (35)(36)

Sugar, Phosphorous, plasma lipoids, serum calcium:

No change or slight increase (blood concentration). (35)(36)(24)(37)(38)

(39)(40)(41)

Inorganic Phosphorous: Converted to organic form. (38)(39)

Serum proteins: No change (32) or increase. (34)

Acid-base equilibrium: Altered in the direction of
slight alkalosis. (28)(38)(39)(41)

Chlorides: May be marked drop. (45)

Oxygen content and capacity of venous blood:
Increased. (38)(39)(46)

Carbon Dioxide combining power: Decreased. (28)(38)(39)(41)(47)

Blood-Immune Bodies.

Agglutinins: Variable data - rise (48) or fall (49)
Complement: No change (50), reduced (51)
Opsonic index: No change. (50)

Gastric Secretion.
Loss of Chlorides. (36)(45)

Sweat.
Loss of from 18 to 26 gm. of sodium chloride in from
3 to 4 liters of sweat in each session. (36) Increased lactic acid content. (51)

Urine.
Amount: Generally temporary oliguria. (34)
Reaction: Unchanged or slightly alkaline. (34)

Metabolic Rate.
Increased 7 per cent per degree of fever. (52)(53)(24)(29)

Electrocardiogram.
Contractions of lowered voltage. (25)(54)
CLINICAL RESUME

Fever therapy should be conducted only in institutions where the work can be properly organized. Treatment of this kind requires the constant attentions of nurse-technician who must be carefully selected and specially trained. Also, the treatment must be supervised at all times by a physician familiar with all the details of the method. The nurse must not leave the patient even for a minute while he is in the cabinet, and the physician must not go beyond immediate calling distance. If the treatments are conducted under these rules, and the patients are carefully selected, no major complications need be anticipated. (17)

In the selection of cases for treatment there are certain contraindications which have been listed as advanced age, cardiac and renal disturbances, arteriosclerosis, pulmonary tuberculosis, aortic aneurysm, rapidly progressive late neurosyphilis and abnormal conditions of the skin which interfere with adequate sweating. (13)

Pre-treatment

The patient should be given an enema the night before a treatment and be sure he gets a good night's sleep. A preliminary sedative should be given 2 hours before the treatment. Bromide grains 30, and luminal grains one,
seem to be an effective sedative.\(^{(20)}\) These are given p.r.n. during the treatment.

If symptoms of brain edema develop, the patient is removed from the cabinet and hypertonic glucose is given intravenously. Ten per cent glucose in normal saline should be given intravenously at the first sign of circulatory failure.

The fluid intake should be kept up during the treatment. Cold fluids are given with no bad effects. Two to four liters of 0.6 per cent saline should be given to replace fluid and chloride loss through perspiration. Vaseline around the lips cuts down the incidence of herpes.

Post-treatment

After the treatment the patient is cooled with an electric fan and sponging of the body. After two to three hours the body temperature usually returns to normal. Cold fluids are given. The patient is not allowed to leave the treatment room until the temperature has returned to normal. If temperature does not return to normal, ice bags to head, cold sponge baths, cold colonic flushes will bring the temperature down.

I will now consider a review of the results obtained by different men in the treatment of the different diseases.
Gonorrhea and its Complications

The gonococcus is one of the bacteria that we know the thermal death time. In 150 strains of the gonococci, in vitro, it is at 106 to 107 degrees F. from 6 to 27 hours. (21) This fact makes the treatment of gonorrhea and its complications especially suited to artificial fever therapy. When it has been possible to estimate the thermal death time of a strain present, a single application of a fever treatment at the temperature and for the necessary number of hours has been advocated. Immediate cure is almost always obtained in those treated in that manner. Good results have been obtained when one-half to three-fourths the thermal death time was given. This suggests the assistance of defense factors in the body. However, the determination of these thermal death times at the present time is not yet practicable, so most men favor a number of shorter treatments in place of the one long session. Their sessions are given not less than twice a week usually for 5 hours. The results from treatment of gonorrhea in the various anatomic sites have been excellent. Results of treatment of ninety-five men who had acute urethritis, of forty-four who had epididymitis, and of several who had prostatitis were excellent. Clinical and bacteriologic cures were obtained in 80 to 90 percent of cases reported by Book, Carpenter, Warren,
T. E. Anderson, Arnold, Trautman, A. E. Bennett, Austin, Desjardin, Hench, Popp, Sheard, Slomb, and Faget. (22)

W. Bierman and E. A. Horomitz of New York City combined the Kettering hypertherm treatment and the Elliot treatment and in forty-one patients he got bacteriologically negatives in thirty-seven after one to three treatments.

There were 143 cases of gonorrheal arthritis, reported by ten different physicians at the May, 1935, Fifth Annual Fever Conference, Dayton, Ohio. Seventy per cent became symptom free. Ten per cent obtained marked relief, and twenty per cent little or no relief. As a rule, the latter had an obstinate chronic type of infection. Much better results are obtained in the acute cases than in the chronic forms.

Kendell et al (13) report thirty-one patients with gonorrheal arthritis, associated with gonococcal infections of the genitourinary tract treated by the Kettering hypertherm. Of these 19 were patients with acute gonorrheal arthritis. After the course of fever treatments the average improvement in joint functions was 77.6 per cent. In three patients there was a complete restoration of joint function. The final average improvement in joint functions in the cases of acute gonorrheal arthritis was 98.4 per cent. Thirteen patients had complete restoration of joint func-
tions. Of the twelve patients with chronic gonorrheal arthritis, the average improvement in joint functions at the end of the course in fever therapy was 62.5 per cent. Four patients had joint functions completely restored. The final improvement in joint function in the cases of chronic gonorrheal arthritis was 38.3 per cent. The smears of the genitourinary tract of 24 of the patients were negative at the conclusion of the fever therapy course. Then, four more became negative in two weeks. Supplemental treatments removed the infection of the genitourinary tract in the remaining three patients.

Desjardine et al. (17) report twenty-nine cases of gonorrhea and its complications treated by fever therapy of which twenty-five were cured. They state that cures are more easily affected in men than in women.

Hench et al. (18) summarized twenty-four cases of gonorrheal arthritis with twenty-two (92 per cent) cured. Failure in two cases (8 per cent) due to inadequate dose of fever.

Carpenter, Book, Mucci and Warren (21) have shown that the thermal death time of fifteen other strains of gonococci in vitro is about five hours from 105.8 to 107.6 degrees F. Thus it is recommended by those who have obtained the best results in gonorrheal arthritis that each dose of fever be at least five hours at 106.7 degrees F.
Others have used an approximate dose (from three to five hours at 104 to 106 degrees F.) The majority have found that only one to three sessions of fever of five hours duration at about 106.7 degrees F. are necessary. When smaller doses were used the results were not as good and more sessions necessary.

The results obtained in treating gonorrheal infections and its complications has already been highly encouraging. Tenney(29) concluded that hyperthermia acts almost as a "specific" for gonorrheal arthritis. Simpson, Kestig and Settler (36) state "the results were uniformly successful". Hench, Slocumb and Popp (18) state "in gonorrheal arthritis, results are so striking and apparently so superior to those obtained by other methods, that we can prescribe fever therapy as the method of choice with considerable assurance".

Syphilis

At the present time the value of fever therapy in the treatment of neurosyphilis has been definitely established beyond any argument. However, there is still considerable difference of opinion as to what type of fever therapy is the best. There are those who believe the malaria treatment is the most satisfactory, and the other group where hyperpyrexia is artificially induced by some outside force such as the Kettering hypertherm.
The works of Carpenter, Book, and Warren (43)(44) have shown several things concerning the ability of the Spirochaeta pallida to withstand fever in vitro. They found that a series of unsustained fever ranging from 105.8 to 107.6 degrees F. would kill Spirochaeta pallida in rabbits with active syphilitic lesions. Also a sustained temperature of 106.7 - 107.6 degrees F. for six hours would destroy Spirochaeta pallida. In order to kill the Spirochaeta pallida it required five hours at a temperature of 102.2 Degrees F., three hours at 104 degrees F., two hours at 105.8 degrees F., and one hour at 106.7 degrees F. These experiments have been confirmed by Simpson. (42)

The accepted fever course for the treatment of syphilis is ten weekly treatments of five hours duration with the fever sustained above 105 degrees F.

Simpson (42) suggests that he has used fever therapy in conjunction with chemotherapy in the treatment of early syphilis. He states that he gets better results using the two combined than of either used separately. He gives the antisyphilitic drug an hour before the beginning of the fever treatment on the basis that the general vasodilatation which occurs during the treatment may permit a greater diffusion of the chemical substances.

He treated twenty-six patients who had primary or
early secondary syphilis with the combined fever and chemotherapy. The cutaneous manifestations disappeared rapidly. The Kahn and Kolmer serologic reactions were reversed to negative in fourteen were less positive in two, remained negative in one, and remained positive in one. The ten who became less positive and the one who remained positive had only been under observations for a period of six to nine months. There has been no clinical or serologic relapse in these patients treated in this manner. He also ran two control groups of patients. Six patients received only fifty hours of fever above 105 degrees F. In two of these there were relapses with the appearance of cutaneous eruptions. In the other four the serum became less positive in three and negative in one. The second group of fourteen patients received thirty weekly injections of Chemotherapy. Of these there were two that had relapses with the appearance of cutaneous lesions. Fever therapy was instituted with prompt disappearance of the lesions. Of the remaining twelve the serology was reduced to negative in five, less positive in six, and more positive in one.

However, as Stokes (42) points out, one must remember that Chemotherapy is available to everyone and has much proven data behind it, while fever therapy is new and at present only available to a limited number, so we
should continue our chemotherapy always and combine it with fever if we can and when we think that it is indicated.

Simpson (42) reports twenty cases with dementia paralytica that he treated with fifty hours of fever therapy and thirty injections of chemotherapy. Twelve had complete clinical remissions and two were restored to a working condition. Therefore, 70 per cent were socially rehabilitated. Four patients were fifty per cent improved and two called twenty-five per cent improved. No relapses have followed treatment. Six of these had had advanced dementia paralytica and four had been in a hospital for mentally diseased. The Kahn and Kolmer serologic reactions were reversed to negative in four, less positive in nine. Spinal fluid reversed to negative in five, less positive in seven, remained positive in six, became more positive in two.

Ten patients with tabes dorsalis who had received chemotherapy were given fever therapy. The root pain was abolished in all ten. One so-called cord bladder was cured. Two ataxic patients restored to normal gait. Six showed improvement in gait and two no improvement in gait.

The combined treatment was given seven patients with the tabetic form of dementia paralytica. They had all had previous chemotherapy and one had had malaria therapy.
There was improvement in mental orientations in six of the patients. One showed no improvement and died seven months later. Disappearance of root pain occurred in all. Four of the five ataxic patients were improved. One patient who had had an ataxic gait for three months was restored to a normal gait. Another had a cure of his cord bladder.

In a series of seven so-called Wassermann-fast patients the serology was reduced to negative in four, became less positive in two and stayed positive in one.

Tuberculosis

Experiences with thirty-four cases of pulmonary tuberculosis indicates that fever therapy is of no definite value and is sometimes harmful. (22) Cavities remain unclosed and sputum remains positive. Fever stimulates metabolism which is known to be harmful in tuberculosis.

Chorea

In a report of twenty-eight cases at the Fifth Annual Fever Conference there were reported very good results. Many were cured and most were notably improved. Associated endocarditis was not a contraindication.

Subacute Bacterial Endocarditis

The report of eight cases indicate that life was made more comfortable and death postponed for a short time. The blood cultures remained positive. There is a danger of emboli due to the increased velocity of the circulation.
Asthma

Treatment of twenty-five cases of intractable asthma of the allergic type that had not been relieved by other forms of treatment, gave 75 percent notable remissions for one to seven months. More treatments gave subsequent remissions.

Peripheral Vascular Disease

It appears that we should be satisfied at the present in inducing vasodilation in these diseases instead of trying to kill some unknown organism. A temperature higher than 102 degrees F. is likely to cause burns due to the poor conditions of the circulatory system.

Staphylococcal Infections

The staphylococci will live over 100 hours in a temperature of 107 degrees F. and so cannot be effected by fever therapy.

Multiple Sclerosis

Satisfactory remissions were obtained in 50 per cent of seventeen cases reported by A. E. Bennett and E. Austin of Omaha, Nebr., and H. W. Hipke of Milwaukee.

Non-specific Arthritis

The results of fever therapy in non-specific arthritis have been disappointing. There were 128 cases reported at the Fifth Annual Fever Conference at Dayton last May and less than 10 per cent became symptom-free. Some 30
per cent received some relief. Best results were obtained in the acute cases.

Hench (18) concludes that of all patients with chronic infectious arthritis, approximately 10 per cent become symptom-free, about 25 per cent are markedly relieved, about 35 per cent were moderately relieved, and about 30 per cent received no relief. Experience has not been broad enough as yet to determine what fever dosage should be used in these cases. They have been using five hour treatments of from 104 to 105 degrees F.

Miscellaneous Conditions

Preliminary observations indicate no marked effect in pyelitis, glomerulonephritis, epidemic encephalitis, or Parkinson's disease. Good results were noted in six cases of osteomyelitis of long bones and in two of intractable osteomyelitis of facial bones.

Sciatic neuritis has been helped.

Mortality

The Council on Physical Therapy of the American Medical Association recently reported the treatment of 4,809 patients with 29 deaths, a mortality of 0.6 per cent. (22) Simpson's last series of 400 cases had no mortalities. They have had one death in 300 cases at the Mayo Clinic.
The following will be a very brief report of clinical observations and results obtained in the work of the University of Nebraska Division of Fever Therapy at the Lutheran Hospital of Omaha, Nebraska. I am using these through the kind permission of Drs. A. E. Bennett and J. P. Person.

The following chart shows the type of cases, the number of cases, and the number of treatments given between November 1, 1934 and March 1, 1936.

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. Cases</th>
<th>No. Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral Syphilis</td>
<td>13</td>
<td>77</td>
</tr>
<tr>
<td>Spinal Syphilis</td>
<td>28</td>
<td>185</td>
</tr>
<tr>
<td>Syphilitic Interstitial Keratitis</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Tabo Faresis</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>6</td>
<td>33</td>
</tr>
<tr>
<td>Chorea</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Rheumatic Fever</td>
<td>7</td>
<td>30</td>
</tr>
<tr>
<td>Toxic Psychois</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Meningococccemia</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Infectious Arthritis</td>
<td>54</td>
<td>233</td>
</tr>
<tr>
<td>Hypertrophic Arthritis</td>
<td>13</td>
<td>62</td>
</tr>
<tr>
<td>Gonorrheal Arthritis</td>
<td>26</td>
<td>104</td>
</tr>
<tr>
<td>Gonorrhea-Men</td>
<td>68</td>
<td>226</td>
</tr>
<tr>
<td>Gonorrhea-Women</td>
<td>24</td>
<td>91</td>
</tr>
<tr>
<td>Chronic Sinusitis</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Asthma</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Dermatitis Herpetiformis</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>2</td>
<td>23</td>
</tr>
<tr>
<td>Malta Fever</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Subacute Iritis</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Bacterial Endocarditis</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Sclero Derma</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>C. C. Ophthalmritis</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Neuritis</td>
<td>27</td>
<td>91</td>
</tr>
<tr>
<td>Functional Psychosis</td>
<td>9</td>
<td>31</td>
</tr>
<tr>
<td>Synovitis</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Arteriosclerosis</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Myositis</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Lues Systemic</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>335</strong></td>
<td><strong>1538</strong></td>
</tr>
</tbody>
</table>
The following is a summary of the results obtained in the treatment of the above cases.

Cerebral Syphilis: 100 per cent of cases returned to normal working status.

Spinal Syphilis: 100 per cent relief of gastric crisis and pain. 100 per cent increase in general condition. 70 per cent improvement in ataxia and cord bladder symptoms.

Tabo Paresis: Same as Spinal Syphilis.

Syphilitic Interstitial Keratitis: This one case cured. Has normal vision.

Multiple Sclerosis: In early cases 25 per cent had almost complete remissions with no recurrence to date. In moderately advanced cases 50 per cent had almost complete remission with slight recurrence in 3 - 6 months. In advanced cases 10 per cent had good remissions with recurrence 3 - 6 months.

Encephalitis: No improvement.

Chorea: Relief usually immediate. Remissions lengthened. Most active cases respond best. Six three-hour treatments for a total of 18 hours of 103 - 104 degrees F. usually suffices. Treatments may be given at 3 - 5 day intervals.

Rheumatic Fever: Excellent results.

Toxic Psychosis: Excellent results.

Meningococcemia: Only case treated was cured.
Infectious Arthritis: In early cases 50 - 75 per cent obtain relief of pain. In late cases 30 - 50 per cent obtain relief of pain.

Hypertrophic Arthritis: 50 percent of cases receive relief of pain only.

G. C. Arthritis: 95 per cent of cases receive immediate cure.

Gonorrhea - all types: 80 to 90 percent cure.

Chronic Sinusitis: No results.

Asthma: An appreciable number of individuals with intrinsic intractable asthma may be given long remissions.

Dermatitis Herpetiformis: One case has been completely relieved for two months.

Bronchiectasis: Marked improvement in both cases.

Malta Fever: No results.

Subacute iritis: Excellent results.

Bacterial endocarditis: No results.

Sclero Derma: No results.

G. C. Ophthalmitis: Excellent results.

Neuritis: Good results.

Functional Psychosis: No results.

Synovitis: Same as G. C. Arthritis.

Arteriosclerosis: No result.

Myositis: Good result.

Lues Systemic: Good result.
There have been two main types of sedation used at
the Lutheran Hospital. (55) One is barbiturates in large
doses just before treatment. This gives fair sedation.
When combined with pantopon by hypodermic it is sufficient
for most patients. The other is Sedormid in massive doses
starting twelve hours before treatment and combined with
Pantopon by hypo. It has been used for only a short time
and seems more successful than the barbiturates. It has
the disadvantage of a prolonged action which renders the
patient groggy the day following the treatment.

Complications.

85 per cent develop herpes simplex with the first
treatment.

30 - 40 per cent of gonorrheal treatments have first
degree burns. Burns are treated with Amertan.

10 - 20 per cent of leustic group have first degree
burns. Burns rarely occur in all other treatments.

1 per cent develop brain edema which readily re-
sponds to hypertonic glucose intravenously, together with
ordinary methods for lowering body temperature. The syn-
drome has many features of ordinary heat exhaustion, ex-
cept the heat regulatory center rapidly gains control with
the above stated aids. The appearance of brain edema is
not a contraindication for future fever therapy treatment
for that patient.
Carbon dioxide and oxygen mixtures are useful in these cases to stimulate respirations. This is sometimes combined with ecoramine, caffeine and occasionally adrenalin as indicated.

3 - 5 per cent of cases develop tetany with carpopedal spasm and muscular twitchings. This condition responds rapidly to intravenous calcium gluconate.

There has been two fatalities. One was a senile arteriosclerotic with cirrhosis of the liver, the other an elderly chronic alcoholic with cirrhosis of the liver. Autopsy on both showed above mentioned cirrhosis of liver, moderate cerebral edema, slight pressure cone, and punctate hemorrhages around the base of the brain.

Any patient not a good surgical risk is not a good risk for fever therapy. Chronic alcoholics are especially hard to handle and do not take the treatments, well.

Before and between treatments, patients are instructed to drink one quart of milk per day to give them calcium, to have a high salt diet, plenty of rest, and force fluids.

During the first hour of treatment the patient is restless, but otherwise not uncomfortable. Patients frequently become panicky during the first hour and further sedation is required. The high temperature together with sedation produces a mild delirium in a small per cent of cases. This disappears following treatment. Sensations
of nausea and even vomiting occurs with some patients, particularly those that drink large amounts of the weak saline solution during the treatment.

There are two main ways in which fever therapy acts in curing disease. One, as in the treatment of gonorrhea, the body temperature of the patient is raise above the lethal point of the organism and actual sterilization occurs. In the other, the body temperature is deleterious but not lethal. Additional factors are marked dilatation of all peripheral blood vessels, the marked increased velocity of blood, the leucocytosis, increase in immune bodies of all types for several hours following the treatment. The efficacy of all medication is apparently increased, probably on the basis of increased circulation and peripheral dilatation.
SUMMARY

1. Fever therapy has a definite place today in the treatment of disease.

2. The Kettering hypertherm is probably the best, safest and most accurate method of hyperpyrexia induction.

3. Fever therapy produces highly satisfactory results in treatment of gonorrhea and syphilis.

4. Fever therapy has satisfactory results in various other diseases.

5. Fever therapy has been somewhat disappointing in the treatment of non-infectious arthritis.

6. Results obtained in the Fever Therapy Unit of the University of Nebraska compare favorably with those obtained elsewhere in the United States.
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