Induced pyrexia: a resume of artificial fever therapy with especial emphasis on recent methods

Robert F. Day
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INDUCED PYREXIA

A Résumé of Artificial Fever Therapy with Especial Emphasis on Recent Methods

By

Robert F. Day

Senior Thesis
University of Nebraska
College of Medicine
1935
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INTRODUCTION
Fever, long regarded as a thing of dread by the medical profession, has been transferred from its phobic role and added to the therapeutic armamentarium of the modern physician. Allegorically speaking, fever has been a "Dr. Jekyl and Mr. Hyde." We are again at the fork in the road, this time following fever as a useful member of the therapeutic highway in contrast to an era of antipyrexia.

Jones (66) states "we are arriving at a more sensible, biological interpretation of fever; instead of striving to reduce the height of fever, we are seeking methods by which we may safely raise the body temperature. Many workers are adding to the testimony of the beneficial effects of this fever which we have feared."

The value of fever is still not appreciated. In our present concept, fever should be regarded as a natural factor produced within the body to aid in destroying an infectious agent and to repair tissue injury. Fever is a part of the defense mechanism of the body and in this capacity is probably equally as important as phagocytosis or antibody production. Furthermore, it may be responsible for the other processes associated with the production of a local or general immunity (62).
HISTORY
HISTORY*

Fever as a therapeutic agent had its origin in antiquity. It was an early observation that mental patients improved following intercurrent diseases accompanied by high fever. However, the knowledge of its beneficial action was empirical and enshrouded with magical formulas and superstitions. Hippocrates and Galen knew that diseases with fever may act favorably on "psychoses". Boerhaave and Sydenham reported similar observations.

Hot baths as therapeutic agents probably had their inception in Greece, where the natural thermal springs were converted into capacious baths. Devices, elaborate in their construction were conceived and dedicated to its administration. Attention focused largely on the temperature of the bath and little on the fever produced in the patient. Frequently a death occurred. The baths were administered by priest physicians and were renowned for their curative virtues. Acute and chronic diseases of infectious origin were treated with hot water and steam baths by our own American Indians as well as by the Ancient Egyptians, Chinese, Jews, Japanese, Negroes of tropical Africa and other aboriginal tribes. Luxurious baths with elaborate heating plants, some of which occupied many acres of territory, were built by the Romans. These baths were the meeting place and social center of Rome, and came to flourish, although in less ostentatious buildings throughout the dark ages. Syphilis, probably imported from America, made these communal baths more unhygienic and added the danger of infection for this was not only a place of social but venereal pleasures as well....and venereal infections. As we would expect, under these conditions

* Gleaned from (64), (36), (37)
Syphilis spread; public opinion associated, and rightfully so, the spread with these institutions; consequently, the bath-house fell into disrepute. A period of poor personal hygiene and bodily filth then became common throughout Europe, bathing being relegated to monthly or bi-monthly baths in wooden tubs in the home. Hot bathing was still considered of value, especially in Finland and Russia, where a steam room closely adjoined the main domicile of many of the peasants. Dr. Claude W. Mason in his lectures on "Tropical Medicine" at the University of Nebraska describes the hot baths of the Finnish people of the present generation. "They heat large stones until it seems the stones would almost burst with the heat. These are then placed on the floor of their bath-house and water poured over them, so that the room is filled with live steam. They then take their steam bath until their skin becomes a fiery red and they are almost par-boiled. Then to top it off, they run from the house and dive into a nearby lake, and beat themselves with branches of young trees until their skin again becomes fiery red."

The Japanese were the first moderns to use intensely hot baths for therapeutic purposes, being aided by the natural hot springs due to volcanic formations of the islands. Neymann and Osborne (65) describe the baths of the Japanese: At Kusatsu, water gushes out of bases of ancient volcanoes at a temperature between 100 and 160 F. There are large communal tanks 4 feet deep, at a temperature between 115 and 128 F. The baths are unbearably hot, so are cooled somewhat as bathers stir it with large wooden paddles. They immerse themselves to the neck and pour hot water over their heads with wooden dippers. They remain in the baths for variable periods chanting songs while the bath master shouts encouragement from
time to time. In about six minutes they are almost par-boiled and bob out with temperature of 103 to 105 F. The temperature continues for a long time and they take about five baths daily. The baths are used for the treatment of Syphilis, Arthritis, Rheumatism, Acute Genito-Urinary infections, Respiratory, Nervous, Digestive and Ocular diseases. The therapeutic effect was formerly attributed to the mineral content. They have been popular throughout the empire since the sixteenth century and locally for several centuries before.

The laity has always been certain of the curative value of external heat. Parents use hot baths as treatment followed by sweats to overcome bad colds and respiratory infections. This form of home treatment has been handed down from mother to daughter for generations. Sweat baths were prescribed by the general practitioner of the middle and nineteenth century and act on a perfectly logical basis of common sense and experience.

In 1848 Koster studied the influence of malaria on mental disease and the erection of an insane asylum in a place that was constantly exposed to intermittent fever was considered.

In 1853 Kostl reported a cure or, at least great improvement in a case of dementia paralytica after the patient had had small-pox.

Schlager in 1857 reported six psychotic patients out of eleven cured after having had typhoid.

Nasse in 1864 noted the favorable influence of malaria on mental disease and pointed out the especially striking results in dementia paralytica. In 1864 and 1874 Rosenblum, in Russia, made use of relapsing fever and malaria in the different psychoses,
HISTORY

syphilitic and non-syphilitic. He did not succeed in gaining followers, but the influence of acute febrile diseases upon paretics was too obvious to be unobserved indefinitely.

In 1883 Phillips demonstrated that temperature could be raised to 103 F. by immersing himself in a hot water bath. He noted the increase in pulse and respiration. This fact had to be rediscovered from its hiding place in the Columbus Medical Journal several times before its importance was appreciated.

Also, in 1883, Fehrleisen reported the cure of lupus following the local injection of a pure culture of streptococci from a case of erysipelas. Old Medical literature contains numerous references to the beneficial effects of a secondary infection in acute diseases.

In 1886 Emmerich was able to save animals from Anthrax by the intravenous injection of living streptococci. Powlowski, a student of Virchow's, observed similar cures in Anthrax by the injection of cultures of the bacillus of Freidlander, B. pyocyaneus, and other bacteria.

Wagner von Jauregg et al made their original proposals in 1887. Wagner-Jauregg was the most persistent in imitating nature's method. He first tried to inoculate patients with erysipelas but was able to cause only a circumscribed infection in the skin. He next used tuberculin but was unable to obtain repeated marked changes in temperature. However, he persisted in this treatment and after ten years reported the results in 69 patients. He thought he had been able in many of these to produce more frequent and more prolonged remissions but no cures. He then tried larger doses of tuberculin. With this modification, he obtained a few lasting remissions; and
the patients were able to leave the institution and return to work. Whether this improvement was permanent in any of these cases is not recorded.

Later Wagner-Jauregg used Besredka's polyvalent typhoid vaccine, which contained living typhoid bacilli whose virulence had been reduced by mixing with typhoid immune serum. This vaccine was given intravenously in increasing doses. The frequency, degree and duration of the remissions were much better than with tuberculin. In the twenty years succeeding his original proposal he was deflect- ed from the direct approach to the subject by intermediate experimen-
tation with non-specific protein pyrexia. Wagner von Jauregg had noted the great improvement in psychiatric patients following some intercurrent acute infection and he attempted to reproduce this in-
fection in patients with dementia paralytica.

Buchner, in 1890 showed that killed cultures of bacilli were equally as efficient as the live bacilli.

Following Frankel's report on the value of typhoid vaccine given subcutaneously in typhoid, Rumpf demonstrated that the same results could be obtained by repeated intramuscular injections of large doses of pyocyaneus vaccine.

As early as 1907, preparations of sulphur were made for sub-
cutaneous injection by the French, chiefly Louis Bory, Delehaye and Piot, and Fleig. Strangely enough, in view of the recent use of injections of sulphur to produce fever, these authors claimed that it reduced the temperature in cases of bronchopneumonia and pulmonary T. B. Nothing of importance then appeared until in 1914 Ichikawa reported that typhoid could be aborted by the intravenous injection of either typhoid or paratyphoid vaccine.
Kraus and Mayza from Argentina reported that colon bacillus vaccine, given intravenously, would abort typhoid. The following year Ludke demonstrated that the same results could be obtained by using a solution of proteose. Hence the name "protein therapy".

In 1917 Wagner von Jauregg inoculated his first patients with malaria. Two of the four patients who were treated at this time, and who showed marked improvement, were still working at their former occupations in 1925. Subsequent to his work, these treatments were begun on a large scale in the Hamburg Clinics of Weygandt and Nonne.

Weichbrodt and Jahnel in 1919 used hot water for the purpose of elevating the temperature of syphilitic rabbits.

In 1921, Meyer-Bisch and Basch reported the use of sulphur in injections of oil for the treatment of arthritis, and studied the abnormal metabolism occasioned by such injections.

Sulphur in oil was suggested for the treatment of dementia paralytica in 1925 by D. F. Tutunji.

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

In 1927 Schamburg and Tseng used hot water to raise the temperature in humans suffering with Syphilis.

Walinski in 1928 introduced hot air for causing induced pyrexia. King et al first applied diathermy to a case of paresis in October, 1928. They repeated some work done by Carl A. L. Benger and Ronald Chrestir, who definitely proved that the general body temperature of animals could be raised by a high frequency current. Rosanoff, a psychiatrist, independently revived the hot bath in this year. Walinski and Rosanoff, independently rediscovered
Phillips method (1883) i.e. raising the body temperature by means of external heat.

In 1929 Mehrtens and Pouppirt, psychiatrists used hot air in central nervous system syphilis.

Neymann and Osborne (65) describe the application of the diathermic apparatus to the field of induced hyperthermia: "Our own thoughts about the therapeutic problems of general paresis brought about our own researches. General paresis is benignly affected and sometimes cured by malaria, recurrent fever and rat-bite fever. Many years ago paresis was treated by threading horse hairs under the skin of the chest of patients, and thus producing huge abscesses, and occasionally by allowing patients to become infected with erysipelas. The injection of bacterial toxins e.g. tuberculin and typhoid to ameliorate the disease is a recent discovery. Milk, suspensions of sulphur in oil, turpentine, and many different foreign proteins have also been used for this purpose. In 1925 Neymann decided that all these had one thing in common i.e. an elevation of temperature. He also knew that the diathermic current produced the sensation of warmth and probably heat within the tissues. He next thought of the possibility of passing high frequency current through the head of a paretic, heating up the brain and thus curing the patient. This was later proven impractical because it was impossible to penetrate the skull with an intense diathermic current without burning the soft tissues and even if a slight heating of the brain occurs, it is promptly barred off by the blood stream. Without coagulation it is impossible to produce a slight elevation of temperature and an active hyperemia by local diathermy.

"In 1925 a physicist was consulted about this problem. The information was given that the diathermic current produced little,
if any, heat within the tissues. Lately this fallacy has been reiterated by two physicians. During the course of unsuccessful attempts to heat up the brain of dogs, we found the body temperature of the animal increased a little, and therefore conceived the idea of elevating the whole body temperature by means of the passage of large amounts of current through electrodes placed on the chest, abdomen and back. In this way, electropyrexia, first came into being. Many discouragements and slow up-hill progress marked our efforts. Production of artificial fever in man can now be said to depend only upon two factors, proper insulation so that the heat obtained is not dispersed into the atmosphere, and proper electrodes which will allow sufficient current to flow through the patient.

"Shortly after we completed our early experiments with diathermy, another group in the East conducted similar experiments with radio waves, which resulted in the radiotherm, a machine which requires no electrodes in direct contact with the patient, but which is costly to operate and sometimes inclined to catch on fire. In its present form is more spectacular than practical. A little later another group became interested in electric heating blankets. This type of treatment is a mere variant of the electric light cabinet method of Walinski."

Simpson of Dayton originated the idea of air-conditioned cabinets through experimentation with the small hot air blowers employed in the radiotherm apparatus for the evaporation of moisture from the patients and for maintaining the temperature after it had been raised by short radio waves. Simpson discovered in the summer of 1933 that patients' temperatures can be raised and maintained consistently by air-conditioning alone without resort to radio waves. His cabinet has proven the most satisfactory apparatus yet devised for routine artificial fever therapy at high temperatures.
PHYSIOLOGY
Hewlett (67) has concluded that: "The febrile temperature is primarily due not to an increase in heat production or to an absolute inefficiency in heat dissipation but to a lack of adjustment between the two."

According to Liebermeister, the heat regulation in fever behaves as if the regulatory centers were "set" to maintain the body temperature at a new level, which new level is maintained in much the same manner as is the normal temperature. More recent writers speak of an increased excitation or excitability of the heat centers which causes them to regulate the body temperature at the new and higher level (67).

During continuous fever there is usually an increase in the total heat production from ten to forty per cent above the normal. Increased heat production alone will not explain the rise of temperature encountered in the febrile state. During moderate exertion, the body can and frequently does eliminate far larger amounts of heat without a significant rise in temperature. More important than increased heat production in producing the febrile elevation of temperature is a relative insufficiency in the heat elimination. The circulatory flow is somewhat slower through the extremities in continuous fevers and the insensible perspiration is but moderately increased, whereas if the temperature of a normal individual be raised to 100.4°F., an increased blood flow through the extremities and profuse sweating is noted (67). In experimental pyrexia the flow through the superficial capillaries, venules and veins appears rapid, and these vessels are much dilated i.e. there is a diminished peripheral resistance (62). However, heat dissipation will also be manifest in the febrile individual if his temperature be artificially raised.
above the temperature of his febrile state. Finally, the febrile patient maintains his body temperature against agencies which tend to reduce it just as the normal person does, i.e. when exposed to cold, his skin vessels contract and he shivers (67). Von Euler has advanced evidence that the blood of fever patients contains some epinephrine-like substance capable of inducing constriction of skin vessels (62). The assumed vasodilation in the muscle area in the early stages of fever may balance the vasoconstriction in the skin and give a decrease in the average peripheral resistance. In this case artificial pyrexia and fever may both be accompanied by lowered peripheral resistance and differ only in the area in which resistance is mainly lowered. In fever, the area mainly involved may even differ according to the stage of fever (49).

THE EXISTENCE OF HEAT CENTERS AND HEAT NERVES

According to Howell (68) "Most physiologists probably are inclined to believe that the variations in heat production and heat dissipation are controlled through excitation or inhibition of the recognized mechanisms, which may be tabulated as follows:

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<th>1. The motor nerve centers and the motor fibers to the muscles.</th>
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"But it may well be that the activity of these mechanisms is controlled and coordinated through a special heat-regulating center in the brain. It seems necessary to assume the existence of some such device to explain the almost constant balance that is main-
tained at the set level of the normal body temperature, and the alterations in this level which we witness in the case of fevers of different intensities."

Modern literature dealing with temperature control appears to become more and more concordant in ascribing the main function of this control to the hypothalamus. Bazett (48) advances evidence to support the hypothesis of the importance of the hypothalamic area. It consists of a histologic study of the brain stem in a small series of cats in which the presence of temperature control to a greater or lesser extent was demonstrated after decerebration at a somewhat anterior level.

NITROGENOUS METABOLISM IN FEVER

During fever there is practically always a negative nitrogen balance. Attempts to overcome this by feeding high protein diets results in an increased nitrogen excretion so that a negative balance still remains. In some cases, the protein loss is equivalent to 200 to 500 grams of muscle per day. During convalescence there is a nitrogen retention and a gradual replacement of the protein lost during the febrile period (67).

Uric acid and purine bases, as well as creatinine, are excreted in increased amounts during fever. The increased excretion of uric acid and purine bases indicate an increased catabolism of nucleoproteins in the body. The increase in creatinine indicates destruction of muscular tissue.

At the present time there seems to be no proof of a definite qualitative change in the character of the protein metabolism during fever. That such a change may be present is suggested by the extensive degenerations in the tissues seen microscopically, and by the epicritical elimination of urea which may well be
derived from degenerated tissue.

Observers in searching for the cause of the increased protein decomposition which occurs in the febrile state are agreed that there are many causes, among which may be mentioned the increased temperature of the body. Another factor in the causation of the increased protein metabolism is partial starvation. A further cause is a resorption of inflammatory exudates, such as takes place during the course of pneumonia, acute rheumatic fever, pleurisy and other conditions.

There appears to be a specific protein destruction in fever which cannot be entirely overcome by dietary measures. (67).

NON-NITROGENOUS METABOLISM

On the usual fever diet about 80 per cent of the heat production is derived from non-nitrogenous material. It is probable that the carbohydrate reserves of the body are rapidly depleted and that the considerable fat metabolism (calculated by Grafe) is due to the partial starvation. With an adequate supply of carbohydrates the combustion of fats as well as of proteins can be restricted.

SALT AND WATER RETENTION

During fever there seems to be a physical or chemical change in the body which leads to a retention of salt and water in the tissues. Concomitantly the concentration of sodium chloride in the blood is abnormally low during the period of salt retention. It thus differs from nephritis where the concentration of chlorides in the blood is relatively high. There is considerable evidence that a redistribution of water takes place in fever, more available water being present in the tissues and less in the blood (67). There is a definite relation between water intake and loss of water by perspiration (2).
Bazett, McGlone, Williams and Lufkin (51) studied the depths of the end-organs to determine their mode of stimulation and thus have an anatomical and physiological foundation for a study on the temperature changes which accompany temperature sensations. These writers reported histologic studies of fresh tissue removed at circumcision. In this tissue, the spots sensitive to cold vary in number from six to twelve per square centimeter, and have an estimated depth of about 0.1 mm. Bazett, McGlone and Brocklehurst (50) show that "a comparison of the latency of sensation with the time taken for heat penetration also allows an approximate calculation of the probable depths of the end-organs concerned." End-bulbs of the Krause type have a distribution similar to the cold spots and average about fifteen to the square centimeter. Spots sensitive to warmth in the prepuce and dorsal skin of the penis are few in number i.e. one or rather less per square centimeter and have a calculated depth of 0.3 mm. These sensory spots are commonly definitely related to visible veins, and the spread of thermal changes along the veins is apt to give mild and somewhat diffuse sensations of warmth. Ruffini end-organs have a distribution agreeing fairly well with that of the warm spots and a depth of about 0.28 mm. (51)

Ebbecke experimented on the temperature sensations that are induced in a limb on release of a circulatory stasis which has been maintained for some time and concluded that sensations of both warmth and cold depended on thermal gradients of varying intensity set up at depths as warm blood entered cooled skin or vice versa. Goldscheider and Hahn criticized and showed that if his experiments were repeated quite different sensations, or no
SENSATION

sensation at all, might be induced if the time intervals employed were varied. Bazett and McGlone (53) noted in the course of their experiments that an intense sensation of warmth might be induced on the release of stasis without any change in temperature level, or the induction of any thermal gradient, so that it might appear logical to assume a chemical stimulus of some type.

EFFECTS OF TEMPERATURE RISE ON THE BODY

Many investigators have studied the temperatures which seem to be safe for the organism to safely withstand. Much of this experimentation has been with animals. Carpenter and Warren (62) have shown that a temperature of 42.5°C is safe for normal dogs, rabbits and guinea pigs, if the temperature is not maintained for more than five hours at this level. Knudson and Schaible (63) have shown that young rats may be exposed to an ultrahigh frequency field for periods of one-half to one hour daily with a rise in body temperature to 40.5°C without any appreciable retardation of their growth, any loss in power to breed, and no abnormal pathologic lesions are produced. These same authors report in another paper (64) that dogs may have their temperature artificially raised to 42°C and their temperature will return to normal quite rapidly, whereas, animals heated above 42.5°C for any great length of time do not survive. Dogs heated momentarily to 44.5°C have survived, however (64).

Observations of man have indicated that a rectal temperature of 41.5°C is safe for a five hour interval, provided, of course, that there are no severe lesions of the cardiovascular system, kidneys or lungs. In some instances, a temperature of 41.5°C was maintained for seven hours in the patients of Carpenter and Warren (62), with brief intervals during which the rectal tempera-
EFFECTS OF TEMPERATURE RISE ON THE BODY

Dr Lynn Hall states that the highest temperature on record and a surviving patient is 113 F. rectal. Excessive heat to the surface of the body has a marked tendency to upset the heat regulating mechanism, thus causing heat stroke (3).

TEMPERATURES OF VARIOUS REGIONS OF BODY

It has long been known that there is a wide variation in the surface temperature of various regions of the body. Neymann and Osborne (2) found that the subcutaneous temperature becomes less and less as one proceeds with thermocouple measurements distally from the thorax and abdomen where the temperature of the depths is about two degrees warmer than the subcutaneous temperature. The temperature of the ankle joint is about a degree F. less than just below the gluteal region and may be as much as three degrees cooler than the subcutaneous temperature of the abdomen. This ratio is maintained whenever penetrating heat is used, but when external heat is used for elevating the body temperature, this ratio is gradually reversed. Exposed or partially exposed surfaces rapidly cool and the temperature of any part near the source of heat rises more quickly than that of other parts. These authors found that the temperature in the lumbar spine, rose rapidly, when penetrating heat was used, to 106 F. but fell over a degree after the current had been turned off. The rectal temperature lagged behind for awhile, but finally exceeded that of the lumbar spine and remained above 108 F. for four hours. The temperature of the cisterna magna, which they believe closely approximates that of the brain itself, was about half a degree lower than the rectal temperature at the height of treatment, and at this time, axillary and lumbar temperatures paralleled the temperature of the cisterna. The subcutaneous temperature of the upper thigh remained lower
TEMPERATURES OF VARIOUS REGIONS OF BODY

during the entire time. There is a quick rise of all subcutaneous temperatures when external heat is applied. With diathermy treatment, the temperatures of the liver, rectum, and deep thigh are parallel, while that of the superficial thigh is between one-half and one degree lower.

EFFECT OF FEVER ON METABOLISM

Dubois has shown that, in general, the rate of metabolism follows Van't Hoff's law; namely, that for every 1 degree C. rise of body temperature there is a 13% increase (67). Metabolism is increased in pyrexia of both origins i.e. infectious and experimental (49). Tenney (60) reports "the rate in one of the arthritic cases was minus 29 before treatment; at a temperature of 104 F., it was plus 6 and after treatment it was plus 1."

CIRCULATION IN PYREXIA

The cardiovascular changes seen in fever are closely resembled in artificially induced fever. An increased pulse rate of 8-10 beats per minute per degree rise over 98.6 F. is noted in both types of fever. Bazett (49) has shown that the pulse rate tends to be faster at any given level when the temperature is rising than when falling. Irregularities, partially dependent on variations in the rate of temperature change, are due to physico-chemical alterations, not to Vagus or Splanchnic stimulation or inhibition. Reflexes play a minor role and probably is the factor responsible for the sudden acceleration of the pulse in beginning circulatory failure induced by exposure to heat; and may also be responsible for the increase in pulse rate above the normal fever level, which may accompany infections with symptoms of toxemia. Grollman has demonstrated an increase of 30 percent in minute volume in man on exposure to mildly warm air ("humidity maintained low to avoid discomfort"). The pulse rates reported did not exceed 85
per minute, an increase of 45 per cent, and the increase in body temperature was described as "slight" (49). Microscopic studies of the capillaries of the nail beds showed an increase in the size and number of capillaries during the height of fever (60). Increases in the minute volume accompany experimental pyrexia but are probably smaller than the changes in pulse rate (49). There is an increase in the size of the wheal in the histamine skin tests in some of the cases of occlusion of the blood vessels of the lower extremities (60). Simon Benson (46) has shown that under experimental conditions, the heart rate varies directly as the temperature applied to the skin. He has indicated that the almost instantaneous response of the heart to the changes in the bath temperatures is a reflex action, probably initiated through the stimulation of temperature nerve endings in the skin. Present indications are that the assumed "skin-heart" mechanism becomes less sensitive with increase in age (69).

CHANGES IN BLOOD VOLUME

The Mayo Clinic reports no change or a slight concentration in the blood volume following fever therapy (70). Knudson and Schaible (64) noted a decreased blood volume in dogs amounting in some experiments to 25 per cent, which usually returned to normal within twenty-four hours.

CHANGES IN THE ACID-BASE EQUILIBRIUM

Raising the body temperature of dogs to 41.7 C. does not produce any great change in the hydrogen ion content of the plasma of dogs, although there is a tendency toward a condition of alkalosis (64). This is in agreement with the recent report from the Mayo Clinic (70) in humans. With higher temperatures, Knudson and Schaible (64) noted a tendency toward acidosis, apparently
caused by a great increase in the lactic acid from increased tissue metabolism resulting in a tissue anoxemia.

**BLOOD PRESSURE:**

The blood pressure level is determined by the relation of the heart output per minute to the average resistance to flow in the periphery; in the latter factor at least, as we have seen above, fever and pyrexia conditions differ. At first the blood pressure (Systolic and Diastolic) rises slightly with the temperature, but when the fastigium, 41.5 C. is reached it usually, and if there are no complications, is rather uniform throughout the fever period, registering a systolic of from 80 to 70 with a diastolic of from 60 to 50 mm of Hg. Occasionally lower levels have been recorded with no serious results. Frequently the diastolic sound may be heard to zero (49).

With mild warmth, the systolic and diastolic both are lowered, and Grollman showed that higher temperatures cause a greater lowering of systolic and diastolic. Using higher temperatures than Grollman, Sayers and Harrington obtained greater lowering of the blood-pressure. Adolph showed that with still higher temperatures a rise in systolic pressure is noted and a fall in diastolic i.e. an increased pulse pressure becomes manifest. The blood pressure responses occasioned by the hot baths are: 1) Drop in systolic and diastolic with mild warmth; 2) Rise in systolic and fall in diastolic with hotter baths; 3) With quite hot baths, a fall in both systolic and diastolic is noted if there are symptoms of circulatory failure (49).

A raised systolic pressure appears to be evidence of a somewhat severe test and often precedes symptoms of distress and circulatory failure. In experimental pyrexia with profuse
sweating, if water is not given, there results a circulatory failure with evidence of diminished blood volume and inadequate venous return. Restlessness is a prominent feature and the symptoms resemble those of hemorrhage. Restlessness appears to be a physiological reflex method of improving venous return and whenever it is a prominent symptom, attention should be directed to this factor (62).

A rise of blood pressure is the rule in inflammatory conditions while the fever lasts, provided the subjects' general condition is adequate to achieve it, and the association of a so-called normal pressure with an infection implies the presence of some toxic or other factor that interferes with the development of the pressor change (49). After a series of treatments, there is a tendency for the blood pressure to remain at a lower level for some weeks.

CHANGES IN THE BLOOD SUGAR

Knudson and Schaible (64) from their experiments on dogs report: "the blood sugar content in most of the experiments shows an increase in some cases amounting to as high as 150 per cent. The greatest increase in blood sugar occurs in those experiments in which the pH has been lowered most. Kemp and Stokes (62) report that the blood-sugar fell rapidly. The increase was manifested throughout the duration of treatment, and does not persist after therapy has been discontinued.

CHANGES IN THE HEMOGLOBIN

There is an increase in the hemoglobin of dogs (64). The slight increase in hemoglobin noted in humans, is primarily due to dehydration.
CHANGES IN THE RED BLOOD CELLS

There is an increase in the red blood cells of dogs (64). The slight increase in red blood cells is primarily due to dehydration but also due to stimulation of the blood-forming organs as is shown by the younger forms of erythrocytes (60). The normal red blood count in male patients suffering from dementia paralytica shows anemic tendencies. The hyperthermia treatments (diathermy) modify the red blood count only in that they make this more constant, and that the lability which characterizes this blood count before treatments has disappeared as a result of the treatments given.

CHANGES IN THE WHITE BLOOD CELLS

There is an increase in the total white cells of dogs (64). According to Hinsie's work in the treatment of cases of general paralysis, "there is an increase of 75 per cent in the number of leukocytes as well as an increase in the staff cells which are the early forms of the polymorphonuclear neutrophiles." This is due to circulatory stimulation of the bone marrow. The maximum increase comes, according to his findings, at about the ninth hour after treatment, returning to the normal level at about the twentieth hour. Tenney's (60) counts "seem to indicate the same finding." The leucocytosis of the dementia paralytic group is not particularly affected by the first few treatments given, but is decidedly increased by the time the entire series of ten treatments are given (diathermy) and this increase persists for at least three days after the completion of therapy. Neymann and Osborne (2) report a relative increase of the polymorphonuclears and eosinophiles, and a corresponding decrease of the small and large mononuclears. The tendency of the eosinophiles to disappear as the fever rises, has no adequate explanation. Bierman (39)
found, in a study of 24 cases of various diseases from which he made 39 determinations, that during treatment with radiations of about a 30 mm. wavelength, there was an initial reduction in the number of white blood cells. This usually was seen at the end of the first or second hour after the beginning of treatment, and varied from two to forty per cent, averaging about 25 to 30 per cent. He found the peak of the leucocyte count usually occurred at the sixth to ninth hour, averaging about 80% where the count was followed to its highest point. In only two instances did the author fail to observe an increase in the number of the white blood cells. The greatest percentage of increase was seen in the staff cell count. He states that "the white cells from the bone marrow first showed the stimulating influence of the hyperpyrexia--the segmented neutrophiles and the staff neutrophiles. The monocytes are the next to give evidence of an increase in their number, and, last, the lymphocytes. When the hyperpyrexia treatments were administered at frequent intervals e.g. every other day, the leukocytic response became diminished and the number of the white blood cells on the days between treatments became lower."

CHANGES IN THE N.P.N.

Knudson and Schaible (64) report an increase in some instances of over 200 per cent in dogs. Urea nitrogen, creatinine and amino-acid nitrogen are also increased due to increased metabolism resulting from the rise in temperature and the oliguria. The N.P.N. is increased (62) (2) as is the uric acid (2). There is a tendency for the non-protein nitrogen to remain at a lower level for some weeks after a series of treatments (2).

CHANGES IN THE INORGANIC PHOSPHORUS

Variable changes were noted in animals, although with a maximum temperature to 41.7 C. there is a marked reduction (64).
Inorganic phosphorus is converted to the organic form (70).

CHANGES IN THE CLOTTING FACTORS

Tenney (60) states that there is a definite increase in the platelets. He noted that in no case was the blood viscosity increased at the height of fever where the loss of body fluids was replaced by a large fluid intake. Eighteen arthritic cases ran a viscosity somewhat higher than normal. As the temperature rose in 14, the viscosity dropped from 0.1 to 1.5 points; two cases remained unchanged, and in four where fluid was not given there was an increase. One patient receiving a 5% sodium chloride solution intravenously had a subnormal viscosity. In one case treated with sodium citrate intravenously before treatment, the viscosity was decidedly lowered. Tenney also noted that the blood sedimentation was faster and there was an increase in the blood plasma in these cases.

CHANGES IN THE BODY WEIGHT

Hench and Slocumb (70) report a gain of 0.5 to 6.0 pounds in 79 percent of the patients treated by artificial pyrexia at the Mayo Clinic and a loss of 0.5 to 6.0 pounds in 21 percent of the patients. Animals lose weight when their temperature is elevated which is dependent somewhat on the length and intensity of the treatment; the weight usually returns to normal within 24 hours (64). Tenney (60) reports there is a loss in weight during the early treatments with radiothermy which is gained as the treatment progresses. Even with an enormous intake, an actual loss in weight occurred after every treatment. Soiland and Warner (61) reported a gain in weight of from 20-30 pounds in nearly all cases.

CHANGES IN THE URINE

No amount of fluid intake seems to affect the urinary output,
which is always sparse, has a high specific gravity, and never exceeds 300 cc. during the ten or twelve treatment hours (2).

**SUMMARY**

Fatherree and others have summarized the various methods for the production of therapeutic fever, as follows:(70)

**Bacteriolysis**

Gonococci: Generally at a temperature of from 106 to 107 F. for about 5 to 6 hours.

Streptococci: No data.

**Blood flow:**

- **Pulse rate:** Increased up to 130 to 150 beats per minute.
- **Circulatory rate:** Increased
- **Cardiac output:** Increased minute volume output.
- **Blood pressure:** Initial rise, subsequent fall.
- **Blood volume:** No change, or slight concentration.
- **Viscosity:** No change (if intake is encouraged).
- **Nail-bed capillaries:** Increased in number and size.

**Blood: Cellular elements**

- **Erythrocyte count:** Generally no change.
- **Erythrocytes-sedimentation rate:** Conflicting data; some workers report little or no change; others, an increase.
- **Leukocyte count:** Initial fall, subsequent rise to 15,000 per cu. mm.
- **Leukocytes:** Increased rate of phagocytosis.

**Blood chemistry:**

- **Nonnitrogenous elements (urea, uric acid, creatinine):** No change or slight increase (blood concentration).
- **Sugar, phosphorus, plasma lipoids, serum calcium:** No change or slight increase (blood concentration).
- **Inorganic phosphorus converted to organic form.**
- **Serum protein:** Some authors report no change; others, an increase.
- **Acid-base equilibrium:** Altered in the direction of slight alkalosis.

*Chlorides: May be marked drop.
- **Oxygen content and capacity of venous blood:** Increased.
- **Carbon dioxide combining power:** Decreased.

**Blood: Immune bodies.**

- **Agglutinins:** Variable data (rise or fall).
- **Complement:** Some reports indicate no change; others, a reduction.
- **Opsonic index:** No change.

**Gastric secretion:** Loss of chlorides.

**Sweat:**

- Loss of 18 to 26 grams of NaCl in 3 to 4 liters of sweat in each session.
- Increased lactic acid content.

**Urine:**

- **Amount:** Generally temporary oliguria.
- **Reaction:** Unchanged or slightly alkaline.
- **Metabolic rate:** Increased 7 per cent per degree of fever.
Electrocardiogram:
Contractions of lowered voltage.

Body weight:
Gain: 0.5 to 6.0 pounds (79 percent of patients treated at the clinic).
Loss: 0.5 to 6.0 pounds (21 percent of patients treated at the clinic).

* Neymann and Osborne (2) report a slight tendency toward an increase.
BACTERIOLOGY
Fever temperatures destroy infectious agents within the body. Some infectious agents are killed by temperatures which the human body can withstand, others are temporarily inactivated, and some are probably heat-resistant to the temperatures which can be induced in the human body. Carpenter and Warren (62) have studied the effect of fever temperatures on the spirochete of syphilis, the gonococcus, and the tubercle bacillus, as well as on other micro-organisms. They found that Treponema pallidum is killed in vitro by a fever of 39 C. in 5 hours, by 40 C. in 3 hours, by 41 C. in 2 hours, and by 41.5 C. in one hour. The gonococcus was more resistant, but some strains were destroyed in 5 hours at 41.5 C. which, for the most part, is the exposure used by them in their clinical studies. Other strains were exposed in from 6 to 8 hours at 41.5 C. but a study of the hourly death rate showed that 99.9 per cent of the organisms were killed during the first 2 hours at this temperature. At the lower fever temperatures (40 and 41 C.) the thermal death-time was correspondingly longer. The tubercle bacillus, however, is still pathogenic for guinea pigs after 200 hours' exposure to 41.5 C.

PHAGOCYTOSIS

The effect of temperature on phagocytosis is most interesting. Commandon made moving pictures of leukocytes and noted that they creep faster from 30 to 35 C. than from 25 to 30 C. At 25 C. he observed them to travel 9.6 microns per minute, while at 35 C. they moved 25.2 microns per minute. As the temperature of the body becomes elevated above normal, the physical property of the leukocyte changes from the gel toward the sol state, thereby becoming more permeable and able to ingest greater numbers of bacteria or other foreign particles. Carpenter and Warren (62) observed from the hourly examination of cervical smears an increased
phagocytosis of gonococci during the course of an induced fever. Fenn, who analyzed the data of Madsen and Watabiki on the effect of temperature on the phagocytosis of bacteria, showed that the rate of phagocytosis is very nearly a logarithmic function of the temperature. (62).
METHODS
There are five general methods for producing artificial fever: Foreign proteins, infectious agents, radiant heat, hot water baths and electrical energy. All methods can be classified as either external or internal heating agents. The inductotherm, radiotherm and diathermy use electrical energy which is absorbed by the tissues and transferred into heat while the other agents merely conduct heat from the surface of the skin, and thus, by conduction, heat the underlying tissues. The slope of the normal physiological heat gradients of the body is not disturbed by the internal heating methods. With external applications to the body surface these normal heat gradients of the body are reversed. Osborne and Markson (3) state that "experience leads to favoring the internally heating methods which do not reverse this natural heat gradient."

FOREIGN PROTEINS

Recently, numerous agents have been recommended as having a common property i.e. the ability to produce a marked febrile reaction. The beneficial effects obtained with pyretotherapy is explained by the theory that the body has a reserve store of nonspecific antibodies for emergencies, the mobilization of which is promoted by nonspecific protein administration. Specific immune bodies are probably also mobilized by nonspecific foreign proteins.

The list of agents employed in pyretotherapy is a long one and includes sterile milk, tuberculin, killed cultures of various micro-organisms, especially B. typhosus, and many proprietary preparations.

Considerable controversy exists as to whether it is actually the fever or rather the whole constitutional response to protein that proves beneficial.
The list of infectious agents used by man in imitating nature's method of curing one disease by the superimposition of another, is much shorter than the list of nonspecific proteins. Except for the use of malaria in central nervous system syphilis, the use of infectious agents is rather obsolete.

**RADIANT HEAT**

With radiant heat, the body is exposed to hot air with a temperature that can be withstood by the skin of the body. The air surrounding the body may be heated in various ways, but in all cases arrangements must be made to prevent heat losses. The peripheral structures of the body are heated first, and the heat is then conducted to the enclosed viscera (62). Many experiments on heating the bodies of animals by this method have shown that such a method is practical.

The Kettering hypertherm is the most recently developed mechanical method in the natural evolution of apparatus for artificially inducing fever by physical means. It is an air conditioned chamber, capable of raising the patient's temperature by circulating humidified heat. Desjardins (71) states it is the method "which appeals to me as the most effective from all points of view." The fever is induced by a simple air heater to raise the temperature of the air and an equally simple means of humidifying the air to any desired degree. The HEATED and HUMIDIFIED air is then CIRCULATED around the patient at the rate of about ten times a minute. A partition at the foot end of the chamber separates the mechanism from the patient. The temperature of the air is controlled by a thermostat, and the desired relative humidity of the air is controlled by a humidistat and by wet and dry bulb thermometric readings. The temperature can
be raised more rapidly with the Kettering hypertherm than with radiant light chambers and the temperature of the patient may be kept at any desired or required level. The patient's body with the exception of the head which is outside, is entirely free within the chamber. This apparatus also does not require electrodes, condenser plates or electrical appliances of any kind. The compartment at the foot end of the box contains the following air conditioning apparatus: 1, a set of three heating elements; 2, a humidifying pan, fed with water from a glass jar outside of the cabinet through a device similar to those used for watering chickens; 3, air blowers which cause the air to circulate and recirculate through the cabinet at a rate of 450 cubic feet per minute; 4, a thermostat to regulate the air temperature, which is generally maintained at 145 to 150 F.; 5, a humidostat to control the relative humidity of the air in the cabinet which is usually maintained at 35 to 45 per cent; and 6, wet and dry bulb thermometers to indicate the temperature of the cabinet and to permit humidity readings. The cabinet consists of a roomy box with a comfortable bed, which may be pulled in and out. Sliding panels are present on both sides of the chamber so that the patient's entire body can be kept under constant observation and the condition of the skin closely watched. The patient is not restricted by confining jackets or anything else and is not burdened by many layers of blanket. It permits the nurse or the attending physician to take care of the patient throughout a session of treatment with the greatest ease. In case of an emergency, also, the chamber can be thrown open and the patient withdrawn in a few seconds.

Krusen states "this cabinet permits giving controlled fevers."
There is a known air velocity, a controlled temperature, and a controlled humidity." (11). Desjardins (71), in giving his opinion of the Kettering hypertherm, states "all these are advantages which do not exist to the same degree with any other method of fever therapy with which I am acquainted."

HOT WATER BATHS

The hot water not only elevates the body temperature, but the immersion also prevents heat losses. This method is impractical if the fever is to be maintained for several hours. Also, it is very depressing to the patient. Furthermore, the prolonged hydrostatic pressure from without may cause passive congestion of the abdominal viscera (62).

ELECTRICAL ENERGY

The inductotherm radiotherm and diathermy are all comparatively recent methods of producing artificial fever by electrical means. Frequently both "diathermy" and "radiothermy" are designated as "high frequency fever". Sometimes the term "ultra high frequency" is used to differentiate radiothermy from diathermy (62).

DIATHERMY

Diathermy is the method in which large, flexible, block tin electrodes are bound anteriorly and posteriorly over the thorax of the patient, and a high frequency current (300 meters) is passed through the body. Heat is produced locally between the electrodes, due to the resistance of the body to the passing current. The heat produced is conducted through the other tissues of the body by the circulation of the blood.

The prime requisites for the successful treatment with diathermy depend on properly constructed electrodes and a machine powerful enough to give sufficient energy. The edges of the
Electrical Energy

Electrodes must be extensive and have a smooth edge because the current has a tendency to concentrate along the edges (42).

The new cuff electrode has added greatly to the comfort of the patient during treatment. Five electrodes are used, one around the trunk, one around each thigh, and one encircling each leg. They are easier to apply than the larger jacket electrodes and are of particular advantage with patients who have deformity of the back or chest. Discomfort to the patient has still further been lessened by the use of a special zipper-type treatment bag which eliminates the excessive weight of blankets necessary for proper heat insulation. (3).

Bishop, Horton and Warren (4) used a cellotex chamber (in order to eliminate the use of blankets which are cumbersome and give the patient a sense of restraint) which covers the patient and prevents loss of heat. There are five carbon filament lights in the foot end of the chamber and three in the head end to maintain the air temperature within the box at a level sufficiently high to compensate for loss of heat by the patient through radiation etc. (usually around 45 C.). They describe the procedure they use with a slightly modified diathermy machine: "After the current has been turned on it is raised as rapidly as the patient permits to between 5000 and 6000 milliamperes. No lubricant appears necessary, since the patient begins to perspire almost immediately. During the first 10 to 30 minutes no change may occur except for the rapid outpouring of perspiration. Then there is a flushing of the skin which may progress to the point where the patient becomes a deep red color (not cyanosis)...Immediately after this the temperature begins to rise and continues to rise at an even rate until the current is turned off. If the
Elevation of temperature has been rapid the rectal temperature may continue upward about a half a degree after the current is turned off, but if the rise has been fairly slow this continued rise will be reduced or may not occur... During the elevation of the temperature the rectal temperature is at first higher than the mouth temperature. When the body temperature reaches about 38 or 39 degrees C. the mouth temperature usually becomes higher than the rectal temperature and remains so or equals it until the current is turned off... As soon as the current is turned off the mouth temperature equals or becomes slightly less than the rectal temperature.

"When the required temperature level has been reached and the current turned off, the electrodes are removed from the trunk and the patient remains in the box covered only by a sheet. The air surrounding the patient is kept at an adequate level, and in so doing the patient's body temperature is maintained at the predetermined height. If, for any reason, the body temperature rises, the surrounding air is cooled off. If it drops the air temperature may be raised as high as it can be tolerated (perhaps 50 C.) and slowly the body temperature is built up to the desired level."

RADIOTHERMY

Radiotherapy is the term used for the method whereby the body is heated in a field of short radio waves that are "broadcasted" from a short wave oscillator (30 meters). The heating in radiotherapy depends upon the same fundamental principle as described above in the case of diathermy, except that with the radiotherm the heat is produced from the electric currents within the body.
which the radio waves induce. The accepted theory of heating is that the body furnishes resistance to the conduction of current between the surfaces adjacent to the opposed plates. The current is conducted through the material for a brief interval at each alternation of polarity of the plates, the corresponding polarities being induced upon the adjacent boundaries of the interposed body. Greater heating is possible at certain frequencies, depending upon the conductivity of the body or solution to be heated.

The radiotherm is constructed on the same principle as a short wave radio transmitter except that the energy is concentrated between the two condenser plates instead of being directed from an aerial. The total energy oscillating in the circuit must pass through an object which is placed as a dielectric between the two plates. With this method no electric current is conducted to the object or organism, but merely the effect of the electric field (the electric wave) is used without requiring any contact with the conductors. Any object or part of an object placed in the electrostatic field acts like a small condenser. The heating in the electric field is principally a property of the electrolyte (in this case the body fluids) and depends on its concentration. For every electrolyte there is a definite degree of dilution at which heating takes place most quickly. There are very definite differences as to the rate of heating of the different body tissues. The field effect is limited almost precisely to the space lying between the condenser plates. All the individual parts are subjected in equal manner to the effect of the field, the degree of heating being dependent only on the chemicophysical makeup of the object. In applying diathermy to bone the heating of the marrow does not amount to a tenth part of the skin, while in the
case of the electrostatic field an equal and even greater warmth can be attained inside the bone as compared with that on the skin. The relative penetration (the heating of deep parts in ratio to that of the surface) is very essentially dependent on the distance of the condenser plates from the surface of the body and on their positions. It is necessary to provide an insulating layer between the plates and the body, glass being the most suitable material for maintaining the distance and ensuring compression at the same time (1).

The patient is placed above the radio between the two plates and may be covered with a celotex cabinet with hot-air dryers blowing to evaporate the perspiration, or he may be placed between the plates wrapped in blankets. When the desired temperature is reached, it may be maintained by increasing voltage, by increasing plate distance or by applying more blankets. When this temperature has been reached, the author (Tenney) removes the patient in the blankets to his bed, placing more blankets and hot water bags about him so that the heat may be maintained from three to four hours longer, or he places shellacked paper cabinets heated with electric light bulbs over the patient (60).

Tenney (60) feels he is using a form of artificial fever which is less hazardous than that produced by intravenous injections, after giving over 1000 treatments. He believes that this method of producing artificial fever is superior to other methods, and that the therapeutic results are better. Soiland and Warner (61) observed that pain of various intensities is quickly modified and frequently relieved, and that this relief is in certain instances more pronounced than with any other mechanical or electrical device with which they are familiar.
Christie and Loomis, and Kahler, Chalkley and Voegtlin expressed the belief that the effect of a high frequency field depends primarily on the production of a rise in temperature in the organism (61). Schereschewsky stated that certain wave lengths (from 15 to 3.8 meters) exert a specific effect on living cells.

THE INDUCTOTHERM

The Inductotherm is a vacuum tube oscillator, generating an alternating current with a frequency of approximately 12,000,000 cycles per second. The cable, through which the current is conducted is a flexible, heavily insulated one which is wound around or about the part to be treated. The cable may also be wound into a pancake type of coil.

An alternating magnetic flux is set up in the coil, having the same frequency as the current in the coil. If a conductive material is placed within the coil, an electromotive force will be induced in it. Eddy currents of the same frequency as the exciting current will flow in the conductive material as a result of this induced voltage. The eddy currents induced in the more conductive materials will be the more intense (7).

ELECTRIC BLANKETS

Wilgus and Kuhns (42) describe the electric blanket in general use as "a blanket about six feet square, and by a connecting cord is simply plugged into an electric socket in the wall. The patient is wrapped in blankets, and covered by the electrically heated blanket. After a cold sponge and a little sleep the patient is ready to about his business." They believe this is the simplest and safest form of fever producing agents. This conclusion follows an experience of two years with the electric blanket.

Neymann and Osborne (2) state that the heat of the atmosphere
surrounding the patient should not be allowed to rise over 130
F. unless the air is kept in constant motion by means of a blower
or turbine. Blanket temperatures of above 120 F. are dangerous
and do not perceptibly quicken the rate of the temperature rise.

SUMMARY

INFECTIOUS AGENTS

1. Considerable risk to life.
2. Often difficult to obtain organisms for inoculation.
3. Fever is not subject to control i.e. severe chills,
   marked lowering of blood pressure at times, and sudden
   rise and fall of temperature.
4. In some cases, an immunity to the disease obstructs
   satisfactory treatment.
5. Patients react differently; some have slight fever,
   some active, and some even immune.
6. Occasionally, the attack so severe that the disease has
   to be terminated by treatment in order to save the
   patient's life.

FOREIGN PROTEINS

1. Uncertainty of producing fever.
2. As a rule do not produce sufficient elevation of body
   temperature to be of great value.

HOT WATER BATHS

1. Impractical if fever is to be maintained for several hours.
2. Prolonged hydrostatic pressure may cause passive congestion
   of abdominal viscera.

DIATHERMY

1. Waves demand that electrodes be placed in good contact
   with the skin.
SUMMARY

2. Least effect on bones and joints.
3. Greatest effect on muscles.
5. Patients markedly disturbed are difficult to treat.
6. Expensive original investment.
7. Danger of burns.
8. Deep-seated organs more or less unaffected.
10. Must have trained attendants.
13. Height of temperature can be controlled at will by increasing or decreasing amount of energy supplied, or by adjusting whatever arrangements are used to prevent heat loss.
14. No toxic substances are introduced into the body.
15. Low percentage of deaths.
16. Treatment may be given at any time and as frequently as the physician chooses.
17. The normal metabolic activity of the body is stimulated by an outside source.
18. A method of study of fever effects is offered with temperature as the only variable factor. Chemical and laboratory research may be conducted on the effects of fever in various conditions.

RADIOThERMy

1. Waves act by having the plates near the body with an intervening air layer between.
2. Act on muscles, bones, joints as well as on the deep-seated organs.
3. Can be directed to a considerable degree.
4. Complicated and expensive.
5. Comfortable for patient because he is free to move about in the chamber used to prevent heat loss and his respiratory movements not interfered with as in diathermy, where electrodes are bound to the chest.
7. Possibly certain wave-lengths have specific actions.
8. Action better the more acute and recent the disease (6).
9. Must have trained attendants.
10. Height of temperature can be controlled at will by increasing or decreasing amount of energy supplied, or by adjusting whatever arrangement is used to prevent heat loss.
11. No toxic substances are introduced into the body.
12. Low percentage of deaths.

**INDUCTOTHERM**

1. Greatest heat in most conductive tissues i.e. vascular tissues (7).
2. Most comfortable for patients having unusually large amounts of subcutaneous fat (7).
3. Easily applied (7).

**ELECTRIC BLANKET:**

1. Too exhausting for some patients e.g. multiple sclerosis, because a therapeutically active fever cannot be produced fast enough.

**KETTERING HYPERTHERM**

1. Temperature raised by CIRCULATING, HUMIDIFIED, HEATED AIR.
2. Has a known air velocity, controlled temperature and controlled humidity.
SUMMARY

3. Easily controlled mechanism.
4. Does not require electrodes, condenser plates, or other electrical appliances.
5. Patient may be observed easily and quickly at all times.
6. No confining jackets.
7. In case of emergency, patient can be quickly withdrawn.
8. Temperature can be raised quickly.
10. Must have trained attendants.
11. Nursing care simpler than with any other method.
13. Height of temperature can be controlled at will.
14. No toxic substances are introduced into the body.
15. Low percentage of deaths.
CLINICAL
Patients for fever therapy must be carefully selected. Thin or normal weight patients stand the treatment better than obese patients, and women better than men (56). In syphilis, late deteriorated cases with marked cell destruction cannot be expected to respond.

CONTRAINDICATIONS FOR FEVER THERAPY

To subject patients to high temperatures, especially as is necessary for gonorrheal infections, it is necessary that the patient have a complete thorough physical examination. Definite contraindications for all types of fever therapy are: patients with evidence of cardiovascular disease; patients with any type of active pulmonary disease; and, cachectic and debilitated patients. Schmidt and Weiss (56) state "there should be no marked evidence of degeneration of the cardiac, renal, vascular, or nervous systems."

Relative contraindications include arteriosclerosis, pulmonary disease, and marked grades of focal infection.

Certain conditions are not contraindicated under proper treatment control. Diabetes can be controlled by Insulin and the diet. Nephritis and chronic arthritis patients must be watched very carefully.

Schmidt and Weiss (56) state that diathermy is contraindicated in patients over 50 years of age. Popp (72) sets 60 as the upper limit for age contraindication.

PRE-TREATMENT

The patient should receive the same care he would receive were he having a major operation. A cleansing soap-suds enema should be given the night before, and a good nights rest ensured. The patient is usually allowed to eat a light breakfast which should precede the beginning of the treatment by two hours or
more. About one to two hours before the treatment, a preliminary sedative should be given.

**TREATMENT**

Simpson points out that it makes little difference what device is used to produce the fever; that the most important factor is that the treatments should be given by a skilled nurse-technician, who has had at least a month's supervised training in this special work, and who will devote her entire time to it. She should be trained to look for danger signs: too rapid pulse, beginning tetany and the like. The patient should not be left for a moment during the treatment. A fan is turned on the head; the face is bathed with ice water; constant sympathetic attention is given by the nurse. A competent physician familiar with the work should be on call at all times during the treatment.

**TEMPERATURE**

The temperature may be raised from 99.6 rectally to 106 rectally by any of the mechanical methods, in from 60 to 120 minutes. The temperature should be checked regularly every 10-15 minutes and more often if indicated. A recording thermometer may be used with any of the methods, except with radiothermy, the current must be turned off to make the temperature observation.

The temperature, pulse, respiration and color of the patient are the guides as to his progress in the treatment.

**SEDATIVES AND OTHER DRUGS**

Neymann and Osborne (2) noted that morphine and hyoscine used together caused difficulties because the temperature had a tendency to rise and get out of control. Hyoscine alone inhibits sweat production and often causes delirium. It is contraindicated during hyperpyrexia treatments.
Luminal, one grain, and bromide, 30 grains seems to be an effective sedative (60). Most of the commonly used barbituric acid derivatives work well with fever therapy as does chloral hydrate, also. These are given p.r.n. before and during the treatment.

Hypertonic glucose is indicated if symptoms of brain edema develop. Glucose, ten per cent, should be given early if there are signs of circulatory failure. Calcium gluconate serves well to allay any symptoms of tetany that might develop.

Some patients require no sedative, while others require considerable. Narcotics, generally, are unsatisfactory and deep narcosis is undesirable. The most satisfactory effect results from the amount of sedative that causes short naps and tends to overcome apprehension, giving the patient the impression of a brief fever period. Almost all drugs cause a preliminary period of excitement before the desired narcosis. They likewise depress respiration and blood pressure. Normally in the absence of drugs, a delirium is frequently noted, especially between 40 C. and 41 C. (62).

**FLUID INTAKE**

Warm fluids e.g. orange-juice, water, lemonade, tea and milk, should be forced during the treatment to replace losses from perspiration. With the Kettering hypertherm cold fluids are given without any bad effects. A 0.6 per cent solution of sodium chloride should be forced to compensate for the chloride loss through the perspiration.

**COMPLICATIONS**

Radiothermic burns are more common than diathermic, but are
very superficial. Electric blanket burns have now been practically eliminated. The most disturbing features are blisters of the heels and in the region of the coccyx. These originate because of the maceration of the skin by voluminous perspiration and the weight and pressure of the patient's own body. They now pad the heels of all patients with cotton and place an inflated rubber ring under the buttocks. It must be remembered that the patient lies in one position between eight and twelve hours. Patients suffering from multiple sclerosis are especially prone to develop such blisters. (55)

Nausea and vomiting may occur toward the end of a session. This ordinarily passes after one attack of vomiting and a series of eructations. The treatment consists of 500-1000 cc. of 10 percent glucose.

Herpes of retina occurred in one case, which, however, gradually but completely disappeared (59). Vaseline around the lips cuts down the incidence of herpes. Popp (72) states that "if the first treatment is given cautiously and not too much emphasis is placed on maintaining a high temperature, herpes can be avoided. It appears that, if the sudoriferous mechanism and collateral circulation are suitably adapted, cutaneous complications do not arise."

Bennett and Austin (73) have summarized the results obtained at the Lutheran Hospital, Omaha, Nebraska as follows:

<table>
<thead>
<tr>
<th>SYMPTOMS</th>
<th>PERCENTAGE TO NO. TREATMENTS</th>
<th>PERCENTAGE TO NO. PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting</td>
<td>25</td>
<td>53</td>
</tr>
<tr>
<td>Herpes</td>
<td>14</td>
<td>36</td>
</tr>
<tr>
<td>Vertigo</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>Headache</td>
<td>9</td>
<td>25</td>
</tr>
<tr>
<td>Burns</td>
<td>7</td>
<td>25</td>
</tr>
<tr>
<td>Cerebral edema and transient hyperpyrexia</td>
<td>1.7</td>
<td>5.5</td>
</tr>
</tbody>
</table>
### TREATMENT

**SYMPTOMS**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage to No.</th>
<th>Percentage to No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>1.4</td>
<td>5.5</td>
</tr>
<tr>
<td>Tetany</td>
<td>1.4</td>
<td>4.1</td>
</tr>
<tr>
<td>Vaso-motor collapse</td>
<td>.9</td>
<td>2.8</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>.9</td>
<td>2.8</td>
</tr>
<tr>
<td>Corneal herpes</td>
<td>.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Acute exacerbation of symptoms</td>
<td>.4</td>
<td>1.4</td>
</tr>
</tbody>
</table>

* More frequent and prolonged in treatments on gonorrheal patients.

/ More frequent in multiple sclerosis, psychotic and luetic groups.

### POST-TREATMENT

Defervescence is accomplished by cooling the air with an electric fan and by sponging the patient's body. The body temperature returns to normal in 2-3 hours. Pulse and respiration gradually subside with the fever. Cold fluids are given. Temperature should be normal before the patient leaves the treatment room and observed at hourly intervals for 4 hours thereafter. If the temperature should go higher than desired after the patient is in bed an ice-bag may be applied to the head. The blankets are then gradually removed, a cool sponge bath is given, and if the temperature from the central origin continues to rise, cold colonic irrigations will control the situation. As the temperature falls and approaches normal, the blankets are gradually removed. A cool sponge bath is given followed by a crash towel massage. The patient is then placed in dry linen and is covered with light blankets after which he is very comfortable.

### SYPHILIS

**MALARIA IN SYPHILIS**

Reports upon malaria treatment in paresis compose at least four-fifths of the long list together with occasional articles upon the use of typhoid vaccine, saprovitan (a saprophitic bacterium obtained from milk), anti-chancroidal vaccine, trench fever diathermy, hot air and hot baths (24). The ideal time to use the malaria treatment, according to O'Leary (25) is when...
only slight evidence has been shown of clinical and serological improvement following the routine antisyphilitic measures, and not to wait until the objective signs of general paralysis are obvious. Malaria therapy is more valuable in the prevention of parenchymatous neurosyphilis than it is in the treatment of it (27). Serologic changes in the blood and spinal fluid were not considered significant in the interpretation of the results, during the earlier experience with malaria inoculation in paresis. More recent work has shown that a reversal to normal of the blood and spinal fluid has paralleled the clinical results in most cases, but such improvement has appeared two or three years after the subjective improvement was noted. These changes in serology and spinal fluid occur irrespective of the amount of subsequent antisyphilitic treatment and indicates that a factor of resistance is involved (25).

In this country, the tertian strain of the plasmodium is used and after seven to twelve attacks, the malaria is aborted with quinine. In England, the quartan strain is used because it causes high temperature without serious symptoms, and may, therefore, be allowed to run for weeks or months. Also, in England, instead of stopping it after seven or eight attacks, the fever is allowed to continue until the patients have acquired tolerance for the parasite (42).

Among reported results of malarial treatment of syphilis are: Wagner-von Jauregg, in 1922, reported on 200 cases of general paresis, 25 per cent of whom had gone into such complete remissions as to be able to resume their former occupations (42).

In England more than 3000 patients have been treated since 1925 and of these, over 20 per cent were sufficiently improved to
be discharged, and 12 per cent "cured". (42)

In 1928 Westphal and Back tabulated 1,568 cases treated in seven of the larger European clinics, including their own at Bonn, with percentages of those returned to work "with slight psychic disturbance" averaging 21.4; of those capable of work, though with defect, about 20 per cent; and of those made worse, or who died, running from 10 to 23 per cent (24).

Wilgus and Kuhns (42) reported 100 patients treated during 1929 and 1930 with the following results: "66 per cent improved, 20 per cent were unimproved; and 14 per cent became worse."

Sioli reports 50 per cent of good remissions, Kirschbaum 52.5 and Gerstman 33 per cent and 33 per cent in the Munich clinic. Other reports range only from 12.7 to 17 per cent (24).

Vallejo Nagera's compilation of 43 authors (quoted by Prussak) averages 29.6 per cent of complete remissions out of 5,000 cases in all. Bunker and Kirby, reviewing results in 156 patients treated from 1/2-4 years previously, found 33.3 per cent still in remission and 17.3 per cent still showing marked improvement. They quote statistics of 1,004 untreated cases at Manhattan State Hospital (1911-18) showing but 3.5 per cent spontaneous remissions (Raynor). (24).

Read and Pasking reported several years ago a series of something over 50 cases with 19 per cent of good remissions obtained during treatment or shortly thereafter. (24).

O'Leary (27) reports: "In the past 10 years 89 patients who had asymptomatic neurosyphilis were treated with malaria when the serologic tests on the spinal fluid had failed to become reversed to negative following intensive use of arsphenamine, mercury and bismuth. In 50 per cent of the cases in which in-
vasion of the nervous system was of mild degree, the serologic reactions became completely negative following malaria therapy, irrespective of whether antisyphilitic treatment was given after induction of malaria. In 39 per cent of cases in which the formula of the spinal fluid was of the paretic type, the spinal fluid factors were reversed to negative following malaria therapy. Among those cases in which the usual antisyphilitic treatment was not given following malaria treatment, there was satisfactory reversal to negative of the spinal fluids in 58 per cent of those in which reports on the spinal fluid had indicated only mild or moderate involvement, whereas among cases in which the formula of the spinal fluid was of the paretic type, in only 30 per cent was there a reversal to negative."

O'Leary (27) reports a relapse to positivity of the spinal fluid in only one case after a negative report had been obtained following malaria treatment, and one death the cause for which could not be found at autopsy. He also reports (25) that malaria has been of value in treating other forms of syphilis than neurosyphilis, namely, interstitial heratitis, and osseous involvement in congenital syphilis as well as various other resistant complications of the disease.

Inoculated malaria has a death rate of about 10 per cent (24), 12.2 per cent according to Bunker and Kirby, and 5 per cent according to O'Leary (25).

Many writers are of the opinion that malaria combines both heat and biologic factors i.e. there is something besides the fever which malaria imparts in causing improvement in syphilis. The English method of treatment is based entirely on the hypothesis that the curative action of the malaria is not on account of the
SYPHILIS

fever but is due chiefly to the continued presence of the parasites and their toxins.

RAT BITE FEVER IN SYPHILIS

Dr. H. C. Solomon, of Boston, in 1925 introduced the use of the rat bite fever organism, Spirocheta Morsus-muris, into this country for the treatment of paresis. He thought this to be less severe on the patient than malaria, and the treatment was comparatively simple and harmless. Arsphenamine easily controlled this benign infection. The spirillum of rat bite fever lives in the blood of rats and mice without producing symptoms of illness. Physicians connected with the Illinois State Hospitals tried this form of treatment, in 1927, on paretic patients. They report: "After one year of observation the following percentages of improvement were noted: 50 per cent of the patients were more or less physically improved; 20 per cent showed from slight to marked mental improvement; 60 per cent did not show any difference mentally; 10 per cent at first showed improvement mentally and then became worse." (42).

This method of treatment was finally discarded because of sloughs and other disagreeable complications as well as poor specific results. It is not now used extensively anywhere.

RELAPSING FEVER IN SYPHILIS

Relapsing fever was introduced by Plant and Steiner (56). It is less dangerous than malaria but has similar drawbacks (22).

TYPHOID VACCINE IN SYPHILIS

Wilgus and Kuhns (42) noted in more than 80 per cent of the cases treated with typhoid vaccine that a modification occurred serologically from a highly paretic curve to a negative one, the average, however, being to a luetic zone curve. Varying degrees
of modification also occurred in the blood and spinal Wassermanns.

Nelson (22) has introduced a variation in the usual technic and has produced fever by combined typhoid vaccines as high as that produced by malaria. By using typhoid vaccine and rather rapidly increasing the dose, chills can be produced at required intervals extending over a period of several weeks (36).

Typhoid vaccine has many advantages over malaria: the patients do not become anemic and the interval between chills can be regulated (36); and may readily be used in place of malaria if it is difficult to obtain Plasmodium vivax, if the patient has had repeated attacks of malaria, if the patient is debilitated, or if only an occasional patient is to be treated (26).

O'Leary (28) reports that the therapeutic remissions in his experience have been less frequent and less pronounced with typhoid than with malaria.

Nelson (22) states "in respect to convenience and safety, they (typhoid vaccine and other proteins) have an advantage over malaria that is well worth using."

In 1927, Dr's. Kunde, Hall and Gerty reported the restoration of 21 out of 49 patients treated (24). Treatment of patients with resistant neurosyphilis by this method has been followed by clinical and serologic improvement (22). Of 100 patients treated at Elgin, during 1927 and 1928, there resulted in improvement, 52 per cent; unimprovement 28 per cent; and retrogression, 20 per cent (42).

SULPHUR IN OLIVE OIL IN SYPHILIS

Knud Schroeder of Denmark, basing his work upon that of Meyer-Bisch in arthritis deformans (derived in turn from the practice of Borg and others from 1911 on), began the treatment of
paresis in 1924. Up to 1929, he had treated 12 patients with intramuscular injections of a one per cent suspension of sulphur in olive oil, administered twice weekly for five weeks in two or three courses interrupted by rest periods of two weeks. Four of the 12 patients had maintained complete remissions. Marcus and Kallman claimed marked improvement in 41 per cent of cases treated by this method. Read (24) treated 14 patients and states "11 have shown marked improvement, and of these 11, 8 appear to be in complete remission, and the remaining 3, though much better are probably hopeless so far as social readjustment is concerned." Wilgus and Kuhns (42) report on 100 patients treated at Elgin, Illinois, during 1928 and 1929 with 58 per cent improved, 21 per cent unimproved and 21 per cent made worse.

Schroeder felt that this method of inducing fever was of value because it was innocuous, controllable, readily available and easily regulated according to reactive idiosyncrasies. Its use is especially recommended in cases not thought suitable for malaria or typhoid vaccine therapy, or where the malarial infection must be stopped for one reason or another before enough febrile rises have occurred, or when the infecting organisms cannot be obtained. It seems to be a procedure which is simple, safe and readily available, and at the same time productive of results (24).

RADIOTHERMY IN SYPHILIS

Hinsie and Blalock of the New York Psychiatric Institute recently reported on 68 patients with general paralysis who were treated by radiotherapy. The results of treatment by radiotherapy about six months after the completion of the treatment were:

Remissions 17 per cent; improved 35 per cent; unimproved 38 per cent; and died eight per cent. The authors conclude that radiotherapy in the production of fever is a less hazardous agent
than malaria (42).

Tenney (60) reports "31 cases received radiothermy in the treatment of lues. In addition to regular antiluetic treatment, these patients received from 3 to 30 radiotherm treatments. Among these 31 cases, there were patients in the first, second and third stages of syphilis, as well as congenital and paresis cases. In these cases, the duration of the disease ranged from 3 weeks to 25 years, and the treatment rendered 10 patients symptom free, 13 improved and 8 unimproved."

DIATHERMY IN SYphilIS

King and Cocke, in 1928, began the treatment of paresis with fever produced by diathermy. These pioneers in diathermy treated 20 cases of paresis, 8 being definitely improved and all gained weight, including a partial mental improvement.

One hundred patients treated by diathermy at Elgin showed 72 per cent to be improved, 11 per cent stationary and 17 per cent retrogressive (42). Neymann and Osborne, and others, have reported similar results.

ELECTRICALLY HEATED BLANKET IN SYphilIS

Wilgus and Kuhns (42) report that about 75 per cent of their patients under this treatment have shown some degree of improvement and about 1/3 have developed such marked remissions that they are "classed among the best workers in the institution (Elgin, Illinois)." They report 78 per cent of 100 patients treated in 1931-1932 improved, 15 per cent unimproved and 7 per cent were deteriorated.

MULTIPLE SCLEROSIS

The treatment of the major group of organic neurological affections has been purely of a symptomatic nature, and therefore little has been accomplished in the past in the treatment of
Multiple sclerosis is probably due to an infectious process, and the improvement reported in the cases of Schmidt and Weiss seems confirmatory of a bacterial origin. (56).

Schmidt and Weiss (56) reporting on a small number of cases treated by diathermy state "hypertonia becomes greatly diminished, which enables patients to resume active movements without fatigue, and the parkinsonian facies is altered to a considerable degree."

The classical multiple sclerosis syndrome has a tendency to run a chronic, progressive, intermittent, remittent course. Spontaneous remissions in the syndrome are almost the rule, thus the success or failure of any therapeutic attempt is difficult to judge. The diagnosis is not circumscribed by definite rigid clinical standards, or by laboratory findings. The existence of two trends is generally conceded, a chronic form, and one with a more acute onset and course.

Neymann and Osborne (55) gave a series of artificial fever treatments to multiple sclerosis patients varying from six to fifty-one in number. Diathermy, radiothermy, and occasionally the electric blanket were employed but in 95 per cent of the cases, diathermy was employed. They recommend a temperature curve with a quick rise to 103.5 F., and a high plateau ranging between 105 F. and 105.5 F. and maintained at 105 F. for from 8-10 hours. Their treatments were given bi-weekly. They divided their cases into three groups; mild, advanced and far-advanced: "The four mild cases could all walk when they were admitted for treatment, but showed many of the major symptoms of the syndrome. These had not progressed to a point where hospitalization was imperative. All four improved to a point where a clinical diagnosis without a
history would be difficult. Two patients still have a positive Babinski on one side. One still shows reduced vision, temporal pallor of the disks and positive Barany tests. One is quite free of symptoms. All have returned to work.

"The next group of eleven were all hospitalized from necessity. After treatment only two of these attained a practically normal gait and one of these...was evidently a form of subacute encephalomyelitis. The other nine all showed improvement in their gait, but still retained some spasticity. About two-thirds of their initial symptoms were absent or improved after treatment. Four were able to return to their occupations; seven live at home in a semi-invalid state. Yet all are quite satisfied with their progress and many have applied for a second series of these strenuous treatments in spite of their sufferings during the long hours of fever.

"The third group of ten cases were more or less hopeless from the start. Four of the six bedridden cases regained the use of their upper extremities and are now able to feed themselves. One even learned to walk. Of the entire advanced group, two were much improved and four lost some of their most troublesome symptoms. Only three left the hospital; two resumed work, and one remained at home, a semi-invalid. One other had improved but all symptoms returned later on. This is the only one of the series that has shown such a course. The cell count was increased above eight cells per c. mm., in five fluids. After treatment, the cell count decreased to normal in two cases. Both of these were much improved clinically. The length of duration of the disease seems to have no bearing on the prognosis. The final outcome is more dependent on the severity of the symptoms at the
MULTIPLE SCLEROSIS

the time treatment is started. Summarizing their results; excellent remissions were observed in ten, eleven others showed distinct improvement. This includes three of the more acute type. After treatment, all these remained clinically stationary for the period during which they were observed from a few weeks to eighteen months. Two of the patients in the advanced group died, one as the result of treatment. It is not a simple matter to control the temperature of such far advanced cases and the greatest caution is urged. The fever may get out of control at any moment, especially if the patient's state is aggravated by massive tremors which in themselves have a tendency to elevate the temperature."

ARTHITIS

The treatment of arthritis by hyperpyrexia was introduced by Markson and Osborne in 1931. The hypertrophic, or degenerative, type of arthritis is now excluded entirely because of the high incidence of cardio-renal damage in these patients. Patients with this type of joint involvement are subject to such accidents as myocardial failure and fibrillation. Cases are now selected from the infectious group because this younger group withstands the high fever without serious danger or discomfort. Infectious is used synonymously with rheumatoid of the British, and proliferative used by some other writers.

Markson and Osborne (3) obtained their best results with a fever of 104 F. sustained for eight hours. Variations from this temperature for brief periods are not contraindicated but the temperature should not be allowed to drop below 104 F.

The treatment should be given once weekly and the height
and duration of the fever should always be determined by the condition of the patient. The number of treatments to be given will also vary with the individual patient.

The Mayo Clinic "Symposium on Fever Therapy" (70) contains the following summary of the "Average results in total cases reported in the literature:

<table>
<thead>
<tr>
<th>DISEASES</th>
<th>CASES</th>
<th>PERCENTAGE</th>
<th>SYMPTOM</th>
<th>MARKED IMPROVE.</th>
<th>MODERATE IMPROVE.</th>
<th>LITTLE OR NO IMPROVE.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Infect.</td>
<td>147</td>
<td>10</td>
<td>25</td>
<td>35</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>(Atrophic)Arth</td>
<td>24</td>
<td>90</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Senescent Arth</td>
<td>14</td>
<td>5</td>
<td>(50)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic Gouty</td>
<td>1</td>
<td>100</td>
<td>(1 case)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chr. Traumatic</td>
<td>2</td>
<td>100</td>
<td>(2 cases)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuritis</td>
<td>6</td>
<td>80</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myositis</td>
<td>8</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bursitis</td>
<td>4</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

"FEVER THERAPY FOR CHRONIC INFECTIOUS ARTHRITIS: 60 CASES TREATED AT THE CLINIC (MAYO)

<table>
<thead>
<tr>
<th>IMPROVEMENT GRADE</th>
<th>IMMEDIATE</th>
<th>LATER (8-11 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3 (Severe activity)</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>2 (Moderately severe)</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>1 (Mild activity)</td>
<td>27</td>
<td>12</td>
</tr>
<tr>
<td>0</td>
<td>10</td>
<td>50</td>
</tr>
</tbody>
</table>

"IMMEDIATE RESULTS OF FEVER THERAPY FOR G.C. ARTHRITIS" (Mayo Clinic)

<table>
<thead>
<tr>
<th>RELIEF, GRADE</th>
<th>ACUTE ARTHRITIS</th>
<th>CHRONIC ARTHRITIS</th>
<th>AVERAGE FOR BOTH, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>44</td>
<td>14</td>
<td>32</td>
</tr>
<tr>
<td>3½</td>
<td>44</td>
<td>29</td>
<td>37</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>29</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Total cases:</td>
<td>9</td>
<td>7</td>
<td>16</td>
</tr>
</tbody>
</table>

GONOCOCCAL INFECTIONS:

Stuhler (74) reports 25 cures out of 29 patients treated at the Mayo Clinic since December, 1933. These were patients with acute or chronic gonorrhea. By cure is meant: Cessation
of discharge, disappearance of gonococci, and of all symptoms that were produced by the presence of the gonococcus. Nine smears were free from G.C. after the first session; 4 after the second; 3 after the third; 2 after the fourth; 4 after the fifth; 1 after the seventh; 1 after the tenth; and, four were not cured. Stuhler is of the opinion that the chronic form responds best. An average of 4.6 treatments were given per patient.

Bennett and Austin (73) report the results obtained with 20 patients receiving a total of 59 treatments. Five of these patients were female and 15 male. Sixteen completed the treatments and averaged 4/ number of treatments:

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>No. Cases</th>
<th>Relieved</th>
<th>Unimproved</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute cervicitis</td>
<td>1</td>
<td></td>
<td>1</td>
<td>Discontinued Rx</td>
</tr>
<tr>
<td>Chronic salpingitis and cervical infection</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>&quot;</td>
</tr>
<tr>
<td>Acute anterior urethritis</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>&quot;</td>
</tr>
<tr>
<td>Chronic prostatitis</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>Recurred in 6 weeks</td>
</tr>
<tr>
<td>Chronic prostatitis and acute epididymitis</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>2 discontinued Rx; one under treatment</td>
</tr>
<tr>
<td>Prostatic abscess</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Para-urethral abscess</td>
<td>1</td>
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They report 12 possible cures, 5 failing to complete the treatments, two improperly treated, and one under treatment. Their experience with the Kettering hypertherm would indicate that a temperature of 106-107 F. for 6-7 hours every 3 days are necessary, with the continuation of local treatment combined with the fever therapy in the chronic cases.

**ASTHMA AND ALLERGIC DISEASES**

Feinberg, Osborne and Afremow (33) have used electropyrexia in intractable asthma and allergic diseases (104 F. for 8 hours, 4 days interval, 2 treatments in a course) and report "a number of severe asthmatic patients treated by this method (diathermy) gave results which are regarded as highly encouraging."
CONCLUSION
Fever therapy is rapidly providing a wide berth for itself in the realm of useful agents to combat disease. Many physical methods are now being employed. Clinical results with all of the methods are about the same. The best method at the present time seems to be the Kettering hypertherm. The author was in one of these cabinets for over an hour, and had a temperature elevation of over 106 F. About the only really uncomfortable portion of the whole procedure is a short period when the temperature is being raised from 101 to 103 or 104 F. The author went into the cabinet about a half hour after a Sunday chicken dinner and had no sedatives, yet the temperature was elevated to 106 F. with only slight nausea and moderate discomfort during portions of the session when the temperature was being elevated rapidly.

The value of induced fever is being established in certain types of diseases. Some, which have hitherto resisted all other forms of treatment, especially diseases of the nervous system, are now showing improvement with this type of therapy.

Whether the effects of radiothermy and diathermy i.e. penetrating heat and other means of producing artificial fever i.e. the application of external heat, are comparable in all respects is as yet unanswered, however, the similarity of clinical results that have been obtained by a variety of fever-inducing agents argues in favor of the premise that the results obtained are chiefly due to the production of the fever.
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