THE HISTORY OF FEVER THERAPY IN THE TREATMENT OF DISEASE*

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THE idea that fever is a method of therapy may be traced back to the early days of written history. "Give me the power to produce fever, and I will cure all disease," is a quotation attributed to Hippocrates more than twenty-three hundred years ago. Ruphos of Ephesus, four hundred and fifty years afterwards, said: "If indeed any were so good a physician as to be able to produce fever, it would not be necessary to look for any other remedy in sickness."

The production of fever as a therapeutic procedure had to wait centuries, however, for advances in chemistry, physics, mathematics, and medical sciences. The development of fever therapy can be divided into empirical and scientific eras. The borderline between these two eras was thermometry which was introduced in the early part of the Seventeenth Century by Galileo and Sanctorius, and developed in the second half of the Nineteenth Century by Wunderlich and Allbutt.

EMPIRICAL ERA

The origin of therapeutic fever lies buried in medical antiquity. While the rays of the sun have therapeutic value, other than their heating effects, nevertheless, early physicians used them solely for these effects. Heat was also applied to locally affected parts of the body and to its entirety by means of hot water, steam, sand, and mud baths. It is probably true that the ancient therapist might not have been aware of the fact that by these physical means he produced a rise in body temperature. However, our present knowledge of thermotherapy leads us to the reasonable conclusion, based upon the descriptions of the techniques used, that sufficient heating energy was frequently employed to accomplish such an elevation of systemic temperature.

Egyptian physicians during the Fifth Century B. C. applied rules for

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sun and heat therapy. In the encyclopedic compilations of Oribasius (325-403 A. D.) of Constantinople, are found quotations from Herodotus, the historian of the Fifth Century B. C., referring to this phase of Egyptian medicine.

Natural hot air caverns connected with volcanic sources were utilized (Oribasius, X, 40). The epic poet Homer (Fifth Century B. C.) clearly established that hot baths for medical purposes were common among the Greeks before the Age of Pericles.

Hippocrates had ideas as to the significance of fever, and modern concepts as to its possibilities. He prescribed hot water and steam baths for "thickened" and "tense" skin, for "spasticity" and for pains of the extremities as well as of the torso. Illustrative is the case history of a man of Athens who was affected with a severe pruritus of his entire body. The skin in all regions was so thickened that he had the appearance of a leper and it was impossible to pinch up the skin anywhere. No one had been able to relieve him. Hippocrates ordered him to go to the Island of Melos where there were hot baths. There he became entirely cured of his itching and the thickening of the skin, but he developed a dropsy and died. This man may have had one of the chronic dermatoses for the treatment of which dermatologists are now finding fever therapy to be of value. It is also possible that this patient may have received burns sufficiently extensive to cause a nephritis which proved fatal.

Among contraindications, Hippocrates mentioned repeated or profuse nasal hemorrhage, which, as an evidence of hypertension, would be included in modern contraindications for fever therapy.

During the reign of Tiberius Caesar, 42 B. C.-37 A. D., Aurelius Cornelius Celsus described the prevailing medical procedures and ideas regarding fever and heat. He wrote of a certain Pretonius who treated persons attacked by fever somewhat as follows: "He had the patient well covered up to excite at the same time a violent heat and thirst. When the fever began to abate somewhat, he made him drink cold water. If he broke out in a violent sweat, the patient was considered cured." "Heat," Celsus wrote, "acts well in eye diseases which are without pain and lachrymation. It is good for all sorts of ulcers but principally those due to cold." The techniques of heat application included wet fomentations, dry packs, steam baths, hot air baths, and sun baths. Celsus claimed that ordinarily heat would "relax the skin and draw forth corrupt humors, and change the condition of the body."

Galen wrote: "It is probable that Erasistratus (an Alexandrian anatomist of the Fourth Century B. C.) was not unaware of the method of treating cases of dropsy by heating in the barrel, a treatment which is highly estimated by other ancient physicians. Indeed, the patients experienced for the entire body an evacuation (sweating) much greater and sooner than in the bath. However, they did not suffer from the heat because they breathed cold air, their heads being outside. If they are deprived of this air, they die quickly." (*Deutil respir.* 4. t. iv.)

Coelius Aurelianus treated wasting, hemoptysis, and dropsy with dry hot air and hot sand baths. A description of the early hot sand bath is found in the works of Oribasius (*Orib.* Col. X, 8). "The summer time is the best because one can then choose the hottest day. Toward morning, there are prepared on the river bank in the deep sand, two or three trenches. These are allowed to become thoroughly heated by the sun. The patient should have digested his last meal and also taken a previous walk or at least had some passive movement. When the air is sufficiently warm and the sand sufficiently heated the patient is laid in the trench and covered with the hot sand as much as he can comfortably bear. The head must be protected from the sun. His face is wiped with a sponge dipped in cold water and if he suffers much he is given something with which to rinse his mouth. If the patient perceives that his body does not heat up at all or that he even becomes chilly because of the sweating he should say so. The attendant will then remove the sand, take him out of the trench, and will place him in the trench alongside in the same way as described above. If necessary, this may be done a third time being guided by the different conditions and according to their strengths."

The American Indians treated fevers with heat. William Penn in a letter to Edward Baynard, a fellow of the Royal College of Physicians, described how an Indian Chief obtained almost immediate relief from an illness associated with fever by the use of hot vapor baths. Among the early Americans, the sweat bath was a favorite therapeutic measure, especially for acute fevers. Arthritis, neuritis, and rheumatism, common among these Indians, were not distinguished from each other, but were all treated alike with the sweat bath. Carolina Indians used hot mud holes for treating various diseases of the extremities. Remittent and other forms of fever prevalent among the inhabitants of Northern Africa, were treated by sweating induced by hot sand and hot water baths.

The Chinese and the Japanese were among the earliest peoples to use their intensely hot springs for therapeutic purposes. In Japan the volcanic formations gave rise to many hot springs. These thermal springs were used for the treatment of all forms of syphilis, arthritis, rheumatism, acute genito-urinary infections, and respiratory, digestive, nervous and ocular diseases. They have been very popular throughout the Japanese empire since the Sixteenth Century and enjoyed local renown for several centuries before that time. Indeed, the use of the thousands of hot springs in Japan was common among all classes of the populace as one of the most important cures long before the introduction of European medicine. At Kusatsu, water gushes out of the bases of ancient volcanoes at a temperature between 100° F. and 160° F. As the water flows into reservoirs, it is unbearably hot, and the bathers stir it with large wooden paddles, thereby cooling it. They then immerse themselves to the neck and pour hot water over their heads with wooden dippers. After three to six minutes of this refined torture, they bob out almost parboiled with a body temperature of between 103° and 105° F.

Scientific Era

The research techniques developed during the Seventeenth, Eighteenth, and Nineteenth Centuries, permitted medical practice to pass from the stage of philosophic argument to scientific reasoning. Galileo in 1595 invented the thermometer, which may be said to have brought science to fever and heat therapy. Galileo's thermometer was the open-air alcohol thermoscope. Shortly afterward, in 1611, Sanctorius introduced this device to clinical medicine. Sanctorius investigated the cause and nature of body temperature. To carry out his studies, he devised the pulsilogium, an instrument for studying the pulse, and applied Galileo's thermoscope. He recognized that the human body has a normal temperature and determined variations from the normal as an aid to diagnosis.

In 1648, Von Helmuth also began to use a clinical thermometer, designed by Leurchon, the Frenchman, who in 1624 gave the name "thermometer" to the instrument.

Ferdinand II, Grand Duke of Tuscany, hermetically sealed the open end of Galileo's thermometer in 1641. Robert Hooke of England, in 1664, proposed that the freezing point of water be taken as one fixed point on the thermometer scale. It is believed that in 1684 he also sug-

gested the boiling point of water as another fixed point.

Fahrenheit described the use of mercury in thermometers in 1714. Herman Boerhaave (1668-1738) of Leyden, the founder of "eclectic" medicine, had been interested in fever and temperature reactions. He directed Fahrenheit to make him some thermometers for clinical use.

In 1742, Celsius of Upsala, an astronomer, proposed "zero" as the boiling point of water and "100" as the temperature of melting ice. The change to modern Centigrade was made independently by two scientists, Christin of Lyons, and Stromer, a colleague of Celsius. Stromer inverted his friend's scale and this revised instrument was used experimentally at Upsala in 1750.

Some of the authors of the Sixteenth and Seventeenth Centuries regarded fever as nature's means of healing. Gomez Pereira and Solenander pointed out the common belief of the Italians that tertiana had a cleansing effect. Primrose quoted the belief of people in England that malaria was beneficial.

An engraving by Jacques Lainet (Paris, 1659) represented the combination of mercury and heat for the treatment of syphilis. Fumigations with mercury were carried out in an oven. The intense sweating along with salivation, was thought to rid the body of disease poisons. "For one pleasure, a thousand pains" was the significant inscription on the oven.

In attempts to discover the exact influence of heat, Boerhaave and his pupil, Prevoost, and Fahrenheit put animals into heated ovens. They found that a dog and a cat died in twenty-eight minutes at a temperature equivalent to 73° C., while a sparrow died in seven minutes.

Influenced by Sydenham's views and by his own observations, Boerhaave finally concluded that fever must not be fought under any circumstances. He wished, he said, that he could produce the febrile curing action by artificial means. "I would be," he said, "the greatest physician if I could produce intermittent fever as easily as suppress it."

John Hunter (1728-1793), the English surgeon, also used the thermometer. Both he and DeHaan opposed the view that the production of heat in the body was due to friction of blood moving in the vessels. George Martine, of Scotland, in 1740 published his clinical-thermometric observations in a paper called "Essays and Observations."

Boerhaave's praise of fever caused a controversy that has persisted up to the present time. Gaub, one of Boerhaave's pupils, believed that

although fever was often salutary, nevertheless, it sometimes was fraught with great danger, especially to the circulation.

In 1790, Metzler made an interesting observation on malarial therapy in a treatise, "On the Advantages of Fever in Long Standing Diseases." This treatise, published in Ulm, was one of the early prophesies of the future therapeutic use of malaria. Metzler wrote: "Vigorot, Broussonet and myself sent patients with congested bowels to such places where they have soon been cured by intermittent salutarious fever."

An important theory on the cause of fever was offered by William Cullen of Edinburgh, in 1777. It was based on the newly acquired facts in the budding field of neuropathology. Virchow one hundred years later was a protagonist of this theory. An elevated temperature of the body, Cullen said, was a paralytic symptom due to depression of a natural influence on heat production. Any disease could become febrile if it extended to the centers of metabolism and suppressed the moderating effect of these centers. Febrile patients were, therefore, subjected to cooling measures by Cullen and his followers.

With rare exceptions, no attempt was made prior to the work of Wunderlich, to obtain more than one or two temperature recordings during an illness. Davy (1788-1829) in mapping out physiologic variations, and Traube (1818-1876), closely following the influence of digitalis on the body's temperature, were among the few who made frequent observations during a twenty-four hour period. The importance of such continued readings escaped them. Traube denied that fever depended upon increased production of heat. Lavoisier's theory of combustion and oxidation had postulated this relationship.

Up to the time of J. Clasius (1850) heat was generally regarded as a material substance. Only after Lord Kelvin (Sir Thomson) in 1849 established his absolute scale of temperature and Clasius and Helmholtz in 1850 worked out the mathematical laws governing heat transformation was the scientific framework for clinical thermometry laid.

In 1868, Carl Wunderlich published his classic on animal heat. Wunderlich demonstrated the diagnostic and prognostic importance of continued temperature observations during the course of a disease. He recorded the temperature of patients every four hours and constructed charts showing its variations. When he stated that fever was a symptom and not a disease, Wunderlich prepared the way for studies on heat production and fever. Wunderlich's method of attaining rectal tempera-

ture curves characteristic of various diseases spread quickly through England and Germany.

The period of the Nineteenth Century that witnessed the introduction of thermometry into clinical medicine was characterized also by advances in knowledge concerning infectious diseases. The record of the temperature of the body became one of the principal means of characterizing various febrile affections and of recognizing complications of these diseases. The close association of infection with fever was soon established and stressed so energetically that at present physicians find it difficult to avoid using one as an indication of the other. Thermometers had begun to make their appearance in numerous English hospitals during 1866-1867, and became generally accepted within the next two years. These were axillary thermometers, large, ten inches long, clumsy, and took five minutes to register. Sir Clifford Allbutt in 1868 reduced their size and devised the clinical mercury thermometer with which we are familiar. Resistance thermometers and thermocouples now permit of the continuous observation and automatic recording of temperature. Thanks to these advances, the thermometer, well-established as the invaluable tool of the diagnostician, has become the compass of the fever therapist.

The practitioners of the ancient and of the medieval world had made therapeutic use of fever produced by physical means on an empiric basis. They did not realize the physiologic significance of the procedure. The voices of those who reacclaimed the value of systemic temperature elevation and stated that fever is a natural mechanism of defense were drowned out under a deluge of antipyretics. Cool packs, showers, and baths, snow and ice were applied with such diligence that at times the doctor in concentrating on his efforts to reduce the fever forgot the patient, and accidents occurred. Less dangerous and simpler antipyretic measures were sought. Sydenham had called attention to the value of quinine in treating the fever of malaria. It came to be generally used for the treatment of other diseases associated with temperature elevation, such as typhus, puerperal infections, and tuberculosis. In these cases quinine proved unsatisfactory. A search for new antipyretics was therefore begun. Salicylic acid, phenol, antipyrin, antifebrin, amidopyrin, followed one another and were prescribed alone, alternately, or together. Chemists, in their laboratory search for antipyretics, discovered many a useful narcotic, analgesic and spasmolytic drug, but the "fever

drug" could not be found.

When Pfluger (1829-1910), as a result of his physiologic studies, ascribed a utilitarian purpose to fever, he was studiously ignored. Welch's supposition, in 1888, that "fever-producing agents light the fire which consumes them" found no response until recent years. Virchow echoed Cullen. Practitioners maintained a continuous attack on temperature elevation in disease. The momentum of these opinions has carried over into our day, so that the alcohol sponge and cold baths still are frequently routine, and the combination of acetylsalicylic acid, phenacetin and caffein has remained a popular method of "reducing the fever."

A clearer and more scientific conception of fever and its beneficial effects was obtained through several revolutionary medical discoveries which resulted in the founding of bacteriology and in an understanding of human metabolism, nutrition, and the physiology of the nervous system. The bacteriologist has shown that, in order to overcome disease, the objective of the clinician should not be the direct suppression of the abnormal elevation of temperature, but rather the destruction of the foreign agents responsible for inflammation and for fever. Further investigations demonstrated that the value of quinine in the treatment of malaria was not due to the influence of this drug upon heat production, heat loss, and heat regulation, but because of its effect upon the plasmodium. The work of men such as Pasteur, Koch, and Behring helped to establish the idea that the body fights for itself, that suffering life helps itself and the art of the doctor should assist the natural power of healing when it is weakened or limited. Modern medicine should no longer concentrate its attention upon the number of degrees of temperature elevation, but upon the profound change in physiologic activity due to this elevation. It should determine to what extent these phenomena are symptoms of the healthy activity of the organism and to what extent they are signs of damage and of loss. We recognize that microörganisms are not the only cause of inflammation and of fever, but that there are a host of thermic, chemical and toxic causes.

As early as 1870 Wunderlich declared that fever is a neuropathologic process. Other outstanding scientists of that time, such as the physiologist Johann von Muller, the surgeon Billroth, and the pathologist, Virchow, agreed that fever is an increase of oxidative processes due to stimulation of the central and peripheral nervous system. Experi-

mental hyperthermia was produced by the famous brain puncture (Warmestich) of Aronsohn and Sachs (1884), who stimulated the corpus striatum, and by Ott (1891), who stimulated the tuber cinereum. The studies of Krehl and his associates further emphasized the neural relationship to fever. The work of Krehl confirms more and more the famous conception of Liebermeister, who had declared that in fever, heat regulation is adjusted to a higher level.

Space does not permit reference to the work of many men who helped develop these fields. These include Lavoisier (1775) who determined the fundamental fact that the quantity of oxygen absorbed and carbon dioxide excreted depends upon food, work, and temperature; Joule, who in 1842 determined the mechanical equivalents of heat; Mayer, Helmholtz, Bischoof, Voit, Rubner, Atwater, Benedict, Lusk, Bazett and many others.

In 1883, W. H. Phillips experimenting upon himself, demonstrated that his temperature could be raised to 103° F. by prolonged immersion in hot water. Fourteen years later, Hill reported the influence of bath temperature upon body temperature and the changes it produced in pulse, blood pressure, and alveolar tension. Others confirmed and added to these findings. These authors included Fox, Sonntag, Weichbrodt and Jahnel, Schamberg, Tseng, Walinski and Mehrtens and Pouppirt.

Kellogg, in 1894, reported that the body temperature, as indicated in the rectum, may rise to 103° F., or even higher, in a prolonged electric light bath. Yet no one thought of using his technique for producing artificial fever for therapeutic effects until 1929, when Kahler and Knollmayer obtained fever temperature by this means.

With the advent of modern electricity, it was soon recognized that one of the effects of an electrical current was thermal. However, no form of electrothermal treatment had been possible until d'Arsonval in 1891 evolved his high frequency current, and showed that it would pass through the human body in a volume as great as three amperes, but without muscular nervous irritation and causing what he called "an unpleasant sensation of heat."

Nikola Tesla, working independently, produced a high frequency circuit and reported his results in the same year as d'Arsonval. He noted the passage of this current through the body and its lack of effects other than heating, which he suggested might be used therapeutically. It remained for von Zeynek, nearly ten years later (1904), working with

von Preyss and von Berndt, to demonstrate the therapeutic application of this current. von Zeynek called the method thermopenetration, while Nagelschmidt finally hit upon the now accepted term *diathermy*.

Notwithstanding the voluminous literature upon diathermy accumulated all over the world, it was not until 1929, nearly forty years after d'Arsonval's discovery, that a sustained fever induced by diathermy was used for therapeutic purposes. Neymann and Osborne, King and Cooke, raised the body temperature by using jacket-shaped electrodes. By means of blankets, they were able to maintain such temperature elevations for several hours.

The recent interest in fever therapy was in a large measure the result of work by Wagner-Jauregg of Vienna and by Whitney of Schenectady. Julius Wagner-Jauregg, after twenty years of observation, began to inoculate paretic soldiers with malaria in 1917. Despite some fatalities and great resistance from his colleagues, his success was so brilliant that ten years later he received the Nobel prize. The beneficial effect of malaria in epilepsy had been known to Hippocrates. Its curative effects in paresis and in insanity had been recorded in more than one hundred and sixty cases before Wagner-Jauregg, according to Maisani. Yet Wagner-Jauregg's work popularized this procedure and established its clinical value so that it received world-wide study.

In order to achieve the same results a host of less noxious proteins than the living malaria plasmodium were tried. Physical agents, such as the hot bath, diathermy, and photothermy were also employed.

In January 1928, Whitney observed that the men working with high-powered short wave tubes employed for long range radio transmission complained of headaches and other discomforts. A physician examining these men before and after work found that exposure to the current developed by these tubes produced two or three degrees of temperature elevation. Although Gosset and his co-workers had treated tumors on geranium plants by means of short waves in 1924, and Schereschewsky had employed currents of very short wave length for the treatment of animal tumors, these workers did not call special attention to the heat-producing effect of these energies. After experimentation on small animals, Whitney placed a number of larger high-frequency oscillators at the disposal of a number of us who were especially interested in the subject. From these and other sources have come new data concerning the physiologic significance of fever and also its thera-

peutic possibilities in the treatment of gonorrhea in all of its manifestations (including cases resistant to the sulfonamides), syphilis of the central nervous system, Sydenham's chorea, rheumatic fever, and in some diseases of the eye and of the skin. A voluminous literature on the subject has been developed consisting of books and articles which have been printed in leading medical journals. At the First International Congress on Fever Therapy held in New York in 1937 much of the data developed in recent years was summarized. There is evidence of the possibility of enhancing the effectiveness of the newer chemical substances by combining their use with purposeful elevations of the body temperature as in syphilis, gonorrhea, and in subacute bacterial endocarditis.

This survey of fever research gives but a bare outline of the painstaking work devoted to this subject in the past years. We tend to view fever therapy as a modern concept because the techniques which we employ to create it are of recent origin. It is therefore of interest to note that this method has been employed by some physicians all through the period of known medical history. Many of the diseases which we treat in this manner today were apparently treated in like fashion during the past centuries. It may well be that we still have something to learn from the ancients, including Petronius who thought that fever should be treated with heat.

In spite of all these efforts of the past, the significance of fever is not sufficiently appreciated today. It is hoped that the precise production of hyperthermia and its control in time and degree by means of the new methods will prove not only a most useful contribution to therapy, but will also start a new chapter in the history of the time-honored problem of fever.

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