What is old is new again: The use of whole-body hyperthermia for depression recalls the medicinal uses of hyperthermia, fever therapy, and hydrotherapy

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Abstract

This review contextualizes the current studies of whole-body hyperthermia (WBH) for depression by reviewing past hyperthermic treatments in medicine and psychiatry. It compares current and historical methodologies and hypotheses of mechanism of action. Hyperthermic treatments for cancer have increased in specificity and efficacy over time, from cautery to local and regional hyperthermic treatments, like radiofrequency ablation and intraperitoneal chemotherapy. Whole body hyperthermia remains under study for the treatment of cancer. In the 1800s, surgeons treated tumors by inoculating them with erysipelas and inducing fever. This treatment was replaced by radiation therapy. In psychiatry, Rosenblum and Wagner-Jauregg began treating mentally ill patients with inoculants and fevers, resulting in the use of the “malaria fever cure” for treatment of dementia paralytica (neurosyphilis). Its use expanded to non-syphilitic psychoses. In the 1930s, there was a less invasive treatment for syphilis, the fever cabinet. All fever treatments were phased out with the arrival of penicillin. In psychiatric hospitals, warm full baths, hot wet packs, and other forms of hydrotherapy were used to calm excited patients. These treatments were replaced by pharmacotherapy. For fever treatment, the understanding of mechanism of action slowly advanced from Coley’s description of the stimulation of the body’s “resisting powers” to the more specific finding, among others, of a rise in cytokines with fever. A reduction in depression in cancer patients treated with WBH has correlated with increases in β-endorphin levels and a theory of thermoregulatory cooling has been applied to the recent use of WBH in depressed patients.

Keywords: whole body hyperthermia; fever therapy; pyrotherapy; hydrotherapy; depression

Introduction

The concept of treating depressed patients with a controlled heat environment for a set duration of time has again taken hold in psychiatry. This was inspired by ancillary findings in cancer and medical patients who were treated with whole-body hyperthermia (WBH) over nearly four decades. In the 1980s, Robins’ group studied WBH in cancer patients, employing a radiant heat device (RHD) that elevated body temperature to 41.8°C for up to 150 minutes. With treatment, three patients manifested relief from pain and/or an increased sense of well-being [1]. In a follow-up study, they looked at neuro-endocrine changes in six cancer patients treated with WBH by RHD and reported elevations in β-endorphin plasma levels and increases in cortisol, ACTH, and prolactin [2]. The relationship between thermal stress (defined by temperature/duration) from WBH and the rise in β-endorphin level was linear. When they looked at mood states in seven WBH-treated cancer patients, using the Profile of Mood States questionnaire, they found a significant decrease in depression (F=2.71; p <0.05) after WBH, lasting up to 72 hours, with a group baseline depression score of 10 (SD=8) decreasing to a post treatment score of 3 (SD=5). They correlated the decrease in depression with increases in plasma β-endorphin levels [3].

Studies employing other methodologies, such as far-infrared dry sauna (FIRS) treatments to improve the quality of life for patients with type II diabetes mellitus [4], chronic fatigue syndrome [5], pain [6], and heart failure [7] are difficult to compare to other WBH studies because they do not record core body temperature. However, after finding that thermal therapy improved general well-being and anorexia in heart failure patients, Masuda et al. studied 28 mildly depressed patients with subjective complaints and appetite loss, half of whom were treated with thermal therapy in a FIRS set at 60°C for 15 minutes, then removed and kept warm for 30 minutes in a room at 28°C. Patients received twenty treatments over four weeks of hospitalization, after which somatic complaints (p < .001), hunger (p < .0001), and relaxation scores (p < .0001) improved significantly, and mental complaints showed slight improvement (p = .054), compared to the non-thermal treatment group [8].
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Whole-Body Hyperthermia in Depression (Table 1)

The above studies anticipate and inform current studies of whole-body hyperthermia (WBH) in patients with depression, studies conducted by a research group at the University of Wisconsin-Madison School of Medicine: one open trial [9] and what is considered the first randomized, double-blind, sham-controlled study [10]. In the second study, thirty patients with chronic, non-treatment-resistant, major depression (MDD) received one of two study interventions, WBH or sham. The WBH was administered with a Heckel HT3000 WBH system.

The Heckel HT3000 WBH system (Figure 1) - in combination with other therapies - is a therapy module used to treat rheumatism, fibromyalgia, muscular tension, arthrosis and degenerative processes, chronic inflammatory processes and infections (Lyme disease) and malignancies. It can provide a rapid and controlled increase in body temperature to one of three levels: Mild (37.5 – 38.5°C), Moderate or fever-like (38.5 – 40.5°C), and extreme (40.5 – 42°C). It does so with a water-filtered infrared-A (wIRA) irradiator above the exposed upper part of the body; leg and foot infrared emitters prevent loss of body warmth. The irradiator penetrates into deep tissues but is gentle on skin. There are two phases to treatment: the irradiation phase and the heat retention phase, when the patient is wrapped in the walls of the tent and the heat is maintained at a plateau level, up to several hours (“long-duration whole-body hyperthermia”). When WBH is given at fever-like and extreme temperatures, there is continuous monitoring of vital functions: core body temperature, ECG and pulse, BP, breathing, and oximetry. The Heckel HT3000 WBH system is used in many capacities, including the delivery of medications to the site of action and increasing the efficacy of chemotherapies and antibiotic treatments. It is believed to augment immunological processes, for example the migration of lymphocytes to inflammatory sites [11].

In Raison’s group’s six-week randomized double-blind study, sixteen patients with major depression received mild intensity WBH for the mean length of 107 minutes; the heat was turned off when the core body temperature reached 38.5°C, after which the patient remained in the WBH device for a cool-down period of 60 minutes. Fourteen patients completed the sham treatment. After the intervention, the participants were assessed with the 17-item Hamilton Depression Rating Scale (HDRS) at 1, 2, 4, and 6 weeks. Twenty-nine patients provided one or more post intervention assessments. Compared to the sham group, the WBH group had significantly reduced HDRS scores across this period, with active improvement during the first two weeks, after which scores remained stable [10].

The positive outcome is based on the theory that “exposure to warm temperature activates the spinoparabrachial pathway and the midbrain 5-HT nuclei to which it projects,” a pathway that may be functioning sub-optimally in MDD [9]. Some patients with MDD have increased core body temperature – a manifestation of decreased activity in the above pathway - and, after treatment with WBH, demonstrate a drop in core temperature (thermoregulatory cooling). In their open study [9], the group observed a correlation between higher core temperature prior to WBH and the extent of antidepressant response at five days post-treatment.

Brief Review of Heat Treatments in Medicine

The word hyperthermia derives from the Greek: hyper meaning a rise and thermē meaning heat. Heat treatment or hyperthermia, which can be applied to parts of the body or to the body as a whole, has been used in medicine since ancient times.

Localized Heat Treatments

Localized heat treatments in medicine began with cautery in the Western world [12-17] and moxibustion in the East [18-21], both of which continue in different forms today. In the early 19th century, galvanocautery burned tumors through the application of electrodes. The Byrne method was developed to cauterize gynecological tumors [22-23]. Following discoveries by Nikola Tesla and Jacques-Arsene d’Arsonval that high frequency, high-tension currents could heat living tissues without obvious harm [24], high frequency sparking (destructive fulguration or electrocauterization) was applied to superficial malignancies. The Keating-Hart method of fulguration added cool air to lower the temperature of the cancerous tissue.

Thermoradiotherapy, also developed by de Keating-Hart, added X-Ray irradiation to the sparking and cooling and was used with inoperable or deep cancers [25]. D’Arsonval established the first high frequency heat therapy unit at the Hôtel-Dieu de Paris hospital in 1895, where some patients were treated on condenser couches (Figure 2). D’Arsonvalization spread throughout the United States and Europe until the 1920s, when diathermy emerged in its place [22,26]. Diathermy (“heating through”) applied high-frequency electromagnetic currents to deep tissues, destroying the tumor by thermocoagulation [25]. Diathermy machines (Figure 3) were used in electrotherapy, and eventually in occupational and physical therapy [26]. Electrosurgery continued to evolve from bipolar surgery in the early 1900s to improvements in cutting and hemostasis with Bovie’s practical electrosurgical device [27-28], to modern loop electrosurgery [17]. Cancer heat treatments evolved into...
modern treatments like radiofrequency ablation - the placement of a needle electrode inside the tumor to produce temperatures up to 100°C - and hyperthermic intraperitoneal chemotherapy, in which a heated chemotherapy drug is placed directly in the abdominal cavity during surgery [17].

Systemic Heat Treatments

For centuries, physicians have noted the connection between infection, fever, and tumors. A French physician by the name of Antione Dieder observed, in 1725, that there were fewer malignant tumors in patients with syphilis [29]. In the 1860s, the German surgeon Carl Busch described a patient with a multiple skin sarcoma of the face who developed erysipelas with fever after tumor resection; the cancer disappeared. Two years later, Busch induced erysipelas in a patient with an inoperable tumor of the neck by placing the patient in a bed “in the immediate vicinity of a case of erysipelas.” The tumor initially regressed but grew back [30]. When Feheleisen discovered the erysipelas cocci (streptococcus), enabling cultivation outside the body, it was possible to inoculate cancer patients with the toxin of erysipelas [31]. Bruns described five cases of sarcoma exposed to erysipelas and fever, which were either “permanently cured” (3/5) or reduced in size [32]. A JAMA review (1893) [30] of 38 cases of malignant tumors (mostly inoperable) where erysipelas occurred – by accident or inoculation – concluded there was “indisputed evidence of the curative effect of erysipelas upon malignant tumors” because “we know positively that in a number of authentic cases it has had a permanent curative action.” Eight cases not in the review were inoculated, had no actual attack of erysipelas, and showed “marked improvement,” indicating there was a substance in the culture “antagonistic to the tumor growth.”

However, physicians continued to inoculate with the goal of producing fever. William Coley initially inoculated sarcomas with live erysipelas [32] but developed a safer heat-killed erysipelas inoculant that he combined with the bacillus prodigiosus (serratia marcescens), called “Coley’s Toxins.” He injected the toxins into the tumor or subcutaneously, with intravenous injection reserved for special cases. He adjusted the dose of toxin to each patient and titrated upward to attain a body temperature of 39°C or greater [33]. While Coley considered several theories of tumor regression – direct destructive action, high temperature destroying “cells of lower vitality” and leading to fatty degeneration and resorption, and “direct antagonistic effect” of the erysipelas bacteria on the “cancer bacillus” [32] – he considered high temperature an important factor in stimulating the body’s “resisting powers” (immune system). Over time, his work produced mixed results in patients with inoperable sarcoma and carcinoma and was not well replicated [34] or accepted [35]. However, Coley was named the “Father of Immunotherapy” and the opinion of his work eventually improved. His daughter (HC Coley-Nauts) reviewed over one thousand of his cases and found that almost five hundred achieved near-complete regression [36]. In her review,
One outgrowth of Coley’s work is the use of the bacilli Calmette-Guerin (BCG) vaccine to treat bladder cancer and, as discoveries in immunotherapy have advanced, so has the understanding of his toxins. It is now thought that Coley’s Toxins bind to and stimulate the Toll-like receptors (TLRs) on the immune cells [38]. Rare trials are being conducted, such as one in Germany in 2007, a CRI funded phase I trial that demonstrated the toxins induce fever and a rise in cytokines; one patient experienced a 50% reduction in his bladder cancer, correlating with increases in cytokines [39,40]. Despite restrictions on the use of these toxins in the United States and England (Cancer Research UK), patients seek out these treatments in clinics in Mexico, Germany, and China [41].

### Heat Treatments in Psychiatry

**Malaria fever therapy**

...we cannot be reproached for using a procedure which is irrational. We have listened to nature; we have attempted to imitate the method by which nature itself produces cures. *Julius Wagner-Jauregg*

In psychiatry, one of the more dramatic – some say desperate – forms of heat treatment was a malarial fever treatment for patients with the manifestations of tertiary syphilis (neurosyphilis), known as general paralysis of the insane ([GPI]) or dementia paralytica [DP]. In 19th century Europe and North America, the increase in the rate of hospitalization for mental illness was, in large part, due to syphilis. When syphilis infected the brain, it produced grandiosity and other manic symptoms, eventually leading to dementia, paralysis and death [42].

For centuries, there were observations about the propitious effects of fever on mental illness; see Whitrow for a summary [42]. While Busch and Fehleisen were exposing patients to erysipelas, an Austrian psychiatrist, Julius Wagner-Jauregg was making observations of his own. In 1883, at the Asylum of Lower Austria in Vienna, he observed a female patient who

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### Table 1. Recent studies of whole body hyperthermia in depression.

<table>
<thead>
<tr>
<th>Researcher</th>
<th>Modality</th>
<th>Core Body Temp (CBT)</th>
<th>Instrument</th>
<th>Results</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robins [3]</td>
<td>Radiant Heat Device</td>
<td>-</td>
<td>Profile of Mood States Questionnaire</td>
<td>↓depression for 72 hrs in 7 cancer patients</td>
<td>Correlates with ↑plasma endorphin levels</td>
</tr>
<tr>
<td>Massada [8]</td>
<td>Far-infrared dry sauna (FIRS) @ 60°C x 15 mins; kept warm @ 28°C x 30 mins; 20 txs in 4 wks</td>
<td>-</td>
<td>Cornell Medical Index &amp; Self-Rating Depression Scale</td>
<td>Improved hunger, relaxation and somatic complaint scores in 28 mildly depressed patients</td>
<td>Inhibits sympathetic nerves → parasymp. nerves predominant</td>
</tr>
<tr>
<td>Raison [9,10]</td>
<td>Heckett HT3000 WBH system @ mild intensity for mean length of 107 mins; cool-down of 60 mins</td>
<td>38.5°C</td>
<td>Hamilton Depression Rating Scale @ 1, 2, 4, &amp; 6 wks.</td>
<td>Greatest ↓ HRS score in 1st 2 wks, after which scores = stable</td>
<td>Some MDD pts =↑ CBT = sign of ↓ activity in the spinoparabrachial (SPB) pathway. Mild WBH sensitizes SPB pathway needed for thermoregulatory cooling &amp; regulation of mood</td>
</tr>
</tbody>
</table>

### Table 2. Types of fevers.

<table>
<thead>
<tr>
<th>Fever</th>
<th>Characteristics</th>
<th>Examples of Causative Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous Fever</td>
<td>Temperature stays elevated ≥ 24 hours; fluctuation not &gt; 1°C</td>
<td>Unintreated typhoid fever and typhus, pneumonia, UTIs, meningitis</td>
</tr>
<tr>
<td>Remittent Fever</td>
<td>Daily fluctuations of ≥ 2°C; lowest point can be nearly normal but doesn’t touch normal</td>
<td>Infectious diseases, such as brucellosis, infective endocarditis, rickettsiae infections</td>
</tr>
<tr>
<td>Intermittent Fever</td>
<td>Fever appears for a period of time, disappears, and reappears in cycles; there can be a large difference between apex and base temperature</td>
<td>Malaria;* Pyrogenic abscesses, tuberculosis, typhoid fever</td>
</tr>
<tr>
<td>- 1. Quotidian fever</td>
<td>24 hour periodicity</td>
<td>P. falciparum malaria; P. knowlesi malaria</td>
</tr>
<tr>
<td>- 2. Tertian fever</td>
<td>2 spikes in 24 hours</td>
<td>Mixed malaria infections; GC endocarditis, leishmaniasis</td>
</tr>
<tr>
<td>- 3. Quartan fever</td>
<td>48-hour periodicity</td>
<td>P. vivax malaria; P. ovale malaria</td>
</tr>
<tr>
<td>- 4. Loycopeter fever</td>
<td>72-hour periodicity</td>
<td>2 groups of P. vivax alternate sporulation every 48 hours</td>
</tr>
<tr>
<td>Relapsing Fever</td>
<td>Fever recur; separated by periods of no fever or low-grade fever.</td>
<td>Malaria, rat-bite fever, borreliia, lymphoma</td>
</tr>
</tbody>
</table>

*At the time of malariotherapy, *P. vivax*, *P. malariae*, and *P. falciparum* were known.

Adapted from:


The Free Medical Dictionary: https://medical-dictionary.thefreedictionary.com/double+tertian+malaria
recovered from mental illness after an attack of erysipelas [43]. In an 1887 paper [44], he reviewed the literature— including reports of the beneficial effects of typhus, intermittent fevers (malaria), erysipelas, and anthrax on mental illness—and he postulated fever therapy as a treatment for psychoses. He considered malaria (which had a treatment and could be induced) and erysipelas (more benign/also inducible) as diseases for further study. However, Wagner-Jauregg’s attempts in 1888-89 to inoculate patients with streptococcus failed. In 1890-91, he injected his GPI patients with the newly-developed tuberculin vaccine, achieved positive results, and abandoned tuberculin injections due to toxicity concerns. He re-considered the use of malaria and injected his first patient in 1917, injecting the patient with the P. vivax- infected blood of a soldier back from the Balkan front. The patient, who was given quinine after nine febrile attacks, recovered and was discharged. Of nine GPI patients infected that summer and followed up for a year, six were reported to be recovered or improved [45,46].

Due to Wagner-Jauregg’s success with another 200 GPI patients, tens of thousands of GPI patients came to be treated with malaria—often coupled with the use of earlier heavy-metal treatments; “half could be expected to resume normal life or improve significantly” and “only one in five failed to respond [47].” In 1927, Wagner-Jauregg received the Nobel Prize in Physiology or Medicine, the first psychiatrist to receive a Nobel Prize [45,46].

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It is interesting to note that, after World War I—with its epidemic of malaria on the Macedonia front—malaria was “unexpectedly found to be the leading cause of psychiatric disorders among soldiers of the Allied powers fighting there [50].” A 1926 paper [51] reported on nine of forty patients who died during treatment or the month thereafter, one by suicide during the “acute hallucinatory confusion” concomitant with fever. In a 1936 review of malarial fever therapy [52], Rudolf wrote of the “fluctuating hallucinations of all the senses” occurring during treatment, a reason that Wagner Jauregg terminated treatment. There were also reports of “paraphrenic states or late psychoses” occurring after treatment, including conditions that were “confusional, hallucinatory, systematized, stuporous, with ideas of reference, manic-depressive, hypochondriacal, depressive, and catatonic” states of hebephrenia and cases of typical dementia praecox. It was difficult to distinguish the psychiatric effects of malarial disease from those of its treatment, quinine, which was observed in the early 1900s to cause personality effects, mania and depression. Over time it has become clearer that quinine alone can produce confusion and delirium [50].

At the time, Wagner-Jauregg’s malaria fever therapy was considered a breakthrough in treating a common and fatal illness and “broke the therapeutic nihilism that had dominated psychiatry in previous generations [43].” Yet, it remained a high risk procedure and was implemented by syphiliologists who practiced in specialized units and hospitals. Some of the risks of inoculation included the risk of blood clots with IV injection, the risk of introducing other pathogens, including additional T. pallidum, and the risk of infected mosquitoes spreading disease. Some of the complications included uremic coma, pyogenic infections, seizures, circulatory collapse, and acute bulbar palsy [51]. According to one review [47], mortality rates varied from 10% (early on) to 1%, with average mortality rates of 2.4% - 5.4%. According to Rudolf, “none of these risks are, however, so great as are those for the untreated patient,” who has “about twice” the risk of the patient treated with malarialotherapy. See Table 2 for fever types and Table 3 for the parameters of malarial treatment.

A review of >2800 cases treated with malaria and malaria/arsenic (from 1926 – 1936) led Rudolf to proclaim: “The failure of so great a proportion, about 70 – 75 per cent of paralytics, to undergo good remission after treatment has led many writers to endeavor to determine the most favourable type of case for treatment [52].” By the 1930s, there were numerous theories on the pathogenesis of paralytic dementia (PD) and the mode of action of malarialotherapy. One theory [53] proposed that the tertiary and parasyphilitic lesions resulted from “hypersensitiveness” in the tissues, effecting an allergic reaction, neuronal death and neuroglia. The opposite view held that the defensive reaction was missing, as evidenced by the lack of history of earlier syphilitic lesions in the PD patient. “Pyretotherapy stimulates the resistive function of the reticulo-endothelial system at a time when this function is flagging under the influence of a chronic infection – syphils.” With febrile paroxysms, the neutropenia of PD led to neutrophilia. And, in an effort to determine the best patients for malaria treatment, a preliminary test with a mild leucogenic agent (e.g. injection of sodium nucleinate or peptone) was done, to determine which patients mounted a satisfactory leucocytic reaction [53].

Despite the failures, malarialotherapy enabled many patients to leave the mental institutions [54] and led to the broad use of the “malaria fever cure” in syphilitic and non-syphilitic psychoses [55], including schizophrenia and manic-depressive psychosis, with little effect in epilepsy [52]. In the 1940s, malaria fever treatment of GPI was supplanted by treatment with penicillin. However, not all malarialotherapy ended.

An NIH study in the 1970s [56] injected penitentiary volunteers with blood infected with a multiply drug-resistant (Columbian) strain of P. falciparum, to find a cure for this resistant strain. Such a study could not be conducted today, following Congress’s passage (1974) of the National Research Act, after which institutional review boards (IRBs) oversaw
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<table>
<thead>
<tr>
<th>Table 3. Malariotherapy: Parameters of treatment.</th>
</tr>
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<tbody>
<tr>
<td>Patient Population*a</td>
</tr>
<tr>
<td>1- GP confirmed by serological exam of blood/CSF</td>
</tr>
<tr>
<td>2- Good health, particularly circulatory and renal systems 3- Best results when treated early in the course</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Known malarial specieb</th>
<th>P. vivax</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. malariae</td>
<td></td>
</tr>
<tr>
<td>P. falciparum</td>
<td></td>
</tr>
</tbody>
</table>

Methods of Inducing Infection

1- Inject benign tertiarial malarial blood SQ or IM (Wagner-Jauregg injected 1-4 cc)
2- Inject infected blood IV: This reduced the “prepatent period” but there was a risk of blood clot
3- By mosquito bite, by placing a jar covered with netting and containing 4-5 infected mosquitoes on the patient’s thigh.a This reduced the risk of other human infections being introduced through blood. Expensive to maintain mosquito colonies.b

Stages

1- Incubation period of 10 – 24 days 2- Primary attack a. Initial stage: gradually 1 fever, intermittent days 3-4 followed by intermission for 1-2 days. No rigor. b. Developed stage: Intermittent fevers with rising spikes and longer paroxysms (10-12 hours); can become double tertian. Parasites increase day 1-3, then temp/parasites moderate. Cold-sponging begun at 105°F to prevent hyperpyrexia. Treatment with quinine after 8 – 16 paroxysms (8-12 for Wagner-Jauregg )
c- Termination stage: Fever reverts to tertian type; severity decreases. In cases of spontaneous recovery (no quinine), parasites persist in the blood after fever abates.

3- Convalescence – Patients are anemic and exhausted; treated with “food, fresh air, and medical comforts.”

Reasons for terminating malarial infection early, by treating with quinine

1- Clinical severity: “persistent vomiting, faintness or collapse during the paroxysm, cyanosis, seizures, undue restlessness, albuminuria and the earliest suggestion of jaundice.”a 2- Hallucinations (Wagner-Jauregg)
3- Hyperpyrexia >105° F 4- Parasite burdens >100,000/mL of blood

Quinine dosing

Wagner-Jauregg: Quinine bisulphate in doses of 7-~2 grams twice daily for 3 days; then 7- aurine (0.5 Gm.) once daily for 14 days, followed by neo-arsphenamine injections.c Others: 1.0 Gm. twice daily for 10 days 10 gr three times a day for 5 days 5 gr three times a day for 10 days

Complications

Highest risk of fatality: first 12 hours after quinine given Uremic coma, pyogenic infections, seizures, circulatory collapse, and acute bulbar palsy c Tendency toward obesity following treatment

*Relatives of the patient informed of risk (Nicol)

Adapted from:


experiments with human subjects [57].

In 1990, Dr. Henry Heimlich wrote a letter to the New England Journal of Medicine [58] in which he argued that neurosyphilis and neuroborreliosis (neurologic Lyme disease) are related clinically and biologically (both are spirochetes) and that malariotherapy be considered for the treatment of refractory neuroborreliosis. Simultaneously, he supported the use of malariotherapy for the treatment of AIDS and participated in Chinese research that inoculated HIV-positive patients with P. malariae vivax [59]. During this time, desperate patients with Lyme Disease (LD) were travelling to Mexican clinics for IM injections of P. vivax-containing blood. Two returned to the United States with parasitemia that responded to chloroquine [60]; one later reported the treatment did not improve her LD. A follow-up CDC report [61] described a Texas patient with LD who self-injected with P. vivax contaminated blood – resulting in “10 paroxysms of fever up to 104.9°F (40.5°C) lasting 12 hours” – and self-treated with chloroquine 21-24 days after his first IV injection; follow-up testing 6 days later detected no malarial parasites. The effect on his LD was not reported.

The CDC warned against the use of malariotherapy for Lyme Disease, calling the treatment an “obsolete practice” for treating neurosyphilis because there were no controlled studies done during Wagner-Jauregg’s time and reason to treatment/duration of remission were unpredictable and variable. They warned against current induction of malarial infection due to concerns about the resulting morbidity, the possibility of infection of the injected blood with pathogens like HIV and hepatitis B virus, and the risk of transmission of malaria to others. According to the CDC, malariotherapy for LD remains experimental, subject to FDA and IRB approval and informed consent [60,61].

Fever Cabinets

Malaria fever therapy led to research into other methods of fever-induction, such as the injection of foreign proteins or colloid sulphur, diathermy, hot-water baths, and fever cabinets [62].

In 1930, an American bacteriologist named Paul de Kruif met Wagner-Jauregg [63] and this meeting led to the development of a fever cabinet that could replace malaria fever therapy for neurosyphilis. De Kruif and his collaborators developed the Kettering hypertherm (Figure 4), an air-conditioned cabinet that enabled rapid elevation and maintenance of the syphilitic patient’s body temperature [64,65]. Moist air blew over the patient, creating six hours of fever from 105° - 106°F [63]. These sessions were given weekly for ten weeks. The best results were obtained in syphilitic patients when the hyperthermia protocol was combined with antisyphilitic chemotherapy (bismuth compounds, iodobismitol or trypsarsamide) injected one half hour before each treatment and given as a follow-up course weekly for twenty weeks [65].

When war became imminent, there was a hope for a rapid treatment that could bring the soldiers with syphilis back to A-1 status, to fight in World War II. De Kruif called his treatment a “one-day cure” for syphilis, a concept that was opposed by the American Medical Association, and he supported the building of a Quarantine Hospital for treatment. In 1942, a new Chicago Venereal Disease Hospital was opened and equipped with ten hypertherm fever cabinets. De Kruif wrote:

“Artificial fever is now so safe and so marvelously controllable, not in a hot box as you call it, but in a warm box. The humid air now used for induction of fever is not above 112° [F], usually 110°. The fever, once induced, is maintained at.
108°—only 2° above the temperature of the patient, so perfect is the insulation. Over twelve hundred patients have been fevered in Dayton during the past eleven years, and in only one can fever be said to have been contributory to death. This means that far over twenty thousand hours of fever have been given with this remarkable safety. And now we don’t burn them at all anymore. And now we have hundreds of neuroluetics cured. And now we have forty-five successive cases of early syphilis one day treatment: fever plus mapharsen [arsenic], and all have reversed clinically and to complete negative by quantitative Kahn [test], with no relapse so far [63].”

De Kruif later acknowledged that 15 to 30% of patients relapsed.

In 1943, penicillin emerged as a treatment for syphilis. At first, it was used together with arsenic, bismuth and heat treatments, but, eventually, after a decade of use, heat treatments for syphilis were phased out [63].

Hydrotherapy

“Kraepelin, the eminent psychiatrist of Heidelberg, regards the continuous bath (98° to 100°) for several hours as the most effective calmative, inasmuch as it often succeeds when medicinal agents fail.” [66] page 228

Hydrotherapy is a method of applying water in disease and includes “the application of water in any form from the solid and fluid to vapor; from ice to steam, internally and externally [66].” In the 1800s, its main effect was thought to be the “thermic and mechanical action of water upon the cutaneous surfaces of the body.” Wilhelm Winternitz of Vienna – known as the father of scientific hydrotherapy – observed that the application of “thermic stimuli” to one part of the body could produce changes in circulation in other parts of the body through dilatation/contraction of blood vessels, depending on the temperature of the stimulus [67]. The skin was extensively studied: cutaneous circulation, nerve endings and the pressure, touch, and temperature senses, skin as an organ of excretion (infectious organisms being found in perspiration), and the skin as a heat regulator. As a result, the centuries-old ‘water cure’ evolved into a scientific remedy [66].

At the time, Dr. Simon Baruch of New York City was a Professor of Hydrotherapeutics and an expert in his field. His 1899 book, The Principles and Practice of Hydrotherapy: A Guide to the Application of Water in Disease for Students and Practitioners of Medicine, describes cold and heated methods of hydrotherapy used in the treatment of both medical and mental diseases [66].

It is important to understand several principles of hydrotherapy extant at the time. Hydrotherapists considered the “action” and the “reaction” of a particular treatment. For example, in a cold procedure, when the cutaneous vessels are contracted (action) a compensatory dilatation (reaction) of the deeper vessels ensues [66]. Secondly, hydrotherapy was considered tonic or sedative. For a tonic or stimulating effect, a cold shower, douche or cold pack was employed and used to treat diabetes, rheumatism, anemia, gout, and digestive disorders [66]. A sedative effect was achieved with a bath at 90°F (“tepid”) – 105°F (“very hot”), equivalent to ~32 – 40.5°C.

In lieu of this paper’s focus, below is a description of hyperthermic procedures only, as described by Baruch:

1. The warm full (whole) bath was a tub bath with the water temperature maintained above the body temperature at 95° to 100° F. The mechanism of action was thought to be “endosmosis” filling the peripheral sensory nerve terminals - considered the outposts of the entire nervous system, conveying all impressions directly to the brain” - with water, rendering them succulent. This succulence diminished the irritability of the nerve terminals, explaining the calming effect of the warm bath.

2. The continuous or hammock bath was a 100° F bath in a deep tub. The patient’s skin was rubbed with mutton suet (or lanolin) and the patient was laid upon a sheet suspended above the bottom of the tub, like a hammock, with a rubber pillow under the head. The tub was covered with blankets on supports and the temperature was regulated by “electrical and other contrivances.” The patient was bathed for hours to weeks and
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Lifted daily from the tub for cleansing, excretion, and renewal of water; some patients slept in the bath under observation. Side effects included insomnia, polyphagia and weight gain. The treatment was thought to decrease “cutaneous irritations” (e.g. fluctuating temperatures) and result in the “regulation and quiescence of important functions, especially of the activity of the central nervous system.” Therefore, it was used for spinal cord diseases, including paraplegias, bladder/intestinal paralysis and the sequelae of meningitis and brain tumors. Because of its capacity to calm cerebral irritability, the continuous bath was used for “general hyperaesthesia, and especially cerebral excitement and delirium.”

3. The hot wet pack consisted of a large blanket and a sheet – dipped in hot water and wrung out – which were wrapped around the patient’s body, excluding the head, and applied for an hour or more and all night if asleep.

At the time, hydrotherapy was considered an advancement in the treatment of certain forms of insanity. For example, it was very important to control the motor excitement of mania to prevent “death from exhaustion in a few days.” Prior to hydrotherapy, these patients were fastened in bed with a straitjacket and given hyoscine, a sedative. When such restraint was prohibited, hydrotherapy was adopted. According to Kraepelin and others, the following diseases could be managed with the prolonged warm bath: exhaustion psychoses, the insomnia of acquired neurasthenia, dementia praecox, the insomnia and agitation of melancholia, and the excitement of manic-depressive insanity [66]. The hot wet pack was considered the best treatment for insomnia among the insane.

While these treatments existed throughout Europe in the 1800’s, they were slower to arrive at American mental asylums. There is a report of the use of prolonged hot baths at Buffalo State Hospital, in 1885, but without the hydrotherapy apparatus [68]. In 1887, after a tour of European asylums, Baruch attempted to expand the use of hydrotherapy into American asylums, whose only baths at the time were “for the purpose of cleanliness [66].” It gradually replaced restraints and sedative medications, and came to include douches, needle sprays, salt glows, electric light baths, wet sheet packs, and continuous baths [69].

In American asylums, the prolonged warm bath proved effective in “acute maniacal conditions, or acute delirium states, characterized by great motor activity.” Increased motor activity (mania) was reduced, as was restlessness, tactile hallucinations, and elevated temperature (delirium); sleep was induced and appetite improved. There was also some benefit in cases of “melancholia with frenzy [68].” Following a hot bath, “cephalic cold” was applied with an ice-cap or ice-collar, neck/forehead compresses, or face sponging. Cephalic cold prevented “cerebral congestion” which could worsen manic attacks and other psychoses [69].

In NYS hospitals, most agitated patients remained in the continuous heated baths for hours to days, although one report indicated that, at a Heidelberg clinic, patients stayed in the continuous bath for nine months [68]. In the late 1930s, Alfred Eisenstaedt photographed excited patients immersed in the continuous flow baths at Pilgrim State Hospital [70]. Figure 5 is a photograph of hydrotherapy equipment used at the Utah State Hospital circa 1940. Hydrotherapy treatments in psychiatric hospitals were phased out with the discovery of antipsychotic medications.

Current Interest in The Role of Infection, Malaria and Fever

Systemic heat treatments like malariotherapy would not occur today, unless under rigorous research conditions, and observations regarding early malariotherapy treatment and duration of remission are considered variable and unpredictable [60,61]. However, interest in Plasmodium infection continues, as well as interest in the effect of fever on medical and psychiatric disease.

For example, in 2014, CDC/NIH researchers decided to look at the effect of co-infection with Plasmodium spp parasites on the survival of Ebola patients in Liberia, and discovered that the co-infected patients had an increased survival rate. They did not consider the role of fever and concluded that the increased survival was the result of an “indirect effect” on the host and not a direct effect on the replication of the Ebola virus. They suggest that coinfection could dampen down the destructive cytokine storm, with increased survival, or, alternatively, increase natural killer cells. If Plasmodium spp coinfection has an immunomodulatory effect, then immunomodulatory drugs could potentially be used to treat Ebola infection [71].

Figure 5. Utah State Hospital hydrotherapy equipment, 1940. The tubs are in the foreground. In the background is a patient shower stall and console that regulated water temperature and velocity. (Courtesy of the Utah State Hospital Historian and Provo City Library, Provo, UT)
In psychiatry, there have been recent observations of the resolution of psychosis following fever from infection. A 2007 case report [72] out of Rome, Italy, describes a man with an acute psychotic disorder whose fever of 40.5°C from a urinary infection led to the resolution of his psychotic symptoms, while off antipsychotic medication. A 2016 case report [73] describes a psychotic patient with strep bacteremia who was intermittently febrile (T_max of 102.74°F or 39.3°C) and also removed from antipsychotic medication, leading to a resolution of psychotic symptoms. One author speculates that the antibiotics used to treat the fever could have psychotropic properties, in this case beneficial ones.

One other current and related area of interest is that of heat-shock proteins, which can be induced by hyperthermia and other physiologic stresses. Heat-shock proteins have a role in regulating immune responses and are potentially neuroprotective.

Summary

Over the last 40 years, research using WBH to treat cancer patients led to observations of increased well-being and decreases in depression, correlating with increases in plasma β-endorphin levels. There were similar findings in patients with chronic medical disease who were treated with far-infrared dry sauna (FIRS). This led researchers at the University of Wisconsin to use systemic heat treatments to raise the core body temperature of depressed patients to a moderate level of 38.5°C, on the hypothesis that depressed patients with increased core body temperature (indicating decreased activity in the spino-parabrachial pathway) will undergo thermoregulatory cooling.

How do these current hyperthermic treatments compare to prior treatments in the fields of medicine and psychiatry? The localized uses of heat treatment, which began as cautery and moxibustion, have advanced in accuracy and continue to be used in surgery and oncology. The methodologies and mechanisms are more straightforward. However, the systemic heat treatments have gone through cycles – evolving and being abandoned over time, without clear understanding of the mechanisms of action.

It is important to distinguish between internal, systemic heat treatments initiated by injection of infective agents (erisypelas, typhus, malaria) that stimulate fever and the external application of heat through the use of heat cabinets, hydrotherapy, and the current, experimental, whole body hyperthermia treatments for depression. With fever caused by infection, the role of heat treatment is confounded by the role of the organism and the treatments for the infection. In the 1800s, when cancer patients were inoculated with erisypelas, it was not clear if the curative agent was the fever or the organism. Was there a substance in the culture “antagonistic to the tumor growth?” Nonetheless, William Coley continued to inject his toxins into cancer patients with the goal of obtaining a body temperature of 39°C or greater, believing that high temperature was necessary for stimulating the body’s “resisting powers” (immune system). The understanding today is that Coley’s Toxins bind to and stimulate the Toll-like receptors (TLRs) on the immune cells [38] and, through fever induction, increase cytokines [39,40]. The production of Coley’s toxins has ended and their use to treat malignancy remains experimental. Sophisticated forms of immunotherapy have supplanted their use.

Wagner-Jauregg injected patients with paralytic dementia with P. vivax malarial blood, producing intermittent fevers and paroxysms and allowing the fever to rise to 105°F. One theory of action was that fever stimulated “the resistive function” of the reticulo-endothelial system, whose function was suppressed by syphilitic infection. Neutropenia progressed to neutrophilia. A more recent study of the role of malaria in increasing survival of Ebola patients [71], postulates that coinfection with malaria decreases the destructive cytokine storm or increases natural killer cells.

Many of these invasive treatments were used at times of desperation – syphilis was a fatal disease with no treatment and the patients were treated as morally defective and institutionalized. It was a time of little or no oversight of human experimentation.

The WBH currently being tested in depressed patients resembles the earlier treatments of fever cabinets for syphilitic patients and hydrotherapy for a variety of conditions, including mental disorders. Hydrotherapy treatments were instituted in an attempt to prevent more desperate situations: for example, the exhaustion and death of manic patients. These treatments were supplanted by the discovery of the antipsychotics and lithium for mania. The effectiveness of hydrotherapy was not fully understood, nor were there blinded, placebo controlled experiments. It is hoped that the current WBH research will elucidate the mechanism of action and allow for safer and more targeted treatments of depression.

References

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