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Balneotherapy in dermatology

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ABSTRACT: Balneotherapy and spa therapy emerged as an important treatment modality in the 1800s, first in Europe and then in the United States. Balneotherapy involves immersion of the patient in mineral water baths or pools. Today, water therapy is being practiced in many countries. Examples of unique and special places for balneotherapy are the Dead Sea in Israel, the Kangal hot spring in Turkey, and the Blue Lagoon in Iceland. Bathing in water with a high salt concentration is safe, effective, and pleasant for healing and recovery. This approach needs no chemicals or potentially harmful drugs. There are almost no side effects during and after treatment, and there is a very low risk to the patient's general health and well-being. Mineral waters and muds are commonly used for the treatment of various dermatologic conditions. The major dermatologic diseases that are frequently treated by balneotherapy with a high rate of success are psoriasis and atopic dermatitis. The mechanisms by which broad spectrums of diseases are alleviated by spa therapy have not been fully elucidated. They probably incorporate chemical, thermal, mechanical, and immunomodulatory effects. The major importance of balneotherapy and spa therapy both individually and as complements to other therapies lies in their potential effectiveness after standard medical treatments have failed to give comfort to these patients.

KEYWORDS: balneotherapy, Blue Lagoon, climatotherapy, Dead Sea, Kangal hot spring, magnesium, mineral waters, selenium, spa therapy, thermal sulfur water.

Water treatment in the forms of balneotherapy and spa therapy emerged as an important treatment modality in the 1800s, first in Europe and then in the United States (1). It was subsequently scoffed at by scientists and declined in popularity for almost 50 years, only to experience a resurgence in popularity over the past two decades, although it has yet to be accepted as a well-established treatment modality for dermatologic and rheumatic conditions. Balneotherapy involves the immersion of the patient in mineral water baths or pools. Mineral waters are natural solutions formed under specific geologic conditions and characterized by a "chemico-physical dynamism." They originate in springs, are bacteriologically pure, and have a therapeutic potential (2).

Mineral waters may be classified in many ways according to their distinctive chemical and physical elements, such as temperature, molecular concentration, chemical composition, and mechanisms of therapeutic action (2). The composition and physical properties of various spa waters vary (3). They are salty, sulfurous, bicarbonated, sulfated, carbonic, arsenical, and ferruginous on the basis of their chemical content. They are also classified as being hypotonic, isotonic, or hypertonic. Water temperature is described as being "cold" (<20°C), "hypothermal" (20–30°C), "thermal" (30–40°C), or "hyperthermal" (>40°C). Spring water may also be radioactive. The waters used to treat dermatologic disorders have varying chemical and physical properties, but they are generally rich in sulfur, hydrogen sulfide, and sulfates (4,5).

Today water therapy is being practiced in many countries which have a variety of mineral springs and muds that are considerably different from one another in their hydrogeologic origin, temperature, and chemical composition (Table 1). Bathing in water with a high salt concentration is safe, effective, and pleasant for healing and recovery. This approach needs no chemicals or potentially harmful drugs. There are almost no side effects during and after treatment, and there is very low risk to the patient's general health and well-being. Waters rich in salts may need to be diluted to avoid irritating the skin, and waters poor in salts may need to be concentrated and their temperatures adjusted.

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Table 1. Chemical analysis of mineral waters

Spring water	La Roche-Posay (France) (64)	Ipati (Greece) (65)	Bugok (Korea) (66)
pH	6.96		9.16
Temperature	13°C	33.5°C	76°C
CO_3	396 mg/L	1.924 g/L	29.3 mg/L
Calcium	140 mg/L	0.8717 g/L	1.99 mg/L
Selenium	0.06 mg/L		
Silica (SiO_2)	30 mg/L		63.5 mg/L
Magnesium	4.9 mg/L	0.2162 g/L	0.24 mg/L
Strontium	0.26 mg/L		0.07 mg/L
Zinc	0.022 mg/L		
Copper	0.005 mg/L		
Potassium		0.066 g/L	2.35 mg/L
Sodium		1.461 g/L	95 mg/L
Chlorine		3.19 g/L	12.8 mg/L
Bromine		0.0084 g/L	
Sulfate (SO_4)		0.0219 g/L	123.5 mg/L
Hydrogen sulfide (HS^-)		0.0019 g/L	
Bicarbonate (HCO_3)		1.924 g/L	29.3 mg/L
Iron			0.04 mg/L
Lithium			0.06 mg/L
Fluorine			3 mg/L

Absorption of salts through the skin seems to be limited, but there are no precise data on this subject. The therapeutic effect would therefore appear to lie in a local interaction between the mineral water and the structure of the skin surface. Mineral waters and muds are commonly used for the treatment of various dermatologic conditions. The major dermatologic diseases that are frequently treated by balneotherapy with a high rate of success are psoriasis and atopic dermatitis. Other conditions treated by balneotherapy include acne vulgaris, atopic dermatitis, alopecia areata, contact dermatitis, dyshidrotic dermatitis, eczema, granuloma annulare, ichthyosis vulgaris, lichen planus, lichen sclerosus and atrophicus, mycosis fungoides, necrobiosis lipoidica, palmoplantar keratosis, parapsoriasis group, pityriasis rubra pilaris, pruritus, psoriasis, rosacea, scleroderma, sebopsoriasis, seborrheic dermatitis, ulcer (chronic), urticaria pigmentosa, vitiligo, and xerosis.

The mechanisms by which broad spectrums of disease are alleviated by spa therapy have not been fully elucidated. They probably incorporate chemical, thermal, mechanical, and immunomodulatory effects (5–8).

Chemical effects

The chemical composition of thermal water or mud varies among spas. It is still not clear which elements are essential and what is the ideal concentration of each element in order to attain an optimal response to treatment. Different diseases may require varying concentrations for optimal therapeutic results. Chemical stimulation is directly related to the particular composition of the mineral waters.

Sulfur, a chemical element, may be present in sulfurated waters as a free or combined ion. Sulfur waters may comprise various combinations of sulfur ions, water, and other ions. The activity of sulfur in the skin seems to be related mainly to its interaction with cysteine and with its catabolites (9,10). Thermal sulfur water exerts beneficial antiinflammatory, keratoplastic, and antipruriginous effects. Sulfur may also interact with oxygen radicals in the deeper layers of the epidermis, producing sulfur and disulfur hydrogen, which may be transformed into pentathionic acid ($H_2S_5O_6$), and this may be the source of the antibacterial and antifungal activity of sulfur water (11). The use of sulfur water in dermatologic practice has been proposed for many different afflictions, including acne. The therapeutic action of sulfur water is related mainly to sulfur's keratolytic effect, resulting in peeling (12,13). Sulfur waters also possess antibacterial and antifungal properties, which explains their use for treatment of infected leg ulcers, tinea versicolor, tinea corporis, and tinea capitis (14,15).

Magnesium is a rate-limiting factor in the activation of epidermal adenylate cyclase and consequently in the production of cyclic adenosine

monophosphate (cAMP). An imbalance of cAMP (decrease) and cyclic guanosine monophosphate (cGMP) (increase) has been implicated in excessive cellular proliferation, a major element of the psoriatic state (16). It was also shown that magnesium in concentrations of 5×10^{-4} M inhibits the synthesis of some polyamines that are involved in the pathogenesis of psoriasis, and that their reduction by magnesium improves the psoriatic condition (17). Magnesium also has an anticarcinogenic effect, and tissues with high concentrations of magnesium have a lower incidence of cancer compared to tissues with low concentrations (18). Finally, magnesium, through its competition with cellular calcium, causes vasodilation, thereby lowering blood pressure (19).

Selenium is an essential trace element. In high doses, it is toxic and inhibits cell growth and DNA synthesis, while small doses of selenium promote DNA synthesis and cellular growth (20). Selenium also works as an antioxidant, an anti-inflammatory, and a protector against ultraviolet A and B (UVA and UVB) light (21).

Thermal effects

Water has high thermal capacity and conductivity and temperatures that rise to 10°C above that of the surrounding air. Thermal stimulation causes vasodilation, enhances blood circulation, and decreases blood pressure.

Short-term thermal stress is known to alleviate pain. Heat increases the secretion of norepinephrine, cortisol, and growth hormone. Plasma prolactin levels have been reported to rise by as much as 14-fold after a sauna bath (22). The analgesic effect of heat may be explained, at least in part, by increased concentrations of β-endorphin concentrations (22). On the other hand, immersion to the neck in tap water heated to 34.5 ± 0.5°C suppressed plasma levels of β-endorphin, adrenocorticotropic hormone (ACTH), and prolactin in eight healthy male volunteers (23). β-endorphins play an important role in immune system function, for example, through their well-known immunosuppressive effects that are partly exerted via interleukin (IL)-10 in different lymphocyte-mediated skin disorders (24). They are normally produced in the central nervous system (CNS). Human keratinocytes under different stimuli (such as heat or UV radiation) can produce and release a pro-opiomelanocortin (POMC), which is the common precursor of the various endorphins (25). It has been hypothesized that under different stimuli, such as mineral water bath or mud bath, human skin can release significant amounts of opioid peptides, modifying the threshold of pain.

Hyperthermia may produce an immunosuppressive effect whereby the mass of lymphatic tissue and both humeral- and cell-mediated immune responses are decreased. T-lymphopenia and eosinopenia may stem from increased glucocorticoid activity. Thermal treatment in healthy subjects has caused hypothalamic-pituitary adrenal axis dysregulation that was manifested by an increase in the circulatory levels of β-endorphin and ACTH concentration, with a concurrent unexplained reduction in serum cortisol levels (26).

Heat may also have an anti-inflammatory effect. In experimental animals, both hyperthermia and the local application of heat have been shown to prevent the development of chronic and proliferative inflammation. These anti-inflammatory effects of heat may result from the increased secretion of cortisol and catecholamines induced by thermal stress (26).

Hyperthermia also has important effects on granulocyte mobility and phagocytic, microbial, and enzymatic activities. Slight hyperthermia (to 38–39°C) has a destabilizing effect on their lysosomal membranes and stimulates immune mechanisms, especially phagocytic migration and bactericidal properties. Other beneficial effects of thermal stimulation include increased extensibility of collagen-rich tissues, such as tendons, fasciae, and articular capsules, an effect which improves the range of motion of involved joints. Hyperthermia also decreases synovial fluid viscosity (27).

Mechanical effects

Balneotherapy may have beneficial effects on muscle tone, joint mobility, and pain intensity. Increased buoyancy and hydrostatic pressure during immersion in spa water, especially with hydromassage and high-pressure showers, may bring about physiologic changes, including increased diuresis and natriuresis, hemodilation, increased cardiac output, and reduced plasma levels (28).

Mechanical stimulation includes a loss of some body weight when the individual floats on water, thus allowing for easier movement. The body resists the flotation force, whereupon the output and the rhythm of the heart increases and breathing becomes deeper.

Immunologic aspects

It has been suggested that absorption through the skin of trace elements present in mineral water and mud packs may affect the immune system (27). The fact that sulfur spa baths have been used successfully in immunomediated afflictions such as contact dermatitis, psoriasis, and atopic dermatitis has led to the speculation that sulfurous mineral waters could play a role in immunoregulation of the skin. The benefit of application of mineral waters to the skin could be related to the modifications of functional subsets of T lymphocytes and to the increased or decreased synthesis and/or release of different cytokines in the skin.

Elution of proinflammatory mediators from the affected skin may be induced by spa therapy as well (29). Sulfur water is capable of inhibiting the proliferation of both normal T lymphocytes and the T cells obtained from the blood of patients with respiratory and cutaneous atopy (5). Sulfur water can inhibit the production and/or release of cytokines, particularly IL-2 and interferon (IFN)-γ, from the Th1 lymphocytes subset. Sulfur water acts mainly on the T memory cells subset. These latter lymphocytes are inhibited in their proliferation rate and in their ability to produce and release cytokines (30). Some thermal water is able to induce a reduction in degranulation of cutaneous basophils in atopic patients (31). Other seems to exhibit a suppressive activity on the cytokine production of Langerhans cells (7) and an irreversible decrease of ATPase-positive epidermal Langerhans cells following treatment with salt from the Dead Sea in both murine ear skin and in humans (32). Finally, one should not forget that the relaxant effect of rest is known to have beneficial effects on the immune system.

Dead Sea

One example of a site where balneotherapy contributes much to the research and treatment of many diseases and conditions, especially psoriasis, is the Dead Sea in Israel. It lies in the southern part of the country and is located in the great Syrian-African rift valley. At about 400 m below sea level, it is the lowest inhabited place on earth as well as being the world's most hypersaline lake. It is famous for its balneologic properties and for providing climatotherapy, especially for ailments of dermatologic and rheumatologic origin (Fig. 1). The highly successful treatment of such diseases

Fig. 1. Sun bath at the Dead Sea. Courtesy of Dead Sea Laboratory, Ahava.

at the Dead Sea is attributed to a variety of natural factors, the major ones being the mineral content of the sea, the thick haze hanging over it, and the filtered radiation. The Dead Sea has a salt content of about 320 g/L, of which potassium chloride, magnesium chloride, calcium chloride, and sodium chloride (with their respective bromides) are the major components, comprising 98% of the salts on a dry weight basis.

The average mineral salt content is as follows: sodium, 1.70%; potassium, 1.30%; calcium, 20.40%; magnesium, 4.90%; chloride, 7.80%; sulfate, 7.80%; and carbonate, 23.20%. Compared to an ocean, the Dead Sea is richer in its proportions of calcium, magnesium, potassium, and bromide, and lower in its proportions of sodium, sulfate, and carbonate (33). The salts and minerals are present in a total concentration of 33%, as opposed to a total concentration of only 3% in the ocean. It has been reported that repeated bathing in the Dead Sea for a certain length of time has a therapeutic effect on some skin diseases, and penetration of Dead Sea minerals through human skin from bathing in this hypertonic salt solution has been scientifically demonstrated and quantified (34). Another mineral-rich constituent of the Dead Sea is its "black mud" (rich in organic substances), also known as "bituminous tar." The therapeutic effect of processed Dead Sea mud is related to its high content of minerals and its ability to retain heat for many hours, thus stimulating blood circulation and clearing the skin of dead epidermal cells (Fig. 2).

The thick haze overhanging the Dead Sea is also rich in minerals. Inhalation of bromides, which are strong sedatives, improves the condition of psoriatics, especially among those whose disease is stress related. The local drinking water

Fig. 2. Peloid therapy at the Dead Sea. Courtesy of Dead Sea Laboratory, Ahava.

is also very rich in bromine. The bromine enters the circulation and internal organs through the skin, albeit not as effectively as when it is inhaled (34). The serum bromine level after a 4-week stay at the Dead Sea was shown to rise by up to fourfold (35).

Other unique and special places for balneotherapy that are especially excellent for psoriasis patients are the Kangal hot spring in Turkey and the Blue Lagoon in Iceland.

Kangal hot springs, Turkey

Kangal hot springs are located 14 km north of Kangal, a small town in the vicinity of Sivas, Turkey. The hot springs consist of five pools. The mean water temperature is 35°C, and the pH is 7.8. Two different types of fish live in the pools of the springs, despite the high temperature of the water. Because of the scarcity of natural food sources in the pools, human skin is an attractive and easy food source for these fish. The fish attack the patient's body, feeding on the squames of a patient with psoriasis lesions. Continuous cleansing of squames increases the effectiveness of UV light and also creates a positive psychological condition. Other factors contribute to the therapeutic effect of the place, such as the chemical ingredients of the spa—selenium, magnesium, and bicarbonate—and the Jacuzzi effect of the pools (36).

Blue Lagoon, Iceland

Geothermal brines are widely used in the world for energy production. They often contain toxic substances like heavy metals, but this is not the case in the Blue Lagoon. The Blue Lagoon is a unique biologic phenomena (37).

The geothermal area on the peninsula is called *Svartsengi* (meaning "black meadows" in Icelandic). A geothermal power plant was built in 1976 in Svartsengi, and the lagoon was formed close to the plant, where warm saline fluid is discharged to the lava field. As implied by its name, the water in the lagoon has a unique bluish-white color, caused by silica particles, which scatter light intensely.

In the Blue Lagoon, there are some noticeable differences compared to the usual UV thalassotherapy. The silica brine and the minerals of the lagoon are unique and not found in other areas in the world. Some of the silica in the water forms colloidal particles that precipitate on the bottom of the lagoon to form a layer of soft white mud. The silica mud has an abrasive effect when rubbed on psoriasis plaques. The conditions in the lagoon might provide a favorable environment for a number of organisms, but only a paucity of flora exist. The dominant algae are the blue-green algae known as *Leptolyngbya erebi* var. *thermalis*. These algae grow very rapidly in the warm water of the lagoon, and they are not found under similar conditions anywhere else in the world (38). The third difference is the period of natural sunlight in Iceland, which is not reliable for treating psoriasis except for a short period in the summer. Bathing in the Blue Lagoon combined with UVB exposure has a very favorable effect on psoriasis (39).

Psoriasis

The Dead Sea is a sulfur-rich spa known to be especially effective in the treatment of psoriasis. The sulfur that penetrates the skin is oxidized and evokes various physiologic responses in the skin, such as vasodilation in the microcirculation, an analgesic influence on the pain receptors, and inhibition of the immune response. Dead Sea therapy for psoriasis is very efficacious. The therapeutic strategy is based on daily exposure of the skin to Dead Sea water and to the sun's UV rays (40). The addition of balneotherapy with mud packs and sulfur baths enhances the improvement observed in both the skin and joints in these patients.

Most kinds of psoriasis respond to the treatment regimen, with the exceptions of generalized

pustular psoriasis and erythroderma. The pioneering pilot studies of Dostrovsky et al. (41) and Dostrovsky and Shanon (42) elucidated the therapeutic effect of heliobalneotherapy for psoriasis in the Dead Sea area. Another study conducted by Even-Paz et al. (43) indicated that sun exposure was the main factor in producing beneficial results for psoriasis in Dead Sea spa therapy, and that bathing in Dead Sea water enhanced the effect of solar radiation. A double-blind controlled study by Halevy et al. (44) evaluated the therapeutic effect of Dead Sea salt in patients with psoriasis. The results indicated a beneficial therapeutic effect for bathing with either Dead Sea salt or common salt as monotherapy for psoriasis vulgaris, although a more enhanced beneficial effect was observed in patients treated with Dead Sea salt.

The chemical effects of Dead Sea spa therapy have been shown in several in vivo and in vitro studies (34,44–49), which showed increased levels of minerals that may play a role in cell proliferation and differentiation (18,50,51). The chemical effects of Dead Sea spa therapy in psoriasis have also been demonstrated in other in vitro and in vivo studies (34,45–49,52) on human and animal skin: their results revealed increased levels of minerals. The possibility that Dead Sea minerals penetrate psoriatic skin has been suggested because of significant elevations in four ions—bromine, rubidium, calcium, and zinc—in the serum of psoriatic patients following daily bathing in the Dead Sea for 4 weeks (34). It has also been shown that Dead Sea minerals penetrate psoriatic skin more than they do healthy skin, and that this penetration may occur even if diluted Dead Sea water is used (34). Of importance is that psoriatic keratinocytes obtained from patients treated with Dead Sea solutions and mud revealed elevated mineral content while retaining normal structure (47,48). Furthermore, it has been shown that the Dead Sea minerals (magnesium and potassium ions) have a specific inhibitory capacity on the uncontrolled proliferation of psoriatic dermis grown in tissue culture (52). These data suggest that the therapeutic effect observed in psoriatic patients following Dead Sea spa therapy may be attributable, at least in part, to Dead Sea minerals, which may play a role in cell proliferation and differentiation (50).

Bathing in high-concentration salt solutions may trigger the elution of various chemotactic and proinflammatory mediators (i.e., elastase and cytokines) from the affected skin of patients with psoriasis (32,53,54). Bathing in tap water or salt solutions has been associated with an increased photosensitivity of the skin to UVB irradiation, and may contribute to the efficacy of balneophototherapy (55,56).

Dead Sea salts themselves exert a beneficial influence on psoriatic skin. It was noted that bathing in the Dead Sea reduced the area of psoriatic microvilli by 64.3% (51). Dead Sea water is particularly rich in magnesium ions. Schempp et al. (57) demonstrate in both in vivo and in vitro studies that magnesium ions specifically inhibit the antigen-presenting capacity of Langerhans cells and may thus contribute to the efficacy of Dead Sea water in the treatment of inflammatory skin diseases. The fact that improvement in the psoriatic condition may be obtained after immersion in simulated Dead Sea salt solution, without any exposure to the sun, indicates that the salt composition of the sea is one of the major factors in the treatment of psoriasis.

Atopic dermatitis

Atopic dermatitis in the “dry” phase may be alleviated by local treatment designed to improve skin moisture and protect against external irritants (58). Bathing can prepare the skin for the application of moisturizers. Acute exacerbation and the weeping forms of the condition must first be given specific pharmacologic treatment (3). Rest and a healthy environment can also be positive factors in healing this disease.

Inoue et al. (59) reported that balneotherapy using Kusatsu hot spring water (Japan) is useful for controlling the skin symptoms of acute flares/exacerbations of refractory cases of atopic dermatitis. It is now widely accepted that patients with atopic dermatitis are prone to cutaneous *Staphylococcus aureus* infection during phases of acute exacerbation and that an increased density of *S. aureus* is found to correlate well with the severity of skin manifestations (60,61). Inoue et al. (59) reported the effectiveness of Kusatsu hot spring bathing followed by immediate application of white petrolatum in controlling skin symptoms of exacerbations of refractory cases of atopic dermatitis. This treatment had no side effects. The hot spring water was thought to act against *S. aureus* because this microorganism was found to decrease in number or to disappear altogether from the skin surface during balneotherapy (61). The bactericidal activity of the hot spring water against *S. aureus* is expressed by the coexistence of manganese and iodide ions in water under

acidic conditions (pH 2–3) (8). In addition to its application as a treatment for refractory cases of atopic dermatitis, an acidic solution containing manganese and iodide ions is used as a disinfectant in various areas of medicine (59).

Pruritus

Bathing can alleviate many types of pruritus, especially the senile form, as well as chronic prurigo. The lesions of these patients are caused by scratching and they benefit from the antiseptic properties of certain waters (3).

Lichen rubra planus

The often prolonged therapy can be administered in combination with bathing. The psychological support provided by the climate and environment is important in these patients for whom treatment is often complex and lengthy (3).

Rosacea

High-pressure showers that erode the epidermis and reduce erythema and telangiectases after the epidermis re-forms were shown to be therapeutically beneficial (3).

Acne

The pustular phase must first be healed with suitable pharmaceuticals. After this stage, mud face masks followed by washing with hot water are reportedly beneficial for improving the condition (3).

Seborrheic dermatitis

The basic treatment of this disease is to relieve inflammation, to suppress skin-resident bacteria, and to keep the skin dry. Yeast (*Pityrosporum ovale*) plays a role in seborrheic dermatitis: by bathing in the Dead Sea, all the resident flora are eliminated and improvement of the seborrheic condition can be expected to follow (62).

Keratolytics, or bathing in hypertonic salt solution, ease the removal of skin fat and scales. Bathing and local washing combined with sunlight or phototherapy has been recommended (3).

Ichthyoses

Symptomatic treatment of this disease consists of moisturizing the skin, adding lipids to the damaged skin, and aiding its desquamation. Baths consisting of fairly large amounts of sodium chloride are very useful for this purpose (63). Contraindications for balneotherapy for individuals with ichthyoses include varicose veins, nonhealed wounds, acute and subacute dermatitis, and hypersensitivity to mineral baths (63). Balneotherapy can be combined with sunlight, phototherapy, or other local or systemic therapy.

The major importance of balneotherapy and spa therapy both individually and as complements to other therapies lie in their potential effectiveness after standard medical treatments have failed to give any comfort to these patients. Therapeutic spas and baths offer an atmosphere of health and physical fitness: if improvement is not achieved through their specific chemical and mineral components, the advantages of relaxation and stress relief should not be underestimated.

References

1. Benedetto AV, Millikan L. Mineral water and spas in the United States. Clin Dermatol 1996: **14**: 583–600.
2. Lotti T, Ghersetich I. Le basi della dermocosmetologia termale. In: Caputo R, Monti M, eds. Manuale di Dermocosmetologia. Milan: Raffaello Cortina, 1995:751–762.
3. Andreassi L, Flori L. Mineral water and spas in Italy. Clin Dermatol 1996: **14**: 627–632.
4. Lin AN, Reimer JR, Carte DM. Sulfur revisited. J Am Acad Dermatol 1988: **18**: 553–558.
5. Valitutti S, Costellino F, Musiani P. Effect of sulphurus "thermal" water on T lymphocytes proliferative response. Ann Allergy 1990: **65**: 463–468.
6. Tishler M, Shoenfeld Y. The medical and scientific aspects of spa therapy. Isr J Med Sci 1996: **32(suppl 3**): 8–10.
7. Wollenberg A, Richard A, Bieber T. In vitro effect of the thermal water from La Roch-Possay on the stimulatory capacity of epidermal Langerhans cells. Eur J Dermatol 1992: **2**: 128–129.
8. Celerier P, Richard A, Litoux P, Dreno B. Modulatory effects of selenium and strontium salts on keratinocyte-derived inflammatory cytokines. Arch Dermatol Res 1995: **287**: 680–682.
9. Benci M. L'impiego dello zolfo nella terapia dermatologica. Current 1994: **1(suppl)**: 8–17.
10. Zunz E. Elements de Pharmacodynamie Special. Paris: Masson and Cie, 1932.
11. McMurtry CW. Dermatologic therapeutics: sulfur. J Cutan Dis 1913: **322**: 399–408.
12. Miller HE. Colloidal sulphur in dermatology. Arch Dermatol Syphil 1935: **31**: 516–525.
13. Hjorth N. Traditional topical treatment of acne. Acta Derm Venereol (Stockh) 1980: **89**: 53–55.
14. Salter WT. A textbook of pharmacology. Philadelphia: WB Saunders, 1952.

15. Parish LC, Witkowski JA. Dermatologic balneology: the American view of waters, spas, and hot springs. J Eur Acad Dermatol Venereol 1994: **3**: 465–467.
16. Vorhees JJ, Duell EA. Imbalanced cyclic-AMP and cyclic GMP levels in psoriasis. Adv Cyclic Nucleotide Res 1975: **5**: 735–738.
17. Lowe NY, Breeding Y, Russel D. Cutaneous polyamines in psoriasis. Br J Dermatol 1982: **107**: 21–26.
18. Blondell JM. The anti-carcinogenic effect of magnesium. Med Hypotheses 1980: **6**: 863–871.
19. Shani J, Kushelevsky AP, Harari M, Even-Paz Z. Sustained decreased of blood pressure in psoriatic patients during treatment at the Dead Sea. Pharmacol Res 1995: **31**: 355–359.
20. Medina D. Selenium and murine mammary tumorigenesis. In: Cohen R, ed. Diet, nutrition and cancer: a critical evolution. Boca Raton, FL: CRC Press, 1986:23–42.
21. Moysan A, Morliere P, Marquis L, et al. Effects of selenium on UVA-induced lipid peroxidation in cultured human skin fibroblasts. Skin Pharmacol 1995: **8**: 139–148.
22. Jezora D, Vigas M, Tatar P, Jurcovicora J, Palat M. Rise in plasma beta-endorphin and ACTH in response to hyperthermia in sauna. Horm Metab Res 1985: **17**: 693–694.
23. Coruzzi P, Ravanetti C, Musiari L, Biggi A, Vescovi PP, Novarini A. Circulatory opioid peptides during water immersion in normal men. Clin Sci 1988: **74**: 133–136.
24. Dubois M, Pickar D, Roth YF, et al. Surgical stress in humans accompanied by an increase in plasma beta-endorphin immunoreactivity. Life Sci 1981: **29**: 1249–1251.
25. Teofoli P, Lotti T, Guarciello V, Panconesi E. Detection of mRNA encoding proopiomelanocortin (POMC) in the A431 cell line. In: Abstract book 3rd EADV Congress, Copenhagen, September 26–30, 1993:352.
26. Cozzi F, Lazzarin P, Todesco S, Cima L. Hypothalamic-pituitary adrenal axis dysregulation in healthy subjects undergoing mud-bath application [letter]. Arthritis Rheum 1995: **38**: 724–725.
27. Sukenik S, Abu-Shakra M, Flusser D. Balneotherapy in autoimmune disease. Isr J Med Sci 1997: **33**: 258–261.
28. O'Hare JP, Heywood A, Summerhayes C, et al. Observation on the effects of immersion in bath spa water. Br Med J 1985: **291**: 1745–1751.
29. Wiedow O, Streit V, Christophers E, Stander M. Liberation of human leukocyte elastase by hypertonic saline baths in psoriasis. Hautartz 1989: **40**: 518–522.
30. Sainte-Laudy J. Etude du pouvoir anti-degranulant de l'eau d'Avene vis-a-vis de basophiles humanis sensibilises. Int J Immunotherapy 1987: **III(IV)**: 307.
31. Morimoto C, Letin NL, Distaso JA, et al. The isolation and characterization of the human suppressor inducer T cell subset. J Immunol 1985: **134**: 1508–1512.
32. Gruner S, Zwirner A, Boonen H, et al. Effect of treatment with salt from the Dead Sea (Tomesa therapy) on epidermal Langerhans cells—a clinical study. Hautartz 1990: **65**: 1146–1151.
33. Even-Paz Z, Shani J. The Dead Sea and psoriasis. Int J Dermatol 1989: **28**: 1–9.
34. Shani J, Barak S, Levi D, et al. Skin penetration of minerals in psoriatics and guinea pigs bathing in hypertonic salt solutions. Pharmacol Res Commun 1985: **17**: 501–512.
35. Shani J, Barak S, Ram M, et al. Serum bromine levels in psoriasis. Pharmacology 1982: **25**: 297–307.
36. Ozcelik S, Polat HH, Akyol M, Yalcin AN, Ozcelik D, Marufihah M. Kangal hot spring with fish and psoriasis treatment. J Dermatol 2000: **27**: 386–390.
37. Ólafsson JH. Therapeutic climatology. The Blue Lagoon in Iceland and psoriasis. Clin Dermatol 1996: **14**: 647–651.
38. Petursdottir S, Kristjansson J. The relationship between physical and chemical conditions and low microbial diversity in the Blue Lagoon geothermal lake in Iceland. FEMS Microbiol Ecol 1995: : .
39. Ólfasson JH, Sigurgeirsson B, Palsdottir R. Psoriasis treatment: bathing in a thermal lagoon combined with UVB treatment only. Acta Derm Venereol 1996: **76**: 228–230.
40. Sukenik S, Giryes H, Halevy S, Neumann L, Flusser D, Buskila D. Treatment of psoriatic arthritis at the Dead Sea. J Rheumatol 1994: **21**: 1305–1309.
41. Dostrovsky A, Sagher F, Even-Paz Z, et al. Preliminary report: the therapeutic effect of the hot springs of Zohar (Dead Sea) on some skin diseases. Harefuah 1959: **57**: 143–145.
42. Dostrovsky A, Shanon J. Influence of helio-balneotherapy at the hot spring of Zohar (Ein-Bokek) on psoriasis: a further report. Harefuah 1963: **63**: 127–129.
43. Even-Paz Z, Gumon R, Kipnis V, Ables DJ, Efron D. Dead Sea sun versus Dead Sea water in the treatment of psoriasis. J Dermatol Treat 1996: **7**: 83–86.
44. Halevy S, Giryes H, Friger M, Sukenik S. Dead sea bath salt for the treatment of psoriasis vulgaris: a double blind controlled study. J Eur Acad Dermatol Venereol 1997: **9**: 237–242.
45. Shani J, Sharon R, Koren R, Even-Paz Z. Effects of Dead Sea brine and its main salts on cell growth in culture. Pharmacology 1987: **35**: 339–347.
46. Shani J, Sulliman A, Katzir I, Brenner S. Penetration of selected Dead Sea minerals through a healthy rabbit skin, from a sustained-release transparent varnish, as a prospective treatment for psoriasis. J Eur Acad Dermatol Venereol 1995: **4**: 267–272.
47. Shani J, Even-Paz Z, Avrach WW, et al. Topical replacement therapy of psoriasis by Dead Sea salts, evaluated by scanning electron microscopy and X-ray fluorescence. Dermatosen 1991: **39**: 49–55.
48. Shani J, Tur E, Wald E, et al. Computerized morphometry of psoriatic keratinocytes after bathing in the Dead Sea bath solutions. J Dermatol Treat 1993: **4**: 195–198.
49. Shani J, Barak S, Ram M, et al. Serum bromine level in psoriasis. Pharmacology 1982: **25**: 297–307.
50. Petrini M, Vaglini F, Carulli G, Azzara A, Ambrogi F, Bertelli A. Effects of lithium and rubidium on the differentiation of mononuclear cells. Int J Tissue React 1986: **8**: 391–392.
51. Vorhees JJ, Duell E. Imbalanced cyclic-AMP and cyclic-GMP levels in psoriasis. Adv Cyclic Nucleotide Res 1975: **5**: 735–758.
52. Shani J, Milner Y, Politi Y, Katzir I, Chomsky O, Brenner S. Inhibition of psoriatic skin cell proliferation in tissue culture by selected Dead Sea salts. Pharmacol Commun 1995: **7**: 21–27.
53. Wiedow O, Wiese F, Christophers E. Lesional elastase activity in psoriasis: diagnostic and prognostic significance. Arch Dermatol Res 1995: **287**: 632–635.
54. Wiedow O, Wiese F, Streit V, Kalm C, Christophers E. Lesional elastase activity in psoriasis, contact dermatitis, and atopic dermatitis. J Invest Dermatol 1992: **99**: 306–309.
55. Boer J, Schothorst AA, Boom B, Hermans J, Suurmond D. Influence of water and salt solutions on UVB irradiation of normal skin and psoriasis. Arch Dermatol Res 1982: **273**: 247–259.
56. Schempp CM, Blumke C, Schopf E, Simon JC. Skin sensitivity to UV-B radiation is differentially increased by exposure to water and different salt solutions. Arch Dermatol 1997: **133**: 1610.
57. Schempp CM, Dittmar HC, Hummler D, et al. Magnesium

ions inhibit the antigen-presenting function of human epidermal Langerhans cells in vivo and in vitro. Involvement of ATPase, HLA-DR, B7 molecules, and cytokines. J Invest Dermatol 2000: **115**: 680–686.
58. Ghersetich I, Tsampau D, Lotti T. L'eau thermale d'avene nel trattamento della pelle sensibile. G Ital Dermatol Venereol 1992: **127**: 29–31.
60. Svejgaard E. The role of microorganisms in atopic dermatitis. Semin Dermatol 1990: **9**: 255–261.
61. Kubota K, Machida I, Tamura K, et al. Treatment of refractory cases of atopic dermatitis with acidic hot spring. Acta Derm Venereol 1997: **77**: 452–454.
59. Inoue T, Inoue S, Kubota K. Bactericidal activity of manganese and iodide ions against *Staphylococcus aureus*: a possible treatment for acute atopic dermatitis. Acta Derm Venereol 1999: **79**: 360–362.
62. Duvic M. Possible mechanisms of effectiveness of Dead Sea balneotherapy. J Am Acad Dermatol 1986: **15**: 1061.
63. Shani J, Seidel V, Hristakieva E, Stanimirovic A, Burdo A, Harari M. Indications, contraindications and possible side-effects of climatotherapy at the Dead Sea. Int J Dermatol 1997: **36**: 481–492.
64. Karam P. Mineral water and spas in France. Clin Dermatol 1996: **14**: 607–610.
65. Katsambas A, Antoniou C. Mineral water and spas in Greece. Clin Dermatol 1996: **14**: 615–618.
66. Seung-Kyung H. Mineral water and spas in Korea. Clin Dermatol 1996: **14**: 633–635.