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SYSTEMIC ASPECTS OF PSORIASIS: AN INTEGRATIVE MODEL BASED ON INTESTINAL ETIOLOGY

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Psoriasis can best be understood from a multifactorial approach that recognizes the systemic aspects of the disorder. Among the various factors thought to be involved in the etiology and pathogenesis of psoriasis, bowel pathology has assumed a noteworthy position in the literature. This article reviews the psoriasis/bowel connection with regard to abnormal bowel structure and physiology in psoriasis patients. Clinical implications of bowel involvement in psoriasis are discussed within the framework of an integrative medicine model that emphasizes natural therapeutics for addressing the systemic aspects of the illness. (Int Med 1999;2:105–113) © 2000 Elsevier Science Inc.

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Psoriasis is a chronic cutaneous disease of unknown causation [1]. Although there is no generally recognized cure for psoriasis, a variety of treatments are commonly used to reduce the severity of symptoms and lessen their impact on the patient's quality of life. Topical therapy may be helpful for symptomatic relief, especially for mild psoriasis. For moderate to severe psoriasis, phototherapy and systemic therapies are the standard medical therapies. However, these treatments are all associated with significant adverse effects. Phototherapy may produce erythema, pruritus, wrinkling, solar elastosis, and an increased risk of skin cancer. Systemic therapies such as acitretin, methotrexate, cyclosporine, hydroxyurea, and thioguanine are all associated with significant systemic toxicity and must be monitored closely [2].

The cost of standard medical treatment for psoriasis is substantial, currently estimated at approximately $1.6 billion to $3.2 billion per year in the United States [3]. There continues to be a need for effective, affordable therapies with fewer side effects. Understanding the etiology and pathogenesis of psoriasis may lead to economical therapies that address the underlying causes of the disease while decreasing adverse effects.

Considered to be an autoimmune disorder with systemic features, psoriasis is known to be associated with joint and bowel disease. This report explores the concept of intestinal pathology as a significant etiological factor in psoriasis. The conceptual basis of the integrative approach advocated in this article is derived from the systems approach of Edgar Cayce as described by Landsford, Mein, and Pagano [4–6]. In essence, the model focuses on intestinal permeability as a primary factor in the pathogenesis of psoriasis. The Cayce hypothesis is that various factors produce a "thinning of the walls of the small intestine—specifically, the jejunum and the lower duodenum. . . . This thinning allows toxic products to leak from the intestinal tract into the circulation; these eventually find their way into the superficial circulation and lymphatics and are eliminated through the skin, producing the plaques of psoriasis" [5, p. 176]. Therapeutically, a variety of natural remedies (such as diet, herbal teas, hydrotherapies, and topical applications) are utilized to heal the gut, decrease systemic toxicity, and provide symptomatic relief.

The literature on bowel structure and function suggests that systemic autointoxication is a plausible pathophysiological pattern in psoriasis. A literature review is provided on the systemic aspects of psoriasis with special emphasis on comorbidity with other systemic disorders. Consideration of the systemic patterns associated with psoriasis may contribute to an understanding of the various pathophysiological processes producing this illness. With this broader perspective in mind, we will consider the abundant body of information on bowel pathology in psoriasis. For completeness, this review draws on sources with differing levels of quality and strength of evidence: experimental reports, clinical studies, and case studies. Most are in peer-reviewed journals; a few are not. It is particularly impor-

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tant to include this diversity of sources in an area in which some practitioners may not conduct controlled studies or may be outside mainstream medicine, yet have contributed valuable clinical insights.

The discussion that follows outlines an intestinal model of psoriasis causation and suggests an integrative medicine approach to psoriasis. Integrative medicine emphasizes cooperation between healthcare professionals of conventional and alternative therapies. From an integrative medicine approach, natural therapeutics directed toward internal cleansing and intestinal healing hold promise in the treatment of psoriasis, in addition to standard medical therapies for this condition.

COMORBIDITY OF PSORIASIS WITH OTHER SYSTEMIC DISORDERS

The term "comorbidity" has been used to describe the overlap of illnesses that tend to occur together. In reviewing the possible sources of comorbidity, Weissman et al. [7] have concluded:

> In comorbidity there is an underlying assumption that separate diagnoses may co-occur for several reasons: one disorder increases vulnerability to the other; one disorder is a different expression of the other; both disorders are due to some third underlying cause, or by chance alone . . . [7, p. 433].

Henseler and Christophers [8] have documented a significant comorbidity of psoriasis with several other conditions including obesity, diabetes, and heart disease. They hypothesized that the concomitance of these systemic disorders may be related to dietary habits, nutritional status, or common genetic factors. Numerous case reports suggest a comorbidity of psoriasis and kidney disease [9–11]. The conceptual significance of this association with regard to autointoxication will be discussed in a later section.

The comorbidity of skin disease with bowel pathology is particular noteworthy. Person and Bernhard [12] observed that the pustular dermatitis associated with small bowel bypass surgery and the cutaneous manifestations of inflammatory bowel disease are well known. These manifestations of skin disease are generally assumed to be due to the absorption of microbial antigens from the bowel. Thus, autointoxication is described as a primary pathophysiological process in the cormorbidity of bowel and skin disease.

Other clinicians have described the association of digestive system surgery with skin disease. D'Amico et al. [13] reported an association of primary biliary cirrhosis and psoriasis. Following implantation of a portocaval anatomosis, the patient experienced remission of psoriasis and psoriatic arthritis. The physicians hypothesized that the blood flow redistribution reduced bowel congestion and decreased the involvement of pathological intestinal flora, particularly with regard to hepatic functioning. Porres [14] noted that jejunoilio bypass surgery resulted in improvement of psoriasis symptoms in a 44-year-old woman. The woman was able to discontinue her psoriasis medication.

Yates et al. [15] also emphasized the comorbidity of psoriasis and bowel disease. To test the hypothesis that these disorders are related, they studied 204 patients with inflammatory bowel disease (116 with Crohn's disease and 88 with ulcerative colitis) and 204 age- and sex-matched controls. They concluded: "The prevalance of psoriasis in Crohn's disease (11.2%) and in ulcerative colitis (5.7%) was significantly greater than in the control group (1.5%). The prevalence of psoriasis in first-degree relatives of patients with inflammatory bowel disease was also increased. It is suggested that there is a relationship between psoriasis, ankylosing spondylitis, sacroiliitis, peripheral arthropathy and inflammatory bowel disease" (p. 323).

Menzel and Holzmann [16] analyzed stool samples of patients with seborrheic eczema of the scalp, psoriasis capitis, or seborrhiasis. The researchers measured pathological flora of the bowel to a high degree in all patients. The flora were predominantly pathogenic yeasts. With regard to treatment, they observed that therapy for the intestine is helpful for the skin disease as well. Numerous studies have emphasized the significance of pathological intestinal microorganisms in the etiology of psoriasis [17–20].

The comorbidity of psoriasis and joint disease is also well known. Approximately 5%–7% of psoriasis patients also have a specific form of arthritis linked to psoriasis [21]. Although the relationship between these diverse manifestations is unknown, the bowel has been implicated as a possible link between skin and joint disease. Most notably, inflammatory bowel disease has been shown to be comorbid with psoriatic arthritis and other illnesses classified as spondyloarthropathies. The concept of spondyloarthropathy links diseases with common clinical, radiological, and genetic features. In addition to psoriatic arthritis, other diseases in this category include ankylosing spondylitis, reactive arthritis caused by urogenital or enterogenic infection, inflammatory bowel disease (ulcerative colitis and Crohn's disease), some forms of juvenile chronic arthritis, and acute anterior uveitis [22]. Furthermore, gut inflammation has been specifically cited as a likely causative factor in certain forms of psoriatic arthritis based on ileocolonoscopic studies of patients with psoriatic arthritis [23].

Fry [24] theorized that the association of small intestine and skin disease may be considered under the following subgroups:

1. A nonspecific relationship in which a primary disease of the small intestine causes nonspecific changes in the skin (e.g., acquired ichthyosis) or, a primary disease of the skin produces nonspecific changes in the small intestine (e.g., dermatogenic enteropathy).
2. A specific relationship in which a particular disease entity of the skin is associated with a particular disorder of the small intestine (e.g., dermatitis herpetiformis).
3. A generalized disease process that affects both the skin and the gut but which is not necessarily confined to these two organs (e.g., systemic sclerosis or polyarteritis nodosa).

Depending on the orientation of the investigator, psoriasis has been placed within each of these subgroups. Pagano [6] regards psoriasis as a nonspecific manifestation of bowel pathology (intestinal permeability) in which toxins leak out of the gut and are eventually relayed to the skin for elimination from the body. Marks and Shuster [25] have emphasized a nonspecific process in which psoriasis is the primary disease producing secondary pathology in the small bowel. De Vos et al. [26] noted that psoriasis may be associated with a particular disorder of the small intestine (celiac disease). The growing literature on the spondyloarthropathies [22] reflects an interest in the systemic manifestations of autoimmune diseases including psoriatic arthritis.

ABNORMALITIES OF INTESTINAL MUCOSAL STRUCTURE IN PSORIASIS

Pursuing the pathophysiology of bowel and skin disease comorbidity, researchers have investigated intestinal permeability as a possible etiological factor. Hamilton et al. [27] explored passive small intestinal permeability in 29 patients with psoriasis using the cellobiose/mannitol differential sugar absorption test, which measures urinary recovery ratio of cellobiose and mannitol. The recovery ratio was abnormal in 7 patients. However, the researchers concluded that these rates were similar to values in a control population, and were not affected by the extent or activity of the skin disease.

Using a different assessment technique, Humbert et al. [28] studied the intestines of 15 psoriatic patients and 15 healthy subjects. Intestinal permeability was evaluated using the ^{51}Cr-labeled EDTA absorption test. The psoriasis group was found to exhibit significantly increased bowel permeability compared to the controls. The researchers concluded: "The difference in intestinal permeability between psoriatic patients and controls could be due to alterations in the small intestinal epithelium of psoriatics" (p. 324).

In seeking to reconcile these inconsistent findings with regard to intestinal permeability in psoriasis, a possible explanation is that absorption of antigens through the bowel wall is primarily through the lymphatic system. The ^{51}Cr-labeled EDTA absorption test is sensitive to lymph movement [29,30]. Thus, the apparent contradiction may provide a valuable clue to the pathophysiology of psoriasis. Absorption of antigens via the intestinal lymphatics may be a significant source of systemic autointoxication. Because the intestinal lymphatic absorption vessels (lacteals) drain fats and proteins from the bowel, increased permeability through the lacteals should lead to increased serum levels for fats and proteins. Hyperlipoproteinaemia has been documented in psoriasis [31] and is thought to be a primary factor in the comorbidity of psoriasis and heart disease [32]. The role of the lymphatic/immune system in psoriasis will be reviewed in a later section.

In addition to bowel permeability, the intestinal mucosal structure of psoriatic patients has also been investigated. Using microscopic analysis of the gut, Shuster and Marks [33] initially reported structural abnormalities of the jejunal mucosa in psoriasis, but later withdrew the claim citing faulty analysis technique and small sample size [25]. Barry et al. [34,35] created a more precise grading system for measuring bowel mucosal architecture pathology that demonstrated differences in jejunal mucosa in psoriatic patients as versus normal controls. The researchers focused on severe psoriasis (greater than 50% surface area involved). "Both the structural and functional intestinal changes described suggest that there is a decrease in the small bowel surface area in patients with severe psoriasis" [35, p. 877]. Thus, smoothing of the intestinal wall in the jejunal area of the bowel is regarded as a feature of severe psoriasis. In addition to the normal controls, an additional comparison group included sick and wasting individuals. The results indicated that pathological changes in the small bowel mucosal architecture are not specific to psoriasis, but may also be found in patients who are sick and losing weight from other causes. The nonspecific aspect of intestinal permeability is consistent with the Pagano hypothesis cited above [6]. More recently, Hendel et al. [36] reported that 6 of 15 patients had abnormal jejunal histology, with short villi.

Michaelsson et al. [37] found that 37 psoriasis patients had highly increased numbers of tryptase-positive mast cells in the duodenal stroma. The authors hypothesized "that there are at least two types of abnormalities in the duodenal mucosa in psoriasis, one type that is present in most psoriasis patients and characterized by an increase in mast cells and eosinophils, and another that is present in a subgroup of patients with antibodies to gliadin and an increased number of duodenal intraepithelial lymphocytes" (p. 866). Michaelsson et al. had previously noted physiological abnormalities in the duodenal mucosa of psoriasis patients involving increased lymphocyte infiltration and IgA antibodies to gliadin [38], and elevated serum eosinophil cationic protein with increased numbers of EG2-positive eosinophils in the duodenal mucosa of psoriasis patients [39].

AUTOINTOXICATION IN PSORIASIS

Autointoxication is an ancient theory based on the belief that intestinal toxins can enter the circulation and poison the body. The concept probably originated in Egypt or Greece. The Greek version recognized a broad range of pathological agents including residues of food, bile, and phlegm as portrayed in the humoral theory of disease [40]. Until the early 20th century, autointoxication was widely accepted and various therapies (such as colonic irrigation) were commonly used for a variety of systemic disorders [41]. Unsupported by scientific evidence, the autointoxication concept fell out of favor several decades ago. However, the growing body of information linking intestinal disease, excessive intestinal permeability, and systemic illness has revived the theory [12,42]. Similar concepts such as multiple chemical sensitivities [43] and endotoxins [40] are also now gaining in favor.

The concept of autointoxication in psoriasis gained support from numerous case reports suggesting that dialysis is effective in the treatment of psoriasis. As early as 1965, dialysis was used by Russian clinicians for the treatment of psoriasis [11]. In 1976 McEvoy and Kelly reported that a uremic patient with psoriasis experienced clearing of skin lesions while being treated with hemodialysis [44]. Numerous subsequent reports documented the efficacy of dialysis in decreasing psoriatic lesions [45–50]. However, a controlled trial with seven patients by Nissenson et al. [51] failed to confirm the efficacy of dialysis for psoriasis. Halevy et al. [52] pointed out methodological flaws in the Nissenson et al. study, especially a predominance of patients with psoriatic erythroderma, a form regarded as particularly unresponsive to dialysis. A notable double-blind, crossover study of five patients [53] resulted in two patients with complete clearing, two patients had more than 75% clearing, and one patient had no substantial response. None of the five patients responded to the sham dialysis procedure.

A study by Sobh et al. [54] compared hemodialysis, peritoneal dialysis, and Goeckerman treatment (coal tar dressings and ultraviolet light). Forty patients with severe psoriasis (greater than 50% body surface area affected) were randomly assigned to treatment groups. Statistical analysis of the data obtained following 10 dialysis sessions showed better response in peritoneal than hemodialysis, and both were better than Goeckerman treatment. The researchers concluded that dialysis treatment is a good therapeutic modality, especially for those with severe lesions in whom mortality and morbidity are high, especially if other potent therapeutic modalities are contraindicated.

Practically speaking, dialysis has not assumed a prominent position among the various therapeutic options available to clinicians. In reviewing the literature, Halevy et al. [10] concluded that "dialysis does have an effect on psoriasis and that this effect is more prominent after peritoneal dialysis than after hemodialysis. The clinical response is not always complete, however, and in most cases short lasting. For these reasons, and because such therapy is not a simple procedure, dialysis is not a practical mode of treatment for psoriasis" (p. 72).

From a conceptual standpoint, the apparent therapeutic efficacy of dialysis is supportive of an autointoxication model of psoriasis. "The mechanism by which dialysis affects psoriasis is unknown. Removal of some substances from the bloodstream is the most likely explanation. These substances could be carried free in plasma or on white blood cells and removed in the peritoneal dialysate during treatment" [55, p. 1179]. The reported increased efficacy of peritoneal dialysis over hemodialysis may be linked to the fact that peritoneal dialysis can remove solutes of higher molecular weight in larger quantities than hemodialysis [56]. Although the psoriasis/dialysis literature is complex and at times conflicting, the overall thrust of this body of data supports the plausibility of an intestinal etiology in psoriasis that involves autointoxication via the absorption and circulation of toxins from the digestive tract. One possible explanation is that, for psoriasis patients whose kidneys are weak or overtaxed, the overload of toxins may enter the superficial circulation and eventually provoke an immune response in the skin.

LYMPHATIC AND IMMUNE SYSTEM INVOLVEMENT IN PSORIASIS

Recently, psoriasis has been grouped with numerous other systemic disorders that are related to immune system dysfunction. One of the seminal events in drawing attention to the autoimmune aspects of psoriasis was the chance clinical observation that psoriasis improved in patients treated with cyclosporine, a drug used to prevent rejection of transplanted organs. Immunotherapeutic drugs have since been used extensively to suppress immune reactions in psoriasis.

Autoimmune diseases are caused by over stimulation of the body's own immune defenses, in which the immune cells attack healthy cells. In psoriasis, immune system T cells become activated and stay turned on causing the skin to constantly regenerate itself. The specific trigger for T-cell activation is unknown, but may be an antigen, a bacterial or viral infection, or an environmental factor. Even bacterial DNA, previously considered immunologically inert, has been shown to trigger immune responses [57].

Although there is no animal model imitating psoriasis completely, some aspects of psorasis (particularly arthritis) may be mirrored in HLA-B27 transgenic animals [58]. Similar to human disease, experimental animals with the HLA-B27 transgene also develop spontaneous inflammatory disease. In addition to HLA-B27, the role of environmental antigens has been implicated in the animal models. Many B27-linked diseases begin after an infection with an enterobacteria, suggesting a role for environmental antigens in addition to an HLA-B27 molecule, but how bacteria interact with HLA-B27 is not yet clearly understood [59].

The human body is in a continuous relationship with the outer environment. Various allergens are known to trigger autoimmune responses. Furthermore, autoimmune disorders have inner, self-perpetuating causes, such as medicines and food materials. It is important to keep in mind that food is a primary source of the external environment that interacts with the immune system within the body. In addition to inherently toxic substances that may be ingested, intact peptides and proteins are absorbed into the circulation [60]. Thus, diet may play a significant role in autoimmune diseases.

The bowel has protection from harmful materials that are ingested. The process of absorption takes place via the microvilli of the intestinal walls. Normal bowel permeability permits assimilation of nutrients while providing protection against pathogens being absorbed into the systemic circulation.

Food-enriched blood from the bowel is processed in the liver where most immune-complexes are removed. The other pathway of intestinal absorption is through lymphatic circulation. The abdominal lymph vessels are channeled

into the thoracic duct, which drains the lymph into the subclavian vein. In both circulatory patterns (blood and lymph), antigens are eventually directed to the liver where they may be removed from the circulation or made harmless to the body's tissues. If the antigens are passed beyond the liver, they will circulate through the lungs, heart, kidneys, and then to the rest of the body where they may disrupt the functioning of various systems. In a healthy body, appropriate bowel permeability and adequate liver and kidney functioning are able to maintain a level of minimal systemic toxicity which can be easily managed by the immune system.

Intestinal permeability can become excessive (so-called "leaky gut syndrome") due to a wide variety of factors including alcohol consumption, bacterial or viral infection, reduced blood flow (resulting from injury, surgery or atherosclerosis), certain drugs (NSAIDS), etc. If the amount of circulating toxins becomes excessive, and if the liver and kidneys are unable to keep up, autointoxication can result. The immune system reacts to antigens producing the characteristic inflammation associated with autoimmune diseases. Psoriatic skin lesions and arthritis are two possible outcomes from this process.

The immune and lymphatic systems are key factors in this process. In addition to the lymphatic vessels in the intestinal microvilli, the intestinal tract is a mucosal immune system lined with lymph nodes (Peyer's patches) and solitary lymphoid nodules [61]. Thus, the mucosal epithelial surfaces of the intestine are important mediators in the interaction between external and internal milieus.

Beyond the intestinal tract, lymphatic circulation has been implicated in the pathophysiology of skin disease with regard to lymphoctye migration into the skin. Jalkanen et al. [62] studied lymphatic circulation patterns in celiac disease (CD) and dermatitis herpetiformis (DH). They observed that "the staining results of inflamed duodenum in DH and CD were identical with those obtained from inflamed skin. Because more specific markers are not presently available in the human system, we cannot exclude the possibility that there is a common lymphocyte–endothelial cell–interaction system for differing sites of inflammation" (p. 791). Lymphatic/immune system involvement in psoriasis is well established, although the precise homing mechanism by which lymphocytes migrate to the skin remains unknown [63–65].

The concept of autoimmune inflammatory response produced by leaky gut and the ensuing autointoxication is not limited to psoriasis and other inflammatory skin diseases, but may also apply to various systemic conditions. For example, Swank and Deitch [42] described the relationship between intestinal permeability, autoimmune inflammatory reactions, systemic disease, and comorbidity in multiple organ failure as a complex process of bacterial translocation:

> It is clear that increased gut permeability and bacterial translocation play a role in multiple organ failure (MOF). Failure of the gut barrier remains central to the hypothesis that toxins escaping from the gut lumen contribute to activation of the host's immune inflammatory defense mechanisms, subsequently leading to the autointoxication and tissue destruction seen in the septic response characteristic of MOF. However, the role of the gut is more than that of a sieve, which simply allows passage of bacteria and endotoxin from the gut lumen to the portal or systemic circulation. It appears, in addition, that the translocation of bacteria and endotoxin may lead to local activation of the immune inflammatory system and the local production of cytokines and other immune inflammatory mediators . . . [42, p. 411].

Thus, in viewing psoriasis as a systemic disorder involving increased autoimmune reactivity in the skin (and to the joints in psoriatic arthritis), the intestinal tract and lymphatic system take on important roles with regard to etiology and pathophysiology of the disorder. Naturally, diet and nutrition also become important in the cause and treatment of psoriasis.

DIET AND PSORIASIS

Based on the substantial literature linking bowel pathology to skin disease, it is not surprising that dietary factors are well represented in the psoriasis literature. There have been numerous dietary approaches for psoriasis dating back many years. Although the literature does support the idea that diet can have significant positive effects on psoriatic symptoms, the evidence is complex and open to various interpretations.

For example, Schamberg [66] reported remarkable treatment efficacy using a low-protein diet. The typical diet contained about 30 g of protein. Typically, patients were hospitalized for 3–4 weeks. Lerner and Lerner [67] reported a 69-year-old man whose psoriasis improved on a low-protein diet and exacerbated on a high-protein steak diet. Roe [68,69] reported good results with a low-taurine diet in psoriasis. Because the principal source of taurine is animal protein, a low-taurine diet is necessarily a low-protein diet.

However, reports from some observers do not support the efficacy of a low-protein diet for psoriasis. Zackheim and Farber [70] failed to see significant improvement in 13 psoriatic patients who were hospitalized for periods of 4–17 weeks. Kwitten and Kantor [71] reported on a 37-year-old man whose psoriasis failed to improve on a starvation diet consisting of one head of lettuce, two medium-sized tomatoes, one cucumber, tea, and 12 ounces of soda daily for 6 days a week. The estimated protein consumption was 4.7 g per day. Interestingly, Pagano [6] suggested that certain foods (including carbonated beverages and tomatoes) contribute significantly to psoriasis. Simplistic models of dietary effects in psoriasis invariably fall short of validation.

Food deprivation has been associated with improvement in psoriatic symptoms. Simons [72] reported that 8 of 13 Dutch prisoners with psoriasis improved in Japanese con-

centration camps in Java in World War II, while on a near-starvation diet. Some researchers hypothesize that psoriasis is exacerbated with weight gain [73,74]. Others have reported remissions with weight loss under conditions of prolonged food deprivation [72]. Although some physicians think that psoriasis diminishes during periods of food deprivation or poor nutrition, there is no consensus on this point [70].

Spiera and Lefkovitz [75] reported dramatic improvement in four psoriatic patients who were placed on a diet believed to be low in tryptophan. The patients substituted turkey meat for regular sources of meat. Symptoms decreased while on the turkey diet and increased when the previous diet was resumed. Later measurements of the tryptophan levels of turkey meat indicated an error in the original calculations—turkey meat is not devoid of tryptophan. Although tryptophan level was probably not a factor in the clinical improvement, perhaps the change in protein sources was influential.

Dietary supplementation with fatty acids (fish oil) has been credited for the improvement of psoriatic patients. Kromann and Green [76] observed a decreased incidence of psoriasis in fish-eating Greenland Eskimos. This finding, combined with evidence for epidermally derived eicosanoids in the pathogenesis of psoriasis [77], led Ziboh et al. [78] to investigate the effect of fish oil dietary supplementation on psoriatic symptoms. Global evaluation showed that 8 of 13 patients demonstrated mild to moderate improvement of their psoriatic lesions. Further studies [79–82] supported the claim for modest improvement in psoriasis for patients consuming daily dosages of fish oil. As with much of the psoriasis literature, the effects of fish oil supplementation are variable. Fish oil has been found to be no better than corn oil [83] or olive oil [84] in reducing psoriasis symptoms. Kettler et al. [85] noted that although 25 patients with plaque-type psoriasis vulgaris showed no significant clinical improvement while taking fish oil supplement, 1 patient with generalized pustular psoriasis show marked improvement. It may be that fish oil is most helpful for certain individuals or specific forms of psoriasis.

Pagano [6] reported significant improvement of psoriasis in patients using a restrictive diet (discussed below) and dietary supplementation with herbal teas (most often yellow saffron and slippery elm) and olive oil. Yellow saffron (*Carthamus tinctorius*) has been shown to possess antiinflammatory [86,87] and immunosuppressive properties [88]. Slippery elm (*Ulmus fulva*) is an herb used traditionally for digestive difficulties, stomach and intestinal ulcers, and colitis. Slippery elm is a demulcent, high in mucilage, noted for its ability to soothe or protect irritated mucous membranes [89–91]. Although herbal therapy has been used effectively for atopic dermatitis [92–95], Pagano appears to be the primary advocate of herbal therapy for psoriasis.

In an epidemiological study of the association between diet and psoriasis, Naldi et al. [96] noted that dietary factors may influence psoriasis and modulate its clinical expression in an Italian population. Notably, increased intake of fresh vegetables and fruit was linked to a decreased prevalence of psoriasis. This study is in agreement with a similar prevalence survey in a Norwegian population [97].

In summary, diet does seem to play a role in the etiology and treatment of psoriasis. In general, a diet of fresh fruits and vegetables and low protein seems helpful. On the other hand, diet is a highly individual matter. Food allergies and sensitivities (e.g., celiac disease) may play a role for certain individuals, whereas other individuals may be relatively unaffected by the same foods. The degree of gut permeability and the system's ability to handle autointoxication are important factors in this regard. The use of dietary supplements (e.g., fish oil) may be helpful for specific individuals. Research has tended to look for "the" dietary factor (whether protein, taurine, oils) that is problematic for psoriasis. A multifactorial model that recognizes human diversity and systemic interactions will probably be most useful in clinical practice. Assessment of individual dietary patterns and reactions could be of use in understanding the process, in both research and clinical settings.

DISCUSSION

Psoriasis is a complex disorder involving a variety of factors. Therefore a multifactorial approach is needed to integrate the various aspects of psoriasis into a plausible model that addresses both the theoretical and clinical dimensions of the illness. The sources cited above suggest the bowel as one possible integrative factor in the etiology, pathogenesis, and treatment of psoriasis. The section below is speculative, and focuses on the central themes of an intestinal model. These include:

- Bowel Pathology: Due to injury, illness, and/or poor dietary habits, a variety of abnormalities in the upper small bowel (duodenum and/or jejunum) compromise the integrity of the intestinal tract. Various microorganisms may be involved in bowel pathology in psoriasis. From a clinical standpoint, screening for microorganisms is an appropriate early step in the assessment process [20,98].
- Intestinal Permeability and Autointoxication: Deterioration of the intestinal wall results in a smoothing effect to intestinal villi and a thinning of the intestinal wall, particularly in the upper portion of the small bowel. Microorganisms and/or other toxins that would normally be eliminated or restricted to the bowel are absorbed into the circulation (autointoxication). Additional bowel permeability studies using the ^{51}Cr-labeled EDTA absorption test as per Humbert et al. [28] are needed to determine the prevalence of intestinal permeability in psoriasis.
- Lymphatic/Immune System Involvement: The lymphatic/immune system is a likely channel by which the pathogens enter the systemic circulation. An immune response to the misplaced pathogens produces the various forms of psoriatic lesion, depending on the type of pathogen and the unique response of the individual system.

- Comorbidity: Because the systemic toxicity associated with intestinal permeability provides access to various organs in the body, toxicity can manifest in a variety of conditions in addition to psoriasis, most notably joint disease. There is a need for further research to clarify the extent of comorbidity and the specific causal relationships between psoriasis and other systemic illnesses.
- Natural Therapeutics: "Cure by removal of cause" via natural healing modalities such as diet and nutritional supplementation can assist with internal cleansing and healing the gut. The sources cited in the preceding section support the notion that a diet consisting primarily of fresh fruits and vegetables and low in protein can be helpful for some individuals with psoriasis. In addition to a cleansing diet, herbal teas, as suggested in the work of Pagano [6], may be helpful in healing the intestine. Specifically, yellow saffron tea and slippery elm are mainstays of Pagano's approach. Avoidance of foods that contribute to systemic toxicity may require careful monitoring of the effects of specific foods or food groups. For example, Pagano observed that the nightshade group (tomatoes, eggplant, peppers, etc.) tends to exacerbate psoriasis.

Psoriasis has a genetic aspect that can be regarded best as a predisposition or vulnerability. The diathesis/stress concept in which a genetic vulnerability is triggered into action via environmental or endogenous stressor is an excellent model of this view of hereditary factors in psoriasis. In addition to a predisposition for skin disease, an individual may also possess hereditary predispositions for other conditions that are known to be comorbid with psoriasis. In other words, the autointoxication manifests most obviously in weak systems of the body. The genetic diathesis may involve a predisposition for increased bowel permeability or a tendency to for the immune system to react to certain toxins. Stressors may be physical, social, or psychological.

Although not directly related to intestinal etiology in psoriasis, treatment compliance is a practical concern for anyone attempting significant lifestyle changes (such as diet). Psychosocial support should be considered as an adjunct to clinical interventions for any condition requiring substantial lifestyle changes. For example, Ornish et al. [99] demonstrated convincingly the role of group support with regard to intensive lifestyle changes for reversing coronary heart disease. Abel et al. [100] recognized the beneficial effects of psychosocial support for stress reduction, improvement of coping skills, and health education in psoriasis patients. Because stress has been linked to increased psoriatic symptoms [101–103], psychosocial support and stress reduction training are reasonable adjuncts to any psoriasis treatment program.

Thus, the therapeutic model advocated in this report is holistic and integrative. The diet is intended to avoid foods that irritate the gut or increase autointoxication. Although each individual is unique, in general the diet is intended to improve assimilation of nutrients and elimination of toxins. Essentially, the diet consists mainly of fruits and vegetables while avoiding fried foods and refined carbohydrates ("junk food"). The nightshade vegetables (such as tomatoes and peppers) are to be avoided [6]. For some individuals, colonic irrigation may be helpful for cleansing the lower bowel and decreasing autointoxication [4,5].

Evidence of the efficacy of this intestinal model rests largely on the numerous case reports documented by Pagano [6]. Pagano conducted more than 15 years of clinical studies resulting in impressive before-and-after photography of the total clearing of severe psoriatic lesions in numerous individuals. Longitudinal case reports of these patients strongly support the contention that the model is effective in healing psoriasis.

Our own clinical observations in cases of psoriasis treated according to Pagano's protocol lend some support to his approach. Seven of the nine patients in one group exhibited decreased psoriasis symptoms; three had essentially complete clearing of skin lesions. In a later group of five patients, all five showed improvement when treated according to the Pagano protocol. More case studies from other investigators and controlled clinical studies will be necessary to confirm these observations.

CONCLUSION

The etiology of psoriasis involves varied factors, both specific and nonspecific. Based on the literature, the bowel pathology model described in this article provides a conceptual framework for understanding certain systemic features of psoriasis. Clearly, intestinal etiology in psoriasis does not account for all the varied manifestations of the illness. Yet it does provide a plausible approach for integration of some of the diverse research and clinical information in the literature.

An integrative medicine model, in which standard medical treatments (which can often provide temporary symptomatic relief) are integrated with natural therapeutics (intended to address more fundamental causes), is proposed as a plausible next step in the treatment of psoriasis. Additional research is needed to further document the clinical effectiveness of this model, to evaluate the role of bowel permeability in psoriasis, and to determine which elements of the treatment protocol contribute to the improvement in symptoms.

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