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Is psoriasis a bowel disease? Successful treatment with bile acids and bioflavonoids suggests it is

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Abstract The gut is the largest lymphoid organ in the body. The human microbiome is composed of trillions of bacteria. The DNA of these bacteria dwarfs the human genome. Diet and ethanol can cause rapid shifts in the number and types of bacteria in the gut. The psoriatic microbiome is similar to that seen in alcoholics; there is a decrease in bacterial diversity and overgrowth of bacteria in the small bowel. Psoriatics often have liver disease and deficiencies in bile acids. Psoriasis is a disease characterized by a leaky gut. All of the comorbidities of this disease are due to systemic endotoxemia. Bacterial peptidoglycans absorbed from the gut have direct toxic effects on the liver and skin. Their absorption, as well as endotoxin absorption, must be eliminated to treat psoriasis successfully. Endotoxin absorption is markedly increased by ethanol and peppers. Bioflavonoids, such as quercetin and citrus bioflavonoids, prevent this absorption. Bile acids, given orally, break up endotoxin in the intestinal lumen. Pathogens, including *Helicobacter pylori* and *Streptococcus pyogenes,* must be eliminated with antimicrobial therapy for any treatment to work. A complete protocol for curing psoriasis is provided.
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Historical perspective

The current model of psoriasis suggests that it is a cutaneous disease, with a genetic predisposition, related to an overproduction of inflammatory cytokines by T cells. The disease is exacerbated by bacterial super antigens. Current therapy is directed at turning off key psoriasis pathways in the skin by targeting TNF with TNF inhibitors, IL-12 with p40 antibodies, products of Th22 stimulation with IL-22 antibodies, and products of Th17 stimulation with IL-17 or IL 17R antibodies, as well as such antimetabolites as methotrexate and cyclosporine. These therapies are directed at antigen-driven cytokines, but the antigen brought to the skin by myeloid dendritic cells is never addressed. I consider this as smoke suppression without mention of the fire. Peptidoglycan (PG) and PG-specific Th1 cells are found in psoriatic plaques.[1] Psoriasis is a systemic disease with such comorbidities such as obesity, insulin resistance, diabetes, atherosclerosis, hypertension, arthritis, and ischemic disease. All of the "metabolic syndrome" morbidities mentioned have been associated with endotoxemia.[2,3] Bill Rosenberg's group[a] in Memphis were very keen on endotoxemia as a cause of psoriasis in the early

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1980s.[4,5] Both endotoxin and IgA immune complexes activate the alternative complement pathway.

Another group demonstrated that 67% of psoriatics have circulating IgA immune complexes.[6] A positive correlation was found between the extent of pretreatment disease involvement and the level of IgA-containing circulating immune complexes. Of the patients with psoriatic arthritis, 80% were found to have circulating IgA immune complexes.[7] Similar findings were noted in an additional study,[8] where it was found that IgA immune complexes did not decrease with successful treatment.

There was interest in cutaneous polyamines in psoriasis in the late 1970s. Polyamines are compounds having two or more primary amino groups –NH. Linear low-molecular-weight polyamines, such as putrescine, spermine, cadaverine, and spermidine, being intimately associated with cellular growth and division, are elevated in psoriatic skin. All dermatologic contributions on polyamines assumed that they were synthesized in the skin, and it was never mentioned that these are bacterial byproducts found in the gut.[9] The exact mechanism of transport to the skin is poorly understood, but within an hour 50% of orally ingested polyamines from food are present in the systemic circulation.[10]

There is no such thing as a polyamine-poor diet for humans, because milk, eggs, meat, and all types of vegetables contain polyamines.[11] The rate-limiting biosynthetic enzyme ornithine decarboxylase, which metabolizes polyamines, is also elevated in psoriatic skin and increases with epidermal proliferation.[12] Nine hospitalized patients were examined at the beginning and end of their psoriasis treatment, and their cutaneous and urinary levels of putrescine, spermidine, and spermine fell significantly as their psoriasis improved. The conclusion was: "Topical therapy may reduce epidermal cell proliferation in psoriasis by lowering polyamine levels."[13] The researchers did not consider that alterations in diet and alcohol intake while hospitalized may have altered absorption of polyamines from the gut.

Psoriatics have been shown to have increased gut permeability, as evidenced by abnormal 51CR-labeled EDTA absorption test results. If given orally, the amount of 51CR-labeled EDTA excreted in the urine tells how much got out of the gut into the systemic circulation. Psoriatics have much more in their urine than controls.[14]

Recent data confirm the presence of gut-derived bacterial DNA in psoriatic blood. The species identified were *Escherichia coli, Klebsiella pneumoniae, Enterococcus faecalis, Proteus mirabilis, Streptococcus pyogenes,* and *Shigella fresneli.*[15] This demonstrates an association between the bowel and psoriasis.

"All disease starts in the gut" is a saying attributed to Hippocrates (470-360 BCE). The concept of "autointoxication" has been applied to many skin diseases[16] and was familiar to the ancient Egyptians.[17] It reached a highpoint in the teachings of Ilya Ilyich Mechnikov (1845-1916) who won the Nobel prize in 1908. One of his sayings was, "Death begins in the colon." The idea that absorption of bacterial toxins caused all sorts of diseases persisted into the 1930s but gradually died of natural causes.[18,19]

Bowel bypass syndrome

I have given a talk titled "Is psoriasis a bowel disease?" many times since 1981. A sketch from that talk is included as Figure 1. The concept was derived from my experience with the bowel bypass syndrome (BBS).[20–22] I started practice in 1975. In the first few weeks, I saw several obese women who had flulike clinical manifestations, papulopustules, erythema nodosum, arthralgias, cryoglobulinemia, and a common history of having had bowel bypass surgery. Histology of the skin pustules was identical to that of an acute febrile neutrophilic dermatosis as described by Robert Douglas Sweet (1918-2001) in 1964.[23] In his description, he said that the syndrome was caused "by a reaction something or other."

The BBS had never been described. I contacted the bariatric surgeon who operated on these patients, and he was kind enough to provide me with a list of 50 women who had undergone this type of surgery. A mail questionnaire to these 50 revealed the presence of BBS in 10 (a 20% occurrence). I studied these 10 women for the next 5 years. I placed bacterial antigens on them and found that the most reactive by far was *S pyogenes* (Figure 2). In some cases, applying a small skin test would trigger a full-blown episode of arthralgias and pustules. I tested these patients for PG antibodies, which were uniformly elevated, as expected. Because psoriasis was considered a neutrophilic disease, I used psoriatic patients' blood as a control. Surprisingly, many of the psoriatic patients had titers as high as the bowel bypass patients.[24]

I corresponded with Sweet, and he suggested skin testing with his syndrome with a battery of my bacterial antigens. The first woman I tried it on developed full-blown neutrophilic dermatosis and required prednisone to stop it. She was in good health, but 2 years later, she developed leukemia. This scared me, but it suggested that bacterial antigens alone were not the cause of this syndrome but rather triggered it if there was an abnormal immune response.

While studying these patients, I read extensively on "reactive arthritis" (RA) (joint pain at a site distant from infection). Reiter's syndrome following *Yersinia* infection was the prototype, and keratoderma blennorrhagicum of Reiter's syndrome may mimic psoriasis.

In studying the BBS patients, I monitored liver function tests regularly and saw very few abnormalities. About half of my patients had to have their intestines put back to their original anatomic positions due to unremitting clinical manifestations. Each of these patients had an open liver biopsy at the time of surgery, and in all cases cirrhotic changes were noted. I concluded that the BBS occurred only when the patient's liver was unable to handle the bacterial toxins absorbed from the blind loop of bowel.[22]

I submitted my findings to the Pacific Dermatology Association as "The Bowel Bypass Syndrome: A Response

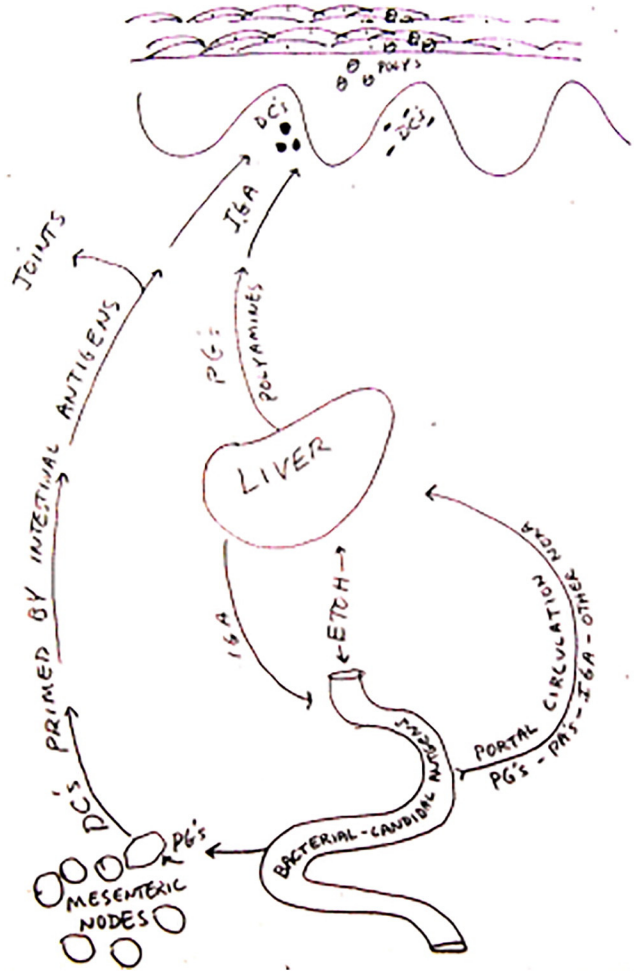

Fig. 1 Sketch from 1981 outlining what is presented in this paper today.

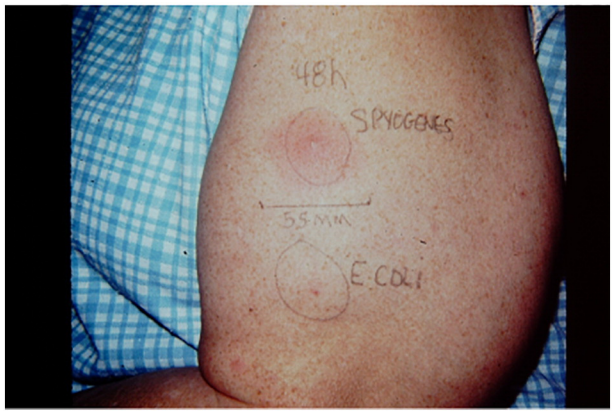

Fig. 2 *Streptococcus pyogenes* skin test.

to Bacterial Peptidoglycans" and the paper won the Nelson Paul Anderson Memorial Essay Contest. I submitted the paper to the *Journal of the American Academy of Dermatology,* and Skee Smith[b], the editor, suggested breaking it into two parts, one published as an editorial with Peter Utsinger, a rheumatologist in Lititz, PA, who also had submitted a paper on the topic.[25] In the editorial, I asked why alcoholics, who also had circulating IGA immune complexes, did not present with arthralgias and neutrophilic dermatoses. I also questioned: "If immune complexes containing bacterial antigens were the cause of the bowel bypass syndrome, why don't patients with hepatitis C whose cryoglobulins contain *E coli* antigens, have bypass syndrome?"[21]

My bypass patients confided in me many secrets about their eating habits. One told me how she had lied about how little she ate to get scheduled for bypass surgery. She said that on the way home from her surgery, she stopped at a donut shop and bought two dozen donuts. She ate 18 on the drive home. I wondered why, if these patients had had bariatric surgery, they were still so fat. It turns out that they played "Beat the bypass." It consisted of milkshakes taken frequently. This works with stomach plication, as well as Roux en Y bypass surgery. A similar high-fat, high-calorie diet is common to many psoriatics. Such a diet causes a profound alteration of the gut microbiome and has interesting side effects that may be responsible for the metabolic syndrome.

In a famous study, referred to by many as "The McDonald's Study,"[26] patients who ate a high-calorie, high-fat breakfast had circulating levels of endotoxin after the meal; however, if they drank orange juice with the meal, their endotoxin levels did not rise.

Endotoxin level can now be easily measured with a simple kit (that was not available when I was studying BPP). In a series of experiments with patients given water; glucose plus water; a high-fat, high-calorie drink; or any of the above plus orange juice, orange juice proved to be protective in preventing endotoxin rise.[26] The endotoxin absorption was prevented by citrus bioflavonoids in the orange juice. In experiments on mice, commonly used emulsifiers, such as carboxymethyl cellulose and polysorbate 80, also caused a rapid rise in the blood levels of endotoxin and signs of the metabolic syndrome, including weight gain, cardiovascular disease, and aging.[27] The "beat the bypass" women were increasing their systemic endotoxin load dramatically by high-fat, high-calorie, emulsified drinks.

Atherosclerosis

One of the major comorbidities of psoriasis is atherosclerosis. Symptomatic atherosclerosis is associated with an altered gut metagenome.[28] An extensive review revealed that bacterial PGs are found in the arteries underlying atherosclerotic plaques.[29,30] Polybacterial and chronic gum pathogens, such as *Porphyromonas gingivalis,* have also been detected in atherosclerotic plaques.[31] Cholesterol, rather than being the cause of these plaques, may be the body's way of covering up toxic PGs absorbed from the gut or mouth.

[b] J. Graham Smith, Jr., MD (1926-2010).

Ecology and absorption of intestinal bacteria

The numbers and weight of the normal human gut microbial flora are astonishing. The word "microbiome" has become a meme in modern medicine. It was first coined by one of my biology teachers at Stanford, Joshua Lederberg (1925-2008). "Microbiota" comes from the Greek "mikros" (small) and "bios" (life). The gut contains 10^{13} to 10^{14} cells per gram with a total weight of around a thousand grams. This is more than 10 times the number of cells in the human body! The metabolic capacity of the gut microbiota equals that of the liver.

Intestinal microbiota

The intestinal microbiota can be considered another organ. Genomes Online database lists 2723 completed and published bacterial genomes[32] and many cannot be cultured. They are identified by molecular tools such as length heterogenicity PCR (LH-PCR) and deep pyrosequencing of bacterial 16sRNA. The Human Microbiome Project, funded by the National Institutes of Health, has generated more than 3.5 terabases of metagenomics sequences. This is truly "Big Data," and identification of bacteria from their DNA sequences is done with super computers and machine learning techniques.[33]

The more than 9 million nonhuman genes in the gut microbiome dwarf the 20,500 that comprise the human genome.[34] Amy D. Proal of the Autoimmunity Research Foundation, in her essay "Inflammatory Disease and the Human Microbiome," said, "It is becoming increasingly clear that inflammatory disease processes are not due to acquisition of any single pathogen. Instead, they appear to result from alterations in the complex microbial communities. It follows that Koch's postulates, which dictate that one microbe must be proven causative of a single disease state, can no longer be supported in the era of the metagenome."[35]

Obligate anaerobes constitute 95% of the total number of bacteria. They outnumber aerobic bacteria by 100-fold to 1000-fold.[33] Ninety-nine percent of intestinal bacteria belong to the 30 to 40 species from the main phyla of Firmicutes and Bacteroidetes, but other species present are members of the phyla Proteobacteria, Verrumicrobia, Actinobacteria, Fusobacteria, and Cyanobacteria.[34]

Microbial density

Microbial density increases from the proximal to the distal gut. The stomach contains 10^1 microbial cells per gram of content, the duodenum 10^3 cells per gram, the jejunum 10^4 cells per gram, the ileum 10^7 cells per gram, and the colon up to 10^{14} cells per gram. Bacterial diversity increases in the same axes and manner as microbial density[35]; however, this may be markedly abnormal in psoriasis and alcoholics.[36]

On the epithelial surfaces bacteria form plaquelike structures. This bacterial film extends into the Lieberkuhn's crypts, in which almost pure strains may exist. The moving flow of luminal contents is surrounded by a tube of densely packed bacteria anchored by extensions penetrating into the epithelial crypts. Well-adapted species, including several *Proteobacteria* and *Akkermansia muciniphila,* reside within the mucous layer close to the tissue.[32]

The jejunum and proximal ileum are essentially sterile compared with the bowel further on. Peristalsis, low pH, lactic acid, bile salts, bacteriocins, pancreatic enzymes, high oxidation-reduction potentials, thick mucin, secretory IgA, and phagocytes (Paneth cells) prevent bacterial overcolonization. The distal ileum and colon are less subject to peristalsis and have very low oxygen tension. Hydrogen sulfide, volatile fatty acids, and urea present in the large bowel encourage anaerobic bacterial growth, as does the extremely low redox potential. Gram-negative, nonsporulating anaerobes, such as members of the *Bacteroides* group, usually outnumber by more than 100 to 1 the "typical" colonic organisms, such as *E coli, Streptococcus faecalis, Proteus vulgaris,* and *Pseudomonas aeruginosa.*

These indigenous bacterial populations are extremely stable and interdependent. Continuous flow culture models of lower intestinal bacteria show that substrate-nutrient competition controls bacterial populations. Many species have tiny ecologic niches, feeding on the byproducts of other bacteria, and in turn producing necessary nutrients for additional organisms. Species that adhere to the bowel wall have a marked advantage over those free in the lumen.

Alterations

Even though indigenous bacterial populations are extremely stable, diet rapidly and reproducibly alters the human gut microbiome. "Work in inbred mice shows that shifting dietary macronutrients can broadly and consistently alter the gut microbiome within a single day"[37] The authors of this publication tested human volunteers with meat-based and plant-based diets and found a rapid (1 day) shift on the meat-based diet between the baseline gut microbiome and the meat-based microbiome. Two days after stopping the diet, subjects gut microbiota reverted to their original structure.[37] The species that changed the most on the meat-based diet were those that exhibited the common theme of bile resistance, being consistent with observations that high fat intake causes more bile acid secretion.[37] While doing this study, the authors noted that foodborne microbes survived transit through the digestive system, especially on the meat diet. They noted: "Many dairy associated microbes remained viable after passing through the digestive tract, as we isolated 19 bacterial and fungal strains with high genetic similarity to microbes cultured from cheeses fed to the subjects."[37]

Indigenous bacteria regularly invade tissues and can be isolated from regional lymph nodes and blood. A dynamic equilibrium exists between indigenous bacterial invaders and host defenses. In a beneficial sense, these bacteria give rise to "normal" antibodies that are important for non–self-recognition and phagocytosis. The composition of the gut microflora controls to a considerable extent the spectrum of microbes

the body can eliminate efficiently via phagocytosis.[22] The indigenous microflora, in common with other ecosystems, share the ability to reject invading microorganisms or pathogens. Before bacterial pathogens can infect humans, there must first be a disruption in the activity of this indigenous flora.

Little is known of the mechanisms, whereby bacteria or macromolecules cross the intestinal epithelium. *Persorption* is a term used to describe the passage of hard particles (such as pollen grains, carbon particles, or starch) between epithelial cells into the blood or lymph vessels of the lamina propria. Ethanol ingestion and starvation markedly enhance this process. Carbohydrate fermentation by intestinal bacteria may produce endogenous ethanol. *Transmural migration* and *resorption* are terms used to describe the passage of viable bacteria across the mucosa. Pinocytosis and intercellular leakage are the mechanisms involved.

Active sampling of intestinal antigens occurs in Peyer's patches, which comprise part of the gut-associated lymphoid tissue (GALT) Specialized M cells in Peyer's patches pinocytose antigens and present them to the underlying lymphoid tissue. The general term, *translocation*, is defined as the passage of viable bacteria to the mesenteric lymph nodes and liver and includes all of the previously mentioned processes.

The immune system of the normal bowel

The small bowel is the body's largest lymphoid organ. It contains half of the total number of lymphocytes in the body, most of them in the Peyer's patches and the lamina propria. Most antibody production in the gut is of the IGA class, but 10% of the cells secrete IgM and 1% secrete IgG. There are 200,000 IgA-producing plasma cells per cubic millimeter in the lamina propria.

Local antibody production does not occur in Peyer's patches. Antigens arriving via M cells interact with dendritic cells (DC), which then "educate" T cells by exposing them to antigen. The "educated" T lymphocytes leave the gut and selectively populate mesenteric lymph nodes. Conversely B-cell immunoblasts migrate from mesenteric nodes to intestinal, respiratory, and genital epithelium via the bloodstream. Most of them "home" to antigen-sensitized areas of the gut. Dendritic cells are also prominent in the skin, synovium, and kidneys, where they initiate localized immune responses to circulating antigens. As many as 3% of blood monocytes are circulating dendritic cells. These sensitized antigen-presenting cells from the gut may selectively populate peripheral tissues such as skin and synovium.[22]

The role of immunoglobulin A in the bowel

B cells primed to produce IgA become plasma cells in the lamina propria of the gut. Some B cells bearing surface IgM may be altered by specialized "T switch cells" in Peyers patches and converted to IgA-producing plasmablasts, which then return to the lamina propria.

In the lamina propria, dimeric IgA is formed from monomeric IgA by the addition of joining chain (J chain). This dimeric IgA is attached to a secretory piece via the J chain as it passes through the intestinal epithelial cells; thus, almost all IgA in the gut lumen is secretory IgA (SIgA). There are two subclasses of IgA: IgA1 and IgA2. Serum IgA is 90% IgA1; in secretions, the amounts of IgA1 and IgA2 are approximately equal. Serum IgA is mostly monomeric and is produced in the bone marrow, spleen, and peripheral nodes. Secretory IgA1 is miscible with the mucous layer in the gut lumen; this allows secretory IgA1 to sit as a monolayer at the mucosal surface. Secretory IgA overlies the mucous layer as a "front line defense." Bacterial IgA1 protease cleaves IgA1 but not IgA 2, and thus the separation of IgA subtypes protects the more vulnerable IgA closest to the mucosa.[22]

Secretory IgA in the gut lumen prevents attachment of bacteria to the mucosa. Complexes made up of agglutinated bacteria and secretory IgA cause increased secretion of mucous by goblet cells. This may trap more bacteria and speed up intestinal transport. Dimeric, polymeric, and aggregated forms of IgA found in the gut are inhibitory to polymorphonuclear leukocytes and monocyte chemotaxis and random movement. IgA does not opsonize bacteria. IgA antibodies can block bacterial lysis by IgG, and complement and secretory IgA can block IgM and IgG-mediated bacterial lysis. These protective qualities dampen potentially damaging inflammatory responses at mucosal surfaces.[22]

Psoriatic patients have been shown to have circulating immune complexes containing IgA.[6–8] The papers on this topic do not distinguish which type of IgA is in the immune complexes, but I suspect that it is SIgA from the gut. IgA immune complexes are also found in alcoholic patients.[38] Ethanol markedly increase absorption of almost any marker of intestinal leakage. A d-xylose absorption test or I51 Cr absorption test is markedly altered by even small quantities of ethanol. Ethanol also changes the bacterial flora in the microbiome, and this altered flora has been implicated in the pathogenesis of alcoholic liver disease.[39]

The peptidoglycan hypothesis

In my bowel bypass patients, skin testing with multiple bacterial antigens produced positive results, but by far the most positive was the reaction to *S pyogenes*. Because *S pyogenes* is not a normal component of bowel flora, and because numerous intestinal bacterial antigens were found in cryoglobulins from the bowel bypass patients, I hypothesized that an antigen common to all bacteria was the underlying cause of BBS. The antigen that best fits this description is the bacterial PG. "Peptidoglycan" is the accepted name for a macromolecule composed of a polymer of *N*-acetylglucosamine and *n*-acetylmuramic acid that has short peptide side chains

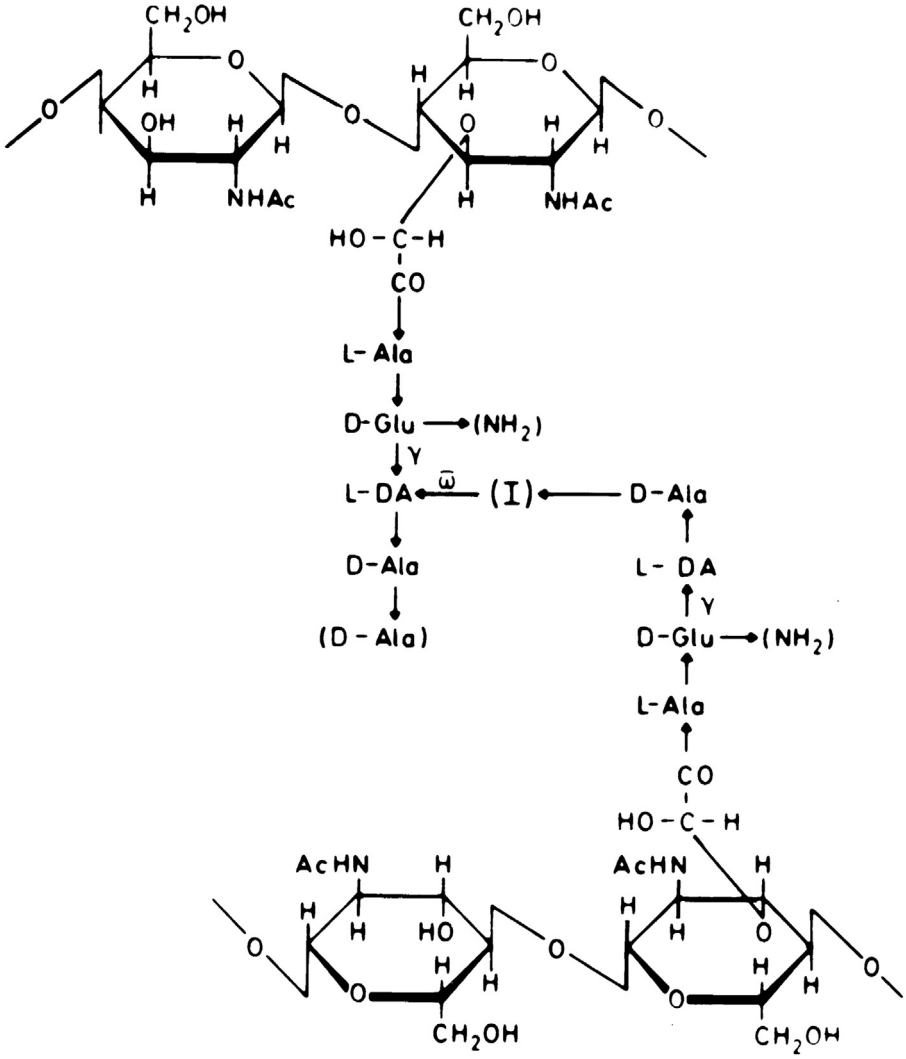

Fig. 3 Peptidoglycan structure.

composed of alternating D and L amino acids (Figure 3). Diamino acids such as diaminopimelic acid (DAP) are found in the peptide side chains and are also found in mesenteric lymph nodes. PGs are responsible for the rigidity of bacterial cell walls.

The PG structure is similar in all gram-negative bacteria. Structural changes, especially in the antigenic peptide side chain, can be caused by changes in the nutritional substrate (microbiome), pH, and oxygen tension in the bowel. Gram-positive bacteria show much variability in the peptide side chain and can be taxonomically classified based on this structure. There is extensive cross reactivity between PGs of gram-positive and gram-negative bacteria; their antigenic determinants may form a common precipitin line without spurring when immunodiffused against purified group A streptococcal antiserum.[20,22]

Some important biologic properties of PGs include activation of complement by the alternative pathway, arthritogenicity, lysis of platelets, activation of macrophage cytotoxicity, and stimulation of both B and T cells (Table 1).

Under normal conditions the body is not exposed to isolated PGs, but rather to whole bacteria, bacterial cell walls, or endotoxins. The cell wall polysaccharide (PS) attached to the peptidoglycan (PG-PS) prevents the biologic effects of the PG from being manifested *in vivo* until the polysaccharide has been enzymatically removed. The half-life of PG-PS complexes is many days, but the half-life of pure PG is 10 hours. Free PG in tissues is chemotactic for polymorphonuclear leukocytes and causes an acute transient edematous neutrophilic reaction.[20]

Peptidoglycans and endotoxins

PGs and bacterial endotoxins are chemically dissimilar. Endotoxins are proteins and produce their effect in 1000-fold lower concentrations than PGs. Some of the biologic properties of PG are similar to those of endotoxin.[40] The cytotoxic effects of endotoxin or its biologically active component, lipid

Table 1 Biologic properties of peptidoglycans *in vivo*

In vivo	*In vitro*
Immunogenicity: B cell activation	Antigenicity: reacts with dendritic cells, T cells, and antibodies
Adjuvant activity: B and T cells	Complement activation
Inflammatory skin lesions	Renders macrophages cytotoxic
Granulomata: internal organs	Inhibition of polymorphonuclear leukocyte chemotaxis
Lesion-enhancing activity	Activation of PA/plasmin system
Localized Schwartzmann reaction	Lysis of platelets with release of serotonin
Antitumor activity	Cytotoxicity for kidney cells, macrophages
Resistance to bacterial infections (nonspecific)	Inhibition of macrophage migration
Pyrogenicity	Gelation of amebocyte lysate

A, are mediated in large part by activation of the alternative complement pathway. Endotoxemia has been demonstrated in both ulcerative colitis and Crohn's disease.[41] There are many similarities between acute psoriasis and endotoxemia, including fever, leukocytosis, increased capillary permeability, elevated liver function enzymes, decreased complement levels, abnormalities of lipid metabolism, and rise of lysosomal enzymes.

The effects of PG and endotoxins may be additive. During endotoxemia or subclinical infection, injection of a very small amount of PG will cause large necropurulent lesions in mice. This is known as "lesion enhancing activity" and is another of the biologic activities of PG listed in Table 1. If bacterial cell walls are injected into rabbits and systemic endotoxemia is induced several weeks later, the previously injected sites will be foci of vascular leakage. Persistence of PG-PS complexes at injection sites has been demonstrated in many animal systems. In tissue culture, human synovial cells produce increased amounts of prostaglandin E2 in response to endotoxin or PG. Increased vascular permeability induced by PGE2 may account for local deposition of antigen or immune complexes.[22] Prostaglandins are markedly elevated in isolated mucosa of IBD. I am unaware of studies of prostaglandins in psoriatic bowel tissue.

Naturally occurring sources of PGs (other than the gut) are from the roots of teeth and especially from the tonsils. Tonsillitis with group A strep is a known trigger for psoriasis and perhaps chronic swallowing of pus from infected tonsils colonizes the small bowel with *S pyogenes*. Most people think that live bacteria do not make it through the acid of the stomach, but this is not so. Live bacteria, fungi, and viruses all make it to the small intestine at least.[37]

The psoriatic microbiome

Identification of gut bacteria is usually done by analyzing the fecal contents. This does not tell anything about bacterial colonization of the small intestine. The microbiome of psoriatic skin has been studied in detail.[42] The microbiome of the psoriatic gut has not. The closest to a modern study using fecal sample DNA extraction and amplification of the V1-V2 16S rRNA gene region and 454 pyrosequencing was done on patients with psoriatic arthritis. This study showed that patients with psoriatic arthritis had decreased bacterial diversity in a pattern resembling the dysbiosis of inflammatory bowel disease.[43] The psoriatic patients had a reduced relative abundance of the genera *Parabacteroides* and *Coprobacillus*. Patients with psoriatic arthritis had reduced levels of *Akkermansia* and *Ruminococcus* (including Firmicutes/Clostridiales and Verrucomicrobiales).

Psoriasis and hidradenitis suppurativa co-occur with inflammatory bowel disease more often than is expected. Patients with IBD have a gut microbiome characterized by a depletion of *Faecalibacterium prausnitzii* and an increase of *E coli*. A study, using a quantitative polymerase chain reaction, compared *F prausnitzii* and *E coli* abundance in fecal samples from healthy controls with samples from patients with psoriasis. Psoriasis patients had significantly lower abundance of *F prausnitzii* in their stool than healthy controls, and significantly higher abundance of *E coli*.[44] Identification and quantification of small bowel bacteria is difficult and is done as a result of gastroscopy investigation of small bowel clinical manifestations. One Russian author, in an online monograph,[45,46] cites several papers by Gumayunova,[47–49] which reveal marked small intestinal bacterial overgrowth (SIBO) in 78.5% of psoriatics. Twenty-one percent of psoriatics had SIBO 10^9 to 10^{11} colony forming units (CFU)/mL. This is comparable to high quantities found in the colon. Bacteria found in the small intestines were *Bifidobacterium* spp. (93%), *Lactobacillus* spp. (84%), *Enterococcus* spp. (65%), *S pyogenes* (9%), and *Streptococcus viridans* (30%).[45] These are all colonic bacteria (except for *S pyogenes*). All psoriatic patients had gram-negative *E coli*, *Bacteroides*, and gram-positive *Clostridium* spp. in the jejunum. Twenty-five percent of psoriatics had *Enterococcus faecalum*, 10% had *K pneumonia*, and 5% had *P vulgaris* in the small bowel. There were no SIBO or pathogenic bacteria in the control group. The correlation between SIBO levels and the severity of psoriasis was noted.[47–49]

Pavlenok compared two groups of psoriatics who had *Helicobcter pylori* infections and no *Helicobacter* infection. *H pylori*–positive patients had intense itching of their psoriatic plaques and *Helicobacter*-negative patients did not. Among psoriatics, 40% were *Helicobacter* positive, and in controls only 5% were positive.[50] Twelve percent of psoriatics were found to be carriers of blastocystosis. These patients were found to have the most severe psoriasis and many of them had psoriatic arthritis.[45]

The Russian studies cited by Peslyak "established that the maximum disturbances of colic microflora are observed in 75% of psoriatics with moderate and at 97% of psoriatics with serious psoriasis."[45] Good studies of the psoriatic gut microbiome need to be performed in other countries as well as the United States.

Alcohol and psoriasis

In 1977, there was a letter to the editor of *JAMA* titled "Does disulfiram cure psoriasis?"[51] Over the years, I have noticed that many psoriasis patients are either alcoholics or heavy drinkers. The tip off clinically is the color of the plaques. Beef steak red psoriasis plaques are almost always associated with alcohol ingestion in my opinion, and as mentioned above, *Helicobacter* infection is associated with plaques that itch.[50] Alcoholics often exhibit hypochlorhydria, which is often found with *Helicobacter* infections.[52,53] Reduced gastric acid production is associated with small intestinal bacterial overgrowth as well as vitamin B_{12} deficiency.

A look at the effects of alcohol on the gut is enlightening because almost everything one can say about the effects of alcohol on the gut applies to psoriasis.

Patients with alcoholic liver disease have quantitative and qualitative changes in the intestinal microbiome. They have increased intestinal permeability and elevated systemic levels of gut-derived microbial products. Intestinal dysbiosis and pathologic bacterial translocation are fundamentals of alcoholic liver disease.[54–56] Dysbiosis can be either intestinal bacterial overgrowth, or qualitative changes in intestinal microbial populations. There is both small and large bowel bacterial overgrowth in alcoholics. Increased numbers of bacteria in the intestines can be assessed by quantitative polymerase chain reaction (qPCR) using universal ribosomal RNA bacterial primer sets in fecal samples or by conventional culture techniques on fecal samples from the small and large intestines. 10^5 colony forming units of bacteria per mL or more of jejunal aspirate indicates bacterial overgrowth. Feeding alcohol to mice causes increase of both aerobic and anaerobic bacteria in the proximal small intestine.[57]

Large intestinal bacterial overgrowth occurs within a week of feeding mice alcohol.[58] Humans with only moderate alcohol intake show small intestinal bacterial overgrowth.[59]

Lactobacillus species are decreased in the bowel of animals and man after ethanol ingestion. Alcohol decreases the levels of long chain fatty acids (LCFAs) in the gut microbiome. Because lactobacilli can use saturated LCFAs *in vivo* and in culture for growth, lower levels of saturated LCFAs could explain suppressed amounts of *Lactobacillus* species in the gut after alcohol feeding. Administration of LCFAs to alcohol-fed mice increased levels of *Lactobacillus* spp., reduced intestinal inflammation, improved intestinal barrier function, and reduced alcoholic liver disease.[60,61]

Feeding probiotics, especially *Lactobacillus*, to cirrhotic patients can markedly decrease small intestinal bacterial overgrowth.[62] Rats treated with probiotics before alcohol feeding do not develop the colonic dysbiosis, which always occurs by week 10.[63]

Alcohol consumption changes many intestinal metabolites. Chronic ethanol ingestion in rats reduces almost all amino acids, including branch-chained amino acids (leucine, isoleucine, valine) and produces perturbations in steroid, lipid, and carnitine metabolism.[64]

Short chain fatty acids (SCFAs) are bacterial fermentation products. SCFAs are lower after ethanol administration. Supplementation of the SCFA butyric acid improves intestinal barrier function after ethanol exposure in mice.[65]

Alcohol also reduces intestinal motility. This may lead to proliferation of luminal bacteria.[66]

Pathologic bacterial translocation of viable bacteria to the mesenteric lymph nodes occurs due to alcohol ingestion. Small intestinal bacterial overgrowth alone may result in bacterial translocation and subsequent liver injury.[67] Bacterial translocation occurs when the intestinal epithelium is damaged and the intestine becomes more permeable. Acetaldehyde, an ethanol metabolite, increases intestinal permeability, and acetaldehyde directly causes tight junction disruption.[68]

Intestinal inflammation is another mediator of barrier dysfunction. Proinflammatory mediators such as IL-1 beta and TNF are increased in the small intestine after ethanol ingestion.[69]

Lamina propria monocytes and macrophages produce TNF after alcohol feeding to mice. These cells produce TNF in the duodenum of humans after alcohol exposure. Inflammation precedes increased intestinal permeability. Intestinal dysbiosis induced by alcohol also triggers this local TNF-driven inflammatory response. TNF-receptor1 mutant mice do not have intestinal barrier dysfunction and alcoholic liver disease. If TNF-receptor 1 is reactivated on intestinal epithelial cells, alcohol feeding produces increased intestinal permeability and liver disease.[58] TNF inhibitors used in psoriasis may have an effect on intestinal permeability via this mechanism.

Lipopolysaccharide (LPS) or endotoxin and PG have been shown to be elevated in the blood of animals and humans after alcohol consumption. The degree of liver injury correlates with endotoxemia in patients with cirrhosis.[70,71] Inversely, selective intestinal decontamination with antibiotics can reduce pathologic bacterial translocation and endotoxemia.[72]

A study demonstrated that oral administration of bile acids to cirrhotic rats abolished small intestinal bacterial overgrowth. It was postulated that cirrhosis decreases bile flow.[73]

The psoriatic liver and bile

I mentioned that my bowel bypass patients had horrendous liver disease, including frank cirrhosis, which did not show up on routine liver function tests. I postulated that the syndrome did not occur until the liver had been hammered by high concentrations of PGs in the portal and lymphatic circulation from the gut.[22] I think that a similar mechanism is at work in psoriasis. Nonalcoholic fatty liver disease is present in 48% to 59% of psoriatics.[71] A study has shown that the severity of nonalcoholic fatty liver disease is associated with gut dysbiosis and shift in the metabolic function of the gut microbiota.[74,75] *Bacteroides* abundance was significantly increased in NASH and hepatic fibrosis patients, whereas *Prevotella*

abundance was decreased. *Ruminococcus* abundance was significantly higher in fibrosis patients. By multivariate analysis, *Bacteroides* abundance was independently associated with NASH and *Ruminococcus* with F≥2 fibrosis.[75] Several Russian studies have described abnormalities of the liver and bile in psoriatics.[45,46] Two hundred and thirteen psoriatics were examined and disease of the liver or bile ducts was diagnosed in 88.[45] In another study, the bile of 67 psoriatics was analyzed by intubation of the duodenum. Twenty-eight of these patients were psoriatics, who had previously been diagnosed with hepatobiliary system disorders. Thirty-nine psoriatics studied had no history of liver problems. Both groups (compared with 15 controls) had significant reduction of bile acid levels in the bile.[45] Fifty Russian psoriatic patients were examined for the presence of circulating bile acids, and they had levels 10 to 20 times normal. The circulating bile acid levels correlated with disease severity and stability.[45] Studies of bile lithogenicity showed that levels of bile acids and phospholipids were significantly decreased in psoriatics. Their lithogenic indices were 2 to 4 times increased over nonpsoriatic controls.[45]

Treatment

Alter the bowel flora toward normal

Treatment of psoriasis begins with altering the bowel flora toward normal. American gastroenterologists don't believe in testing for *Blastocystis hominis*, but they do believe in *H pylori*. If either of these organisms are present, the patient's psoriatic plaques will itch. If itching is present I will test for and treat *H pylori*. *B hominis* can be occult. It is known to produce intestinal inflammation, arthritic clinical manifestations, fatigue, flatulence, and abnormal bowel habits.[47] It can be successfully treated with the probiotic *Saccharomyces boulardii* given by mouth daily for 2 months.[76] This yeast is resistant to antibiotics and can eliminate the toxin of *Clostridium difficile* by production of a protease that cleaves *C difficile* toxin A. It also stabilizes barrier function and strengthens enterocyte tight junctions, restores to normal levels colonic short chain fatty acids (SCFAs), and inhibits TNF production in the gut.[76]*Lactobacillus rhamnosus* was mentioned in the section on alcohol as beneficial to the alcoholic microbiome. This probiotic is readily available over the counter and I suggest that it may have benefit in psoriasis as well.

Azithromycin has been used to successfully treat psoriasis.[77] I like to start with 4 months of this given as 500 mg for 4 days with a 10-day rest before the next 4-day course, or clarithromycin 250 mg/day for 4 months. These antibiotics will eliminate *S pyogenes* but will not significantly alter gram-negative coliform bacteria or anaerobes. *S boulardii* is always given along with antibiotic therapy.

Sulfasalazine will markedly improve 40% of psoriatics who are treated with this drug alone.[78] Sulfasalazine inhibits TNF binding to its receptor[79] and inhibits nuclear factor kappa B.[80] Interestingly, both inflammatory cytokines are also inhibited by *S boulardii*.[76]

Break up endotoxin with bile acids

In a study by Hungarian authors,[81] the common bile ducts of rats were cannulated and the rats were fed lipopolysaccharide (LPS) (endotoxin). The bile-deprived rats all died, and radio-labeled LPS was found in their blood. If the rats were given the bile acid sodium deoxycholate with oral LPS, they all lived and no LPS could be found in their blood. The authors concluded that the bile acid broke up endotoxin in the gut and prevented its absorption. Bile acids also prevent bacterial translocation to mesenteric lymph nodes.[82]

Dr. Bertok then went on to study Hungarian patients with psoriasis, whom he treated with bile acid therapy.[83] In this seminal study, the authors stated that "Under normal conditions the bile acids act as detergents (physico-chemical defense) and can protect the body against enteric endotoxins by splitting them into nontoxic fragments and thus preventing the consequent release of cytokines." Their thesis was that psoriatics had bile deficiency (as previously shown in Russian studies). These authors studied 800 psoriatics and 500 were treated with dehydrocholic acid for 1 to 8 weeks. Of those treated, 434 became asymptomatic (78.8%). Of the 249 patients who received conventional therapy, only 62 (24.9%) showed clinical recovery over the same time frame. Two years later, 319 of 551 patients treated with bile acids (57.9%) were asymptomatic. The authors stated, "The actual results of the present study are even better than now reported, although it cannot be determined precisely, as many patients (n = 73) did not come back for checkup examination after they had gotten better. From incidental information received from such patients' relatives or acquaintances sent to us for treatment we learned that the patients themselves had now been symptom free."[83]

Both groups of patients in the Hungarian study were advised to avoid hot spices (pepper, red pepper, horseradish, bay leaf, etc), alcohol, raw onion, garlic, and carbonated soft drinks. They were also recommended to eat a high-fiber (vegetables, fruits, etc), low-meat, low-fat diet. These recommendations would obviously push the gut microbiome toward health and reduce absorption of endotoxin even if bile acids were not given. The role of alcohol and endotoxin absorption has been discussed, but pepper has not. Even small amounts of pepper will markedly alter a D-xylose absorption test, indicating intestinal leakage. "Bioperine" is added to many poorly absorbable phytonutrients such as curcumin to increase absorption. Bioperine is another name for black pepper. I was unaware garlic, onions, bay leaf, and carbonated soft drinks also favor endotoxin absorption, but I am not going to argue with success. I tell my patients absolutely no alcohol or anything that tastes hot on the tongue, and I mention carbonated drinks as well.

A study reported about Japanese patients who were treated for psoriasis-associated nonalcoholic fatty liver disease with

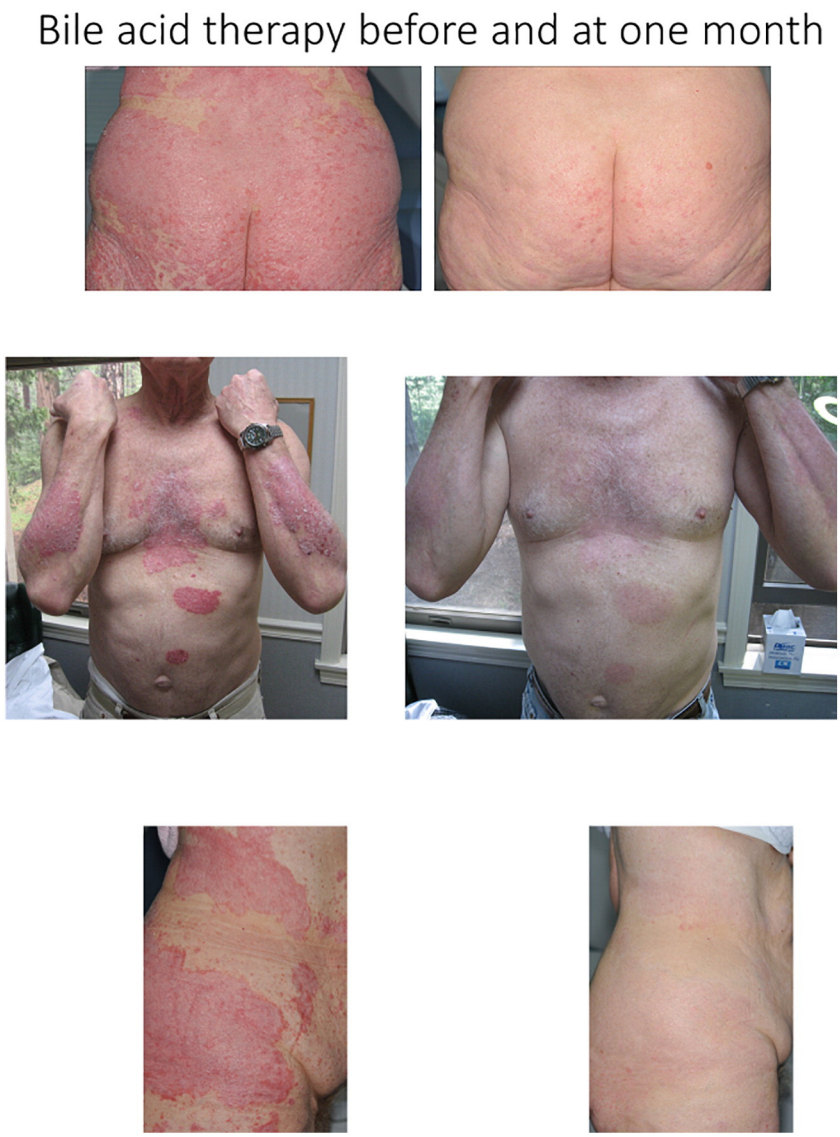

Fig. 4 Before-and-after photos of patients undertaking bile acid therapy.

ursodeoxycholic acid (UDCA). Their psoriatic skin lesions "dramatically resolved."[84] They did not make the connection between bile acid ingestion and endotoxin destruction in the gut. Their conclusion was that UDCA suppressed elevated phospholipase A2 activity in the skin as its mechanism of action.

I have treated numerous psoriatics with bile acid therapy and its associated diet with incredible results (Figure 4). I have used several over-the-counter (OTC) products (no financial interest [NFI] in any). "Bile acid factors" by Jarrow Formulas contains 1000 mg total bile acids per capsule (from bovine/ovine bile concentrate) and Ox bile from Allergy Research Group which comes in 500 and 125 mg capsules. Both are available online and OTC. The only side effect has been mild diarrhea, and so I start with the lowest concentration and have the patient take one capsule each time he/she eats. The dose can be increased as tolerated.

Inhibit absorption of endotoxin with bioflavonoids (and inhibit phosphoryl kinase)

In the "McDonald's study" mentioned at the beginning of this essay, it was shown that orange juice taken with a high-calorie, high-fat meal prevented the rise in circulating endotoxin levels[26] caused by ingestion of emulsified lipids.[85] Other studies have shown the same effect of orange juice on endotoxin absorption,[86] and bioflavonoids have been shown to inhibit the absorption of endotoxin and prevent the metabolic syndrome,[87,88] especially quercetin.[89,90]

Quercetin is the "backbone" for other bioflavonoids such as rutin, hesperidin, naringin, and tangeriten. It is a potent antioxidant, anti-inflammatory agent. It inhibits the manufacture and release of histamine and inhibits collagenase. It inhibits intestinal absorption of endotoxin by its action on tight junctions in intestinal epithelium. It is also a potent phosphodiesterase

inhibitor.[91–93] Aminophylline has been used to treat psoriasis,[94] and more recently, the phosphodiesterase inhibitor apremelast has come to market. I mention these to show that quercetin gives a "twofer" in treating psoriasis, and if one considers its ability to inhibit phosphoryl kinase, we may have a "threefer." Phosphoryl kinases are associated with tissue growth. The development of specific inhibitors against the kinases may be beneficial in the treatment of proliferative diseases.[95–100]

Madeline Heng, Camarillo, CA, has written several papers on the effect of elevated phosphoryl kinase in psoriatic epidermis[101,102] and has shown that it can be suppressed by topically applied curcumin.[101,102] Curcumin, however, is very difficult to absorb,[103] and a number of commercial products containing "bioperine" (black pepper) have been promoted to increase its absorption. Unfortunately, this also increases endotoxin absorption. The best OTC curcumin products (NFI) contain "Meriva." This is a curcumin compounded with soy lecithin in a liposomal form that markedly improves absorption. It has been used to treat psoriasis with very favorable results.[104] Curcumin is a great adjunct to psoriasis therapy, but quercetin has many of the same effects and inhibits endotoxin absorption. As a result, I would recommend quercetin over curcumin, but both in combination are even better.

Healing the liver

Psoriasis may not occur until the liver is overwhelmed by gut-derived PGs and endotoxin. One of the best agents to heal the liver is silymarin, a compound present in the seeds of milk thistle.[105] There are many products on the OTC market, but one I have found most efficacious, compared with other forms of silymarin, is "Legalon," manufactured by Madeus in Germany. This product also effectively treats porphyria cutanea tarda.[105] None of the other OTC forms of silymarin I have tried proved to be efficacious. This same product is now sold in the United States as "Thisilyn" in 140 mg capsules (NFI). Chronic hepatitis C patients may also be helped with oral silymarin and ursadeoxycholic acid.[104] Silymarin alone improves liver function.[106–108]

Conclusions

Anyone on a high-fat, high-calorie (Western) diet has low-grade endotoxemia, which causes the metabolic syndrome, and obesity. The higher levels of endotoxemia associated with psoriasis, alcoholism, and hepatitis C surely cause the comorbidities of these conditions. There may be an underlying genetic predisposition in psoriatic individuals to eliminate bacterial antigens through the skin, a cathartic event whereby increased epidermal turnover sheds scales full of bacterial byproducts. The microbiome of patients with chronic fatigue syndrome has been studied extensively. Researchers can look at the characteristic pattern of bacteria in fecal samples and identify patients with this disease from the pattern detected.[109] The psoriatic gut microbiome has not been studied in this manner but needs to be. It is possible that dietary manipulation of the microbiome can treat psoriasis and its comorbidities.[87,110,111]

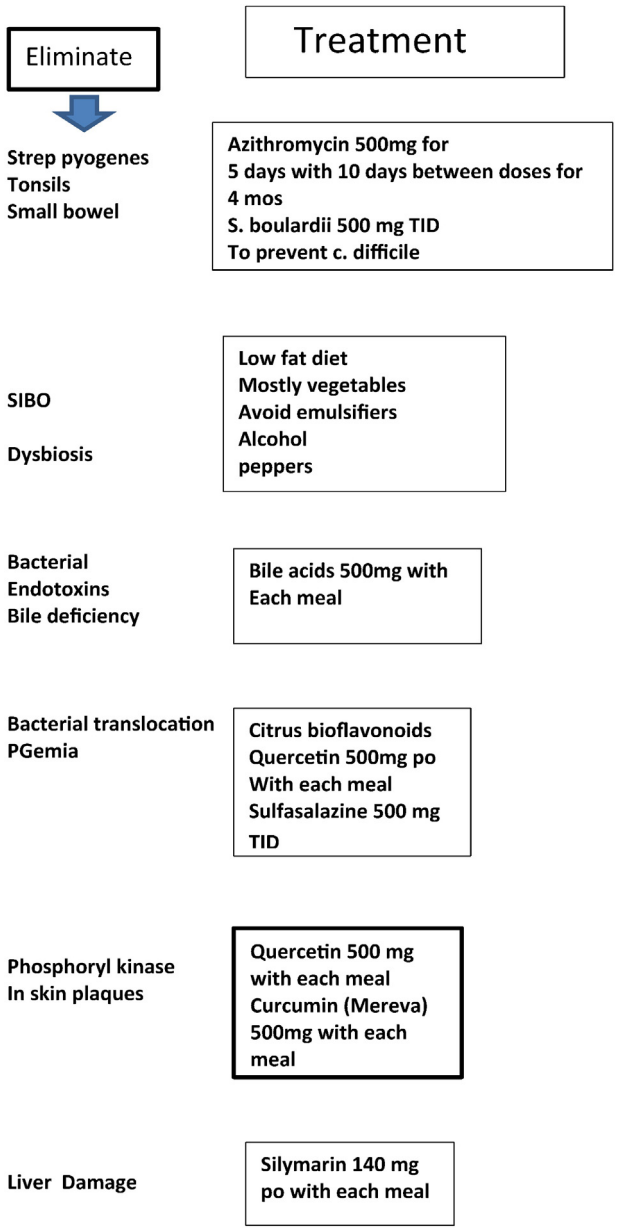

Fig. 5 Treatment algorithm. SIBO, small intestinal bacterial overgrowth.

Using the methods outlined here, psoriasis can be converted from "a career" to an inconvenience that is curable. The problem with using the therapies recommended is that most psoriatics have given up and are depressed. This therapy requires no alcohol, a diet shifted toward vegetarian, and a cereal bowl full of pills every day for 3 months or more. It is work. I recommend weekly visits and hand holding with encouragement and support, while the patients undergo this regimen. I have seen numerous patients "cured" of their psoriasis.

A treatment algorithm that summarizes this essay is presented as Figure 5.

Addendum

Since this manuscript was accepted for publication, a new publication has appeared about the psoriatic microbiome.[112]

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