January 2005 Issue | Stephen E. Chiarello, MD

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Welcome to *Functional Medicine Update* for January 2005. It is the beginning of another New Year, one that heralds the 24th anniversary of FMU. Thanks to all of you who have been with us over the years. For those of you who may be new to FMU, we hope you will find it an enjoyable and helpful tool in the development of your practice and in the management of patients with complex, chronic disease.

Functional Dermatology

In this issue, we are going to focus on a new topic functional dermatology. This subject derives nicely from the December 2004 issue of FMU, which focused on gastrointestinal (GI) immune system function and its relationship to pre- and probiotics. Our interview with Dr. Mary Ellen Sanders helped us to understand much more about the usefulness of various species and strains of bacteria that favorably influence gut immune function.

We are fortunate to have a skilled physician for this month's Clinician/Researcher of the Month interview. Dr. Stephen Chiarello, an internist, and dermatologist will be speaking about his years of clinical experience using integrative/functional medicine. I am going to lay the groundwork for the interview by talking about functional dermatology. The skin is part of the messaging system for the body's immune function. Therefore, imbalances of immune function are often reflected as dermatological conditions.

12th Annual Symposium on Functional Medicine

I have a reason for selecting functional dermatology as this month's topic. The 12thInternational Symposium on Functional Medicine will focus on The Immune System Under Siege: New Clinical Approaches to Immunological Imbalances in the 21st Century. In preparation for the symposium, it seems appropriate to start off the year by talking about ways of clinically assessing immunological imbalances, beginning with the skin. If we know how to read the skin, it may lead us to a better understanding of where certain immune system imbalances originate.

The 12th Annual Symposium on Functional Medicine will be held May 24-28 in Palm Springs, California, at the four-star Westin Mission Hills Resort. I believe it will be one of our most interesting symposia as it relates to integration of the plenary sessions and workshops. We have scheduled a remarkable group of clinicians and researchers who will address immune system challenges that confront our society, their manifestations in terms of certain diseases, and their amelioration using integrative and functional medicine approaches.

There will be two pre-conference courses at the symposium. The first has received rave reviews from past participantsDynamics of Practice Management for the Functional Medicine Clinic, to be held on Tuesday,

May 24. The second pre-course will be held on Wednesday, May 25--Understanding Immune Modulation from the Thymus Dependent-1/Thymus Dependent-2 Perspective. This course is designed to prepare attendees for subsequent information they will receive at the plenary sessions and workshops. We hope you will join us.

Let me return to functional dermatology and discuss using the skin as a marker, a clinical observation point, for imbalances in the immune system. The epithelial tissue shares a common origin across the variety of different tissues in the body, including the gut mucosa, the lining of the eyes, the tongue, the skin, the gingiva of the mouth and periodontal tissue, and the lung mucosa. All of these are similar in some physiology and embryological origin. Where do the skin's immune messages come from? What triggers some of the inflammatory processes that result in adverse dermatological conditions?

The GALT as the Seat of the Immune System

Part of the story goes back to the seat of the immune system, the gastrointestinal-associated lymphoid tissue (GALT). We talked about the GALT at some length in the December 2004 issue of FMU. The gut may be the triggering tool for various types of immunological dysfunction, but it is not the only site of origin. Airborne allergens trigger immunological dysfunction, as well as various types of infections and ischemic events. There are multiple triggers that can initiate immune imbalance, but we should always keep the GALT in mind when looking at dermatological problems. In fact, the skin is the reflecting pond of the state of the immune system in the body at large.

We need only go through the litany of different dermatological conditions to see the strength of their connections to immunological imbalance, beginning with the most dramatic immune dysfunction of the late 20th century HIV infection. As we age, we may experience increasing levels of skin-related dysfunctions from opportunistic infections, ranging from thrush to various types of skin cancers. Certain autoimmune diseases lead to dermatological conditions, such as scleroderma, myasthenia gravis, or various types of psoriatic arthritis. Conditions related to food allergy, mediated through gut response membrane-binding receptivity, are also associated with skin inflammation, such as urticaria.

Responses to certain xenobiotic drugs that can initiate the immune system include rashes, hives, or certain other dermatological conditions. There are conditions associated with dysbiosis that accompany atopy in infants and children, e.g., colic and eczema. In cutting across the full range of the medical lexicon and looking at conditions that are often associated with imbalanced immune system function, there are dermatological signs that reflect an interrelationship between those conditions. The skin is an important reflecting pond that can be used for measuring immunological status.

If you did not fully believe that before, you will now, in view of the emergence of new mechanisms related to various skin disorders. Take psoriasis, for example. Psoriasis is a fairly severe skin condition involving flaking, plating, and exfoliation of the skin, with potential for infection. The physiological mechanism that initiates psoriasis is not well understood. It has only begun to emerge over the past ten years. This has culminated recently in a series of interesting papers in The New England Journal of Medicine that set the tone for what we are going to be talking about in this month's issue of FMU.

Immunologic Targets in Psoriasis

A recent article appeared in The New England Journal of Medicine, titled "Immunologic Targets in Psoriasis."1 I want to discuss this article in some detail. If you have been following FMU for some time, and are aware of what is happening in the field of immunology, you will hear some familiar terms. In this

article, the authors discuss two new studies describing the positive clinical effect of drugs that were historically used for the management of arthritis, but have now been found to be useful in the treatment of psoriasis, suggesting there may be a common etiological factor associated with arthritis and psoriasis. Both of these conditions have immunological modulators. They may share common triggering effects or mediators which, depending upon the tissue, produce differing symptoms, but both involve inflammatory processes.

These drugs, etanercept andefalizumab,modify the expression of various types of proinflammatory cytokines, such as tumor necrosis factor alpha (TNFa) or the aLb2 integrin, also known as leukocyte-function-associated antigen 1 (LFA-1). LFA-1 is important in the process by which T cells cross blood-vessel walls, enter tissue, and are subsequently activated by antigens. This implicates some kind of allergy-potentiating effect that might act as a trigger. If giving a drug that impedes integrin (e.g., movement of lymphocytes) can block psoriasis, this means the signaling process is being blocked, an interaction between the lymphocyte and an antigen. It's important to note that the antigen might come from a variety of sources, including food.

It is interesting to note that etanercept and efalizumab work by different mechanisms, but both drugs have been shown in separate clinical studies to have positive benefit on the remediation of psoriasis symptoms. Because they both treat inflammation from different perspectives, a mechanism seems to be the underlying cause. That is, they may target the same mechanism, even if they work at different places within that mechanism leading to inflammation triggered at the site of the skin. In addition, these drugs have been approved by the FDA for use in the treatment of arthritis, suggesting that there is a common mechanism associated with these inflammatory conditions (e.g., skin inflammation, psoriasis, and arthritis).

These drugs have demonstrated efficacy in rheumatoid arthritis and inflammatory bowel disease (IBD), as well as psoriatic arthritis. There are additional anecdotal reports of their efficacy in immune and inflammatory diseases. There are now published papers indicating their value in the treatment of psoriasis. There are a variety of different medical specialties, all of which could call these drugs their ownrheumatologists, gastroenterologists, and dermatologists. Perhaps the drugs know no medical specialty. Perhaps they interact with a mechanism of inflammation. Regarding how these inflammatory conditions specifically interrelate with dermatological problems, it is necessary to take a step back into understanding how biologic agents work. Let us look at LFA-1 and TNFa as they relate to the immunological features of the skin.

"Skin is endowed with special features that protect it from injury or infection, and a limited number of factors, including the cytokine TNF-a, transmit danger signals from injured tissue to the immune system. The release of TNF-a from cells in the skin induces the production of other cytokines and chemokines and modifies endothelial surfaces in cutaneous postcapillary venules, facilitating the extravasation of leukocytes."1

Barrier function is lost, there is a leaky membrane, and white cells cross that barrier.

"These leukocytes exit vessels and enter the dermis through a multistep process involving several molecules, including LFA-1. Leukocytes are then attracted along chemotactic gradients and can begin to mediate effector functions, such as the killing of pathogenic bacteria or fungi."1

The useful purpose of this inflammatory process is to quench infection that could ultimately cause injury. As in any immunological imbalance, when the inflammation is over-activated, a friendly process in the host can become an injurious process, leading to a psoriatic condition.

"One of the prominent effector molecules produced by these infiltrating leukocytes is TNF-a. Fundamentally, this process is a form of immunosurveillance of body surfaces for danger signals, a phylogenetically ancient process that is central to innate immunity."1

This process can be activated by signals coming through the bloodstream that potentiate the skin's sensitivity to environmental stimuli. There are internal as well as external stimuli that increase the relative activation of this process and can participate in immune imbalance, which becomes like a dog chasing its tail, perpetuating inflammation of the skin.

"Adaptive immunosurveillance is the domain of T cells. Each T cell has a different specificity for antigen conferred by its unique T-cell receptor, and getting the right T cell to the right place at the right time is a major logistic challenge for the immune system. This puzzle is solved by the specific migration patterns of different subgroups of T cells."1

This is where we begin naming various types of T cells as sub-populations.

"Naive T cells shuttle between blood and lymph nodesa process that is dependent on LFA-1. Once in lymph nodes, these T cells mingle with dendritic cells that have recently migrated through the lymphatics from the peripheral tissue. These dendritic cells have left the peripheral tissue because danger signals (such as TNF-a) induced their migration and maturation, and they are uniquely powerful activators of T cells that bear the correct receptor antigens they have internalized."1

Now, there is a potentiated system with increased proinflammatory potential. The Th1/Th2 balance is shifted toward a higher level of inflammatory mediators being produced.

"When they are thus activated, nave T cells divide and multiply, express new molecules on their surface, and are instructed to become effector memory T cells. This immunologic memory extends to the anatomical location, so that a T cell that is educated in a skin-draining lymph node will express molecules that facilitate its subsequent entry into skin..."1

This ties into what is also occurring on the mucosal surfaces in the gut and activation of the GALT. This is a similar argument to one we could imply for gut lymphoid epithelial cells, as well as those of the skin itself, again showing the connection between gut and skin.

"The pathologic release of TNF-a and other cytokines strongly up-regulates the expression of endothelial E-selectin and ICAM-1, as well as chemokines, on the luminal aspect of the skin vessels..."1

The newly expressed molecules circulating in the skin can more efficiently enter through the vascular bed and begin to initiate the perpetuation of the inflammatory process. Recruitment begins, resulting in a concentration of immune cells at the site of the presumed injury or inflammation, which perpetuates the problem. Overly activated TNF-a contributes to the orchestration of inflammation that continues to be seen as chronic psoriasis. This process is self-perpetuating and is reversible only when the activation of T

cells within the lesion is blocked. That is the nature of how immune-modulating drugs have had some success in the treatment of psoriasis or arthritis. They block various steps along the production process for the inflammatory mediators.

Given the activity of these molecules, it is not surprising that blocking with LFA-1 or TNF-a has therapeutic effects in psoriasis. This is also true in IBD or arthritis because they share common mechanisms. The mechanisms of the perpetuation of immune imbalance are being interrupted. Most therapies currently available for psoriasis have dose-limiting toxic effects, which seems to be the problem with using some of these medications.

Are there things one can do from an environmental standpoint, or by harnessing functional and integrative dermatology, to manage these inflammatory conditions? We are starting to witness the emergence of functional dermatology from a mechanistic perspective, built on environmental modulators of the inflammatory system specific to the epithelial surfaces.

Catabolic/Anabolic Balance

I have been speaking to the concept of proinflammatory mediators, the cell types they are derived from, and how they are perpetuated. In general, these proinflammatory cytokines are catabolic mediators. They are the same players we associate with other kinds of infectious conditions and malignancies associated with cachexia, muscle loss and, in extreme cases, wasting disorders. It depends upon the place of residence or production of these mediators and the levels that encounter different kinds of physiological shifts in the catabolic/anabolic balance. In general, the higher the production level of proinflammatory mediators, the more catabolic the shift in physiology. In more extreme cases, imbalance of Th1 and Th2 immune system function may be associated with alteration in the catabolic/anabolic balance, shifting toward anabolism, which includes muscle-wasting, cachexia, and many other things we see in acute disorders. It is a question of degree, whether acute or chronic, and where the patient resides on that continuum of events. The skin is a barometer of some aspects of the balance related to Th1/Th2 activity.

Treatment Strategies

How does one evaluate what type of therapy to use and where to intervene in individuals with psoriasis or problems related to inflammation imbalance in epithelial tissue? We would use the same approach we alluded to in the December 2004 issue of FMU--try to rebalance the immune system. Start with the GALT, move out to the peripheral lymphocytes and to liver-related immune function as encoded through the Kupffer cells (the embedded white cells in the liver), and try to find specific ways of reestablishing immune function balance in those tissues. Clearly, if there is a full-blown state of inflammation in any one of these epithelial tissues, there are drugs derived from clonal biotech procedures for blocking certain aspects of the inflammatory cascadethe TNF-a or LF-1-blocking agents. But in the case of chronic inflammation, it may be best to utilize environmental and functional intervention first. These drugs, if we were to use them too early as treatment modalities, might have potential adverse side effects. Because of their strength in blocking the inflammatory cycle, they may also block the ability of the immune system to function. Inflammation processes occur for a reason, that being to help defend against infection and other things associated with transformed cells that may become malignant. If that function is too greatly suppressed, there is risk of opportunistic infection due to a suppressed immune system, or perhaps secondary malignancy.

Proinflammatory mediators such as TNF-α and IL-1 participate in breakdown of local tissue. They create

a catabolic shift in metabolism. Therefore, if there is a Th1/Th2 imbalance and activation, there may also be an anabolic/catabolic imbalance, leading to poor tissue integrity. In inflammation, there is a breakdown in the integrity of the skin. We have often talked about "leaky gut syndrome". One can have "leaky skin syndrome", as well, as a consequence of an inflammatory process that leads to the breakdown of the skin's barrier defense against bacteria and exogenous toxins that might have access to the body.

I am now quoting from an interesting paper that appeared in *Current Opinion in Clinical Nutrition and Metabolic Care* that discusses the role of proinflammatory cytokines and how they participate as catabolic mediators in the breakdown of tissue integrity.[2] The gut mucosa, the skin, the blood brain barrier, or the pulmonary epithelia, when subjected to high levels of catabolic proinflammatory mediators, all lose their integrity. They become "leaky"; they become penetrable to larger molecular weight substances. That creates a secondary set of conditions that leads to dysfunctions in those particular areas.

An interesting report appeared in *The New England Journal of Medicine*, titled "Treatment of Skin Papillomas with Topical α-Lactalbumin-Oleic Acid.".[3] Alpha-lactalbumin is an immunologically-active milk protein. Investigators developed a specific α-lactalbumin-oleic acid (found in olive oil) complex and tested this in a trial on skin papillomas. They found this specific complex resulted in beneficial and lasting effects on skin papillomas. How does this work? That is an interesting question. This was a double-blind, placebo-controlled trial with 40 patients in which α-lactalbumin-oleic acid or saline placebo was applied daily for three weeks. The second phase involved an open-label trial of another three-week course of α-lactalbumin-oleic acid. Two years after the end of the open-label phase of the study, 38 of the original 40 patients were examined, and long-term follow-up data were obtained. In the first phase of the study, the lesion volume was reduced by 75 percent or more in all 20 patients in the α-lactalbumin-oleic group, and in 88 of 92 papillomas. In the placebo group, a similar effect was seen in only three of 20 patients. From these observations, let us see if we can understand something about the immune system of the epithelium.

"Cutaneous viral warts are common, benign, usually self-limited papillomas with a preference for the hands and feet. A wide variety of local therapies based on destruction, keratolysis, immunostimulation, or antimitotic effects have been tried for the treatment of cutaneous warts, but most of the clinical trials of these local treatments have been of low quality."[4]

A recent report revealed that simple preparations containing salicylic acid are the only topical treatments for which there is good evidence of efficacy and safety. However, in the paper in*The New England Journal of Medicine*, utilizing a topical application of α-lactalbumin-oleic acid on cutaneous viral warts resulted in a significant treatment effect.

There is something about this particular type of protein. What does it do?

"The protein lipid complex travels through the cytoplasm to the nucleus, where it binds with high affinity to the histones and nucleosomes of transformed cells. Interaction of the complex with histones and chromatin in the nuclei of the transformed cells prevents transcription, cell replication, and chromosomal recombination and causes disruption of the chromatin structure and fragmentation of DNA. Healthy, differentiated cells, in contrast, survive challenge with α-lactalbumin-oleic acid and show no apoptotic changes, making the substance rather specific for transformed cells."[4] The cells have gone through some kind of transformation as a consequence of a viral infection. This story relates to human papilloma virus

(HPV) and some of the relative risk factors it has to female cancers.

"HPV plays a key role in the development not only of cutaneous warts, but also of laryngeal papillomas, genital warts, vulvar intraepithelial neoplasia, cervical carcinoma and possibly cutaneous squamous-cell carcinoma. To date, more than 90 types of HPV have been identified and their genomes sequenced. More than 100 additional partially sequenced isolates require further characterization."[4] This is a highly intragenus class of viruses associated with these infections.

"HPVs may be classified on the basis of their tropism as either genital (mucosal) or cutaneous. Genital HPVs are subdivided into high-risk and low-risk types, according to their malignant potential and cell-transforming capacity in vitro. The cutaneous HPVs may be subdivided into the classic types associated with cutaneous viral warts such as verruca vulgaris and verruca plantaris (the lesions treated by Gustafsson et al.) and the so-called epidermodysplasia verruciformis types.

"Numerous hyperkeratotic skin lesions and actinic keratoses develop in organ-transplant recipients, and these lesions have a strong potential to evolve into cutaneous squamous-cell carcinoma."[4]

This is tied to UV radiation exposure and sun-damaged skin, a separate category from HPV viral infections or warts. Yet, they share common mechanisms relating to DNA injury, whether viral-induced injury or induction by ionizing UV radiation. Would there be a similar effect on anti-transformation with the α-lactalbumin-oleic acid complex on skin-induced cutaneous lesions as there is on HPV viral infections like warts? By mechanism, there is some argument that it may be anti-transforming in both cases.

The hair follicle is a possible reservoir for the epidermodysplasia verruciformis types of HPV. In an immune-compromised or immune-altered situation, the virus starts to proliferate and injures and transforms cells. The α-lactalbumin-oleic acid complex appears to have an interesting effect on modifying transformed cells through an immunological mechanism associated with apoptosis, or cell death, of the transformed cell, leaving the host cell completely untouched. Here is an immunological-specific, environmental agent that seems to work only through regulation of transformed cells, i.e., it becomes a chemotherapeutic agent by recruiting the immune system cells and altering the physiology of the transformed cell in such a way that it undergoes cell death, or apoptosis. This is a remarkable part of the story. A milk protein given in a specific complex with a fatty acid can induce a positive effect when given topically on an epithelial surface that is transformed by a virus, or perhaps transformed by UV radiation injury.

What about all the gut epithelial tissue constantly being exposed to some 50 tons of food that is put into our mouths over the course of a lifetime? What information do those food particles and fragments impart to receptor sites of our immune system on the surface of the gut epithelium? That is a question which has not yet been fully answered, but which is certainly at the core of functional medicine thinking. There may be molecules from food that turn on proper immune function and serve as activators of immunosurveillance, and there may be those that turn off surveillance, or that activate specific immunological vigilance associated with inflammation. These may occur at the same time, depending upon individual genetic uniqueness. The food of one can be the poison of another, which comes back to the concept of food allergy and inflammation.

The paper on the use of topical α-lactalbumin-oleic acid for the treatment of skin papillomas is more interesting from a fundamental mechanism perspective than it might seem. It begins with a discussion about cell/cell interaction, surface effects on membrane receptors, and the difference between a transformed cell that has undergone immunological alteration versus a host cell. The discussion evolves to how cells respond to these messages, and how the immune system may be recruited into recognizing that there is a foreigner on board and excising it before it has a chance to do injury. This information may lead to new therapeutic tools that can be used for restoring Th1/Th2 immune balance so as to take charge of foreign or transformed cells that create injury while, at the same time, not upregulating and perpetuating inflammatory disorders. The inflammation needs to be localized and controlled, leading to cellular apoptosis and death, and to be quenched and regulated. The process of clonal growth and decline of immune cells is dependent upon the regulation of the Th1/Th2 immune system.

The inflammation and immune-recognition process I have been describing relates to an balance between Th1/Th2 lymphoycytes and their function, which is both mediated by and responsive to the states of oxidative chemistry in the tissue. If there is a shift in the inflammatory state by increased production of TNFα and IL-1, there is also a shift in the redox potential of that tissue, leading to a higher state of oxidation.

More reactive oxygen species (ROS) are produced during times of immunological upregulation and inflammatory processes. The recognition that oxidants are part of the microbicidal killing process and serve a useful role, is an important part of the developing understanding of the mechanism by which the immune system works. In the same way that anything good at one level may be bad at too high a level, that is the case with oxidants produced during times of inflammation activity. ROS at one level can be a friend to the normal body defense system, but at a higher level, when activated in the skin or gut epithelium and perpetuating a chronic long-term state, can become destructive. That has recently been described in a review in *Free Radical Biology & Medicine*.[5] The author discusses reactive oxygen species in the immune response and how they interrelate to tissue activity and integrity of the immune system, but also tissue injury upon excessive upregulation.

The process of tissue-specific inflammation occurs as a consequence of upstream regulation through nuclear factor regulations, such as nuclear factor *kappa* B (NFκB). NFκB is one of the nuclear regulatory factors released in the cytoplasm from its inhibitor kappa B (IκB) by activation of a phosphorylating enzyme called inhibitor *kappa* B kinase (IκK). This kinase enzyme phosphorylates the inhibitor, and the inhibitor falls off the NFκB subunits. That allows the NFκB to move from the cytoplasm of the cell to the nucleus, where it sits on the regulatory portion of genes and facilitates the expression of 100 or more inflammatory signals, some of which regulate the production of TNF-α, IL-1, and other inflammatory mediators.[6] The activation of NFκB is a tissue-specific process that relates to a specific host tissue. We do not usually talk about generalized inflammation. We talk about tissue-specific inflammation mediated through activation of NFκB that comes from upstream messages delivered to the cell. Those messages could be things such as bacterial wall cell debris like lipopolysaccharides (LPS), or inflammatory cytokines produced by another tissue at a distanceparacrine effects that initiate the release of NFκB in the cytoplasm so it can travel to the nucleus.

This begins a multiplication effect that occurs when the oxidative inflammatory storm begins. It may be seen on the skin, but it may have originated somewhere else as a low-grade chronic inflammation, perhaps in the gut or the liver. There are other interrelated processes. It may be localized on the skin as a

consequence of a wound, injury, or infection. When the skin is inflamed, we think of oxidative stress, catabolic shift, proinflammatory mediators, and imbalance of Th1/Th2. Where else in the body does inflammation reside? Is it solely linked to the skin, or are there other things of low-grade inflammatory potential going on at the lymph nodes, the GALT, in the circulating white cells, or at the hepatic level?

There are a variety of nutrition modulators being observed for these processes, including the amino acid L-arginine, which affects lymphocyte phenotypes of the GALT and which can help regulate the balance of inflammation. There are some good studies being published on the use of supplementary L-arginine for immune balance in the gut. One of these papers appeared in the *Journal of Parenteral and Enteral Nutrition*.[7]

Omega-3 Fatty Acids and Gut/Skin Inflammation
Omega-3 fatty acids also play an important role in regulating NFκB and the proinflammatory condition, which has been associated with not only the management of the gut, but also of the skin. There are clinical studies utilizing gram doses of omega-3 fatty acids for management of both gut and skin inflammation, again showing common mechanisms.

I hope I have left you with some interesting thoughts about the interrelationship of inflammation to clinical conditions in which the skin may be seen as a reflection of imbalance in the immune system. Let's move to the discussion with our Clinician/Researcher of the Month.

INTERVIEW TRANSCRIPT

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JB: It's time for our Clinician/Researcher of the Month. We are pleased and privileged to have Dr. Stephen Chiarello, who comes to us with a broad range of experience in the field of integrative/functional dermatology. Dr. Chiarello practices at the Dermatology and Skin Cancer Center in Port Charlotte, Florida. In speaking with him and reading the information he passes out to his patients, I can see why he is not only a successful physician, but a successful person. He puts his patients first, and has an innovative way of communicating with them in the mutual development of treatment programs.

It's a great pleasure to have you with us on FMU, Dr. Chiarello. I would like to begin by asking how your career led you into the area of integrative and functional dermatology?

Dermatology versus Internal Medicine
SC: I am a Board-certified dermatologist, as well as a Board-certified internist. That has helped me a lot. In my dermatology days at Dartmouth, I was constantly at loggerheads about practicing dermatology versus practicing internal medicine. I kept shaking my head and thinking, well, aren't they both the same? Aren't they all connected? And they certainly are. You have shown us how everything in the body is connected. I love your statement about the skin being the gut, the gut being the brain, the brain being the skin, and so on. They're all connected.

The thing that pushed me into an integrative/functional approach to medicine was my patients. Our

patients are the most important aspect of our practices. Obviously, we're trying to alleviate problems they present with. Being a specialist, it's easy to truncate their problems, put them in a box, spit out some kind of preconceived notion, hand them a pill or a cream, and send them on their way. But if we truly want to solve our patient's problems, we have to look at them from an integrative/functional point of view. We have no choice.

What got me into this field was my desire to make a difference in terms of patient outcomes and not use a band aid approach. I often ask my patients if they want a fish so they can have a meal that day, or do they want me to teach them how to fish so they don't have to come back and see me, and can take care of the problem themselves. Ultimately, my patients and their need to be treated are what pushed me into this field. Of course, I had the combination of both specialties to help me.

JB: Yes, it must be useful to see how different perspectives are woven together. Maybe that's often how people get channeled. Many doctors don't have the breadth of experience across different disciplines that you had in your training. I'm sure that helped you to make the connections and decide that diseases don't occur as isolated, independent units. Would you tell us about some conditions you often see that are amenable to an integrative/functional approach, and how they are different from the traditional perspective?

SC: A good example is one you have often alluded to and spoken eloquently aboutsyndrome X. I'm also a cosmetic surgeon, and I've developed a lot of different techniques for things such as cosmetic skin resurfacing and skin cancer removal. Syndrome X bridges both gaps. I see patients who want liposuction and I see patients with hirsutism. When I see patients on a daily basis, I check them from head to toe. That's something I have always done. If you don't look at the whole problem, I don't see how you can come up with the whole solution.

Syndrome X Symptomatology

What do I see in someone with syndrome X? For instance, there's hirsutism. Instead of just using my laser on a hirsute patient, I know there is likely something behind that condition. For instance, it's a tip-off for polycystic ovary disease in some women. Oftentimes, they are heavy with truncal obesity. They come in for liposuction. Yes, we can take their fat away, but we also create scenarios for them that help them get back to the real problem, the problem of lifestyle choices, or perhaps some genetic predisposition or predilection toward a particular condition. In these cases, it might be fat deposition or hirsutism.

Another part of syndrome X which is epidemic in many of my patients is skin tags. I see lots of them. These have also been associated (weakly, but more so than not), with underlying conditions such as malignancies, colon polyps, and acanthosis nigricans, a velvety appearance that occurs mostly in the axilla, but which can be seen in the neck. This is often found in patients with dysinsulinemia, high glucose, or high insulin levels. In a sense, their insulin results in growth hormones on the skin which produce skin tags. They produce acanthosis, an increase in the epidermal velvety appearance. Another common problem is folliculitis. We have both skinny and fat people with syndrome X.

Carbohydrate Pimples

I see lots of patients with carbohydrate pimples. Whether those pimples are driven by Candida (yeast overgrowth) or bacteria overgrowth, with immunosuppression caused by sugar overloading, I really don't know, but they are invariably there and are a great tip off for syndrome X. And of course, fat distribution

is important. These patients tend to have tinea versicolor, another indication of immunosuppression, as well as fungal infections. I could go on and on. To the extreme, patients might have xanthalasmas or anthomas.

Pattern Recognition

In doing a complete and comprehensive skin exam, you quickly pick up patterns. I have been pushing dermatologists for years to remember that pattern recognition is so important in what we do. In fact, that's true for any health professional. Pattern recognition is learned by looking at the whole and then developing, if you will, a library of ideas along with visualization that allows you to quickly get down to the problem later on. You become very good at what you do because you look and you see. Syndrome X is a wonderful example of that.

Psoriasis

Thirty to 50 percent of my patients have psoriasis, another common condition that is amenable to integrative/functional dermatology. Every patient with psoriasis is out of control and their lives are out of control. It might relate to stress, poor lifestyle choices, being overweight, poor food choices, not taking vitamins, or making poor health choices when it comes to exercise. These are stressed people who are inflamed. They may have a genetic predilection toward psoriasis, but what sets them off is the way they live. If you give them a cream or an injection, you can take care of the fish for that day, but if you create lifestyle changes for them, their bodies take care of themselves, and they return to a non-inflammatory state and a healthier equilibrium. It may not be exactly the equilibrium you want them to be at, but it's a healthier form of homeostasis, and it gives the body a chance to turn itself around and quiet the psoriasis. I cannot control psoriasis in patients who will not make healthy lifestyle choices.

The Paleolithic Diet and Adolescent Acne

JB: I'd like to come back for a moment to syndrome X. We had an interview on FMU earlier this year with Dr. Loren Cordain. He talked about the Paleo Diet. He and his colleagues had just published a paper on the Paleolithic Diet (a high, unrefined carbohydrate diet) and adolescent acne. Dr. Cordain's response to the study was that he felt almost all adolescent acne was a consequence of insulin and glucose dysregulation. When the appropriate diet for stabilizing insulin and glucose was used, the acne resolved. That sounds very reminiscent of what you've observed in your practice pertaining to syndrome X, hyperinsulinemia, and some other dermatological conditions. Do you see a connection between the two in your work?

Acne, Carbohydrate Restriction, and Stress Reduction

SC: I do. The studies originally done on the non-connection between sugar and acne were incorrect. They were studies based on calories and acne, after which they drew the conclusion that sugar was OK. One of Dr. Cordain's studies was a very small study, but an excellent one. I believe it was done with patients who lived on an island who had the healthier diets versus the poor diets that we're used to hearing about. I see this every day. Acne is inflammatory. If you look at acne under the microscope, it's pustular, and full of neutrophils and inflammatory content. Anything that helps to decrease inflammation will help to decrease the manifestations of the acne as well as a predilection for it. I put all my acne patients on carbohydrate restriction. I try to put them on healthy carbohydrates; that is, low glycemic index carbohydrates. I love berries. I try to have them stick with berries and I get them off the high glycemic index type of diet. I also encourage them to exercise. Exercise, of course, helps to regulate glucose and insulin. I also try to get them to learn and apply anti-stress mechanisms in their lives. Nobody can go through life without stress. I

try to teach them ways to anticipate their stress levels and turn them into constructive energy rather than the destructiveness that results in inflammation. I believe that if acne is not directly caused by dysinsulinism, it certainly can be terribly aggravated by that particular condition.

Acne and Antibiotics

JB: Let me propose a kind of "fun" hypothesis that I'd like to get your opinion on. Historically, in adolescents, acne has been treated by administering antibiotic therapy and that has a pretty good clinical effect in causing remission. It's always felt that the success of antibiotic treatment demonstrates that acne is caused by some kind of bacterial infection. Could it be possible that the real effect antibiotics have is mediated through the gut? Aren't we synthetically modifying gut flora in such a way that it alters immune function and reduces the inflammatory message from the gut, which has a systemic effect, in combination with the changing hormones of adolescence that influences the skin?

SC: Absolutely. That's thought to be one of mechanisms of how it might work. Tetracycline, in and of itself, is antiinflammatory. I use tetracycline in treating pemphigoid, for instance, which is a bullous immunological process. The tetracycline is antiinflammatory, and it may not be working at all in destroying "bacteria". Bacteria very quickly become desensitized from tetracycline. Tetracycline might be tagged as an anti-bacterial, but it is also very antiinflammatory.

Probiotics, Acne Rosacea, and H. Pylori

The question of dysbiosis and gut problems is also very intriguing. I put my patients on tetracycline if they have difficult acne, and it quiets down the inflammatory process. If I don't use tetracycline, I put them on a probiotic. I use one that has 15 billion bacteria and 16 strains. I tell the patient that acne is inflammatory, and there are certain bacteria in the gut that are very inflammatory and we want to replace them with healthy bacteria. This quiets down their immune system. It gets them back to homeostasis again, resulting in a non-inflammatory state. I see this a lot in my adult patients with acne rosacea. There have been a number of articles, pro and con, about the direct association between acne rosacea and H. pylori. The probiotics have been shown to crowd out the H. pylori in the gut and resolve some of the problems associated with H. pylori and ulcers. Probiotics also help to resolve H. pylori associated with acne rosacea, which is very inflammatory.

The Gut/Skin Connection

The gut/skin connection is profound. I like to think of the skin and the gut as contiguous. I consider that we are like sophisticated, mobile, coelenterates. The skin is the outside lining that protects us. That connects directly to all the mucosal elements of our bodythe gastrointestinal (GI) tract, eyes, lungs, and so forth. It's as if we're in an envelope and we filter food through its inter-aspects. Our envelope is controlled or protected by the inside lining which is connected to the outside lining. They're always talking to each other and it works both ways. The internal manifestations of skin disease and the external manifestations of internal disease are profound. All we need to do is, as I have mentioned in some of my articles, make the connection. You've pointed that out so many times. You have to think outside of the box and make the connections. Connectivity and becoming an advocate for our patients is what we have to do.

It's a tough job. There's so much information out there. There are so many connections to be made. People like you have made it easier for us to see that we need to make these connections and apply them to our patients in a caring and resourceful way so that they can be effectively put into practice and benefits derived from them.

Skin Tags

JB: You mentioned a term earlier that may not be familiar to those outside the field of dermatology, and that is skin tags and their relationship to insulin resistance. Would you define what skin tags are?

SC: Skin tags are little annoyances that grow out from under our skin. They're usually seen in the axilla area. They might be on the neck. They are tiny little papillomas. They're there for no reason and they seem to appear in adulthood, or they sometimes come out early in young, obese patients. I can tell you about my own personal experience with skin tags. I was at one of your lectures in Miami and I had a blood sugar test done. I had eaten a donut and my blood sugar was way up. A gentleman told me that even though I had just eaten, my blood sugar was very high. I was running, exercising, eating all the right foods, and taking vitamins, but my weight was up to 195. I was getting pimples in my hair. I was getting skin tags, and I wondered what was going on. In addition, my blood sugar was up. I was moving, imperceptibly, into the range of syndrome X. I cut out some healthy foods that were calorie-rich, like nuts and seeds, and I stopped eating in-between meals. I dropped 30 pounds, the skin tags fell off, and the pimples resolved.

JB: That's an interesting case history. Thank you for sharing it. At the Functional Medicine Research Center, I have seen reports of many people who come in as a consequence of being involved in one of our clinical trials, but the conditions you just described come with them as part of their overall health profile. They often have resolution while they're in one of our programssuch as an intervention focused specifically on insulin sensitization or hormone balancingand all the other things seem to clear up, as well. That confirms your concept about the web and the skin being a lens that we focus on to make the connections visible.

Examining the Mouth

SC: They're so easy to see. The skin is so available. Unlike some of the other invasive procedures we have to do, where we must guess and look at shadows, the skin is there. It calls to us and says a lot. I love to look inside patients' mouths because I can see many things associated with poor vitamin and nutrition. Or, I observe what the skin looks like, for example, in smokers. The associations involve many parallels. Macroglossic patients have very slimy-looking tongues. Or, I examine the mouths of patients with gingivitis, which has now been clearly associated with increased incidence of cardiac disease.

It seems obvious that if there is an area of chronic inflammation that is going to result in seeding bacteria into the bloodstream, the bacteria are going to end up somewhere and be inflammatory. If they happen to wind up in your coronary arteries, the body is going to create an inflammatory reaction against them. Then, cholesterol comes in and, before you know it, you have plaque.

Toothpaste with Coenzyme Q10

When I see this inflammatory situation in my patients, I'll even go so far as to suggest, and even sell them, a toothpaste I found with CoQ10 in it that I find very helpful. I'm sure my patients wonder why their dermatologist and internist is selling them toothpaste, but it goes back to caring about them. I really care about my patients. As their physician, I want to do all I possibly can for them. I may not be able to do it all, but at least, I can point them in the right direction so they get better. One of the tenets of functional medicine and the way it works is making the connections. And, yes, you have to love your patients enough that you'll go through the difficult, sometimes frustrating task of guiding them into wanting to return to health. We can coach them. We try very hard, but we can't make a basket for them.

They have to put the ball in the basket themselves.

Motivating Better Lifestyle Choices
One of the hardest things to accomplish is to motivate patients who are in a "funk" because of poor lifestyle choices. They don't think straight. They don't sleep well. They don't exercise. Their lives are gray and black and physicians need to move them, in a caring way, to a state of health where they can look back to where they were. Oftentimes, they don't see how their life choices have brought them down a very rocky, miserable path until they come out of it and look back. It's almost like looking at depression. After you've been there, you look back and think about what it was like. When people regain their health, they look back and ask how they got there. The real problem is they did get there, and how do we turn them around? It's a slow process, and not one that everyone is going to buy into.

You need to be very resourceful. That is so important. I can give one of my patients a $2000-a-year program on weight reduction that includes all the nutritional supplements. But I can't give that to most of my patients because they can't afford it. So, I've come up with a 51 cents-a-day nutritional program for them, which is a compromise, but it's something they can do, something that pushes them in the right direction. We have to realize what we can do for our patients. We also have to make it possible for our patients to succeed, keeping in mind their limitationspsychological limitations, money limitations, and limitations in terms of where and who they areand try to tailor it in a unique way so they can succeed. Success for them may not be the success we place on ourselves. But even if they do a little bit better, even if they get back to a somewhat improved homeostasis, that's enough to be encouraging.

Offering Hope and Encouragement
I also feel we should never discourage our patients. There should be no point at which we dont offer them hope. If you just tell them what's wrong, that's discouraging, and you may be beating them deeper into a hole which they'll never get out of. You need to be very patient, but at the same time, a little detached. We're coaches, not players. If we understand that, we can go home at night and relax. We can't take on the burden of our patients. We can only help them take on their own burdens and work through them. I think that's also true in our own personal lives. I cannot understand how physicians and medical healthcare providers can be good advocates for their patients unless they walk the walk and talk the talk. We all struggle with some of the same issues every day. Should I have this pizza? Shall I run tonight? Shall I take these vitamins? Do I handle my stress situations or do I let myself get out of control? If we don't address our own problems and deal with them on a day-to-day basis, I don't see how we can be believable and credible to our patients. Patients love it when I share some of these personal health issues with them and tell them we're struggling together. That brings the whole thing home and melds the patient/doctor relationship.

JB: I want to compliment you. That whole philosophy is the foundation of what we would call the patient-centered medicine concept that underlies one of the tenets of functional medicine. It underlies the tenets of any good medicine, whatever it may be called. The way you've articulated it is motivating to all of us. Since you practice in Florida, many patients probably come to see you with problems of aging skin and sun exposure. How do you deal with aging of the skin, skin resurfacing, and the sun-damaged skin complex?

Categories of Importance
SC: It boils down to categories of importance. I'm a cosmetic surgeon and I have patients who want to

look beautiful, or better. Behind that lies another intriguing question. Why do they want to look beautiful and better? For some, it's the beginning of a whole new lifestyle. Many who come in for liposuction are already motivated. Many of them don't know how to get healthy again, but this is the first step. I put them on a nutritional program and talk to them about lifestyle changes. I do the liposuction, follow them through, and try to help move them along their way. That's a nice entry point for those who are looking for cosmetic improvements.

Some of my patients who are wrinkled and old-looking are very healthy, but they've let their skin get unhealthy. There's disequilibrium between the way they look and the way they feel. Some of them tell me they feel great, but they feel they look like they're 105 years old. They ask what I can do for them. I tell them their program might be good from a health standpoint, but that we should try to fix their psyche so they will look the way they feel. That combination is dynamite. It propels these people into energy they've never had before.

Educating Patients

I invented a unique triple procedure on resurfacing skin, the results of which are outstanding. As a physician, it's wonderful to watch them grow into a new sense of good feeling. When those things are combined, it sings for them. For those with skin cancers or precancers, I do a comprehensive skin exam. Smokers are more prone to cancer. Or, if they're out in the sun a lot, they're more incidentally prone to internal malignancies. I tell them about recent articles published in the literature. It gives me a window into looking at their skin and trying to get them to incorporate healthy lifestyle choices. I tell them that if they take antioxidants or use them on their skin to protect themselves, it's going to make their skin and their bodies healthier. If they're healthier on the inside, they're going to be healthier on the outside.

Sun Screen and Vitamin D

JB: That raises an interesting paradox. As we try to lower the risk to melanoma and use higher SPF formulations, it cuts down on the amount of some of the near UV radiation necessary for activating the precursor of vitamin D (ergosterol), into its vitamin D component. Then we wonder if that person is going to have a vitamin D insufficiency. How do you recommend we handle that apparent paradox?

SC: From a clinical point of view, I would be guessing at the chemistry. I try to put all my patients on a nutritional regimen that includes taking extra calcium, magnesium, and vitamin D every day. I tell them not to go out into the sun anymore. In our environment, sun, at 15 minutes a day, is usually plenty to get enough vitamin D and vitamin D conversion. For someone with healthy skin, that's not going to adversely affect them. For a black patient or anyone with a darker complexion, that's not going to be a problem. But for someone who's already beaten himself or herself up royally in the sun, I tell them I've removed 20 skin cancers and that they can't go out in the sun. I make sure they get enough vitamin D, calcium, and magnesium. And I make sure they absorb it. I'll get a probiotic on board. I'll make sure they're eating the right foods. That's the answer. In this day and age of science, they're able to have our cake and eat it, too.

JB: That's a marvelous answer. I have one last question about the interrelationship between potential food allergies and dermatological conditions. How do you address that?

Food Allergies and Dermatological Problems

SC: Food allergies are difficult to put your finger on. It's difficult for allergists; it's difficult for nutritionists; it's difficult for everybody. Elimination diets are tedious and tough, but they're necessary.

My atopic individuals have a tendency toward allergies, hay fever, asthma, migraine headaches, or hives, especially at a very young age, and they often have food allergies. Many outgrow them, but at that point in time, they need elimination diets. I can't do everything for everybody, nor do I pretend to be an expert in medicine. There's a time when a physician has to refer to other resourceful practitioners to help him with a patient. That's when I would call in a nutritional expert and an allergist to work through those diets with a young patient.

Dermatitis herpetiformis is a condition that used to be rare, but it's not rare anymore. As with celiac disease, it's a very common problem. What's uncommon about celiac disease is that we havent been very good at detecting it. Food intolerances in our lives are profound; they're common, and we're just beginning to recognize them.

One very clear cut form of food intolerance is dermatitis herpetiformis, a bullous, painful eruption that usually occurs on extensor surfaces. This condition is associated with gluten or wheat sensitivity. Those patients must go on strict, gluten-free diets if they wish to maintain a skin free of annoying blisters.

JB: This has been an extraordinary interview. You have discussed such a breadth of topics. You've described the philosophy of your practice and how you relate to your patients, and how you've leveraged your background, both in internal medicine and in dermatology, to create an integrative/ functional medicine approach to dermatological conditions. It is truly innovative and very motivating for all of us to hear about. I know this has been time out of your practice today and we very much appreciate what you've shared with us. This will be a model for many of us who may be on the fence trying to figure out exactly how we can convert our practices into something that's more integratively and functionally-based, so as to develop the kind of patient/physician relationships that you've described. Thank you so much.

SC: Jeffrey, I want to thank you for actualizing this for me. What I've done is take the tenets that I've listened to so carefully over the years and apply them to my practice, thereby giving myself a chance to act more like a specialist than a technician. That requires the kind of thinking and teaching that you and your institution have been professing for many years. Everyone is taking notice and saying that this standard of care is the way it should be. This is medicine for the 21st century.

JB: Thank you very much. That's a marvelous way to end. We wish you the very best and we'll check in with you soon.

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