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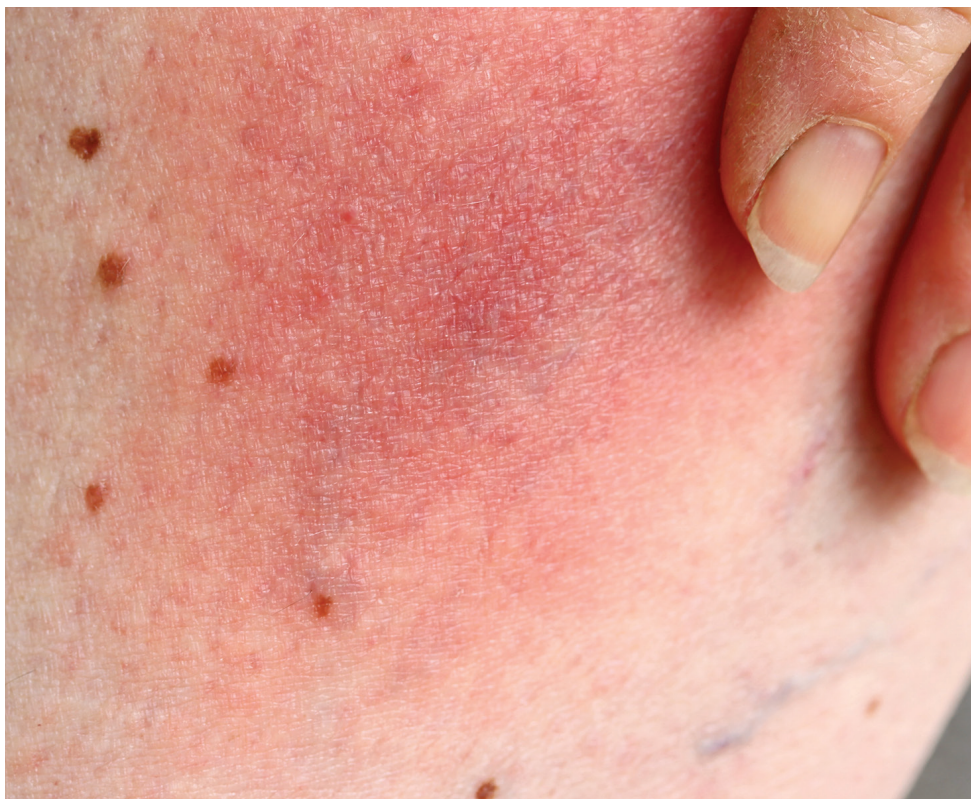
Tolle Totum

Mast Cell Activation

Skin is Just Scratching the Surface

THALIA HALE, ND



Mast Cell Activation (MCA) is demanding awareness in functional medicine practices, especially among practitioners working with patients with chronic complex illnesses and infections such as chronic dysbiosis, Sick Building Syndrome, and Lyme disease and its associated infections.

MCA patients may appear complex in nature, as the syndrome affects multiple systems in the body; this can result in an array of seemingly unrelated symptoms. Fortunately, as naturopathic doctors we have a foundational understanding that the body is wholly connected.

The Role of Mast Cells in the Body

Mast cells (MCs) are a subset of our white blood cells derived from bone marrow.

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Tolle Totum

Eosinophilic Cellulitis

A Mysterious Case of Flower-shaped Lesions

ELISABETH BASTOS, BSC, ND, RACU

Wells syndrome, also known as eosinophilic cellulitis, is a rare benign disease characterized by pruritis, edema, bullae, and urticarial plaques on the limbs and/or trunk.[1] The typically 1-time lesion outcropping may spontaneously resolve within 3-4 weeks; however, the lesions can also reoccur repeatedly, with the cycle continuing for several years.[1] This was the case with my patient.

The cause of Wells syndrome is currently unknown, although there is some scientific speculation of autoimmune involvement. Possible triggers can include infection (viral, fungal, parasitic), leukemia, and certain medications.[2]

There is no proven cure for Wells syndrome. Treatments to manage symptoms usually include oral or topical corticosteroids, although antifungal drugs, antibiotics, immunosuppressants, and/or antihistamines are sometimes also employed.[2]

With the patient in this case study, early stages of her lesion could easily be confused with ringworm, illustrating the importance of a biopsy to rule this out.

The dermatologist and I attempted to identify the source of the eosinophil activation, but with no clear answers resulting. In turn, this case illustrated to me that even when the root cause is yet unclear, understanding functional immunology, even at a basic clinical level, can open enough doors to validated treatments that enhance quality of life.

Eosinophils at the skin level are known to cause symptoms of itching and swelling, which can make day-to-day life difficult for affected individuals. Steroids are a common, albeit unproven, treatment for this syndrome; however, this patient has only 1 kidney and refused the drug based on her concerns of nephrotoxicity and anemia risks.

Some research on Well's syndrome has suggested reducing inflammation by targeting reductions in tumor necrosis factor-alpha (TNFα). Natural substances found to target and reduce this inflammatory cytokine were incorporated in this patient's treatment plan.

Combining naturopathic medicine and a functional immunology approach that improves the body's natural healing ability is especially important in conditions for which there are no other suitable treatment options, no known cure, and a high probability of prolonged suffering. In this case, using some knowledge of the immune

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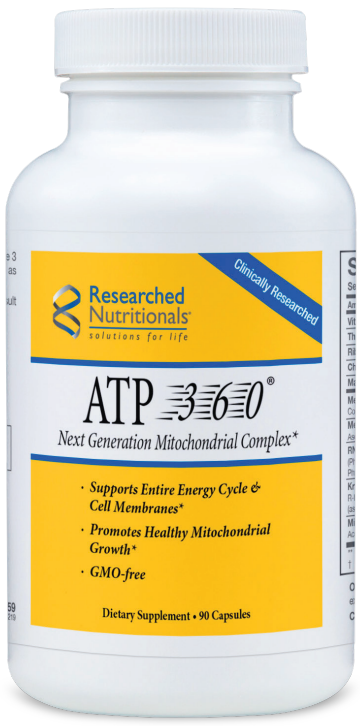

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Upon leaving the bone marrow, MCs become a part of our body's first line of defense. The highest concentrations of these cells are found in the skin, epithelial lining of the lungs, nasal passage, conjunctiva, and digestive tract. This positioning is key, as MCs predominate in the areas where our cells come into contact with the outside world.

If a harmful substance enters our environment, it is perceived as dangerous when the antigen attaches to the mast cell. This causes the basophilic granules within the mast cell to release histamine, heparin, inflammatory cytokines, and other mediators into the extracellular environment. The physiologic effects of histamine release by MCs include vasodilation, increased capillary permeability, bronchoconstriction, and smooth muscle contraction.[1]

Since first studied by Paul Ehrlich in 1878, MCs have primarily been considered part of our innate immune response and mostly involved in allergic and anaphylactic responses. But in the last 3 decades, further studies have revealed that our knowledge of these cells has been limited.[1]

Our MCs play a part in adaptive immunity by recognizing invaders such as viruses, fungi, parasites, and bacteria. They interact with a number of other immune cells to potentiate physiologic and immunologic responses to environmental changes.[1]

When MCs respond appropriately, they are immunomodulatory and support tissue healing, vascular homeostasis, angiogenesis, bone and tissue remodeling, and immune tolerance.[1] When in a maladaptive state, however, MCs can inhibit Th1 immunity and shift a greater emphasis to Th2 immunity, resulting in patients feeling allergic, inflamed, and unable to respond adequately to chronic infections.

Mast Cell Activation

Overstimulation of MCs, which leads to a large release of histamine and inflammatory mediators, has been shown to contribute to chronic allergic/inflammatory disorders, autoimmune diseases, cardiovascular disease, and cancer.[1] Dermatologic findings can be merely 1 clue to underlying immune and inflammatory dysregulation. This overstimulation of MCs can result in multi-systemic symptoms, including those listed in Table 1 (those accompanied by an asterisk are the most common manifestations of MCA that I see in practice).

MCA has a number of comorbidities, including:

- Ehlers-Danlos Syndrome (EDS)[2]
- Electrohypersensitivity[3,4]
- Irritable Bowel Syndrome (IBS)[5]
- Inflammatory intestinal disorders[5]
- Periodontal disease[6]
- Postural Orthostatic Tachycardia Syndrome (POTS)[2]
- Sick Building Syndrome[7-9]
- Small Intestinal Bacterial Overgrowth (SIBO)[10]

The severity of symptoms depends on a number of factors, including the number of MCs involved in the reaction; the amount and type of allergen-specific IgE; the triggering allergen; the presence of triggering cofactors such as exercise, alcohol, or acetylsalicylic acid (aspirin); the presence of comorbidities; the tissue microenvironment; and the cytokines/chemokines involved.[11]

If your patient is complaining of many of the symptoms and conditions listed in Table 1, it is important to take MCA into account as a potential contributing diagnosis. There are 2 subclasses of Mast Cell Activation Syndrome (MCAS): primary (clonal) and secondary (nonclonal). For the purposes of this article, I will be focusing on secondary MCAS, which encompasses IgE-mediated, direct, and idiopathic MCA.[12]

Table 1. **Manifestations of Mast Cell Activation**

Dermatologic Manifestations: • Angioedema • Dermatographia • Dermatitis with pruritis • Erythema • Generalized pruritis* • Hives* • Hypersensitivity to insect bites* • Skin flushing • Sun sensitivity	Gastrointestinal Manifestations: • Abdominal bloating* • Abdominal cramping • Constipation • Diarrhea* • Gastroesophageal reflux* • Peptic ulcer disease • Sensitivity to probiotics
Musculoskeletal Manifestations: • Arthralgias • Myalgias • Osteoporosis	Cardiac/Pulmonary Manifestations: • Heart palpitations* • Hypotensive syncope/Near-syncope* • Tachycardia • Wheezing
Ear/Eyes/Nose/Throat Manifestations: • Conjunctival injection • Rhinitis, especially after meals* • Sinus congestion	Endocrinologic Manifestations: • Blood sugar instability* • Fatigue • Orthostatic hypotension*
Brain/Neurological Manifestations: • Anxiety* • Cognitive deficit/Brain fog • Headaches*	Urinary Manifestations: • Dysuria • Polyuria*

Work-Up for MCAS

The likelihood of MCA being present is high when 2 or more of the Table-1 symptoms are present and your patient is responsive to drugs that block MC mediator effects, mediator production, and/or mediator release.

The current minimal diagnostic criteria for MCAS, as of November 2020, are as follows[11]:

1. Typical clinical symptoms indicative of multi-organ involvement, usually meeting the criteria for anaphylaxis
2. Serum tryptase greater than 1.2 x baseline value + 2 ng/mL during a flare of symptoms is considered indicative of MCA and/or a clear increase in another mast cell-mediated marker
3. Responsiveness to medications that manage MCA, mast cell mediator release, and/or mast cell mediator effects

Elevations in serum histamine and/or serum tryptase strongly support the diagnosis and the ability to use the marker(s) as a therapeutic guide. The challenge faced with random testing of serum histamine and tryptase is that these markers are extremely transient; thus, a normal value cannot rule out MCA.

Managing & Monitoring MCA

In our office, we focus on chronic diseases like Sick Building Syndrome and chronic infections like Lyme disease and its coinfections, gut dysbiosis, chronic viruses, and parasitosis. About 80% of our patients have some degree of MCA symptoms and often do not have elevated tryptase levels. Most of these patients have a number of associated symptoms (often without anaphylaxis) and elevated inflammatory markers and respond positively to mast cell treatment.

Treatment of MCA can be intense, as it most often requires strict dietary management and other lifestyle interventions in addition to pharmaceutical/nutraceutical interventions. In order to objectively assess the patient's condition and help guide management and treatment of MCA, we have found the inflammatory marker Matrix Metalloproteinase-9 (MMP-9) to be very helpful.

MMP-9 is a key effector in immediate-type allergic reactions and is also well known to contribute to the pathogenesis of a variety of non-allergic inflammatory responses. This extracellular matrix-destructive enzyme is involved in tissue remodeling, embryonic development, wound healing, angiogenesis, and more. When improperly unleashed by mast cells, this enzyme sets up a cascade of inflammatory cytokines and chemokines (see Table 2 for interpretation of levels).[13-15]

In an in-office study, we obtained MMP-9 values from 22 of our patients before and after a 3-4-week low-histamine diet and no MC stabilizers. After the diet trial alone, we observed a 39% decrease in MMP-9 levels. In addition, patients reported symptomatic improvement, including reductions in anxiety, fatigue, arthralgias, headaches, congestion, abdominal pain, loose stools, reflux, pruritis, and more.

Inflammatory markers can be elevated by numerous conditions, but being able to objectively show patients their progress has been imperative for treatment compliance.

Triggers for MCA

Whether based on symptoms and empiric treatment and/or lab work-up, one of the greatest challenges in treating patients with MCA is identifying and appropriately treating the triggers for their condition. As mentioned briefly above, pathogens and any other harmful substances can trigger mast cells to become overstimulated.

Triggers to take into consideration include, but are not limited to, the following:

- Mold/Mycotoxins[7-9]
- Electromagnetic frequency (EMF) exposure[3,4]
- Impaired detoxification
  - Methylation
  - Glucuronidation
- Heavy metal exposure[16]
- Chemical/Pesticide exposure[17]
- Estrogen dominance[18]
- Viruses and retroviruses[19]
- Fungal infections[20]
- Parasitic infections[19,21,22]
- Bacterial infections[19,20]
  - Dysbiosis via viruses/fungi/bacteria/parasites
  - *Mycoplasma pneumoniae*
  - *Chlamydia pneumoniae*
  - Lyme disease and its associated infections
  - *Streptococcus* species
- Emotional stress/Trauma[23]
  - Limbic system impairment
  - Vagus nerve impairment

Treatment for MCA

Dietary Interventions

Our office has observed that dietary intervention is the first step in managing patients with MCA. It is imperative for these patients to limit their exposure to additional histamine and triggers during the course of treatment.

There are 2 major rules for a low-histamine diet:

1. Avoid high-histamine foods, including fermented foods
2. Avoid leftovers

Leftovers and fermented foods allow naturally occurring bacteria to break down amino acids into histamine. Once histamine has been created within food, it can no longer be destroyed. We thus recommend that patients prepare their food immediately upon purchasing, and to freeze any leftovers for later consumption.

Table 2. **MMP-9 Interpretation**

MMP-9 Level (ng/mL)	Interpretation
0-983	Normal reference range
≤ 250	Normal; mast cell activation unlikely
250-399	Consider mold and/or mast cell activation
>400	Mast cell activation highly likely

Even food sitting in the refrigerator is susceptible to degradation.

Helpful guides are available, such as the "All I Can Eat" phone application, which may help people understand histamine levels in foods.

Other potential food triggers to consider include oxalates, lectins, and salicylates. For obvious reasons, most patients do not do well on a combination of more than 2 restricted diets, as it can become overwhelming, both mentally and physically. Patients limited to only a few tolerated foods often have other triggers that require attention, like limbic system and/or vagus nerve impairment, or mold.

Environmental/Lifestyle Interventions

As mentioned above, it is critically important to explore the triggers of a patient's MCA and to address them in the necessary order. Outside of dietary intervention, various environmental and lifestyle factors may support a patient's healing process:

- Reduction of EMFs[3,4]
- Inclusion of mindfulness, meditation, limbic system/vagus nerve support[22]
- Reduction of exposure to water-damaged buildings[7-9]
- Transitioning to organic foods[17]
- Addressing sources of heavy metals[16]

Pharmaceutical & Nutraceutical Interventions

Once we have addressed dietary, environmental, and lifestyle influences on one's presentation of MCA, we then introduce pharmaceutical and/or nutraceutical support to further stabilize their condition. By focusing on the foundational components early on, we find that we need fewer MC stabilizers and can use lower doses effectively for management. Most of our patients are on 3-4 MC-stabilizing agents, including probiotic strains that reduce histamine levels.

Pharmaceuticals

Pharmaceuticals used in the management of MCA include[18]:

- 1st Generation H1 Anti-histamines
  - Chlorpheniramine – mildly sedative: 1 daily with food
  - Diphenhydramine – highly sedative: 1 daily if needed
- 2nd Generation H1 Anti-histamines
  - Decreased central effects, resulting in less sedation
  - Fexofenadine: 1 daily with food
  - Loratadine: 1 daily with food
  - Cetirizine: 1 daily with food
  - Levocetirizine dihydrochloride: 1 daily with food
- Other Anti-histamine Support
  - Selective H1 receptor inhibitor/ Mast cell stabilizer – Ketotifen 1 mg (compounded): 1 daily with food
  - Mast cell stabilizer – Cromolyn sodium (prescription/compounded): 100-200 mg 2-3 times daily, 5-10 minutes before meals
- H2 Anti-histamines (Rarely used in our practice due to long-term GI effects)
  - Ranitidine
  - Cimetidine
  - Famotidine

Nutraceuticals

Nutraceuticals used in the management of MCA include:

- Quercetin, 250 mg: 2-3 times daily with food[24]
- Luteolin, 100 mg: 2-3 times daily with food[25,26]
- Curcumin, 200 mg: 1-2 times daily with food[27,28]
- Holy basil, 200-300 mg: 1-2 times daily with food[29]
- Pantethine, 450 mg: 1 twice weekly to every other day, with food[30]
- Fisetin: 1 cap 2 times daily[31]
- DAO, 600 µg: 2-3 times daily, 10-15 mins before meals
- Homeopathic preparations of histamine: 1-3 drops 1-3 times daily, sublingually

Probiotics

Similar to SIBO patients, patients with MCA may have worsening symptoms when taking probiotics, and thus need specific strains to avoid aggravating histamine levels.

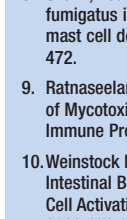
- Probiotic strains to avoid in MCA:
  - *Lactobacillus bulgaricus*
  - *Lactobacillus casei*
  - *Lactobacillus reuteri*
  - *Streptococcus thermophilus*
- Histamine-neutral strains:
  - *Lactobacillus acidophilus*
  - *Lactobacillus lactis*
  - *Lactococcus lactis*
- Probiotic strains supportive of MCA:
  - Soil-based probiotics
  - *Bifidobacterium infantis*
  - *Bifidobacterium longum*
  - *Lactobacillus gasseri*
  - *Lactobacillus rhamnosus*
  - *Lactobacillus plantarum*
  - *Lactobacillus salivarius*

Summary

The unfortunate truth is that our environment has become increasingly toxic. Because mast cell activation can impact so many different organ systems and functions, the assessment and treatment of MCA has become a cornerstone in our treatment of chronic and complex patients. By reducing immune and inflammatory overexpression via specific dietary and lifestyle interventions, identification of MCA triggers, and the use of targeted nutraceuticals and probiotics, we are able to adequately address MCA and restore optimal health in our patients.

References 28-31 available online at ndnr.com

Patients limited to only a few tolerated foods often have other triggers that require attention, like limbic system and/or vagus nerve impairment, or mold.



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system and biology allowed for a treatment plan that gave the patient relief beyond what was expected from her conventional care team.

The Patient

A few years prior, I had been treating D.A. in my office for almost-daily hives. With non-suppressive treatments and dietary elimination of problematic foods (found via the Carroll Food Intolerance Method®), the hives had not been an issue for the patient for well over a year.

A consideration in this case regards what environmental factors might be allowing this new Th2-dominant immune expression to manifest, such as infections, allergens, or stress.[3] Another consideration is genetic contribution, with defective dendritic cells (antigen presenters) making an individual prone to severe Th2-mediated skin conditions.[4] With the genetic possibility in mind, it felt even more important to directly support the immune balance, as the removal of triggers might not be the whole story.

D.A. presented for her first consult regarding this skin condition in August of 2020 after 5 months of continuous, non-tender but severely itchy lesions. She reported having no time periods without the emergence of new lesions. With her diagnosis of eosinophilic cellulitis, we would expect, with her current pattern, that she would have continual lesions for years.

D.A.'s symptoms started in June 2020, when she noticed 1 small pimple-like eruption on her arm (Figure 1). The lesion then grew to include raised red borders and a clear skin-colored center (mimicking ringworm, to an extent) (Figure 2); then it became completely red with edematous bullae around the edges, resembling flower petals (Figure 3). The lesion would lose its puffy edges and remain red-purple in a bruise-like expression at its maximum size, and then would eventually fade. Over the 5 months preceding our consult, multiple lesions would be in various stages on her arms.

In a biopsy report dated June 23, 2020, the pathologist ruled out a skin fungal rash, Sweet Syndrome, and also autoimmunity. This was an important report for me, as, like many doctors, I would have been inclined to assume some sort of fungal infection, considering how the lesion looked at various points of development; research also suggests the possibility of this kind of lesion being autoimmune in nature. Either of these assumed causes would have influenced the direction of treatment. The biopsy revealed eosinophil infiltration (Th2 immune activity) and some lymphocytes (T1 cellular activity) in the skin lesions.

Topical steroid cream was prescribed at the start of her skin problem in June. When the patient reported no change after a few weeks, it was discontinued.

Evaluation

D.A. and I dove into some blood work together. White blood cell (WBC) percentages (a functional immunology approach) provide clues as to whether infection might be an immune imbalance trigger.

Optimally, eosinophils are under 2% in those with allergic history. In this patient, eosinophils measured 2.5% (Table 1). Hay fever or urticaria can cause increased eosinophils, but she denied both. Despite the absence of systemic allergic symptoms, I would still add in Th2 support, since the biopsy findings of local tissue elevation of eosinophils confirmed Th2 activity. The dermatologist also ruled out several parasites as a possible cause, including the worm Strongyloides. Fungal infection is another big player in eosinophil elevation/Th2 dominance, but this was ruled out with the biopsy. The WBC percentages on the CBC helped to move our focus away from any consideration of viral or bacterial involvement, as the absolute numbers and percentages of monocytes, lymphocytes, and neutrophils were all normal (Table 1).

Table 1. **CBC Results**

Biomarker	Result
Neutrophils	63.6% (optimal)
Lymphocytes	26% (optimal, lower end)
Monocytes	7% (WNL)
Eosinophils	2.5% (high)
Basophils	0% (WNL)
Urine pH	6
Urine leukocyte esterase	High
HbA1c	WNL

(WNL = within normal limits)

Because hollow organ inflammations and infections can produce Th2-dominant immune expression[5] and would also hinder our efforts to balance her immunity, a urine test was performed and her sinus and lung health was assessed. Her lungs were normal on auscultation, and there were no findings that suggested sinusitis. High leukocyte esterase on urine chemical testing indicated a urinary tract infection or risk of it.

D.A. reported higher stress than normal due to COVID restrictions, which set the stage for Th2 immune imbalance.[3] Lifestyle interventions such as prayer[6] and walking outdoors were suggested, as they are proven to assist in lowering stress responses.

January 2021 AM serum cortisol levels (drawn within 2 hours of waking) were 326 nmol/L (RR, 135-537 nmol/L), confirming that it was safe to move ahead with treatment to support her endogenous corticosteroid production.

Auricular testing suggested distress

> Optimally, eosinophils are under 2% in those with allergic history. In this patient, eosinophils measured 2.5%. Hay fever or urticaria can cause increased eosinophils, but she denied both.

potential in the colon[7] and liver, so treatment was selected to support these organs, especially due to their influence on the immune system and skin.

Treatment Goals

After gathering information, I find that listing management goals to organize treatment targets is helpful, especially when a condition has unknown etiology and the treatment is based on an understanding of functional medicine and biology (vs researched proof of effective treatments). My goals were as follows:

- Control allergy reaction at the skin, ie, eosinophilic infiltration. Although the dermatologist did not identify parasitic infection, I chose to use treatment that targets microbial disinfection that might also kill any missed parasite-like activity known to trigger increases in eosinophils.
- Per auricular testing result, lower the microbial load with formulas that also support the health of the liver and colon
- Support Th1 cellular immunity in case of missed microbial burden, as some lymphocytes were found in the lesion biopsy and an increase in Th1 can drive down the Th2 dominance that promotes the skin allergy response
- Reduce TNFα to decrease auto-inflammation cycling that can continue even after the root cause has been removed
- Per research on this skin disease, consider autoimmune risk. With this in mind, reduce inflammatory STAT3 (signal transducer involved in the inflammatory response).[8]
- Reduce Th17 cytokine potential that allows more tissue damage that can aggravate Th2-mediated inflammation[9]
- Improve natural corticosteroid activity in order to reduce inflammation potential
- Optimize detoxification ability and reduce toxic load, considering her history of 16 mercury-based amalgams that were only fully removed in September 2019 (approximately 9 months prior). Mercury has been shown to shift immune modulation towards Th2 dominance, even when no preexisting inflammation exists.[10]
- Future goals include addressing insomnia in order to further reduce inflammation and immune imbalance. Scalp acupuncture with electro-stimulation would be ideal, at 2 treatments weekly for 2-6 weeks.

Figure 1

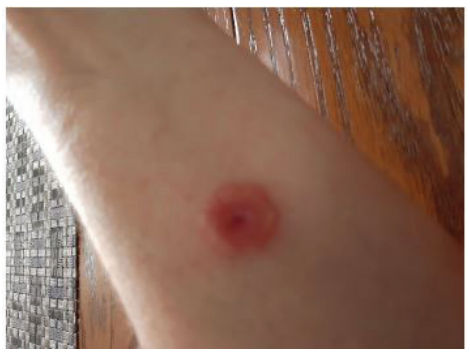


Figure 2

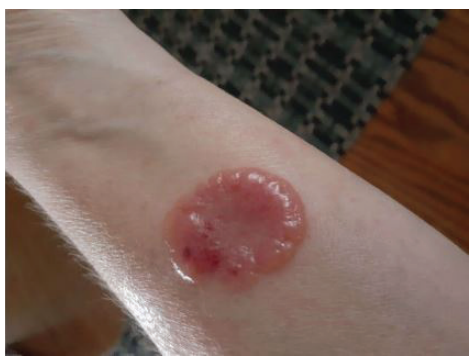


Figure 3

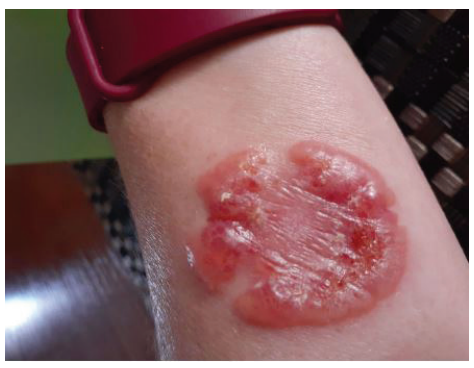
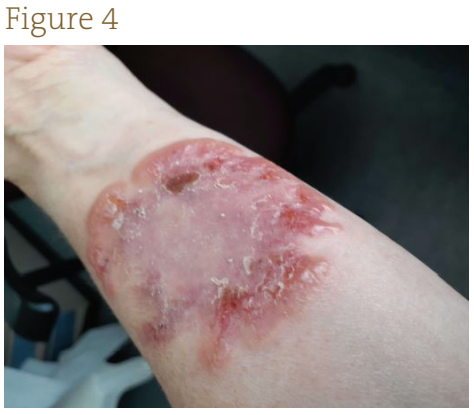


Figure 4



The Plan

Here are the specific treatment recommendations I made to D.A.:

- Avoid problematic foods, as indicated by the Carroll Food Intolerance Method®, to reduce toxicity from poor metabolism
- Avoid lectins found in gluten by eating a gluten-free diet, as gluten lectins can aggravate skin pathology
- Take custom-formulated Th17-reducing capsules containing daily doses of resveratrol (500 mg), lipid-based curcuminoids (200 mg), and quercetin (700 mg)
- Reduce Th2 immune dominance by taking encapsulated daily doses of combined quercetin (1400 mg) and N-acetylcysteine (NAC) (2400 mg)
- Support detoxification and reduce Th2 imbalance potential with liposomal glutathione (sunflower, not soy-based) (800 mg/day)
- Use homeopathic topical disinfectant ointment to naturally prevent bacterial infection of blistered areas, especially if they were to break open
- Enhance endogenous corticosteroid production with *Ribes nigrum* (bud extract) (½ tsp twice daily with water)
- Improve Th1 immunity/cellular immunity with berberine-based capsules
- Reduce TGF-beta (inflammatory cytokine) with a combination of curcuminoids and *Boswellia serrata*, taken on an empty stomach
- Support general healing with zinc (15 mg/day)
- Use *Juglans nigra* herbal orally for disinfection, also to target the liver and colon
- Take a complex homeopathic drainage preparation for skin and large intestine, at a dose of 10 drops twice daily for 4 weeks
- To address local itching, use homeopathic Psorinum 200c – 1 pill every 3 days as needed when itchy skin presents

Follow-ups

In November 2020, D.A. was 3 months into treatment. New lesions were continuing to emerge; however, she reported that they were now growing to only 50-75% of the size of prior lesions and were resolving and drying up faster despite no topical steroid use (Figure 4). She also reported much less itching.

One month later, on December 11, 2020, D.A, reported, "My skin is so much better, I would say by 95%, and the itching is almost gone." Furthermore, no new lesions were showing at this time. The patient reported this by email, and the rash was not examined in the office on this day; however, photos showed purplish marks on the skin, with no bullae or raised lesions.

Conclusion

Naturopathic medicine, including a functional medicine approach, allows a practitioner to view a case for its multiple layers and elements of imbalance, rather than just through the lens of a disease name. In this case, looking for treatment based on a disease name would not have led us very far, as research has delivered no clear guidance regarding treatment. In Well's syndrome, the outcome for a person experiencing repeat lesions for at least 4 months is grim, with an expected course of continued repeat lesions for 2 years, plus, often followed by spontaneous resolution. It is presumed that since D.A. reported having 95% resolution of her skin lesions, with no new outcropping of lesions, only 9 months into her condition, that the 4 months of naturopathic treatment likely facilitated a faster road to recovery than expected. This case sheds light on how naturopathic doctors are well equipped to improve the quality of life in our patients with difficult skin diseases.

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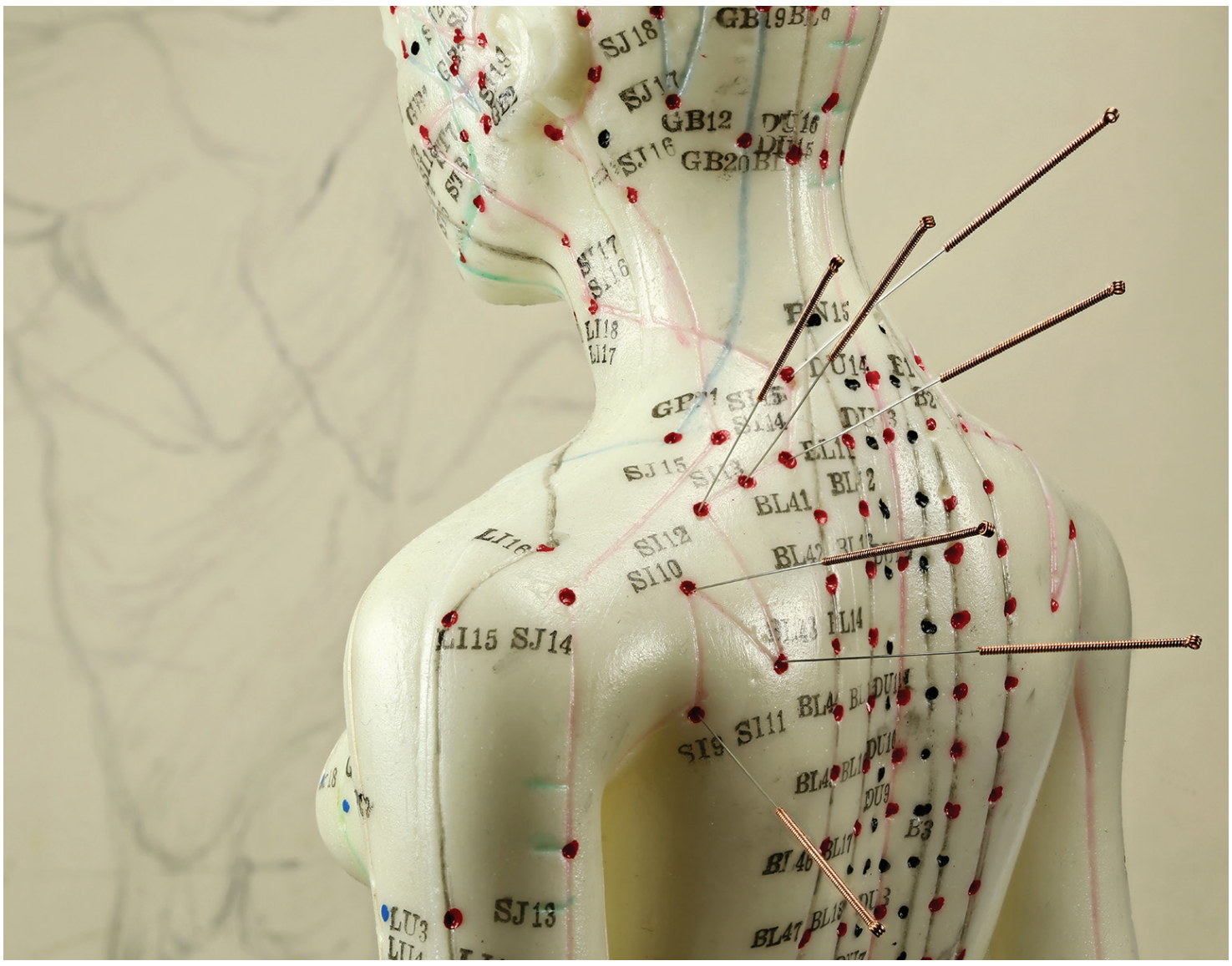
Optimizing Recovery

Using Acupuncture, Trigger-point Injection, & Red Light Therapy

JANNINE KRAUSE, ND, EAMP



Since NASA released its research findings in the early 1990s, red light therapy has been touted as an excellent tool for wound healing and reducing pain and inflammation. Since then, technology and delivery methods have advanced, as have the novel ways in which clinicians can incorporate and pair treatments with red light therapy. This article will introduce you to methods you can use to help your patients recover effectively from the stress of their day and workouts.

Red light therapy can be thought of as a booster to just about any treatment protocol you might use, since it increases the effectiveness of other treatments by increasing circulation.

Consider this: The majority of your patients are likely stressed out, fatigued, and struggling to recover from their day, including workouts, assuming they are able to get them in. Being stuck in fight-or-flight mode interferes with general circulation, which leaves organs and chronically injured areas, such as tendons and ligaments, starved for oxygen and other nutrients. Tissues that lack adequate circulation remain inflamed and are slow to heal.

Decreased circulation also makes it tough for cells to remove byproducts of the

energy-making process. As a result, your patients end up with malnourished cells that struggle to make ATP and to detoxify. That inability to get the cells what they need and to detoxify is a primary cause of fatigue in your patients, and it's happening on a daily basis, not just post-workout.

Mitochondrial Nutrition

Red light therapy works by stimulating cells with specific wavelengths of red light (660-680 nm is the ideal) that turn on red light receptors in the mitochondria to make ATP. Red light therapy alone can be effective; however, most patients will be lacking some of the nutrients necessary for optimal mitochondrial function. It's also possible that your patient is not making sufficient amounts of glutathione, your body's natural janitor, to clear out the byproducts of ATP production. Here are some of the key mitochondrial nutrients that will help your patients get the most benefit from red light therapy:

- Nitric oxide
- Coenzyme Q10 (CoQ10)
- B vitamins
- Magnesium
- L-carnitine
- Alpha-lipoic acid
- N-Acetylcysteine (precursor to glutathione)

Chances are you've had your patients take many or all of these nutrients to help with energy production. But have you combined these specifically with red light therapy to get the most out of your treatment protocols? Perhaps you haven't seen ideal results with supplementation and are thus considering IV therapy or injections to optimize your patients' results. Combining intramuscular injection therapy with red light therapy is a great way to optimize results.

Red light therapy, much like acupuncture and trigger-point injections, has a stimulating effect on the local area being treated. Once you've determined which nutrients are needed to help your patients maximize their mitochondrial energy-making processes (I recommend white blood cell testing), it's time to add in a stimulating therapy.

Stimulating Circulation

Because red light therapy has limited potential due to its depth of penetration – most devices report 1-3 mm of penetration, with 10 mm on the maximum end – it is helpful to pair the therapy with another tool that increases circulation on a deeper level. This is why I have incorporated acupuncture and trigger-point injection therapy to enhance the effects of red light therapy.

Any puncture to the skin stimulates the body to increase circulation to that area. By using a tool that is able to penetrate up to an inch or more into the muscle tissue, you promote a stronger stimulatory effect on the circulation.

In Traditional Chinese Medicine, pain from injury and disease are described as having roots in poor circulation. You may be familiar with the terms, *qi* and blood deficiency, or *qi* and blood stagnation. These terms describe a lack of energy-making ability in an area of pain or injury, but also a lack of blood flow in these areas. So, what better way to stimulate blood and *qi* flow than to use acupuncture combined with red light therapy?

Another way to stimulate *qi* and blood flow is through the use of trigger-point injections. These injections are typically used to target the neuromuscular junction, the region where the nerve enters the muscle. This is a great spot to not only increase circulation, but also to deliver nutrients to the malnourished nerves and mitochondria of the muscle cells.

Trigger-Point Injections

Whether a patient has chronically tight and tense muscles due to stress, poor posture, or an acute or chronic injury, using trigger-point injections with vitamins, nutrients or peptides combined with red light therapy can be an excellent way to optimize patient results. By delivering nutrients directly to the affected area via an injection and promoting regional circulation at the same time, you are more effectively targeting the problem area and promoting faster results.

Since all patients come with unique needs and deficiencies, it's important to target your injection therapy to your patient's individual needs. Here are some injectable nutrients and peptides that are commonly indicated in my patients:

- A proprietary combination homeopathic – to help heal chronic or acute injuries
- MIC* B12, or B12 alone – to stimulate cell metabolism
- MIC* Carnitine, B1, B5 – to stimulate cell metabolism
- B Complex, or B6 alone – to stimulate cell metabolism
- BCAAs (branched-chain amino acids) – to stimulate muscle recovery
- CoQ10 – to boost energy production in a weak, locked long upper-back muscle
- NAD+ – to boost energy in a weak or chronically injured tendon or muscle region
- Glutathione – to enhance cellular detoxification
- Pentadecapeptide, containing 15 amino acids – to stimulate repair of tendons, ligaments, and muscles from injuries

*MIC = methionine, inositol, choline. These nutrients accelerate the breakdown of fat in the body, especially in stubborn areas such as cellulite-prone areas.

These nutrients and peptides can be combined to cover all aspects of your patient'scondition. It is also possible to utilize bio-puncture techniques, where acupuncture points are injected with homeopathic formulas for healing, in combination with red light therapy.

Recommendations for Success

Red light therapy, acupuncture, and trigger-point injections can all be combined in 1 visit. If you are not an acupuncturist, you can utilize myofascial techniques to promote local circulation. Treatments combining these therapies are typically performed 1-2 times per week for 4-10 weeks for acute conditions, with resolution commonly occurring in the 4-5 week range; chronic conditioning can take up to 10 weeks.

After injections and acupuncture needles are placed, red light therapy is applied to the affected area for 20 minutes; total treatment time is 50 minutes. If you use injections and red light therapy alone, treatment duration is 30 minutes.

After you have completed a series of treatments, it is recommended to have the patient consider returning for monthly sessions that address the enhancement of general circulation and mitochondrial support as a method to prevent injury and sustain the results already achieved. It's also recommended to have your patient consider the purchase of a home red light therapy panel to further enhance the benefits of the red light therapy.

By engaging your patient to participate in their continued care, you will see the long-standing benefits of promoting circulation: minimal or no pain, fewer injuries, and increased energy levels. Additionally, by seeing your patients once a month, you gain more insight into their daily struggles, obstacles, and routines. This allows you to help them on a deeper level to create a life that supports their health goals.

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Estrogen-Deficient Skin

Benefits from Topical Estrogens & Phytoestrogens

KATIE STROBE, ND

Menopause is a pivotal time in a woman's life that is characterized by decreased estrogen levels due to declining ovarian function. Biological aging accelerates throughout the body's tissues and is particularly noticeable on the skin, which loses structural integrity. The alterations to the skin include decreased vascularity, fibroblast production, collagen, and elastin, and increased matrix metalloproteinases (MMPs). These changes result in increased atrophy, wrinkling, dryness, and impaired wound healing. Research has demonstrated that oral estradiol can prevent and reverse these changes. Yet not every woman is a candidate for this type of therapy. The purpose of this article is to provide an overview of estrogen's role in the skin and to explore cutaneous interventions that work through the estrogen receptors. Specifically, this includes estriol and the phytoestrogens: genistein, daidzein, equol, and resveratrol.

Aging & Estrogen-Deficient Skin

With advances in research and medicine, women are living longer; however, the age of menopause remains stable at around 51 years old. Therefore, women are spending a significant amount of their lives in estrogen deficiency. Estrogens are steroidal hormones mainly produced by the ovaries in 3 main forms: estrone (E1), estradiol (E2), and estriol (E3). Estradiol makes up 80% of the estrogen in a women's body during her reproductive years. There are 2 types of estrogen receptors: ERα and ERβ. Estradiol binds equally to ERα and ERβ, estrone preferentially binds to ERα, whereas estriol has an affinity for ERβ.[1]

As skin ages, it becomes more susceptible to trauma, which can lead to increased bruising and lacerations. With a growing geriatric population, the burden of wound healing has increased. Estrogen has been shown to increase transforming growth factor-beta (TGF-β) levels, which enhances the quality and rate of wound healing.[2] In one study, men and women with punch biopsy wounds were treated with topical estrogen or a control for 7 days.[3] Compared to the control group, both men and women in the estrogen group showed higher collagen and an 18% decrease in the wound size. These findings illustrate that topical estrogen supports wound healing in both elderly women and men.[3]

Estrogen's Regulation of Skin Structure

The role played by estrogen in the skin includes maintaining thickness, regulating moisture, supporting elasticity, and facilitating would healing.[4] Some of the key structural components regulated by estrogen are collagen, elastin, water, and extracellular matrixes. Numerous studies indicate that in estrogen-deficient skin (EDS), these components are decreased.[5,6]

1) Collagen

A hallmark of aging skin is the accumulation of collagen breakdown products, which results in decreased mechanical tension and, as a result, wrinkle formation. Collagen gives the dermis its structural and mechanical integrity, and it makes up 70-80% of skin's dry weight.[7] The predominant form of collagen in the skin is collagen type I (80%); collagen type III makes up the remainder.[8] There is a strong correlation between menopausal EDS and decreased collagen levels.[8-13] In the first 5 years after menopause, as much as 30% of type I and type III collagen is lost.[5] Moreover, with each postmenopausal year, total collagen decreases by 2.1% for 15 years.[5] Oral, subcutaneous, and topical administration of estrogen have all been demonstrated to prevent collagen decline and to increase collagen content in the skin.[8,9,14-16]

2) Elastin

Elastin fibers are interwoven with collagen in the dermis to facilitate recoiling after transient stretching of the skin and to prevent overstretching. In EDS, structural changes to elastin fibers accelerate the loss of skin elasticity, which contributes to wrinkle formation.[17] Clinical studies indicate increased elasticity with topical application of estrogen.[14,18-20]

3) Water

The content of water in the skin is dependent on evaporation rate and dermal hydration.[9] Glycosaminoglycans (GAGs) in the dermis contain large amounts of water and are thus critical for hydration of the skin.[21] Another major player is hyaluronic acid (HA), which supports moisture content and also helps spread soluble factors and nutrients in the dermis.[22] Estrogen stimulates an increase in GAGs and HA, which leads to higher water content in the skin. Estrogen induces epidermal growth factor expression in keratinocytes, which increases HA expression.[21,23] Additionally, estrogen

With advances in research and medicine, women are living longer; however, the age of menopause remains stable at around 51 years old. Therefore, women are spending a significant amount of their lives in estrogen deficiency.

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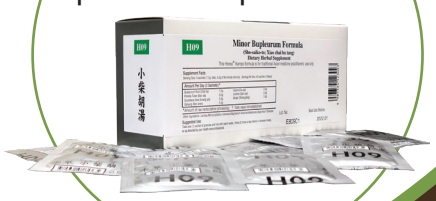

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supports water content in the skin through the promotion of sebum production in sebocytes, which results in moisture retention.[3] Clinical studies demonstrate that topical estradiol and estriol can increase GAGs and HA, thereby increasing the water content of the skin.[24,25]

4) Extracellular Matrix & Oxidative Damage

The extracellular matrix (ECM) is composed of water, polysaccharides, and structural proteins, and serves as a structural support for cells. In addition, the ECM provides a transport system for waste products and nutrients, and it lubricates cells.[26,27] Reactive oxygen species (ROS) such as hydrogen peroxide can cause significant damage to the ECM.[28] ROS can activate pathways for producing matrix metalloproteinases (MMPs), which are enzymes that break down collagen. An altered oxidative state is found in estrogen deficiency and can cause decreased collagen production.[29] In a human fibroblast cell culture study, estrogen was shown to increase survival of keratinocytes and fibroblasts exposed to H_20_2.[29] Experimental data indicate that estrogen can protect the skin from oxidative damage.[10]

Topical Therapies Targeting Estrogen Receptors

Estriol

As mentioned above, estriol (E3) is one of 3 main forms of estrogen. During pregnancy, estriol is produced by the placenta in high amounts, but in much lower quantities the rest of the time. Emerging evidence demonstrates that estriol has immunomodulatory properties and could thus be helpful in autoimmune diseases such as rheumatoid arthritis, thyroiditis, psoriasis, uveitis, and multiple sclerosis.[30] Currently, estriol is most widely known for its topical uses in gynecology to manage vaginal atrophy and urinary tract infections in postmenopausal women.[31,32] Now, dermatologists are looking at the topical use of estriol for its ability to support skin health, particularly in postmenopausal women. One of the allures of estriol is that it is a weak estrogen and believed to provide protection for menopausal symptoms without increasing the risks correlated with stronger estrogens.[33]

Dermatologists are looking at the topical use of estriol for its ability to support skin health, particularly in postmenopausal women. One of the allures of estriol is that it is a weak estrogen and believed to provide protection for menopausal symptoms without increasing the risks correlated with stronger estrogens.

In a clinical trial, Schmidt et al examined whether topical estradiol and estriol could reverse changes in aging skin.[14] Perimenopausal and postmenopausal women applied either 0.01% estradiol or a 0.03% estriol cream to the face and neck for 6 months. To evaluate possible systemic changes in hormone levels, serum levels of estradiol, follicle-stimulating hormone, and prolactin were checked monthly. Skin was checked before and after treatment via corneometry and skin profilometry for parameters such as skin elasticity, skin moisture, wrinkling, and pore size. In 10 cases, biopsies were included, and collagen types were analyzed via immunohistochemistry. The results showed that serum levels of estradiol were slightly increased in the estradiol group but not in the estriol group. Both treated groups showed a significant decrease in wrinkling, increased collagen fibers, improved moisture, and vascularization. Overall, the study showed that "both estrogen compounds were found to be highly effective in preventing or treating skin aging in perimenopausal women, clinically, by measurement data, and by an increase in collagen Type lll."[14]

Phytoestrogens

Phytoestrogens are polyphenolic plant compounds that exhibit estrogen-like effects in animals. They are structurally similar to 17β-estradiol and they weakly bind to estrogen receptors. There is growing interest in utilizing phytoestrogens to fight skin aging, since they have been shown to have antioxidant and anti-inflammatory properties, especially in postmenopausal women.[25,34-36] Additionally, phytoestrogens have been demonstrated to increase skin collagen levels, decrease collagen degradation, and increase hyaluronic acid and moisture in the skin.[37-40] Phytoestrogens have 4 phenolic classifications: stilbene, coumestan, lignan, and isoflavone.[41] The phytoestrogens we will take a closer look at are genistein, daidzein, equol, and resveratrol.

In a controlled clinical trial, 234 women applied an isoflavone cream to their face, neck, and 1 arm (with the other arm serving as the control) for 12 weeks.[4] Skin roughness and wrinkles improved by 39.2% and 22% respectively. Facial wrinkles decreased by 22%, and skin looseness decreased by 24%.

1) Genistein

Genistein is the main isoflavone found in soybeans and fermented soy foods. An animal study demonstrated interesting

results for genistein with regard to skin cancer prevention, skin elasticity, photoaging, skin dryness, and wrinkles.[38] One of the mechanisms by which genistein reduced skin aging in this study was by inducing the expression of VGEF and TGF-ß, which has the effect of increasing the thickness of skin collagen.[38] Additionally, genistein inhibits collagen degradation through the regulation of MMPs.[37] Genistein also exhibits antioxidant properties and has been shown to reduce ROS by regulating glutathione levels; this results in increased cell proliferation and viability rates.[42] Multiple clinical trials, in which topical 4% genistein cream was applied to the faces of postmenopausal women, showed significant improvement; in some cases, genistein performed better than estradiol.[43]

2) Daidzein

Like genistein, daidzein is a phytoestrogen isoflavone that is found mainly in soy foods. It has been shown to play a role in prevention and treatment of osteoporosis, cardiovascular disease, diabetes, cancer, and skin diseases.

In cultured dermal fibroblasts, daidzein was shown in a dose-dependent manner to stimulate estrogen receptor transcription, with up to a 2.5-fold induction compared to the control. Daidzein also increased the expression of collagen type IV, fibillin-1, and elastin in dermal fibroblasts.[36] Daidzein's pharmacological effects are believed to be due to its various metabolites, such as trihydroxy isoflavone and equol.[36]

3) Equol

Equol is found naturally in white cabbage and is produced from daidzein via bacterial metabolism in the gut. Equol has been shown to selectively bind to ERβ, which is abundant in fibroblasts in the dermis and keratinocytes in the epidermis.[36] This binding to ERβ initiates the transcription of antioxidant enzymes such as glutathione peroxidase and superoxide dismutase.[36] In a human dermal model, equol was shown to stimulate the production of type I and type III collagen and to downregulate MMPs (which degrade collagen).[44]

4) Resveratrol

Resveratrol, a powerful antioxidant polyphenol found in grapes, has grabbed the attention of researchers investigating a range of its anti-aging properties.[45] Recent studies demonstrate its protective role in the skin through many mechanisms. In human gene expression assays, resveratrol increased the expression of a variety of anti-aging genes, including sirtuin 1 activator, proliferating cell nuclear factor, nerve growth factor, collagen, elastin, and superoxide dismutase.[40] Additionally, resveratrol downregulated dermal aging genes, such as calcium-binding proteins and MMPs.[40] Resveratrol has been shown to act upon cell signaling pathways connected to UV-mediated photoaging. Specifically, in keratinocytes exposed to UVA radiation, resveratrol lowered ROS in a dose-dependent manner compared to the control.[43]

Summary

The decline of estrogen levels in the skin is a key endogenous cause of skin aging in women. Traditionally, women have used oral estradiol to reduce menopausal symptoms such as wrinkles. However, there can be side effects of this therapy, and it is not indicated in all women. Thus, topical application of estrogen continues to gain recognition as a practical, convenient, and effective means of administration. The use of locally applied low concentrations of estriol, a weak estrogen, has been demonstrated to support skin thickness, increase hydration, improve elasticity, and enhance wound healing with few side effects. Activation of estrogen receptors by phytoestrogens is another method to improve skin health that is gaining recognition. There is still research to be done; however, in the meantime, targeting cutaneous estrogen receptors with topical estriol and phytoestrogens to support skin health in postmenopausal women shows promise.

References 17-45 available online at ndnr.com

Katie Strobe, ND, graduated from the University of Washington with degrees in zoology and chemistry. She then embarked upon several research projects at the Institute for Systems Biology, where she researched medical topics such as immunology, infectious disease, genetics, microbiology, and systems biology. Dr Strobe's research led to publications in high-impact scientific journals, such as *Nature* and *PNAS*. She later followed her passion to move from "bench to bedside" and earned her naturopathic doctorate from Bastyr University in Seattle, WA. During this time, Dr Strobe received several prestigious awards, including a training grant from the National Institute of Health. Facebook: https://www.facebook.com/profile.php?id=100010018719360

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The Anti-Aging Effects of DHEA

CARRIE DECKER, ND

This review of literature, pertaining to the effects of DHEA on aging, stems from a clinical case I saw early on in my practice when I was seeing patients in a variety of smaller towns in Wisconsin. Not surprisingly, many of them were what you might expect of Wisconsinites: hardy, dependable folk, never to miss a day of work on the farm despite every imaginable weather system moving through. The case I am speaking of involved an elderly gentleman, nearly 80 years of age, who was still doing everything it took to run his dairy farm. He didn't come in for a specific problem; rather, he was looking for support with his energy levels. (If the reader doesn't have familiarity with the amount of effort this gentleman's day-to-day occupation demands, it should suffice to say that it would leave me feeling exhausted as well!)

This patient came in with a box of numerous self-selected supplements, likely purchased in response to many infomercials and print media targeting an aging population. After reviewing the supplement facts for each and every product, I found that this elderly rotund gentleman was taking 300 mg of DHEA each day. Although at the time I wasn't quite sure if any long-term safety data were available for that high of a dose, especially in the elderly, it definitely wasn't a dose I was ready to recommend. I advised that he limit his DHEA intake to 50 mg daily and have further labs done to rule out common causes of fatigue, like anemia, hypothyroidism, or other pathology. He never came back for a return visit, so I have nothing more to say about his case specifically.

I'm probably not alone as a practitioner, outside of those who specialize in anti-aging therapies or hormone replacement, in lacking knowledge of the wide array of clinical research on DHEA with regard to aging, as well as its safety at higher doses, such as this case. Herein, I will review the research in this realm, as well as studies related to DHEA and sexual health, which is also a common challenge with aging.

DHEA: The Basics

DHEA and its sulfated form, DHEA-S, are the most abundant steroid hormones in the human body.[1] They are primarily produced in the adrenal cortex, with smaller amounts of DHEA being synthesized in the ovaries and testes. Research suggests that DHEA and DHEA-S are also produced in the brain.[2] DHEA is a precursor to estradiol, estrone, testosterone, and 5α-dihydrotestosterone (5α-DHT).[3] DHEA has roughly 1/20th of the androgen potency of testosterone.[4]

Much like estrogen and testosterone, levels of DHEA and DHEA-S decrease with age and are approximately 25% of their peak values by age 70.[2,5] Thus, we see substantial research regarding DHEA and its supplementation surrounding common concerns with aging: libido, bone health, body composition, metabolism, and skin integrity and appearance.

> In all individuals taking 50 mg/day of DHEA for 1 year, there was a significant increase in skin hydration and sebum levels, and facial yellowness decreased. There also was a significant increase in epidermal thickness on the dorsal hand in the individuals whose baseline DHEA-S levels were in the lowest quartile.

One of the first questions on practitioners' minds is what impact DHEA supplementation has, not only on levels of DHEA and DHEA-S, but also their downstream hormone metabolites, estradiol and testosterone. Concerns about prostate hyperplasia and hormone-sensitive cancers exist with therapies known to augment these hormones, and are well justified.

Effect of DHEA Supplementation on Hormones

In a small short-term study designed to look at the effects of DHEA supplementation on hormone levels, 24 healthy elderly adults, ages 60 to 79, were given 25-50 mg of DHEA for 8 days. Blood levels of DHEA, DHEA-S, and several downstream hormone metabolites were assessed on days 1 and 8.[3] Supplementation of 25 mg of DHEA was adequate to restore DHEA-S levels to that of young adults, while at 50 mg the level remained in the normal range for young men but exceeded the upper normal level for healthy women.

On the day it was taken, supplementation of DHEA significantly increased levels of DHEA, DHEA-S, and estrone in both men and women. A significant increase in estradiol level was seen in women but not in men on day 8 only.[3] In men, DHEA supplementation increased testosterone non-significantly, while in women, on day 8 a significant and dose-dependent increase in testosterone was seen. It is noteworthy that a similar increase in *total* testosterone was observed in the men and women; however, it was only significant in the women, as baseline levels were less than 1/10th that of the men.[3]

In this short trial, no accumulation of steroids (DHEA, DHEA-S, testosterone, estradiol, and estrone) was observed, with the area under the curve (AUC) at day 8 for these hormones not being statistically different than on day 1. Comparing hormone profiles from day 1 to day 8, in women, a trend towards increased estradiol and estrone levels (suggesting hormone accumulation) was observed, but was not significant. The authors of the study concluded, "No worrying transformation to androgen and estrogen was recorded; indeed, the limited increased estradiol in aged women could be predicted to be beneficial."[3]

In a longer follow-up study designed as a randomized, double-blind, placebo-controlled trial (RDBPCT), a population of 280 men and women, ranging in age from 60 to 79 years, were given 50 mg of DHEA or placebo daily for a year.[5] With supplementation, DHEA-S levels were restored to "normal youthful levels" in both sexes. In men, there was no significant increase in testosterone. In women, however, testosterone levels in 14 subjects were significantly higher by month 6, exceeding the normal range for menstruating women. There was a trend of increasing estradiol levels in men at month 12, whereas in women this increase was significant, with levels falling within normal ranges of the early follicular phase of menstruating women. No adverse effects associated with DHEA supplementation were noted, and there was no significant change in the prostate specific antigen (PSA) levels in the men.[5]

Long-Term DHEA Use in Individuals 65+

In this aforementioned 1-year study of DHEA supplementation at 50 mg/day, numerous clinical parameters were also assessed.[5] Changes were most noteworthy in the women, particularly those over 70 years of age. DHEA supplementation positively affected bone health, decreasing bone turnover in women over age 70, and significantly improved most parameters related to libido in this age group of the women as well. In all individuals taking DHEA, there was a significant increase in skin hydration and sebum levels, and facial yellowness decreased. There also was a significant increase in epidermal thickness on the dorsal hand in the individuals whose baseline DHEA-S levels were in the lowest quartile.[5]

The overall findings of this study were well summarized in the authors' conclusion: "A number of biological indices confirmed the lack of harmful consequences of this 50 mg/day DHEA administration over one year, also indicating that this kind of replacement therapy normalized some effects of aging."[5]

Additional human studies in aging individuals (typically 65 years or older) have shown that long-term

DHEA supplementation at 50 mg/day for 6 months to 2 years may decrease insulin resistance, triglycerides, and the inflammatory cytokines interleukin (IL)-6 and tumor necrosis factor (TNF)-α[6]; enhance the effects of weight training on muscle mass[7]; decrease arterial stiffness[8]; improve bone mineral density (BMD)[9]; and decrease visceral and subcutaneous fat.[10] At a dose of 25 mg/day for 6 months, DHEA supplementation also improved cognitive scores in women with mild-to-moderate cognitive impairment.[11]

In these studies,[5-11] no serious adverse events attributed to DHEA supplementation were reported; however, over the long time-period, there were some serious adverse events in the older population included in the studies. Mild adverse events included increased acne and facial hair growth in a small number of the women. There were no changes in PSA levels and liver function tests, and no increases in mammogram or Pap smear abnormalities in the studies in which these parameters were assessed.

Interestingly, a study of middle-aged practitioners of Tai Chi found that these individuals had significantly higher levels of DHEA-S and lower levels of cortisol, shedding light on a potential mechanism by which this practice enhances longevity.[12]

Other Specific Applications

DHEA & Libido

In addition to the findings in women age 70 and older, DHEA may improve libido in younger individuals, primarily females. In postmenopausal women, age 50 to 60, DHEA at a low dose of only 10 mg/day for 12 months was shown to significantly improve sexual function and frequency compared to the control intervention (400 IU of vitamin D).[13] In a population of men and women with hypoactive sexual desire disorder, at a dose of 100 mg/day for 6 weeks, treatment with DHEA significantly improved sexual arousal and satisfaction in women. In the men, however, no improvements were seen.[14]

It is not uncommon for women to have sexual side effects from oral contraceptive (OC) use, with a small but still substantial percentage experiencing a decline in libido.[15] In women taking OCs, the addition of 50 mg/day of DHEA significantly improved numerous markers of sexual function, which had declined with initiation of the OC medication.[16] The women who had higher free testosterone levels during DHEA administration were found to experience greater effects of DHEA on sexual arousal and desire.

In women, DHEA conversion to testosterone by the adrenals is the primary source of testosterone; hence, with adrenal insufficiency, women often experience a decline in libido. In men, however, sexual function and testosterone levels are largely preserved.[17] Multiple studies have shown that 50 mg of DHEA is a suitable dose for women with adrenal insufficiency, in addition to other indicated treatments.[18-20] This dose also supports improvements in hormone levels, metabolic parameters, well-being, anxiety and depression, and frequency of sexual thoughts and interest. Furthermore, DHEA has been shown to improve alertness, stamina, and sexual interest or activity in women with hypopituitarism when added to other indicated hormone replacement therapies.[21]

Supplementation with DHEA has been shown to enhance sexual arousal in postmenopausal women acutely as well. In a RDPBCT with crossover, oral administration of 300 mg of DHEA significantly increased both the mental and physical arousal response to viewing an erotic video 60 minutes later.[22] However, a similarly designed study did not show a significant effect in premenopausal women.[23]

Erectile Dysfunction

Multiple population studies have shown an inverse relationship between DHEA levels and the incidence of erectile dysfunction (ED).[24,25] In addition to being a testosterone precursor, DHEA's demonstrated anti-inflammatory and vasodilatory effects suggest its potential benefit in the treatment of ED.[26]

There is not a preponderance of evidence that suggests DHEA may be useful in ED, although 2 studies have demonstrated a positive impact. In one small prospective study without placebo, supplementation with 50 mg of DHEA for 6 months was shown to improve ED in the men who were naïve to both hormone replacement and treatment for ED.[27] Men with hypertension and those with ED having no known organic etiology both saw significant improvements in multiple International Index of Erectile Function (IIEF) sub-scores after treatment, while those with diabetes mellitus and neurological disorders did not see any change.

In a RDBPCT of men with ED without subclassification of etiology, treatment with 50 mg/day of DHEA for 6 months was associated with significantly higher scores on all IIEF domains compared to placebo[28]; however, the study had a fairly high dropout rate, especially in the placebo group, due to an insufficient response to treatment.

Other Groups

DHEA has also been shown to improve various markers of bone health in women with anorexia nervosa[29-31] and in women taking glucocorticoids for extended periods of time, ranging from 6 months to more than 3 years.[32-34] In these studies, the dose of DHEA ranged from 25 to 200 mg, with the period of treatment being up to 1 year. In the study administering the highest dose (200 mg) for the longest period of time (1 year), no adverse effects were reported; however, there was a significant increase in testosterone, but not estradiol, levels.[33]

Intravaginal Use

Multiple studies have shown that intravaginal preparations of DHEA improve dyspareunia, vaginal tissue atrophy, and related genitourinary symptoms in postmenopausal women.[35-37] Long-term treatment with intravaginal preparations, at doses of up to 13 mg/day, has been shown to be very effective for these local tissue-related complaints, with little to no change in serum sex steroid levels.[38]

Potential Contraindications & Adverse Effects

With DHEA, mild adverse effects are typically not seen acutely, but can be seen with prolonged use. Testing of DHEA levels to ensure they are not high or in the high-normal range prior to therapy initiation may help prevent untoward effects. Adverse effects are mild and may include complaints of oily skin, hair growth, acne, and body odor[39,40] – signs we typically associate with increased testosterone levels. However, hair *loss* can also be seen, as DHEA converts to more potent androgens in the hair follicle, which can interfere with hair growth.[41] Studies suggest that the other epidermal effects also may be related to steroidal production in the skin,[42] which oral DHEA supplementation additionally enhances, and to which some individuals may be more sensitive.

As mentioned, in men, long-term studies have shown DHEA did not have adverse effects on prostate markers.[5,28] In elderly women – although a small, yet significant, increase in estradiol level has been seen with daily supplementation of 50 mg of DHEA – in the studies that also examined mammography and Pap smear results, no increase in abnormalities was observed.

Clinically, DHEA is often used at a low dose initially, and if there are no significant adverse effects, the dose is gradually increased to levels shown to be effective. To the knowledge of this author, studies have not shown DHEA supplementation to be safe in individuals with a history of breast or hormone-sensitive cancers, and therefore should be avoided in this population.

Closing Comments

Given the inevitable decline in DHEA and its downstream hormones that we all experience with aging, it is no surprise to see substantial research with DHEA supplementation focused on age-related changes. Much like the benefits we see with the replacement of estrogen and testosterone, similar effects may be seen with DHEA. While estrogen and testosterone are prescription only, because DHEA is considered a dietary supplement in the United States, it is available for use by practitioners without prescribing rights as well as by consumers. Thus, it is important to understand both its clinical indications as well as its potential for mis-use – such that the next elderly gentleman you see in your practice with a chief complaint of fatigue is correctly advised of more appropriate alternate interventions.

References 10-42 available online at ndnr.com

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Barch Birk

JACOB SCHOR, ND, FABNO

My wife and I have retreated to a small lakeside summer cabin in Maine to winter the pandemic. Doing so has made social distancing easy; there are no people with whom to socialize. The cabin was built 40 years back for summer weekends, not for winter use, so we have stockpiled firewood, topped off the propane tanks, and have taken to collecting birch bark, or "barch birk" – a spoonerism that has become part of our vocabulary.

Birch Bark

Birch bark is an excellent bark for starting fires. It ignites easily and burns intensely – characteristics that are undiminished by rain, sleet, or snow. This ability to start a fire quickly and reliably during the winter seems desirable; we hoard bark like neurotics hoard their lorazepam.

> We hoard bark like neurotics hoard their lorazepam.

Remarkably, birch bark doesn't decay. Fallen birch trees rot away, leaving hollow tubes of bark. One can shake out the contents of an appropriately sized birch log, and employ the resulting cylinder as an approximation of a hat (see photo). Social distancing may eventually be associated with a deteriorated sense of appropriate attire.

Birch trees are instantly recognizable by the bark's coloration. It is strikingly white. Most tree bark is dark colored, combinations of gray and brown. Nature hasn't made many things quite as bright white as birch bark. By the same token, few things in nature are quite as black as the markings on birch bark.

Birch trees are the most northern dwelling of all deciduous trees, their range extending to northern Alaska and east to Nunavut. They are the first trees to return when forests have been clear-cut, and one can imagine them following closely behind retreating glaciers after the last Ice Age. It is their white reflective bark that makes birch trees so cold-tolerant. Most trees try to absorb the sun's heat through their bark to lengthen their growing season. Birch trees have taken the opposite approach. In the far north, midwinter thaws threaten their survival because they can trigger the sap to flow too early. Subsequent cold spells would freeze the sap, injuring or killing the trees. Reflecting away the sun's warmth and staying dormant through the winter thus provides a survival advantage.

This whiteness and reflective qualities of the bark are due to the chemical betulin, a powdery white substance that separates the thin bark layers. Betulin typically makes up a quarter of the bark's dry weight, though in some species it constitutes almost a third of the weight.[1] Betulin is both hydrophobic and quite flammable, so is responsible for the bark's waterproofness and fire-starting trait.

Doctrine of Signatures

These attributes of birch bark are of interest when considered in the light of the Doctrine of Signatures (which states that a plant's appearance suggests its medicinal uses). Discussion of the doctrine quickly becomes parochial, dividing those who believe in some divine messaging within the appearance of plants from those who cannot comprehend how random evolution might result in some cosmic hint of how a plant can benefit humans.

Our colleague, Robin Dipasquale, wrote a beautifully descriptive article on the medicinal uses of birch bark for this publication 6 years ago.[2] In it, she wrote,

> *Under the doctrine of signatures, the skin is structured like layers of bark, indicating the use of birch for skin conditions. Native Americans prepared a mushy paste by boiling and pounding the inner bark, so it could be spread on inflammatory skin conditions, ulcers, cuts, and wounds, where it would diminish swelling and prevent infection. The harvesting of the bark is best done when the sap is flowing and when the moon is close to full, for this is when the water is running and the tree is more willing to let go of its bark.*

Betulinic Acid & CA

The most interesting recent research published on birch bark is in fact related to skin. John Pezzuto's report that betulinic acid was capable of killing melanoma cells first caught my attention in 1995.[3] His initial extract was, according to the *New York Times*, derived from birch bark in a wood pile that had been left to rot for several years:

> *A woodpile near Dr. Pezzuto's laboratory provided about 50 pounds of bark that had dropped off logs. …. Dr. Pezzuto's research team put melanoma cells under the skin of mice near the right leg. Once the cells formed tumors large enough to feel, each mouse got six doses of betulinic acid, one every three days, injected into the abdomen. In one group of five mice, the treatment shrank tumors by 70 percent in two animals and 40 percent in two others. In four of five mice with a different strain of melanoma, the tumors virtually disappeared.*
>
> *(NY Times, 1995)*[4]

Betulin, in the bark, is the precursor of betulinic acid, which is considered the far more biologically active form. The conversion can be accomplished industrially via simple oxidation-reduction protocols.[5] In Pezzuto's case, though, it sounds like some sort of natural microbial degradation did the trick.

In a paper published in 2003, Pezzuto detailed betulinic acid's mechanism of action, including a troubling revelation, that "[cancer] cells treated with betulinic acid generate ROS. Preincubation of cells with antioxidants blocks the process of programmed cell death, and prevents the phosphorylation of p38…"[6]

As a profession, we naturopathic doctors have favored using antioxidants to treat cancer, while most medical doctors have hesitated. Pezzuto's findings should have given pause to those who've been certain that treating cancer patients with high-dose antioxidants is beneficial under all circumstances. If the anticancer effect of betulinic acid is nullified by antioxidants, we should wonder whether other natural substances might behave similarly.

We've seen a steady stream of research on betulinic acid published in the decades since Pezzuto's paper. In-vitro work has shown that…

> *Betulinic acid (BA) … has been investigated … for a plethora of beneficial properties, including anti-cancer, anti-inflammatory, anti-angiogenic, immune-modulatory, and anti-HIV effects. In particular, BA has been reported to be effective in vitro against tumor cell lines of different origins, and also in vivo, in animal models of cancer. …. BA has also an anti-metastatic effect via the prevention of the epithelial-to-mesencymal [sic] transition in highly aggressive melanoma cells.*
>
> *(Gheorgheosu et al, 2014)*[7]

A search on PubMed yields recent studies on betulinic acid's potential for treating cancers of the breast,[8,9] ovaries,[10] lungs,[11] pancreas,[12] colon[13] (including cancer stem cells[14]), liver,[15] and prostate.[16] The list could be longer, but this should suffice to convey the idea that betulinic acid is being tested against a broad range of cancer types.

There are other aspects related to oncology that are worth noting. A 2009 study of betulinic acid in combination with standard chemotherapy drugs indicates that it may be useful in targeting drug-resistant tumors.[17] The compound also enhances the anticancer effect of hyperthermia[18] and potentiates radiation therapy.[19,20]

Absorption Problems

The problem with betulinic acid, similar to some other natural compounds, is absorption. It is hydrophobic. Recent studies are employing nanoparticles as a work-around to get it absorbed.[21-24] While betulinic acid is exciting in test tubes, getting it to work in animals (and humans) has been challenging.[25] This isn't the first natural product to present absorption problems. It is surprising not to find supplement vendors offering products designed to enhance absorption.

Topical Uses

Although betulinic acid might not absorb as well as we would like, topical transdermal application seems to work. A non-randomized pilot study, published in 2006, that used birch bark extract to treat actinic keratoses in humans is "encouraging."[26] Twenty-eight patients with actinic keratoses were treated with either betulinic acid in a topical birch bark extract (sold in Germany as a cosmetic) or with a combination of betulinic acid and standard cryotherapy. In 79% of the patients using only birch extract, more than 75% of their lesions had cleared after 2 months. The clearance was 93% in the patients receiving the combination treatment.[26]

The author modeling a birch bark hat (Photo by Rena Bloom, ND)

Topical use of birch extracts does seem promising. Two 2020 reports from Lisa Weber in Hannover, Germany, describe positive results using topical betulinic acid for treating melanoma in skin samples from gray horses, a breed that has a strong genetic predisposition to skin cancer.[27,28]

Wound Healing

Another topical use of birch bark extracts that has received recent attention is to aid wound healing.

A patented topical oleogel extract of birch bark was approved in 2016 by European regulators to accelerate wound healing.[29] The oleogel was shown to hasten wound healing by more than a day in patients who received skin grafts (n=217).[30].

And in a study of 37 burn patients who had half their wounds treated with the patented oleogel birch bark extract and the other half with a standard disinfectant gel, time to wound closure dropped from 8.8 days to 7.6 days for the wounds treated with the oleogel.[31]

What's next?

Given that many skin cancer patients undergo surgery, we must contemplate whether using a topical birch ointment such as this European wound healing gel, or perhaps the German cosmetic formula, might not only help them heal faster, but also whether some modicum of anticancer effect might seep through the skin. Birch bark and its derivative, betulinic acid, have potential, yet seem underutilized in practice.

My imagination quickly runs wild with the idea of steeping birch bark in a hot tub and then soaking patients in it. Or perhaps covering them in a paste of pulverized birch bark and then drying it in a sauna.

References available online at ndnr.com

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The Skin

An Outer Reflection of Inner Aging

CHRIS D. MELETIS, ND

The human skin is the largest organ of the body. It comprises 15% of body weight and has an average surface area of around 2 m^2 (21.5 square feet).[1] The skin has a high turnover rate, with epidermal skin cells replacing themselves approximately once every 27 days.[2] The skin contains and constrains the trillions of other cells that constitute the "us" that resides within. The skin is our interface between our internal and external environment. It is highly complex, with several layers of tissues, each different in their cellular composition. Skin provides important functions, including prevention of water loss and acting as a barrier against harmful substances. Unfortunately, more than 100 million people, one-third of the US population, have at least 1 skin disease.[3]

Contrary to the usual advice to not judge a book by its cover, the appearance of the skin can actually reveal the inner health of a patient. The question is how do we as clinicians employ this fact as the proverbial reading of the tea leaves of what the past, present, and future may hold for our patients? Our clinically trained eye and our subconscious inner voice can discern how Patient X, Patient Y, or Patient Z feels based upon how they look during their visit. If they look unwell, that might guide our treatment. In contrast, if a patient has a radiant glow, sparkle in their eye, and exude vibrant health, we have an inkling that all is well. Even young children can look across a room and proclaim in their innocence that Aunt Betty or Uncle George doesn't look well. Interestingly, skin blood perfusion and oxygenation impact the way we perceive a person's health and can even influence the way people choose their mates.[4] However, as clinicians, we look for specific aspects of a patient's appearance (see Table 1) that can provide clues as to the state of their health.

It is not a foreign concept to clinicians to use cellular lifespan measurements to determine nutritional and wellness status. For example, we use the lifespan of red blood cells (RBCs), which live some 90-120 days, to glean insight into our patients' health. In addition, by measuring glycosylated hemoglobin (now designated HA1c) and mean corpuscular volume (MCV), we can discern trends towards microcytic anemia (most commonly iron deficiency) or megaloblastic anemia (which frequently reflects a deficit in B12 and/or folate). Further insights are possible with measurements of RBC zinc and RBC magnesium. Our skin is nothing more than a collection of cells such as fibroblasts and keratinocytes. Therefore, it is equally important that we support a healthy lifespan of skin cells by addressing the factors mentioned in this article. In addition to discussing these primary factors that affect the aging skin and offering recommendations, I'll delve into the connection between the health of the skin and the health of the internal body.

Skin & the Mitochondria

Addressing the health of the mitochondria is an often-overlooked way of improving aging skin. It is also a way of building a stronger foundational wellness that may result in outward changes that reflect inner health. It is now thought that mitochondria are important modulators of skin physiology.[5] For example, mitochondria oversee keratinocyte differentiation via production of reactive oxygen species (ROS), which are needed for epidermal differentiation and hair follicle development.[6] Mitochondria are also involved in the function and pigmentation of melanocytes.[5] Further support for the mitochondria's involvement in skin health lies in the fact that 10% of patients who have primary mitochondrial conditions exhibit skin manifestations including rashes, pigmentation abnormalities, and blueness of the extremities (acrocyanosis).[5] Moreover, several skin disorders are associated with changes in mitochondrial energy metabolism, including Dupuytren's disease, atopic dermatitis, and melanoma.[5] Per Feichtinger and colleagues, "Thus, we assume that mitochondrial involvement is the rule rather than the exception in skin diseases."[5]

Ultraviolet-B (UVB) radiation causes mitochondrial dysfunction and may be the primary mechanism by which long-term sun exposure can age the skin.[7] Supporting mitochondrial health can therefore be beneficial for aged skin and in certain skin conditions. Mitochondrial rejuvenators of interest include coenzyme Q10 (CoQ10),[8] alpha-lipoic acid,[9] and resveratrol.[10,11] CoQ10 and alpha-lipoic acid are used both topically and orally for skin health.

> UVB radiation causes mitochondrial dysfunction and may be the primary mechanism by which long-term sun exposure can age the skin.

Lipofuscin, Telomeres, & the Skin Microbiome

Lipofuscin & Age Spots

Lipofuscin is a pigment composed of lipids, proteins, and carbohydrates, and it increases with age. It is produced by the synthesis of free radicals, which generate waste products, including lipofuscin.[12] This age pigment is not just an indicator of aging; it has also been shown in animal studies to interfere with critical chemical and biological pathways that cells need in order to function effectively.[12] Mitochondrial dysfunction can cause cells to age faster and to build up lipofuscin.[13]

Lipofuscin accumulation in the skin is associated with dark, smooth, brown spots known as age spots or liver spots. They are most common on the tops of the hands, but also occur on the chest and cheeks of the face. These should not be confused with the UV-induced pigmentation caused by another pigment, melanin. However, lipofuscin is not only found in the skin; it can also accumulate in neurons, cardiac myocytes, retinal epithelial pigment cells, and hepatocytes.[14] Therefore, age spots on the hands or face should serve as a red flag for other conditions, including age-related macular degeneration and neurodegenerative disorders such as Alzheimer's and Parkinson's disease.[14] In one study, an antioxidant supplement containing selenium as L-selenomethionine (300 µg), zinc (45 mg), vitamin C (270 mg), vitamin A (2.7 mg), vitamin B6 (6 mg), and vitamin E (465 mg) was given to elderly people and caused a significant drop in RBC lipofuscin.[15]

Telomeres

The accumulation of lipofuscin is not the only culprit in the aging process. Lipofuscin combines with other factors, including the shortening of telomeres, the protective "caps" on the ends of chromosomes that slow their degradation. A certain amount of telomere shortening is necessary to prevent cells from becoming cancerous. However, excessive telomere shortening, which occurs with aging, is associated with a number of health disorders and aging itself.[16] The enzyme telomerase is responsible for maintaining telomere length. A deficiency of this enzyme in mouse models was associated with telomere shortening and skin aging.[16]

In humans, evidence of the connection between telomere shortening and skin health is found in a disease called dyskeratosis congenita (DC), which is associated with mutations in the gene that codes for telomerase.[17] Patients with this disease often have reticulated skin pigmentation.[18] People with DC have short telomeres, indicating that skin disorders that occur in these patients can be reduced by supporting telomere length.[17]

There is other evidence supporting the relationship between telomeres and skin health. Studies of human skin keratinocytes have found that regulation of telomere length and telomerase activity is important in these cells.[16] Telomere shortening in fibroblast cells of the dermis is associated with epidermal damage.[16]

Since the skin acts as an environmental barrier for the body, it is exposed to ROS, which are involved in telomere shortening and aging skin.[16] In part because of their exposure to ROS, telomeres in skin cells may be especially vulnerable to accelerated shortening.[16] With excessive sun exposure, UV radiation damages DNA and increases telomere shortening.[19] In fact, skin aging and sun damage share a common pathway that involves impaired telomeres.[19] As telomere length shortens, lipofuscin also increases.[14]

Natural strategies for supporting telomere health include supplementing with an isolated extract of *Astragalus membranaceus*[20] as well as resveratrol[21] and other antioxidants that inhibit overproduction of ROS.

Skin Microbiome

The saying "cleanliness is next to godliness" may not apply to the skin. It's possible to be too clean. Although in clinical practice we often acknowledge the gastrointestinal microbiome, oral microbiome, and the female reproductive microbiome, we often neglect to think about the skin microbiome.[22] This is understandable, as research into the skin microbiome only began relatively recently.[22] Frequent washing has been shown to alter the skin microbiota.[22] Furthermore, the moment our patients place any topical substance, natural or synthetic, on their skin, they are at risk of altering their skin microecology and thus the diversity or pathogenicity of their dermal microbes. Even a natural substance can alter the skin microbiome in a deleterious fashion, either acutely or chronically. What is strong enough to help may be strong enough to harm. For example, I have witnessed many overzealous patients reporting back on the caustic effects of full-strength tea tree oil on sensitive skin.

Wound Healing & Tissue Perfusion

It's also important to remember that our skin must breathe. Consequently, even a simple barrier of a topical agent can alter oxygenation of tissues and compound the effects of already-poor capillary oxygen delivery in some patients. In patients with cardiac issues who have decreased perfusion or in people with conditions such as peripheral artery disease, the ability of the skin to breathe becomes even more important.

Blood flow perfuses the body with oxygen, nutrients, hormones, cells, products necessary for wound healing, and platelets.[23] As an example of how inner health is linked with outward appearance, blood flow to the skin plays an important role in wound healing. Individuals with heart disease or diabetes mellitus have reduced microvascular perfusion, resulting in slower wound healing.[24] Researchers believe that because aged-garlic extract increased microcirculation in patients with an increased risk for cardiovascular events, it may also improve wound healing.[24]

Since the early 1990s, I have observed that something as simple as using an oxygen tent with a simple oxygen generator can help tissue healing when properly employed, while at the same time identifying and removing the obstacles to cure. Oxygen is not only essential to wound healing; it also guards against infection.[25] Oxygen's role in wound healing is a vast and complex topic. More information can be found in my free ebook, *Oxygen: Nature's Gift of Life and Health*, available by emailing me at: NaturalMedMan@hotmail.com.

Nitric Oxide

Nitric oxide (NO) is a molecular messenger involved in skin health. Balanced levels of NO produced in the skin support the maintenance of the skin barrier and regulate blood flow in the microvasculature. When the skin is exposed to UV light or is wounded, higher levels of nitric oxide synthase are produced, which trigger other more complex reactions.[26] After the skin is exposed to UV radiation, there is a burst of NO that helps initiate melanogenesis, erythema, and immunosuppression while at the same time protecting keratinocytes against apoptosis caused by UV radiation.[26] In skin wounds, increased NO synthase activity helps send infiltrating white blood cells to the site of injury and initiates the inflammation necessary for a healing response.[26] Because tissue perfusion is so important for wound healing, and because NO is a vasodilator, utilizing a nitrate-rich supplement that

Table 1: **How the Skin Talks**

Condition of Skin	Possible Meaning
Tenting	Dehydration
Pallor	Anemia; impaired circulation; sympathetic/parasympathetic imbalances, etc
Jaundice	Liver disorder; hemolytic anemia, etc
Flushing	Vascular, neurological, or endocrine imbalances
Rashes/Dermatitis/ Eczema	Internal and external altered homeostasis; nutritional imbalances; gastrointestinal dysfunction; immunological disorder, including viral, spirochete, or bacterial infection, or allergy
Dermatitis herpetiformis	Celiac disease, etc
Psoriasis	Polyamine, cytokine, or immunological imbalances; liver disorder, etc
Hives/Urticaria	Internal and external altered homeostasis; immunological over-reactivity; hematological disorder; mastocytosis; carcinoid syndrome
Dry/Moist/Oily skin	Dehydration; imbalanced essential fatty acid intake; impaired circulation; thyroid or gonadal dysfunction
Thin skin	Senescence; low growth hormone; high cortisol; thyroid dysfunction; vascular insufficiency, etc
Acne	Endocrine, biochemical, or skin microbiome imbalances
Rosacea	***Helicobacter pylori*** infection; hypochlorhydria, etc

Note: These are functional clinical considerations, and the list is not exhaustive.

contains beetroot may help deliver oxygen to tissues.[27]

Hyaluronic Acid: A Natural Moisturizer

Moisture content in the skin also impacts skin aging and its ability to heal. Hyaluronic acid (HA) is a polysaccharide and a glycosaminoglycan that acts as a natural lubricant in the skin, between joints, and in the vitreous humour of the eye. More than half of the HA in the body is concentrated in the skin.[28] HA levels fall with aging and may play a role in the increased dryness and wrinkling of aged skin. HA is important for skin hydration and wound healing. Wounded tissue that is high in HA does not form scars when healing.[28] HA is found in many topical skin lotions[29] and can be injected into the skin,[30] but it can also be used orally. Oral supplementation with HA can have beneficial results not only in the skin, but also on joint health.[31]

Epigenetics & the Skin

Epigenetics refers to heritable alterations in gene expression that do not involve changes in the DNA sequence. Epigenetic mechanisms include DNA methylation, histone modification, chromatin remodeling, and RNA interference. Epigenetics serve as the rheostat determining integrity, readability, and sustainability of both the cells themselves, and the DNA and mitochondria within. Epigenetic changes in the skin can be triggered by lifestyle factors such as psychological stress,[32] poor diet,[33,34] and lack of sleep,[35,36] in addition to exposure to UV radiation.[37]

Antioxidant consumption may lead to beneficial epigenetic alterations in the skin.[38,39] Dietary antioxidants that protect the skin from UV radiation damage include carotenoids and polyphenols, such as apigenin (a flavonoid occurring in numerous herbs, fruits, and vegetables), quercetin, curcumin, silymarin, proanthocyanidins, and resveratrol.[40] It should also be noted that nicotinamide reduces inflammation and arrests the reduction in ATP levels that occurs after exposure to UV radiation; nicotinamide has also been shown to have other beneficial effects in cell culture, rodent, and human studies, indicating that supplementation with this nutrient may have clinical usefulness.[41]

Skin as a Detox Organ

The skin is the barrier protecting us from the outside world. Consequently, when exposed to toxins, the skin can become a doorway leading to full body toxicity. The skin is frequently exposed to toxins such as phthalates and parabens from plastic, personal care products, and other sources. Toxins can permeate all layers of the epidermis, the skin's uppermost layer, and subsequently be carried away into the bloodstream by the capillaries of the dermis.[42] Butylparabens are known to easily penetrate the stratum corneum layer of the skin.[43] Furthermore, human research indicates that dermal absorption is an important source of phthalate toxicity.[44]

Even something as seemingly harmless as sunscreen may contain toxic, carcinogenic chemicals that can impact skin, cells, and hormones.[45] Chemicals often found in sunscreen, such as homosalate, octisalate, avobenzone, octocrylene, octinoxate, and oxybenzone, mimic hormones and disrupt testosterone, estrogen, and thyroid pathways in human cell lines and rodent studies.[46,47] Other components of sunscreen promote oxidative damage in vitro and in cultured human fibroblasts.[48] The toxicity of some chemicals in sunscreen is triggered by sunlight exposure, which leads to DNA damage and overproduction of ROS, according to in-vitro studies.[49,50] Choosing a sunscreen without toxic chemicals can support skin health. A good source for determining the safety of sunscreen brands is the Environmental Working Group (EWG)'s website.

Conclusion

Skin is an outward mirror of our inner cells. More often than not, the skin can serve as a real-time measure of overall health. Factors affecting the skin include mitochondrial health, lipofuscin levels, telomere length, the skin microbiome, HA concentrations, epigenetics and lifestyle factors, and oxygen perfusion. Skin cells, like other cells in our body, need sufficient antioxidants. The need for antioxidants may increase, depending on sun exposure and/or exposure to environmental toxins. Addressing all factors involved in skin health can lead to a vibrant appearance on the outside and optimal health on the inside.

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Aging Gracefully with Cannabis

ROB STREISFELD, NMD

As society appears to have a growing acceptance and increased understanding of plant-based diets, dietary supplements, and even medications, *Cannabis sativa* is back in the spotlight.

With over 500 compounds currently identified within the plant, including cannabinoids, terpenoids, flavonoids, and micronutrients,[1] the opportunity to integrate Cannabis into a functional, healthy lifestyle brings with it tremendous potential for a wide range of health conditions and demographics.

Cannabis & Healthy Aging

While an immense amount of Cannabis research is currently aimed at the treatment of specific diseases and conditions, there is also a need to investigate the plant's preventative and health-promoting benefits. One area where this approach for utilizing Cannabis has garnered significant interest is healthy aging. As the number of elderly people in our population continues to climb, quality of life and overall well-being are becoming greater areas of focus for this demographic. Efforts at anti-aging and growing old gracefully can all be supported by the correct use of Cannabis.

Pain Management

One area where this applies is pain and inflammation. Consuming Cannabis either orally or topically has been shown to reduce pain and inflammation in users.[2,3] A growing body of research has revealed that the production of proinflammatory cytokines and other inflammation mediators in osteoarthritis-induced joint pain is accompanied by activation of the endocannabinoid system, suggesting a mechanisms for the anti-inflammatory and analgesic effects of cannabinoids targeting cannabinoid-2 (CB2) receptors.[2]

THC and/or CBD have been shown to be effective against neuropathic pain in diabetes, various autoimmune diseases, intractable cancer pain, and other disorders.[2,3] Pain reduction by Cannabis in itself is of great value, but especially so when combined with a reduced dependence on prescription opioid-based medications in users of Cannabis.[4,5]

Sleep

A second area where Cannabis can be of benefit to the elderly is sleep. We all need quality, restful sleep to maintain our health. Too often, though, especially in aging, an underlying stress or imbalance impacts a person's ability to fall asleep, stay asleep, or have restorative sleep. This can result from a variety of factors, such as disrupted circadian rhythms due to one's work schedule, hormonal fluctuations, life circumstances, etc. Cannabis has been shown to impact sleep; however, its effects can be dramatically different depending on which phytocannabinoids are being utilized. For example, some phytocannabinoids, such as tetrahydrocannabinol (THC), may assist in falling asleep but may compromise long-term sleep quality, whereas others, such as cannabidiol (CBD), may improve REM sleep.[6] Research related to nightmares, post-traumatic stress disorder (PTSD), and other sleep-related factors is ongoing.[6-8]

Cognitive Function

We cannot fail to mention cognitive function when it comes to aging. Over the past 80 years or so, the term "reefer madness" has unscientifically referred to a supposed negative impact of Cannabis on cognitive stability. While it is not recommended to consume delta-9-THC before at least 18 years of age unless medically necessary, there are today a growing number of successful, fully-functional adults who consume Cannabis regularly, if not daily. Many even tout Cannabis as a way to help manage their attention-deficit/hyperactivity disorder (ADHD).[9]

Recent human and animal research suggests that cannabinoids such as CBD may actually improve cognition and could even benefit individuals suffering from Alzheimer's disease.[10]

Nutrition

Finally, Cannabis research over the years has helped to identify nutritional benefits from consuming various parts of this plant. Malnourishment is often a significant issue among people over age 65[11]; thus, essential fatty acids, protein, fiber, and micronutrients become increasingly important in this population. Integrating nutrient-dense, plant-based foods into the diet such as hemp seeds offers a solution, with an increasing number of options available.[12]

Summary

Cannabis has been shown to promote health and vitality for thousands of years across numerous cultures. Modern research supports the incorporation of Cannabis into one's daily regimen, in some form or dose, as it holds tremendous benefit for all ages, but especially those >65 years of age.

While it is inevitable that we all age, how we age and the steps we take to live our best life is up to each person individually. Staying mobile and without pain, improving one's diet, getting enough sleep, and keeping fit, both physically and mentally, are all fundamental to aging gracefully. We can confidently add Cannabis use to this list, as we continue to study this amazing plant for its benefits in the areas of health and happiness for all ages.

Some phytocannabinoids, such as THC, may assist in falling asleep but may compromise long-term sleep quality, whereas others, such as CBD, may improve REM sleep. Research related to nightmares, PTSD, and other sleep-related factors is ongoing.

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Why I Love Cannabis Topicals

Clinical Pearls for Topical Cannabis Use

JAKE F. FELICE, ND, LMP

The purpose of this paper is to describe one clinician's experience with medical cannabis.

Why Cannabis Topicals?

Non-steroidal anti-inflammatory drugs (NSAIDS) and opiates represent the mainstay of pharmacological treatment for pain. Their use is increasing over time[1-3] and they are associated with very significant morbidity and mortality.[4-7] Viable alternatives to opiates and NSAIDS are desperately needed. Medical cannabis possesses very low toxicity, can be used along with opiates, is effective for pain, is generally well tolerated, and is associated with significant decreases in the use of both NSAIDS and opiates.[8-11]

Cannabis topicals are an ideal introduction to the world of medical cannabis for cannabis-naïve patients. One reason is that topical products, even the ones containing tetrahydrocannabinol (THC), do not give patients a head high. Also, because cannabis topicals bypass the digestive system, they avoid first-pass metabolism in the liver and therefore pose no risk for potential herb-drug interactions.

Topical cannabis products include infused oils, lotions, and balms that can be applied to the skin. They are an affordable and increasingly accessible modality for pain relief, itch, and inflammation. New transdermal innovations, including transdermal patches, are fast arriving in the cannabis and cannabidiol (CBD) markets. Consumers throughout all 50 states now have access to hemp-derived cannabis topical products via online purchasing.

This paper focuses on clinical pearls and applications that this plant has taught me over the last 15 years. For those readers who are interested in a more in-depth look at the research than is covered in this paper, please see my online article "Topical Cannabis: Research Review."[10]

The skin is the largest organ of the body, yet its importance is often neglected by clinicians. It acts as a barrier and is our first line of defense. Skin is responsible for critical transmission of biologic information, exchanging and receiving data from events in the external environment, and transmitting them to our internal organs and immune system. This biologic information travels via neural, endocrine, and immune cell messaging, as well as via the endocannabinoid system (ECS) to regulate local and global homeostasis.[12]

A large percentage of my patients use topical cannabis products combined with oral cannabis products, and report positive results when combining these delivery methods. This makes sense given the synergistic coordination between peripheral, spinal, and central sites of the ECS in the central nervous system.[13-19] Additionally, it is likely that additive or synergistic effects are occurring not only between different cannabinoids, such as THC and CBD, but also between topical cannabinoids and topical opiates.[18]

Applications & Clinical Pearls

Topical cannabinoids may significantly improve skin barrier function,[20] which is an essential feature in addressing itch.[21] Certain phytocannabinoids that enhance sebum production may be effective in treating dry-skin syndrome.[22] Evidence from cell-culture, human, and animal studies also demonstrates potential applications for topical cannabinoids in the following areas:

- Acne[22-24]
- Wound healing[25-27]
- Myositis[28]

One easy way to enhance absorption of cannabinoids across the skin barrier is to use an alcohol-based tincture of cannabis as a spray. In addition, applying copaiba oil or castor oil to the skin after using the cannabis spray may help drive the cannabinoids through the epidermis.

- Psoriasis[29]
- Eczema[20,30,31]
- Arthritis[32-35]
- Multiple sclerosis[36]
- Contact dermatitis[37-39]
- Atopic dermatitis[37]
- Neuropathic pain[40-42]
- Post-operative pain[17]

Additional properties of topical cannabinoids derived from in-vitro and animal studies include inhibitory effects on sebocyte proliferation[23] and differentiation, tumorigenesis, inflammation, sensation of pain, and itch.[12,21]

Topical cannabis products are dose-dependent, meaning that a critical amount (concentration) of cannabinoids contained in topical preparations is essential for achieving optimal relief.[10] Also, the more cannabinoids one applies to the skin, the more effective they are. Cannabinoid concentration is an important consideration when making product recommendations to patients; ie, they should be informed of this concentration-dependent attribute when they are shopping online for the most effective products.

It is also important to explain to patients that topical cannabis products are not miracle drugs. They should be informed that cannabis topicals are mildly effective for pain and are typically short-acting, providing relief that typically lasts between 4 and 5 hours. Frequently, multiple applications may be necessary for maximum relief.

Patients can be reassured that, according to the limited available human research, topical cannabis products are generally well tolerated.[43,44] Because absorption of topicals can be enhanced by carrier ingredients such as ethanol,[45,46] attention to the carriers with which a topical cannabis product is delivered is important in order to ensure efficient transmission across the skin barrier.

One easy way to enhance absorption of cannabinoids across the skin barrier is to use an alcohol-based tincture of cannabis as a spray. In addition, applying copaiba oil or castor oil to the skin after using the cannabis spray may help drive the cannabinoids through the epidermis. These oils have been shown in animal models to penetrate well and possess anti-inflammatory and pain-relieving properties in their own rights.[47,48] An anti-inflammatory oil can offer potential additive and synergistic effects when given along with cannabinoids. "Driving" agents such as dimethyl sulfoxide (DMSO) may also be considered.[49] DMSO also has anti-inflammatory properties,[46] though it may not be as well tolerated as a cannabis topical.

Shock wave therapy or ultrasound can also enhance absorption of topical cannabis by helping drive the topical through the epidermis immediately following its application.[50,51] This might be a consideration for clinicians who already have this equipment in their offices.

CBD in Sunscreens

Research indicates that the ECS plays a role in the detection of tissue injury.[52] Interestingly, the ECS is also involved in protecting skin from ultraviolet (UV) radiation.[53,54] Specifically, topical cannabinoids may offer protection after UV sun exposure.[55] A recent study described dose-dependent protective effects of CBD on UV-exposed melanocytes and keratinocytes.[56] Because CBD does not exhibit absorption in the UVB spectra, this effect was thought to be due to the scavenging of reactive oxygen species rather than the blocking of UV exposure.[56]

Topical CB2 Agonism

Beta-caryophyllene in Topicals

Stimulation of cannabinoid receptor-2 (CB2) has been shown in mice to reduce neuropathic pain.[57] Beta-caryophyllene is a terpenoid in cannabis that acts as a CB2 receptor agonist and has been demonstrated to specifically diminish neuropathic pain in animals.[58] Beta-caryophyllene has also been shown to contribute to the entourage effects of cannabis.[59] I have personally found products rich in beta-caryophyllene to be advantageous for pain, especially when there is an element of neuropathic pain involved.

Although I am unaware of any peer-reviewed research specifically examining the effects of topical cannabis products containing high levels of beta-caryophyllene, the animal research gives us reason to consider these in topical formulations. This is an area that will benefit from future research.

The high concentration of beta-caryophyllene in oils such as copaiba oil[60] makes them ideal as carrier oils for topical cannabis products. Black pepper and rosemary also contain large amounts of beta-caryophyllene, thus can be added as support herbs to a topical botanical formula containing hemp or cannabis.[59] Many cannabis products come with certificates of analysis (COAs), and patients can be instructed in how to search for and read COAs online at the manufacturers' websites.

Echinacea

Another botanical compound that stimulates the CB2 receptor is *Echinacea*. Its alkylamide molecules bind to the CB2 receptor, even at low nanomolar concentrations.[61]

Multiple naturopathic physicians have found that *Echinacea* can positively impact neuropathic pain in shingles. Incorporating *Echinacea* into a tincture with cannabis may therefore be helpful as a topical when treating this condition. The vesicles that occur during shingles do not react well to lotions or creams due to their fragility, and the fragile, sensitive skin barrier can be disrupted by the pressure required to apply these products. A topical spray can be applied to the area so that the patient does not have to touch the skin directly.

I have also had numerous patients report moderate relief from flank pain during the passage of kidney stones after applying topical cannabis to the skin overlying the site of the pain.

Conclusion

Because topical cannabis products are generally well tolerated and do not cause a head high, these products can be an ideal choice for introducing patients to the therapeutic benefits of cannabis. Topicals are affordable, easy to apply, well tolerated, and do not adversely interact with systemic pharmaceutical drugs. While it is apparent that much more human research is needed to fully assess the potential benefits and limitations of the topical application of cannabinoids, their low toxicity along with high potential for benefit provides a good rationale for clinicians to consider topical cannabis lotions, creams, salves and patches in their treatment regimens.

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Incorporating Echinacea into a tincture with cannabis may be helpful as a topical when treating neuropathic pain in shingles.

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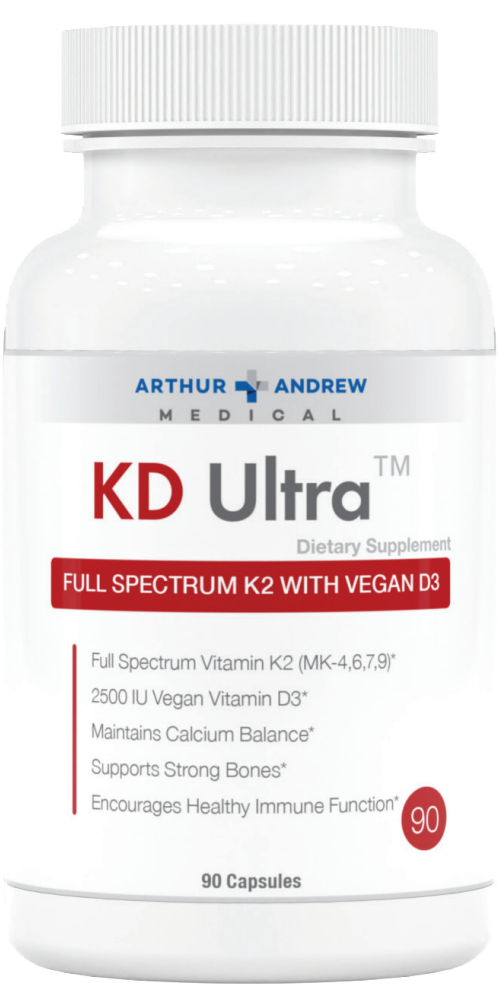

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Notes from the Field

December, 2020

JARED L. ZEFF, ND, VNMI, LAC

The following is not an article prepared for a medical journal. Not every statement of fact is cited or referenced. This is a commentary on the medicine, a running set of observations about practice in the field. It's not meant to be a peer-reviewed presentation; rather, these are notes and thoughts from a practicing naturopathic physician, a primary care doc in general practice.

Science & Naturopathic Medicine

I have been thinking a lot lately about science. I think of medicine not as a science, but as an art informed by science. Conventional medicine, and many in our little profession, understand the best medicine as "evidence-based." "Science" is the primary source of evidence in evidence-based medicine. There is a hierarchy to evidence. I would say that this ranges from anecdotal evidence, personal clinical experience, and the agreement of colleagues, to small studies, larger studies, and meta-analyses. But there is also tradition, and medicine is rich with it. Personal experience is also evidence, though weaker than that of a large study that is appropriately controlled and analyzed, and the subjects of which are properly selected, and the question being explored or tested is properly framed, etc. There are sources of evidence that are more trusted, such as the Cochrane Library and the *New England Journal of Medicine*. We have also learned over the past decade and longer that there is significant fraud in science, as well as many sources of error, such as selection bias in the publication of journal articles.

> *It is simply no longer possible to believe much of the clinical research that is published, or to rely on the judgement of trusted physicians or authoritative medical guidelines. I take no pleasure in this conclusion, which I reached slowly and reluctantly over my two decades as an editor of The New England Journal of Medicine.*
>
> *(Marcia Angell, MD, former Editor-in-Chief at the New England Journal of Medicine)*

This quote by Dr Angell is from her article in the *New York Review of Books* titled, "Drug Companies and Doctors; a Story of Corruption,"[1] which details significant and various ways that published research is manipulated such that it cannot be trusted. But this is the basis of "evidence" in evidence-based medicine, the medicine touted as "science-based." What does this leave us, and where does it lead us?

This is my 42nd year of practicing naturopathic medicine. I began at a time when things were different. The profession was fractionated. There were no journals that catered to us or even to "functional medicine." The only journals that came close were in the field of homeopathy; the National Center published a good journal. And there were some journals of clinical nutrition. But if I wanted to know what worked, I contacted an older doctor who could advise me. In my early days in practice, I made many phone calls to John Bastyr, Bill Turska, Harold Dick, Ravi Sahni, Robert Broadwell, and a few others. To me, the gold standard of evidence in naturopathic medicine was the experience of my elders. I trusted them and their advice, and mostly because it worked; I could rely upon it.

When I began practicing naturopathic medicine, the profession was fractionated. There were no journals that catered to us or even to "functional medicine." The only journals that came close were in the field of homeopathy. And there were some journals of clinical nutrition. But if I wanted to know what worked, I contacted an older doctor who could advise me. To me, the gold standard of evidence in naturopathic medicine was the experience of my elders.

A Brief History of Medicine

Reliability and understanding have been the goal of medicine forever. In the pre-scientific age, there were physicians, of course; I think that medicine, or healing, is one of the very oldest of human endeavors. The history of medicine is the story of the quest for understanding why people become ill and how to relieve and reverse illness: What works? What is reliable? To a great extent, this quest is directed by one's understanding of reality. If one supposes that illness is caused by evil spirits, then the quest becomes one of understanding the spiritual world and how to protect oneself and remove the influence of the evil spirit. The physician then becomes the shaman. One's understanding of *cause* becomes the guide for determining the solution.

For much of history, the cause of illness was considered to be an imbalance among the various elements that make up the person. This is true in ancient Chinese medicine, Indian medicine, Persian medicine, Greek, Roman, and European medicine. In the Greek tradition, which became the Roman and European, an imbalance in the elements and humors was posited as causative, and this ruled for nearly 2000 years, from around 500 BCE to around 1500 CE. The 4 elements – earth, fire, air, and water – were thought to compose all matter. The 4 humors – blood, phlegm, yellow bile, and black bile – were the fluids and elements of life. The elements of matter and the elements of life must be in balance to produce health, and an imbalance caused illness.

There were other theories, such as the Hippocratic. But this Aristotelian model of elements and humors predominated until the Hippocratic was rediscovered, around 1500 CE. Even with what we might consider to be a fundamentally wrong theory guiding them, physicians did help. Some things they did quite well. They set bones. They treated a number of illnesses with the medicines available and did some good. Even in ancient times, they did trephining, a form of brain surgery in which the skull was opened to relieve the pressure of a hematoma from concussion. We know these operations were successful because there are many skulls that show healing of the tissues after such surgeries. Much of medicine is based upon experience, the repetition of what has worked in the past.

Beginning around 1500 CE, in Europe, a new method began to develop, which we call "science." Hippocratic writings were reintroduced in the West, and a medicine divorced from humoral theory and based upon observation was seen from an ancient authoritative source. Thinking began to open and challenge the orthodoxy that had ruled for centuries. By the 1600s, Harvey wrote with accuracy about the circulation, and the microscope was introduced, and the scientific revolution began. Newton published his *Philosophiae Naturalis Principia Mathematica* in 1687, considered by many to be the most significant book in modern science, and the scientific basis of knowledge was firmly established. Medicine now had a new system for

generating reliability and understanding.

In the early 1800s, Pierre Louis, the French physician and scientist, began the examination of medical evidence with statistical analysis. In 1816, Francois Magendie published *Elements of Physiology*, the first modern textbook of physiology. In 1848, Rudolph Virchow, MD, published *Cellular Pathology*. In 1865, Claude Bernard published *An Introduction to the Study of Experimental Medicine*. These 3 texts established the scientific basis of modern medical practice. The discovery of penicillin in 1928 launched the modern age of miracle medicine, which firmly established the conventional medical profession as the standard and dominant profession in medicine, with their new-found ability to cure lethal infections.

Modern science becomes the defining and definitive force in medicine. Evidence and reliability are based now upon dispassionate observation and analysis. And this is what I learned in naturopathic medical school.

The Philosophy is a Constant

As I continued to practice and build my own experience, I rediscovered naturopathic philosophy, our clinical theory. What I have found during my 40+ years of practice is that the philosophy is true, it never changes (built upon natural law), and it is a reliable source of clinical guidance. What we may call science-based evidence tends to change constantly. We see this in the practice of conventional medicine. Things that were used in practice 10 years ago are now "outdated," and many things that were relied upon 20 years ago and 30 years ago have been discarded and forgotten. There are various reasons for this, which could be a different discussion. But the philosophy that guides naturopathic practice never changes. I still use the same things I used 40 years ago – the hydrotherapy, the same botanicals and homeopathics, the dietary basis of healing (which Hippocrates spoke about). They still work. They still get my patients well. They worked 100 years ago and will work 100 years from now. I have added new things and continue to look for new ideas and techniques and medicines. But the basics and the foundation do not change.

What I have found during my 40+ years of practice is that the philosophy is true, it never changes (built upon natural law), and it is a reliable source of clinical guidance. What we may call science-based evidence tends to change constantly.

I have often said the following, or something like it when teaching: You could take a knowledgeable naturopathic doctor, drop them naked pretty much anywhere on earth, and they could be practicing effectively in a very short time. They would find in their surrounding environment most of what they would need to improve the health of their patients and treat their diseases. Water, food, botanicals, earth: in these are our medicines, if you know how to use them. If you understand the principles of health and healing, you can apply these simple and available things in a variety of ways to accomplish the easing of pain and the treatment of disease. Certainly, I like the comfort of my office, my botanical and homeopathic medicinary, the various pieces of equipment that make examination and treatment easier. But I can accomplish much with just my hands, wild plants, water and earth, and my knowledge and experience of the processes of healing and of illness. The process of healing and the philosophy that articulates and explains it have always been the same. I know I can rely upon it.

I have practiced in rough field conditions. For many years, I set up and ran first-aid stations at various Native American ceremonies, deep in the hills or forests or desert. Often, I would spend my time walking around, outside the camps, looking for and harvesting the medicines I would need, beyond what I might have brought with me. I would treat everything from acute infections to heat exhaustion to kidney disease with these simple medicines at hand, along with hydrotherapy and similar techniques. These medicines have always worked and always will.

And if you understand why people become ill and how to reverse this, healing is generally available (refer to Lindlahr and Hahnemann).

Science: A Double-Edged Sword

Science is the observation of phenomena, the search for patterns or logic within the observations, the testing of one's assumptions regarding these observations, and the application of one's conclusions in the real world. It is based upon a natural openness and a natural skepticism. It is also the accumulation of these observations over time. If someone tells me that "the science is settled," unless one is referring to gravity or Newton's Laws, the natural skeptic in me wants to challenge that and test it out.

When I was hearing that we are in the throes of catastrophic anthropomorphic climate change that will destroy our societies in a few years, the first place I went to was old climatologists, those at the end of distinguished careers, and I read what they had to say about it. In general, they pointed out the flaws in these assumptions. Their careers were already made, or they were retired, so they had little to lose and could be perfectly honest. They did not need new grants, so they had little concern about pleasing those in control of the money. I examined graphs of climate change over the past million years, demonstrating a number of warming and cooling periods, including ice ages. We emerged from the past ice age about 10 000 years ago, and are in a similar warming cycle that has occurred several times over the past million years, none of which were driven by the human creation of CO_2 by burning fossil fuels. It is not warmer now than it was in the past warming cycles. And it was warmer about 1000 years ago, during what was called the Roman Warming period, than it is now. And humans thrived during this Roman Warming: less disease and more food. So, I am skeptical of the claims of catastrophic anthropogenic global warming. This does not relieve me of the responsibility to steward the earth's resources and monitor my own "footprint"; as a naturopath, I must respect and care for nature. But it relieves me of an unfounded existential fear that seems to plague many young people today, and it reminds me to keep an open mind in the face of popular science and the politics surrounding it.

I apply this same skepticism to my own work and to what I hear and read regarding medicine. Why did the recommended levels of cholesterol suddenly drop to "200" about 30 years ago? This was the work of a committee of doctors, self-appointed, several of whom were receiving significant financial support from the pharmaceutical company that held the patent for the first statin drug (see John Abramson, MD's book, *Overdosed America*[2]). On what basis did they make this recommendation that we all take for granted? When I was first confronted with apparently vaccine-injured children in my early practice, which I doubted at first, I began to seek the safety studies that I expected from the CDC or FDA. What I found was that such research was not being funded. I could not find significant safety studies. I found instead that vaccine manufacturers were exempt by law from liability. I became more skeptical. Where is the science, and what is its basis?

Science has given us the greatest progress in medicine in the history of humankind. But it is also corruptible. As John Bastyr taught us, we should follow the science and use it as a guide. But the philosophy of our medicine is not corruptible. It is constant. It is based upon the observations of nature. It is a better guide.

Respectfully,

Jared L. Zeff, ND, VNMI, LAc

Jared L. Zeff, ND, VNMI, LAc, is a licensed doctor of naturopathic medicine and a licensed acupuncturist. In addition to functioning as Medical Director at the Salmon Creek Naturopathic Clinic in Vancouver, WA, Dr Zeff taught on the faculty at National University of Natural Medicine in Portland, OR, where he was also Dean from 1988 to 1993, and holds a professorship in Naturopathic Medicine. Dr Zeff is a graduate of the University of California, NCNM, and the Emperor's College of Traditional Oriental Medicine. He, along with Pamela Snider, is the author of the AANP's Definition of Naturopathic Medicine, and the Therapeutic Order concept.

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The Importance of Gut Health

Part 2

JAMES SENSENIG, ND

This column is transcribed from a weekly live conversation produced by the Naturopathic Medical Institute (NMI). The goal of NMI is to preserve and promote the principles of naturopathic philosophy through clinical application, in your offices and in your communities, every day. On October 11, 2017, Dr Jim Sensenig spoke on the importance of gut health. In this lightly edited transcript (by Emily Kane, ND), the second part of a 4-part article, Dr Sensenig discusses why the gut could be considered a second brain.

"Second Brain"

Work done in the earlier part of the last century considers the gut as a second brain. This concept was popularized in the 70s and 80s by a medical doctor named Michael Gershon.[1] He looked at how the gut can function completely independently of any input from the brain, hence the idea of the second brain.

When it was noticed that the neurons in the gut could function without signals from the brain, one source suggested that this is more or less "on-site digestion," ie, not having to be directed by the brain. If we had to depend on the brain to govern what was happening in the digestive tract, we could very well all be dead, because the first and most primitive of our needs is to have nourishment.

There are around 100 million neurons in the enteric nervous system, which means that there are more neurons in the enteric nervous system than there are in the central nervous system. In light of this, it would make sense that the second brain could actually be considered the first brain, in the sense that it is the one part of our system that can act without instructions from above.

> We grew up in a culture where we blame bugs, in general, and we blame specific ones for illness. Not only that, but we have this belief that, for instance, if I am sick with a bug and sneeze on you, you are going to get sick too.

It makes sense that the gut's surface area is so huge, since it is our first exposure to our environment, albeit our internal environment, through our foods and everything else that we are consuming.

Bacterial System (Biome)

Bacterial Load: Part of Who We Are

There was some testing done in the New York City subways, where they took thousands of swabs of DNA from all over the subway system, from the seats to the handles, etc. Half of the DNA they collected was not recognized. It was from microbes or other critters that had not been sequenced, so there was no way to identify where the DNA was from. The majority of what they did collect was from microorganisms.

One of the researchers commented that this makes it look like we are living in this huge rain-forest-type environment, where we are surrounded all the time by hundreds of millions of species of bugs that we do not even know about or understand.

We grew up in a culture where we blame bugs, in general, and we blame specific ones for illness. Not only that, but we have this belief that, for instance, if I am sick with a bug and sneeze on you, you are going to get sick too. The reality is, we are living in this ocean of microorganisms that are around us all the time, and, yes, we might be exposed to some more than others; but the idea that individual bacteria are causing some kind of illness seems rather ludicrous on the surface. Lindlahr would say in his book *Nature Cure*[2] that it is a delightfully simple idea that a single microbe would cause a problem like that.

Many Functions and Effects

Going back to the "second brain" idea and all that nerve tissue in the gut, another way to think about it is that this is the site of initial exposures. This is where we are exposed to 90% of the microbes that we encounter. I suppose the gut has to be exquisitely sensitive; it has to be able to receive information and somehow distinguish good from bad very quickly. It has to decide, as it were, what can be let in and what cannot be let in.

Some people theorize that this is how we evolved such a highly sensitive system. That leads you to all kinds of interesting ideas that we can talk about in naturopathic medicine about one's gut – going with your gut, feeling from your gut, and how your emotions and your external environment affect your gut, and also how your gut affects those areas as well.

In some ways this bacterial system, which is sometimes referred to as the biome, is really part of who we are. It is 3 pounds of our body weight. And it is not really separate from us. It is more like a synergistic relationship: we need the bugs, and the bugs need us.

The biome has many different functions. For example, the health of the gut mucosa is directly dependent on which critters are there, in what amounts, and at what levels. Even this new idea, sometimes called enterobacteriology, has something to do with not only which species are commensal and which ones are pathogenic, etc, but also what part of the gut they live in.

The health of the mucosa strongly influences the health of the mucosal barrier, and its functioning is dependent on the resident bacteria, and vice-versa, because, there again, it is not cause and effect but more of a synergistic relationship. The function of the mucosal surface is itself incredibly important, as we know.

Microbes Linked to Mental State and Behavior

There is more and more evidence suggesting that different microbes or species affect us in different ways, even impacting our moods. It has been speculated that some microbes are associated with anxiety, for example. Other microbes are associated with panic disorder, etc. That is an interesting concept all on its own. Think about the implications there for the mental/emotional side of things.

That gut bacteria partially determine our current mental state raises an interesting question about cause and effect:

Is the biome determining our mental state, or does our mental state affect the biome? With many digestive diseases, we see that kind of relationship, like how stress affects the gut, etc.

The leaky gut phenomenon contributes to a whole host of problems that we are encountering in today's clinical practice, including all kinds of autoimmune diseases, food sensitivities, inflammatory responses – systemically in some cases – and also behavioral problems, particularly the whole autism spectrum disorder.

Food can affects behavior in several ways. One of them is a direct effect of a food on the biome itself. If you have an overgrowth of yeast, specifically *Candida albicans* and its friends, you may have a problem with a dietary substance, perhaps carbohydrates, where there is an increase in the growth of yeast in response to the carbohydrate load, which in turn elaborates certain neurotoxins that affect behavior.

Another way that foods affect the digestive system is through humoral IgG. Although it is not a true allergic reaction, there is a delayed hypersensitivity that can affect people as well.

Some of the high-molecular-weight proteins that are not properly digested by enzymes in the alimentary canal can reach the general circulation, where they are literally attacked by different enzymes within the bloodstream and broken down through a series of bond cleavages. When large molecular-weight proteins, like casein and gluten, for example, are broken down in this way, small sequences of amino acids are released that would not ordinarily be seen under normal digestive circumstances. And these peptides have an opioid-like effect.

This was first found in some of the research conducted on autistic kids to look at why they were responding to foods the way they did. That opioid-like effect is exactly that. You may know these opioids as urinary peptides or protein opioids. The 2 that are most familiar are gliadomorphins (from the gliadin protein in gluten) and caseomorphin (from dairy protein). There are people who react very strongly to those proteins. When you take a person with a food opioid reaction off of those foods, you will see symptoms that mimic exactly opioid-withdrawal symptoms.

What does this have to do with the gut? Those foods become problematic for us only when the system that is designed to break down these foods in the digestive tract cannot do it properly and we become overwhelmed by the consequences. This is an over-simplification of it, but the gut is definitely at the base of it. In this sense, your digestive system is the center of your personal physical universe.

This is exactly what our predecessors have always told us. We have to be cognizant about our food and the quality of it. We have to eat under circumstances that allow us to digest properly. We want to be in a restful, quiet environment; we do not want to overeat; and we do not want to combine foods that have individual or specific digestive requirements.

Dealing with the Diet

I was once asked by a patient if I knew anything about the GAPS Nutritional Program. GAPS is an acronym for Gut and Psychology Syndrome.[3] It is a moniker that an American-trained pediatrician, who now lives in London, has used to describe her work. Basically, she is saying that the whole of the autism spectrum, from learning disabilities and neurological and psychological disorders, to immune disorders and even frank autism, can be categorized in a way that directly relates to the gut and to foods.

> When large-MW proteins, like casein and gluten, are not properly digested in the GI tract, small sequences of amino acids are released that would not ordinarily be seen under normal digestive circumstances. And these peptides have an opioid-like effect.

Her protocol for treating these problems is to normalize gut function and deal with diet. Dealing with diet means focusing on taking things out of the diet, eliminating certain foods, and eating certain other foods.

The part of dietary changes that is often minimized or overlooked is the part about making sure the digestive system works properly and that the pH is changed. Oftentimes, people ask me if they have to be off of a particular food forever. The theoretical answer would be no, assuming we can correct their digestive function. The practical answer, though, is that many people have to be off these things forever because we cannot correct their digestive function 100% or because once the immune system is involved, it has that molecular memory where it is not going to change unless we can desensitize the person in various ways.

James Sensenig, ND, was a 1978 graduate of NCNM in Portland, OR. For over 40 years he maintained an eclectic practice in Hamden, CT. Over the years, Dr Sensenig held prominent positions in the various naturopathic colleges and the AANP. A champion of classical naturopathic medicine, Dr Sensenig received an Honorary Doctor of Naturopathic Philosophy degree from CCNM, and received numerous awards for his dedication to teaching the principles of naturopathic medicine.

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A Scientific Education

Part 3

FRASER SMITH, MATD, ND

In my previous 2 articles, we examined how science and medicine have become intertwined as our contemporary forms of health care took shape. We also looked at how naturopathic medicine retooled its educational systems 50 years ago and emerged with a consistent system of physician-level training. There are challenges that the profession faces, as always, but we have done a good job of rising to meet them.

This month, we'll attempt to see how advances in science might evolve into revolutionary tools and how that might impact medicine. As an important branch of the healing arts, naturopathic medicine will make use of these advances. The progression of health-related science and technology will impact all fields, and that includes us.

Will we be able to keep pace with the demands of a rigorous education? Will the very personalized model of health care we offer become more powerful and data driven? Or, is that a mirage that will yield to a decline in the need of experts like us? Do our fundamental principles and ontological grounding in the *Vis Medicatrix Naturae* have a place in the future of scientific medicine, or will it simply become relegated to the historical dustbin of intriguing ways to describe something that is now actually understood on a scientific basis? Or, will that very understanding turn the tables and leave reductionist, pathology-focused medicine behind, and a new era of systems-thinking provide a medical home for doctors like us?

Data, Doctors, and Decisions

We've already seen a change in how clinicians can make decisions based on evidence. The ability to access and retrieve precise information to support diagnosis and treatment decisions is completely different in this era of ubiquitous search engines and databases. These search engines can also sort information and differentiate results between case reports, animal studies, randomized controlled trials, and systematic reviews. As time goes on, this trove of knowledge will become deeper and the access will be faster. But at some point, the gargantuan collection of publications a doctor can access becomes too much to manage. Even in 2010, one commentator on this phenomenon calculated that 1 medical article was published every 26 seconds.[1] So we will likely see the use of a very sophisticated AI assist function, which not only guesses what we want (which Google and other search engines attempt to do now), but in some sense also "thinks" along with us.

Clinical Decision Support

This leads to the concept of clinical decision support, which is already an embedded feature of many Electronic Health Records (EHR) systems.[2] But the manner of that decision support will likely become more sophisticated. This is partly the drive to automate. This has a darker side, which is the removal of human interaction and human performance in daily life. But it also has an upside, which is that it can leverage physician time for patient support and give them more of a firm foundation on which to make decisions.

The other driving force here is that some of these support functions will be so vast in the aggregation of data and the computations of it, that it will be virtually beyond what anyone can do. DNA is a type of code,[3] and gene expression and repression happens at multiple levels. Imagine the time when we can retrieve precise information about the impact of a drug, nutrient, herb, or an entourage of all these, based on a patient's specific genome. This might be expressed as a probability of efficacy or potential harm. The sheer number of variables will require real-time assistance.

The human genome has already been sequenced, but it will take many decades for the implications of various genes and their associated disease risk factors and treatment options to become clear. We know a little bit about this now. We'll know much, much more by 2050. It's possible that this will be another area that allows for stochastic (random) events, and doctors will know levels of probability.

Systems Thinking

The naturopathic principle *Tolle Totum* speaks from a wisdom in natural medicine that human beings, like natural systems, function as an integrated whole. The science of understanding whole systems is advancing, and this can have an impact on our field.[4] Whole systems are interconnected and sensitive to stimuli – one change here causes a reaction somewhere else. Some disruptions to a whole system are easily absorbed, and others can be highly disruptive. Again, we already know something about this, and sometimes even use small disruptions purposefully.[5] Some phytochemicals, such as compounds in the Cruciferae family of vegetables, present a mild input to the cell "as if" there were real oxidative stress, and the result is an uptick in the production of Phase 2 enzymes. Medical doctors stopped using alpha-blockers to treat hypertension because they cause vigorous counter-reactions in the body. *Tolle Totum* is an attitude, a humility about the complexity of people and their physical frame.

> Tolle Totum is an attitude, a humility about the complexity of people and their physical frame.

Predictions and Fictions

Plenty of well-informed physicians, research scientists, and journalists have taken their best shot at envisioning medicine of the future. A very enjoyable attempt to do this was recently made in the University of California San Francisco's alumni magazine.[6] The authors put medical predictions for 2050 into a 4-quadrant diagram, with Game-Changing versus Overhyped on one axis, and Fiction versus Prediction on the other. In the Game-Changing and Prediction quadrant, we see things such as lab-grown organs, but also superbugs due to increased drug resistance. In the Overhyped and Fiction quadrant, we see both AI "doctors" delivering primary care and the medical resident work-week shortened to 40 hours.

There is a good dose of common sense in this alumni-created prediction model, in that events and practices that most of us never saw coming will arrive, while some developments we had feared will not materialize as anticipated. I personally doubt that the doctor on call will be a quantum version of the omniscient "Dr. Know" of the Spielberg film, *A.I. Artificial Intelligence*.

But things are progressing. I received an alumni email this week from the University of Toronto. A research group there has been studying how cardiac muscle regenerates, especially post-myocardial infarction. The cells must regenerate in a certain vector, with a specific alignment.[7] They are working to create stem cells that will grow in a certain direction and, when hopefully introduced to a human heart, will lead the way for some section of a damaged heart to heal.

Naturopathic Medicine Sesquicentennial

With this kind of truly regenerative medicine here now, and with its certainty to develop rapidly, what does that mean for naturopathic medicine? As mentioned in last month's article, it certainly vindicates many of the principles and beliefs of our medicine. But if the healing is delivered at this level of technology, do our methods with long histories, such as botanical medicine, really mean all that much? Perhaps that is our future too, that naturopathic doctors will be regenerative and gene-based practitioners with a proud but quaint history of those who used outdated methods but had the right idea about healing.

Can Low Tech Be High Science?

Or maybe it's not so cut and dried.

Allopathic medicine already specializes in helping to preserve life and limb when pathology has advanced beyond the self-repair phase (leaving aside the fact that this is concluded too hastily in many cases). Someone with catastrophic injuries from a motor vehicle accident might benefit enormously from the ICU and trauma surgery, but also from the reconstructive surgery and rehabilitation that is incredibly advanced in 2021.

Naturopathic medicine is really on the other side of the boat. We're looking at how to help the body's bioregulatory systems stay in balance. We look at physiological imbalances and how they are rooted in disturbances to the determinants of health. We also always attempt to hear and understand the personal narrative of our patients so that we can attempt to understand how best to help them.

There is nothing inherent in increased access to meaningfully organized data that precludes us from using it in our practice. More refined information about diagnosis and our naturopathic modalities is welcome, and in many ways it will serve us better than high-quality but rare and very reductionistic Cochrane-type systematic reviews that barely scratch the surface of our medicinal toolkit. Evidence that is more attuned to individual treatments seems like a good development.

And, in practical terms, with a predicted 9.7 billion people on earth by 2050, it's not realistic to think in terms of on-demand drug delivery or designer organs for all. Our healthcare system is already stressed under the exigencies of a disease care model. More speed, more processing power, more energy, etc, might not be the sole solution to our problems.

Educating to the Future

What might this mean in the education of a naturopathic doctor who might reach mid-career in the 2040s? There is no doubt that helping students to understand how data might meet decision-making is going to be very relevant. The habits of thought that come with incorporating best evidence into diagnosis and treatment, as our students are now taught, certainly lend themselves to a willingness to use much more powerful analytic and predictive tools that are headed our way. But it seems that a more purposeful and focused study of enhanced clinical decision-making is going to be essential.

Our students already learn genomics and nutrigenomics, but this might have to elbow out the sheer volume of time spent on anatomy and some other subjects. A naturopathic doctor in any era needs to know the difference between the cauda equina and the sella tursica, but something might have to give, as the relationship between genes, response elements, chaperones, environmental signals, etc, and how these work as a whole, might simply be a language that the naturopathic doctor of the near future must be extremely literate in.

Maybe one career path for naturopathic physicians will be to perform those higher-technology-enabled regenerative procedures, like injecting germline therapies based on precise indications. It certainly has some relation to the healing power of nature.

The pedagogies in *how* the curriculum is delivered seem to be gradually becoming more self-directed. Pedagogies that use the learning science behind serious games – not limited to virtual reality, but definitely using game principles – are a topic of upcoming columns here.

It could be that powerful assistance for physicians from (possibly quantum) computing might shock even those of us who have seen computers progress from room-sized mainframes to pocket-sized dynamos. Aided by advanced genomics employed using a whole-systems framework, and enabled by such light-speed computing, a naturopathic doctor a few decades from now might be the primary care doctor that people need.

The naturopathic doctors we train now need to be like pilots of a Dreamliner. They won't be manually or by memory operating all the subsystems of the machine, and some of it might even be over their heads. But they will be responsible to guide it, and to take charge when needed, even sometimes using old-school knowledge and methods. The genomic, data analytic, computational, and interventional technologies that are on the horizon are like that. They'll take us to many places. And yet, an educated and creative problem-solver, with real compassion for the suffering, will be a doctor that many patients want as their own – just like the patients who seek out naturopathic physicians today.

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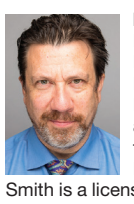

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A Comprehensive Approach to Supporting Collagen Integrity: Beyond Collagen Supplementation

Dr. Christine Chen, ND

When patients ask their doctors about skin care supplements, collagen support often comes to mind. However, is direct supplementation of collagen the best choice for enhancing collagen health?

Collagen accounts for ¾ of the skin's dry weight and 1/3 of the human body's total protein. Aging, as well as exposure to free radicals, such as UV light and smoking, causes a decline in collagen production. This causes the structural integrity of the skin to deteriorate, increasing wrinkle formation and joint degeneration.

1) Building Blocks

The structure of collagen is a triple helical protein consisting of three chains with characteristic repeating sequences (Gly-X-Y)n. The fundamental structural unit of a single collagen molecule is around 300nm long and 1.5nm in diameter. Each chain contains around 1050 amino acids. As we know, only single amino acids, di- and tri-peptides can be absorbed in the small intestine and provide benefits in collagen synthesis. [1-3] Without pre-hydrolysis, collagen cannot be absorbed by human body. Hydrolyzed collagen consists of single amino acids and short-chain peptides.

Health Canada's Natural Health Product monograph only allows "hydrolyzed" collagen to be claimed as a "source of the amino acids for the maintenance of good health, involved in protein synthesis and to help in collagen formation". Supplementing with hydrolyzed collagen is no different than taking amino acids or other short chain peptide supplements which contain r building block amino acids such as **Glycine, Proline and Lysine**.

However, with age, the body's efficiency in producing collagen decreases. **Could promoting the formation and reducing the degeneration of collagen be more important than just simply providing the building blocks?**

2) Essential Cofactors

Hydrolyzed collagens are often marketed as 'the only means' to supply building blocks of collagen for the content of modified amino acids unique to the collagen fibers, such as hydroxyproline and hydroxyllysine. However, our body can readily convert the amino acids into those unique forms with the help of essential cofactors.

Vitamin C is the essential cofactor for the hydroxylation of hydroxyproline and hydroxylysine.[4] (Figure 1) In the synthesis of collagen, glycine and L-proline first join to form "procollagen". Procollagen is then modified by the addition of hydroxy-proline and hydroxy-lysine, requiring vitamin C as a cofactor. Each reaction of hydroxylation devours one molecule of vitamin C; therefore, it is not hard to imagine the importance of adequate vitamin C intake as the number of hydroxylation reactions is already exorbitant for just daily collagen regeneration, let alone other biochemical reactions.

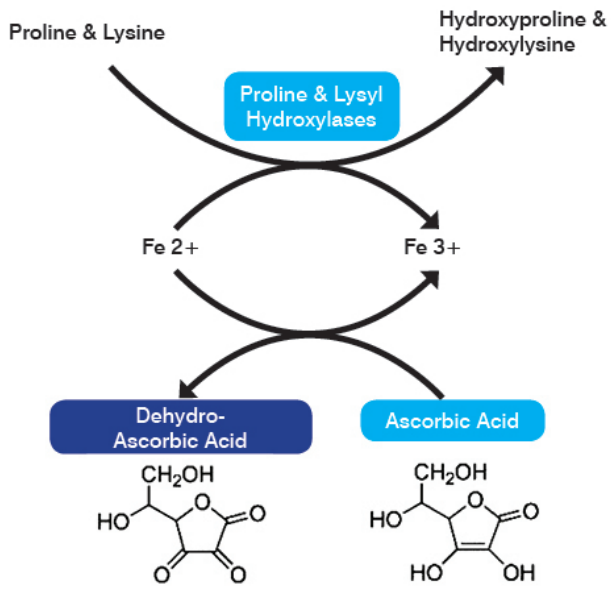

Figure 1. The hydroxylation of proline and lysine

Vitamin A has been shown to stimulate collagen synthesis while reducing the expression of matrix metalloproteinases, enzymes that degrade extracellular matrix including collagen fibers.[6]

Silica in trace amounts is able to facilitate the formation of glycosaminoglycans (i.e. hyaluronic acid) and collagen in connective tissues and bones via its binding of hydroxyl and polyols.[6]

3) Antioxidants Against Free Radicals

Collagen is the only protein in our body susceptible to fragmentation by free radicals. Collagen fibers are good targets for reactive oxygen species because the helix-stabilizing amino acids - 4-hydroxyproline - are easily disrupted by these superoxide anions.[7]

As we age, the body's ability to quench free radicals drastically reduces, resulting in collagen breakdown and loss of scaffolds in the skin tissue. Therefore, supplementing various sources of antioxidants is essential in protection against collagen degradation.

Vitamin C & E are part of the body's main antioxidant mechanism to help regenerate the reduced glutathione. Scavenger antioxidants such as coenzyme Q10, trans-resveratrol, and oligomeric proanthocyanidins, can further improve the antioxidant status of the system.

4) Other Lifestyle Interventions

- Moderate to high-intensity exercise at least twice a week– the mobilization of tissues can provide direct mechanical stimulation of the fibroblasts to synthesize collagen fibers.[8] The effect of collagen stimulation peaks within 72 hours after exercise. [9]
- Anti-inflammatory Diet [10]
- Optimize HPA Axis function with regular sleep cycle[11]

Treat the Whole Person (Tolle Totum)

Supplementing collagen building blocks may start to lose its edge as our body's ability to synthesize collagen fibers declines with age. Therefore, the more important aspect of treatment should be supporting patients via other mechanisms and interventions that include removing offending factors to collagen integrity, protecting the existing collagen scaffolds from degeneration, and promoting the process of collagen regeneration.

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