Stress, Microbiota and Immune Balance: How to Navigate the Underlying Immunology on an Individualized Basis‡

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Speaker Disclosure

Samuel F. Yanuck, D.C., FACFN, FIAMA

I am a paid medical advisor for Pure Encapsulations. I have no other conflicts of interest to disclose.

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Learning Objectives

• Review the four core factors in immune dysfunction and their cascade into the broader immunological picture

• Explore bi-directional connections between dysbiosis and inflammation

• Explore bi-directional connections between stress and inflammation

• Understand how to select the appropriate nutritional modalities to support a balanced immune response in your patients‡
The Four Key Dysfunctions Virtually EVERY Functional Medicine Patient Has…

- Inflammation
- Anti-Inflammatory
- Stress
- Dysbiosis
- Autoimmunity
- Chemistry
Identifying the Primary Drivers of Chronic Illness

- **Dysglycemia**
- **Food & Environment**
- **Detox Defects**
- **Hormones**
- **Vascular/O2 Defects**
- **Others**

**Key Core immune dysfunctions of chronic illness**

**Key immune system changes they cause**

**Key immune consequences of those changes**

**Additional factors driving immune dysfunction**

- **Inflammation**
- **Dysbiosis**
- **Stress Chemistry**
- **Innate Immunity**

- **Brain Inflammation**
- **Autoimmunity**

**Th17 Status**
- Higher Th17 activity drives tissue destruction in autoimmunity

**Th1 Status**
- Low Th1 status further reduces innate immunity
- Low Th1 status drives increase in Th2 cell populations. Th2 increase further dampens Th1
- Low Th1 status increases vulnerability to infection

**Th2 Status**
- Low Th1 status allows dysbiosis to flourish

**Diminished Response**
- Reduced innate immunity lowers Th1 status
- Infection is a main driver of inflammation

**Co-Activation**
- Infection
- Inflammation
- Dysbiosis
- Stress Chemistry
- Innate Immunity

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Key Opportunities for Intervention: NFkB and STAT3

The Role of an NFκB-STAT3 Signaling Axis in Regulating the Induction and Maintenance of the Pluripotent State

Jasmin Roya Agarwal and Elias T. Zambidis

Nuclear factor-κB — a pivotal transcription factor in chronic inflammatory diseases

CD4 T cells: Fates, functions, and faults.

Interleukin-17 and Type 17 Helper T Cells


<table>
<thead>
<tr>
<th>Th Group</th>
<th>Cell Products</th>
<th>Cell Target</th>
<th>Infectious Agents</th>
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<tbody>
<tr>
<td>Th1</td>
<td>Interferon-γ</td>
<td>Macrophages</td>
<td>Intracellular bacteria</td>
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<td></td>
<td>Interleukin-2</td>
<td>Dendritic cells</td>
<td>Fungi</td>
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<td></td>
<td>Interleukin-12R</td>
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<td>Viruses</td>
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<td>Th17</td>
<td>Interleukin-17A</td>
<td>Neutrophils</td>
<td>Extracellular bacteria</td>
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<td>Interleukin-17F</td>
<td></td>
<td>Fungi</td>
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<td></td>
<td>Interleukin-21</td>
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<td></td>
<td>Interleukin-22</td>
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<td>Interleukin-23R</td>
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<td>Th2</td>
<td>Interleukin-4</td>
<td>Eosinophils</td>
<td>Parasites</td>
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<td></td>
<td>Interleukin-13</td>
<td>Basophils</td>
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<td></td>
<td>Interleukin-5</td>
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**Interleukin-17 and Type 17 Helper T Cells**


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<thead>
<tr>
<th>Target-Cell Type</th>
<th>Products Released</th>
<th>Biologic Effect</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrophage, dendritic cell</td>
<td>Interleukin-1, TNF, Interleukin-6 CRP</td>
<td>Inflammation</td>
<td>Infections, Psoriasis, Graft rejection</td>
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<tr>
<td>Endothelial cell</td>
<td>Interleukin-6, Coagulation, MMP</td>
<td>Vessel activation</td>
<td>Reperfusion injury, Thrombosis, Atherosclerosis</td>
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<tr>
<td>Fibroblast</td>
<td>Interleukin-6, Chemokines, Growth factors, MMP</td>
<td>Matrix destruction</td>
<td>Multiple sclerosis, Crohn's disease</td>
</tr>
<tr>
<td>Osteoblast</td>
<td>RANKL, MMP, Osteoclastogenesis</td>
<td>Bone erosion</td>
<td>Prosthesis loosening, Periodontal disease, Rheumatoid arthritis</td>
</tr>
<tr>
<td>Chondrocyte</td>
<td>MMP</td>
<td>Cartilage damage</td>
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</tbody>
</table>
Stress Drives and Is Driven By Inflammation
The Four Key Dysfunctions Virtually EVERY Functional Medicine Patient Has...
“Further instantiating the link between inflammation and depression are data demonstrating that psychosocial stress, a well-known precipitant of mood disorders, is capable of stimulating inflammatory signaling molecules, including nuclear factor kappa B, in part, through activation of sympathetic nervous system outflow pathways.”

**Stress → Sympathetic Upregulation → ↑NFkB → Inflammation → Neuroinflammation → Depression**
Nuclear factor-κB mediates inflammation

Nuclear factor-κB mediates inflammation

Inflammation and Its Discontents: The Role of Cytokines in the Pathophysiology of Major Depression

Biol Psychiatry. 2009 May 1;65(9):732-41. Miller AH, Maletic V, Raison CL.
Inflammation and Its Discontents: The Role of Cytokines in the Pathophysiology of Major Depression

Biol Psychiatry. 2009 May 1;65(9):732-41. Miller AH, Maletic V, Raison CL.
Influence of Dysbiosis & Other Infections
The Four Key Dysfunctions Virtually EVERY Functional Medicine Patient Has...

- Inflammation
- Autoimmunity
- Dysbiosis
- Stress Chemistry

Autoimmunity

Stress

Chemistry

Dysbiosis

Inflammation
Multiple Mechanisms of Immune Suppression by B Lymphocytes
Immune adaptations that maintain homeostasis with the intestinal microbiota
Epithelial-cell recognition of commensal bacteria and maintenance of immune homeostasis in the gut
Inflammation

Autoimmunity

Brain

Chemistry

Dysbiosis

Th17

Status

Th2

Status

Innate Immunity

Infection

Dysglycemia

Food & Environment

Detox Defects

Hormones

Vascular/O2 Defects

Others

Additional factors driven by immune dysfunction

Key

Core immune dysfunctions of chronic illness

Key immune system changes they cause

Key immune consequences of those changes

Additional factors driving immune dysfunction

Identifying the Primary Drivers of Chronic Illness

Core immune dysfunctions of chronic illness

Key immune system changes they cause

Key immune consequences of those changes

Additional factors driving immune dysfunction

Infection is a main driver of inflammation

Reduced innate immunity lowers Th1 status

Low Th1 status further reduces innate immunity

Low Th1 status increases vulnerability to infection

Low Th1 status allows dysbiosis to flourish

Higher Th17 activity drives tissue destruction in autoimmunity

Low Th1 status drives increase in Th2 cell populations. Th2 increase further dampens Th1

Low Th1 status drives increase in Th2 cell populations. Th2 increase further dampens Th1

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Epithelial-cell recognition of commensal bacteria and maintenance of immune homeostasis in the gut
Epithelial-cell recognition of commensal bacteria and maintenance of immune homeostasis in the gut


“For example, although pathogenic bacteria induce TLR- and NLR-mediated NF-κB activation, in vitro studies have demonstrated that commensal bacteria such as Lactobacillus spp., Bacteroides spp. and Escherichia coli (as well as attenuated strains of bacteria that are normally pathogenic, such as Salmonella spp.) can actively inhibit this pathway.”
Epithelial-cell recognition of commensal bacteria and maintenance of immune homeostasis in the gut
Immune adaptations that maintain homeostasis with the intestinal microbiota
Dendritic-cell control of pathogen-driven T-cell polarization

Nat Rev Immunol. 2003 Dec;3(12):984-93, Kapsenberg ML
Immune adaptations that maintain homeostasis with the intestinal microbiota
Inflammation rather than nutritional depletion determines glutamine concentrations and intestinal permeability

“RESULTS: The presence of inflammatory activity had significant negative effects on glutamine concentrations in contrast to the presence or absence of nutritional depletion. Similarly, intestinal permeability increased during active inflammation but not in depleted patients.”
Leaky Gut and Autoimmune Diseases


“Besides an *increase in blood–brain barrier permeability*, multiple sclerosis (MS) patients may also experience an increased permeability of intestinal TJ. Yacyshyn and coworkers have demonstrated that **25% of MS patients** studied had an increased intestinal permeability.”
Leaky Gut and Autoimmune Diseases

“To challenge this hypothesis, we measured serum levels of zonulin in MS patients with different subtypes – relapsing-remitting [RRMS] vs. secondary-progressive [SPMS] – and activities to ascertain whether expression of zonulin into peripheral circulation can differentiate these two groups. Approximately 29% of patients with either RRMS or SPMS had elevated serum zonulin levels (a percentage similar to increased intestinal permeability in MS patients reported by Yacyshyn et al), with overall average serum levels ~2.0-fold higher than in controls. Interestingly, patients with RRMS in remission showed serum zonulin levels comparable to controls.”
Dysbiosis / Inflammation Co-Activation

- Dysbiosis → NFκB Activation → Inflammatory Cytokine Production
- Dysbiosis → APC Presents Food with Kill Signal → Food Sensitivity
- Dysbiosis → Th17 Cell Activation → Autoimmune Tissue Destruction
- Inflammation → Loss of Innate Immunity & Th1 Response → Dysbiosis
- Inflammation → Glutamine Depletion → Loss of Tight Junctions → Intestinal Permeability → Loss of Tolerance of Foods & Microbiota → Inflammation
Applications
Identifying the Primary Drivers of Immune Balance

- **Glucose Metabolism**
- **Food & Environment**
- **Detox Defects**
- **Hormones**
- **Vascular Function**
- **Others**

Other factors affected by immune homeostasis

**Brain Cytokine Activation**

**Self-Tissue Response**

**Cytokine Activation**

**Stress Chemistry**

**Alterred Intestinal Microbial Balance**

**Innate Immunity**

**Th1 Status**

**Th2 Status**

**Th17 Status**

**Key**

- Core changes in immune balance
- Key immune system changes they cause
- Key immune consequences of those changes
- Additional factors affected by immunological homeostasis

Reduced innate immunity lowers Th1 status

Low Th1 status further reduces innate immunity

Low Th1 status affects natural defenses

Low Th1 status affects microbiome

Low Th1 status affects microbiome

Low Th1 status affects microbiome

Affects lung, sinus, GI, and bladder mucosal tolerance

Changes in tissues (e.g., joint, connective tissue, thyroid)

Reduced innate immunity lowers Th1 status

Low Th1 status drives increase in Th2 cell populations. Th2 increase further dampens Th1

Low Th1 status affects natural defenses

Low Th1 status affects microbiome

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Affects lung, sinus, GI, and bladder mucosal tolerance

Key immune consequences of those changes

Additional factors affected by immunological homeostasis

Core changes in immune balance

Key immune system changes they cause

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<table>
<thead>
<tr>
<th>Clinical Objective*</th>
<th>Product Name</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target Cytokine</td>
<td>Curcumin 500 with Bioperine®</td>
<td>1 capsule, 1-3 times daily, between meals</td>
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<tr>
<td>Activation</td>
<td>Order Codes: CUB51 / CUB56</td>
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<tr>
<td>Target Self-Tissue</td>
<td>EPA/DHA essentials</td>
<td>1-2 softgel capsules daily, with meals</td>
</tr>
<tr>
<td>Response</td>
<td>Order Codes: ED11 / ED19</td>
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<tr>
<td></td>
<td>Nrf2 Detox</td>
<td>1 capsule, 1-3 times daily, with meals</td>
</tr>
<tr>
<td></td>
<td>Order Code: NRF6</td>
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<tr>
<td></td>
<td>Resveratrol</td>
<td>1-5 capsules daily, with or between meals</td>
</tr>
<tr>
<td></td>
<td>Order Codes: RE1 / RE6</td>
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<tr>
<td></td>
<td>Vitamin A 3,000 mcg (10,000 IU)</td>
<td>1 capsule daily, with a meal</td>
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<tr>
<td></td>
<td>Order Code: VAC1</td>
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<tr>
<td></td>
<td>Vitamin D₃ 125 mcg (5,000 IU)</td>
<td>1 capsule daily, with a meal</td>
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<tr>
<td></td>
<td>Order Codes: VD52 / VD51 / VD6</td>
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<tr>
<td>Modulate the Impact</td>
<td>Phyto-ADR</td>
<td>1 capsule daily, between meals, or as directed by a health professional</td>
</tr>
<tr>
<td>of Stress (Stress</td>
<td>Order Codes: PHY1 / PHY6</td>
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<tr>
<td>Chemistry)</td>
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<tr>
<td>Support Microbial</td>
<td>A.C. Formula® II</td>
<td>2 capsules, 1-3 times daily, just before meals, with 6-8 oz water</td>
</tr>
<tr>
<td>Balance</td>
<td>Order Code: AC21</td>
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<tr>
<td></td>
<td>MicroDefense®</td>
<td>1 capsule daily, just before a meal, with 6-8 oz water, for 2-3 months, or as directed by a health professional</td>
</tr>
<tr>
<td></td>
<td>Order Codes: M121 / M129</td>
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<tr>
<td>NSK-SD® (Nattokinase)</td>
<td>100 mg</td>
<td>1 capsule, 2 times daily, 12 hours apart, with or between meals</td>
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<tr>
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<td>Order Codes: NS11 / NS16</td>
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<tr>
<td>Support Th1 Response</td>
<td>Arabinogalactan</td>
<td>1 capsule, 3 times daily, between meals</td>
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<td></td>
<td>Order Codes: ARA1 / ARA9</td>
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<tr>
<td>Support Innate</td>
<td>Black Currant Seed Oil</td>
<td>2 capsules, 1-2 times daily, with meals</td>
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<tr>
<td>Immunity</td>
<td>Order Codes: BL1 / BL2</td>
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<tr>
<td></td>
<td>Liposomal Glutathione</td>
<td>1 softgel capsule, 1-2 times daily, with meals, or as directed by a health professional</td>
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<tr>
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<td>Order Codes: LSG3 / LSG6</td>
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<tr>
<td></td>
<td>NAC (N-Acetyl-L-Cysteine) 600 mg</td>
<td>1 capsule, 1-3 times daily, between meals</td>
</tr>
<tr>
<td></td>
<td>Order Codes: NA63 / NA61 / NA69</td>
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<tr>
<td>Modulate Th2 Response</td>
<td>NAC (N-Acetyl-L-Cysteine) 600 mg</td>
<td>1 capsule, 1-3 times daily, between meals</td>
</tr>
<tr>
<td></td>
<td>Order Codes: NA63 / NA61 / NA69</td>
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<tr>
<td></td>
<td>Quercetin</td>
<td>2 capsules, 1-2 times daily, between meals</td>
</tr>
<tr>
<td></td>
<td>Order Codes: QUI / QU6</td>
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<tr>
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<td>Target Cytokine Activation</td>
<td>Curcumin 500 with Bioperine®&lt;br&gt;Order Codes: CUB51 / CUB56</td>
<td>1 capsule, 1-3 times daily, between meals</td>
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<tr>
<td>Target Self-Tissue Response</td>
<td>EPA/DHA essentials&lt;br&gt;Order Codes: ED11 / ED19</td>
<td>1-2 softgel capsules daily, with meals</td>
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<td>Nrf2 Detox&lt;br&gt;Order Code: NRF6</td>
<td>1 capsule, 1-3 times daily, with meals</td>
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<td>Resveratrol&lt;br&gt;Order Codes: RE1 / RE6</td>
<td>1-5 capsules daily, with or between meals</td>
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<td>Vitamin A 3,000 mcg (10,000 IU)&lt;br&gt;Order Code: VAC1</td>
<td>1 capsule daily, with a meal</td>
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<tr>
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<td>Vitamin D₃ 125 mcg (5,000 IU)&lt;br&gt;Order Codes: VD52 / VD51 / VD56</td>
<td>1 capsule daily, with a meal</td>
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<tr>
<td>Modulate the Impact of Stress (Stress Chemistry)</td>
<td><strong>Phyto-ADR</strong>&lt;br&gt;Order Codes: PHY1 / PHY6</td>
<td>1 capsule daily, between meals, or as directed by a health professional</td>
</tr>
<tr>
<td>Support Microbial Balance</td>
<td><strong>A.C. Formula® II</strong>&lt;br&gt;Order Code: AC21</td>
<td>2 capsules, 1-3 times daily, just before meals, with 6-8 oz water</td>
</tr>
<tr>
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<td><strong>MicroDefense†</strong>&lt;br&gt;Order Codes: MI21 / MI29</td>
<td>1 capsule daily, just before a meal, with 6-8 oz water, for 2-3 months, or as directed by a health professional</td>
</tr>
<tr>
<td></td>
<td><strong>NSK-SD® (Nattokinase) 100 mg</strong>&lt;br&gt;Order Codes: NS11 / NS16</td>
<td>1 capsule, 2 times daily, 12 hours apart, with or between meals</td>
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<td>Support Th1 Response</td>
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<td>1 capsule, 3 times daily, between meals</td>
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<tr>
<td></td>
<td><strong>Black Currant Seed Oil</strong>&lt;br&gt;Order Codes: BL1 / BL2</td>
<td>2 capsules, 1-2 times daily, with meals</td>
</tr>
<tr>
<td>Support Innate Immunity</td>
<td><strong>Liposomal Glutathione</strong>&lt;br&gt;Order Codes: LSG3 / LSG6</td>
<td>1 softgel capsule, 1-2 times daily, with meals, or as directed by a health professional</td>
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<tr>
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<td><strong>NAC (N-Acetyl-L-Cysteine) 600 mg</strong>&lt;br&gt;Order Codes: NA63 / NA61 / NA69</td>
<td>1 capsule, 1-3 times daily, between meals</td>
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<td><strong>Quercetin</strong>&lt;br&gt;Order Codes: QU1 / QU6</td>
<td>2 capsules, 1-2 times daily, between meals</td>
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Password: immunemastery

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Webinars

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