The Role of Integrative, Functional Medicine in the Management of Autoimmune Inflammatory Arthritis

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Healthy Immunity = D.I.R.T.

- **Detective & defensive:**
  - Identifies potentially threatening molecular structures: stranger signals
  - Mounts responses appropriate to level of threat: danger signals
- **Internally Regulated (homeodynamic):**
  - Immune responses are tightly controlled & actively resolved by multiple genomic and enzymatic mechanisms
- **Restorative:**
  - Repairs damage that ensues from injury or adversarial encounters
- **Tolerant: actively unresponsive or anergic to**
  - Self antigens
  - Innocuous microbial antigens (commensals)
  - Food and harmless environmental antigens

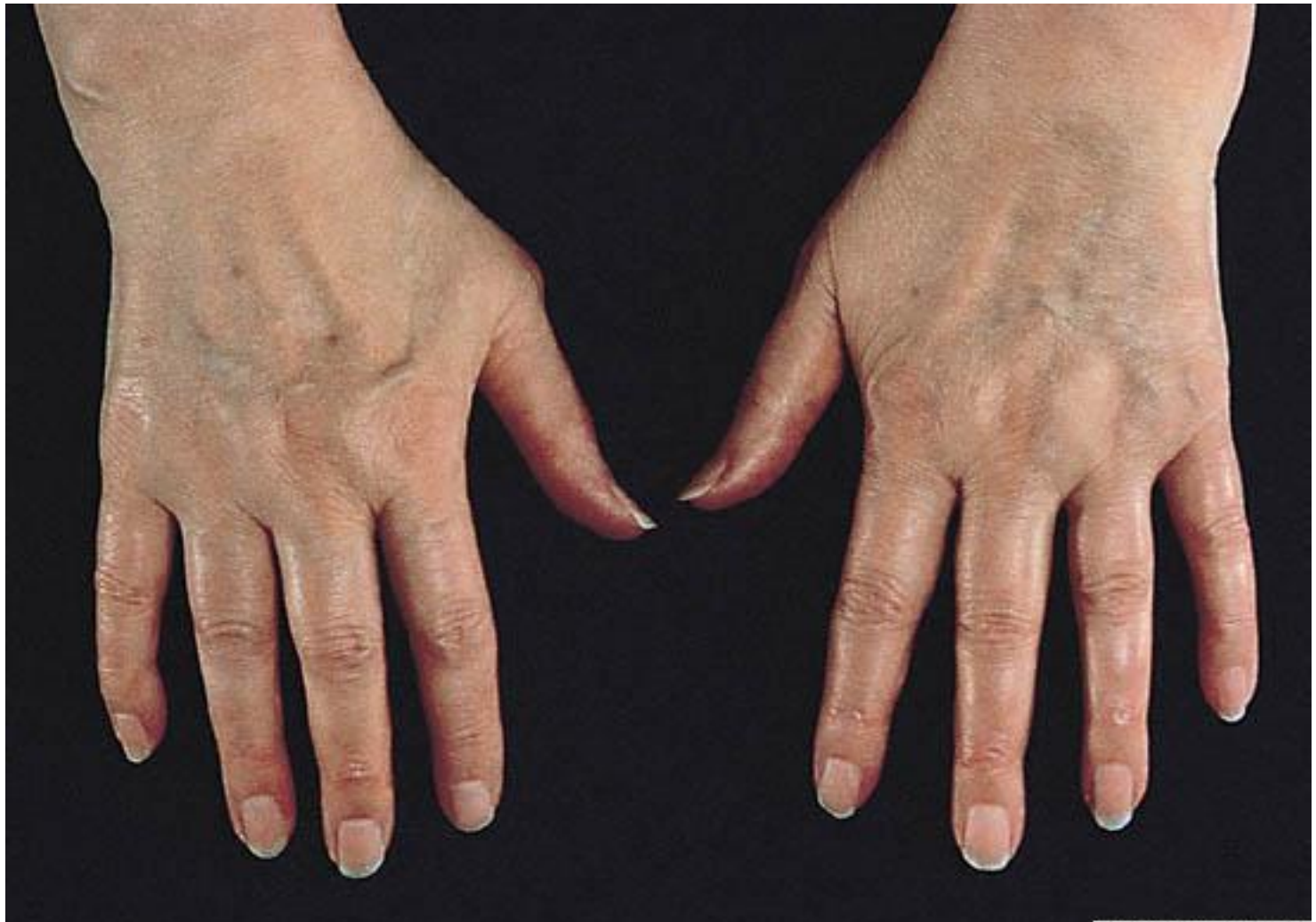
Horror Autotoxicus

- Term coined by Dr. Paul Ehrlich (German bacteriologist)
  - Father of modern science of immunology
  - Winner of Nobel Prize in medicine (1908)
- Ehrlich believed autoimmunity incompatible with life:
  - Immune response could ONLY be towards foreign antigens (”stranger” molecules)
  - Self-reactive lymphocytes are silenced or tolerized
- This belief was long unchallenged despite counter evidence (e.g., lupus autoantibodies; AI hemolytic anemia)
- Autoimmunity and autoinflammation eventually acknowledged in 1940-50’s as *underlying cause* of many chronic diseases

"Mild forms of the autoimmune response probably occur naturally in most people."

National Institute of Environmental Health Sciences, NIH
Press release: September, 1999
www.nih.gov/news/pr/sept99/niehs-28.htm

Symmetric Synovitis in Early Inflammatory Arthritis



Incidence of Rheumatoid Arthritis
(World Health Organization)

- In 2019, **18 million people worldwide** were living with rheumatoid arthritis
- About **70%** of people living with rheumatoid arthritis are **women**, and 55% are older than 55 years
- 13 million people with rheumatoid arthritis experience severity levels (moderate or severe) that could benefit from rehabilitation.
- While **rheumatoid arthritis** is a **systemic autoimmune disease** that affects multiple body systems, the joints of hands, wrists, feet, ankles, knees, shoulders and elbows are most often affected

Inflammatory Arthritis

StatPearls [Internet], January, 2023

- **Arthritis can be broadly classified into two categories, inflammatory arthritis and non-inflammatory arthritis.**
  - ***Comment: this distinction is not as clear as originally thought***
- **Differentiating whether arthritis in a patient is inflammatory or non-inflammatory is the crucial first step towards further diagnosing and managing the patient.**
  - ***Diagnoses is a starting point rather than the end point***

Inflammatory vs Non-inflammatory Arthritis, A True Dichotomy?

- An aberrant immune response is thought to be the primary driver of inflammatory arthritis, while biomechanical factors (wear and tear; trauma) are thought to be the primary causes of non-inflammatory arthritis
- Rheumatoid arthritis (autoimmune) and gout (autoinflammatory) are some of the most common forms of classic inflammatory arthritis
- Osteoarthritis is traditionally thought to be a non-inflammatory, degenerative disorder, but is increasingly being considered an autoinflammatory disease that involves synovitis

Ther Adv Musculoskelet Dis. 2013 Apr; 5(2): 77–94

Case Study (n=1): Rheumatoid Arthritis

- 36 year old white female
- HPI: healthy until 2 yrs prior, onset of symmetrical stiffness & swelling in hands/feet
- Labs: Rheumatoid Factor+
- Rx'd with NSAIDs - partial relief but temporary. Sx progressed to elbows/knees
- Forced to curtail sports
- Worried about side effects with continued use of drugs

Case Study: 36 yo with RA

- Initial Rx: elemental diet fast (rice protein powder) for 3 days, followed by modified elimination diet
- After fast, stated: "Best I've felt in two years."
- Started supplement regimen:
  - Gamma Linolenic Acid (GLA), 900 mg qd (borage seed)
  - Curcumin/ginger extracts
  - Bromelain: 2500 mcu bid
  - Antioxidants (A, E, C, zinc, selenium, bioflavonoids)
  - Glucosamine sulfate, 1500 mg qd

gamma-linolenic acid treatment of rheumatoid arthritis. A randomized, placebo-controlled trial

- **Treatment with 2.8 grams GLA daily for 6 months resulted in statistically significant and clinically relevant reductions in the signs and symptoms of disease activity in patients with RA.**
- **Overall meaningful responses (at least 25% improvement in 4 measures) were also better in the GLA treatment group (14 of 22 patients versus 4 of 19 in the placebo group; P = 0.015)**
- **GLA at doses used in this study is a well-tolerated and effective treatment for active RA.**
- **GLA is available as a component of several plant seed oils and is usually taken in far lower doses than were used in this trial. It is not approved in the United States for the treatment of any condition, and should not be viewed as therapy for any disease**

Zurier, et al, Arthritis Rheum. 1996 Nov;39(11):1808-17 (University of Massachusetts)

A vegan diet free of gluten improves the signs and symptoms of rheumatoid arthritis: the effects on arthritis correlate with a reduction in antibodies to food antigens

- Sixty-six patients with active RA were randomized to either a vegan diet free of gluten (38 patients) or a well-balanced non-vegan diet (28 patients) for 1 yr.
- Twenty-two patients in the vegan group and 25 patients in the non-vegan diet group completed 9 months or more on the diet regimens. Of these diet completers, 40.5% (nine patients) in the vegan group fulfilled the American College of Rheumatology 20 improvement criteria compared with 4% (one patient) in the non-vegan group. Corresponding figures for the intention to treat populations were 34.3 and 3.8%, respectively.
- The immunoglobulin G (IgG) antibody levels against gliadin and β-lactoglobulin (whey protein) decreased in the responder subgroup in the vegan diet-treated patients, but not in the other analyzed groups
- The data provide evidence that dietary modification may be of clinical benefit for certain RA patients, and that this benefit may be related to a reduction in immunoreactivity to food antigens eliminated by the change in diet.

Rheumatology 2001;40:1175–1179

Is **gliadin** (or other lectins) a common trigger for autoimmune diseases OR could it cause **chronic leaky gut**, which results in long-term increases in antigenic & toxic load? (OR both…)

Case Study: 36 yo with RA

- Lab: multiple +IgG foods
- Rx: oligoantigenic diet (gluten and dairy free); ↑ deep sea fish, low saturated animal fat, ↓ nightshades
- 1 month later: slightly better. Added EPA-DHA: 1500 mg; ↑ GLA to 1200 mg
- 2 month follow-up: 50% better, jogging & walking again; Rx'd minocycline (100 mg/d) and probiotics
- 4 month follow-up: "almost back to normal," had improved within 4 days of starting antibiotic

Benefits and risks of minocycline in rheumatoid arthritis

- Minocycline, a semi-synthetic derivative of tetracycline, has been extensively studied as a therapeutic agent for rheumatoid arthritis.
- The antirheumatic effect of minocycline can be related to its immunomodulatory and anti-inflammatory, rather than to its antibacterial properties
- Summarizing the data of 3 double-blind studies, we may conclude that minocycline may be beneficial in patients with rheumatoid arthritis, especially when given early in the disease course or in patients with a mild disease.

P Langevitz, et al, Drug Saf, 2000 May;22(5):405-14

Case Study: 36 yo with RA

- 7 month follow-up: “100% better”; only remaining symptom was pain in one finger, otherwise at full activity level; had tried stopping either minocycline or supplements but symptoms recurred.
- 1 year later, retested IgG-food complexes and modified diet accordingly, otherwise same program.
- Follow-up two years after initial visit. Did well, then stopped minocycline for several months. Had one flare and restarted, better within two weeks. Decided to stay on it, along with supplements, “permanently.”

Autoimmune Disease: Broadly Defined

- **Self-directed tissue inflammation, resulting from loss of tolerance by aberrant dendritic cell, B & T cell responses with development of immune reactivity towards native antigens**
- **Pathophysiology is ongoing & multifactorial: organ or tissue-specific antibodies may predate clinical disease by many years**
- **Adaptive immune response (antibodies, activated T lymphocytes) *appears* to play predominant role in clinical disease, although innate immunity may be the ultimate driver.**

PLoS Med, 2006, Vol 3(8): 1242-1248

Scientific American

March, 2007

New PREDICTORS of Disease

Molecules called predictive autoantibodies appear in the blood years before people show symptoms of various disorders. Tests that detected these molecules could warn of the need to take preventive action

By Abner Louis Notkins

A middle-aged woman—call her Anne—was taken aback when one day her right hand refused to hold a pen. A few weeks later her right foot began to drag reluctantly behind her left. After her symptoms worsened over months, she consulted a neurologist. Anne, it turned out, was suffering from multiple sclerosis, a potentially disabling type of autoimmune disease. The immune system normally jumps into action in response to bacteria and viruses, deploying antibodies, other molecules and various white blood cells to recognize and destroy trespassers. But in autoimmune disorders, components of the body's immune system target one or more of the person's own tissues. In Anne's case, her defensive system had begun to turn against her nerves, eroding her ability to move.

Every story of autoimmune disease is sad—but collectively the impact of these illnesses is staggering. More than 40 autoimmune conditions have been identified, including such common examples as type 1 (insulin-dependent) diabetes, rheumatoid arthritis and celiac disease. Together they constitute the third leading cause of sickness and death after heart disease and cancer. And they afflict between 5 and 8 percent of the U.S. population, racking up an annual medical bill in the tens of billions of dollars.

Recent findings offer a way to brighten this gloomy picture. In the past 10 years a growing number of studies have revealed that the body makes certain antibodies directed against itself—otherwise known as autoantibodies—years, and sometimes a decade, before autoimmunity causes clinical disease, damaging tissues so much that people begin showing symptoms. This profound insight is changing the way that doctors and researchers think about autoimmune conditions and how long they take to arise. It suggests that physicians might one day screen a healthy person's blood for certain autoantibodies and foretell whether a specific disease is likely to develop years down the line. Armed with such predictions, patients could start fighting the ailment with drugs or other available interventions, thereby preventing or delaying symptoms.

Those interventions may not be easy to find; most likely, preventive therapy would have to be tailored specifically for each condition. In certain disorders, such as myasthenia gravis, autoantibodies participate in the disease process, and so blocking the activity of the particular autoanti-

"NOVEL CRYSTAL BALL: One day Y-shaped molecules called autoantibodies in a patient's blood may tell doctors whether a patient is "brewing" certain diseases and may even indicate roughly how soon the individual will begin to feel symptoms."

Autoantibodies: New Predictors of Disease

- **Autoantibodies are made years--sometimes a decade--before clinical autoimmune disease**
- **Well over 10 million people test positive for ANA, years before symptoms appear**
- **Antibodies against citrullinated peptides (antiCCP = anti-cyclic citrullinated peptides), can appear >10 years before clinical appearance of RA**
- **Antibodies against tissue transglutaminase (tTG) can appear 7 years prior to symptomatic celiac disease**

Scientific American, 3/07

Autoimmune Disease: "Delayed Gratification"

- **Many autoimmune diseases do not develop spontaneously, but instead evolve through an extended germination period before they become clinically evident…**
- **This implies the presence of additional environmental factors that dampen or amplify the process over time.**

Ligands for RAGE (Receptors for AGEs)

Could the increase in Autoimmune Inflammatory Arthritis and other ADs Result from Unhealthy Diets?

- **Excessive processed foods**
- **Refined carbohydrates**
- **Trans fatty acids**
- **Excessive arachidonic acid (vs omega-3 fats)**
- ***Insufficient vitamins A & D***
- **Insufficient antioxidant phytochemicals**

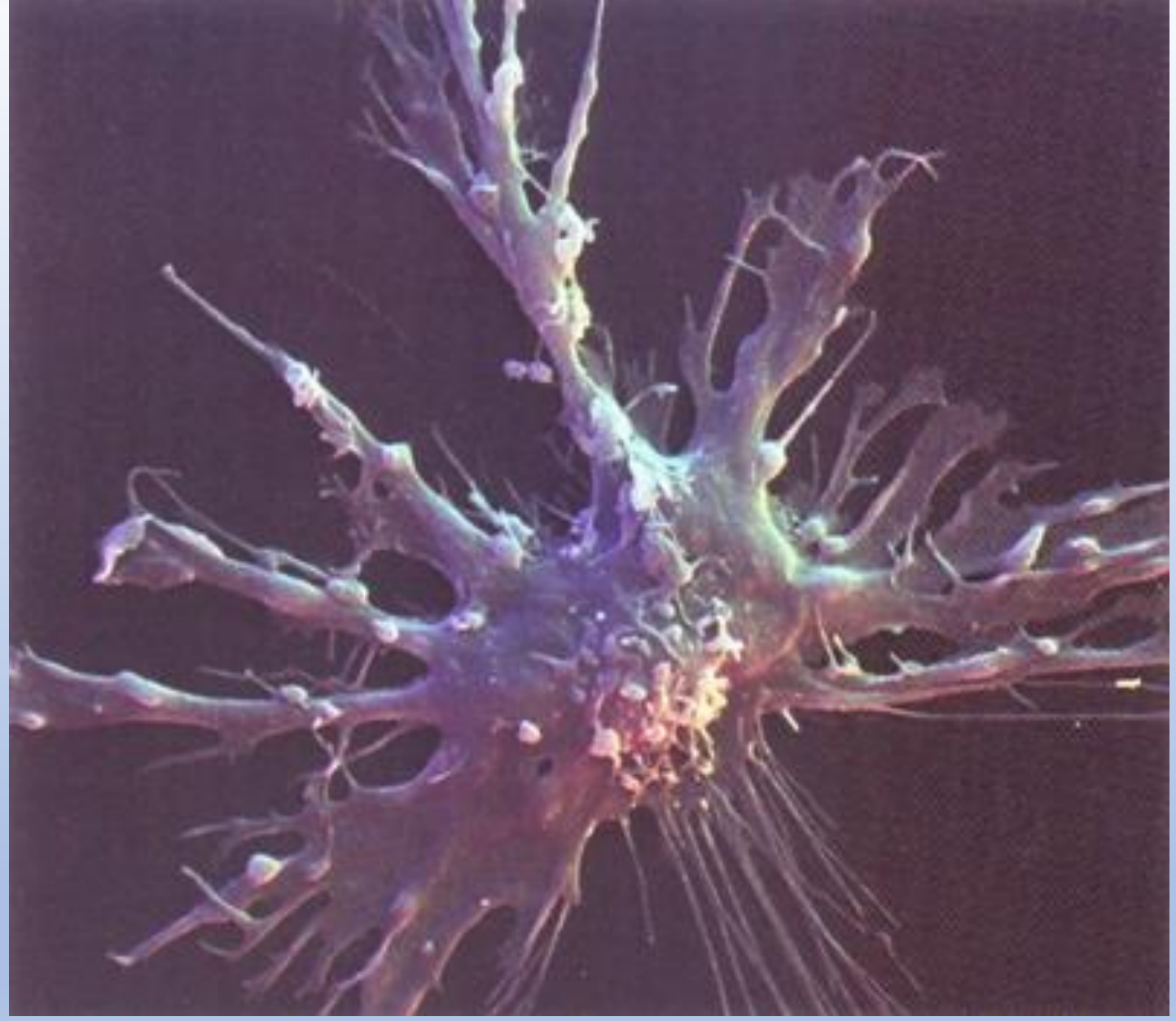
Rancid PUFAs, long-chain saturated fats, refined sugars & AGEs…

- increase inflammation and free radical production,
- which damages tissues & DNA (bystander effect),
- creating "foreign-like" tissues that break immune tolerance…

Danger Signal Theory

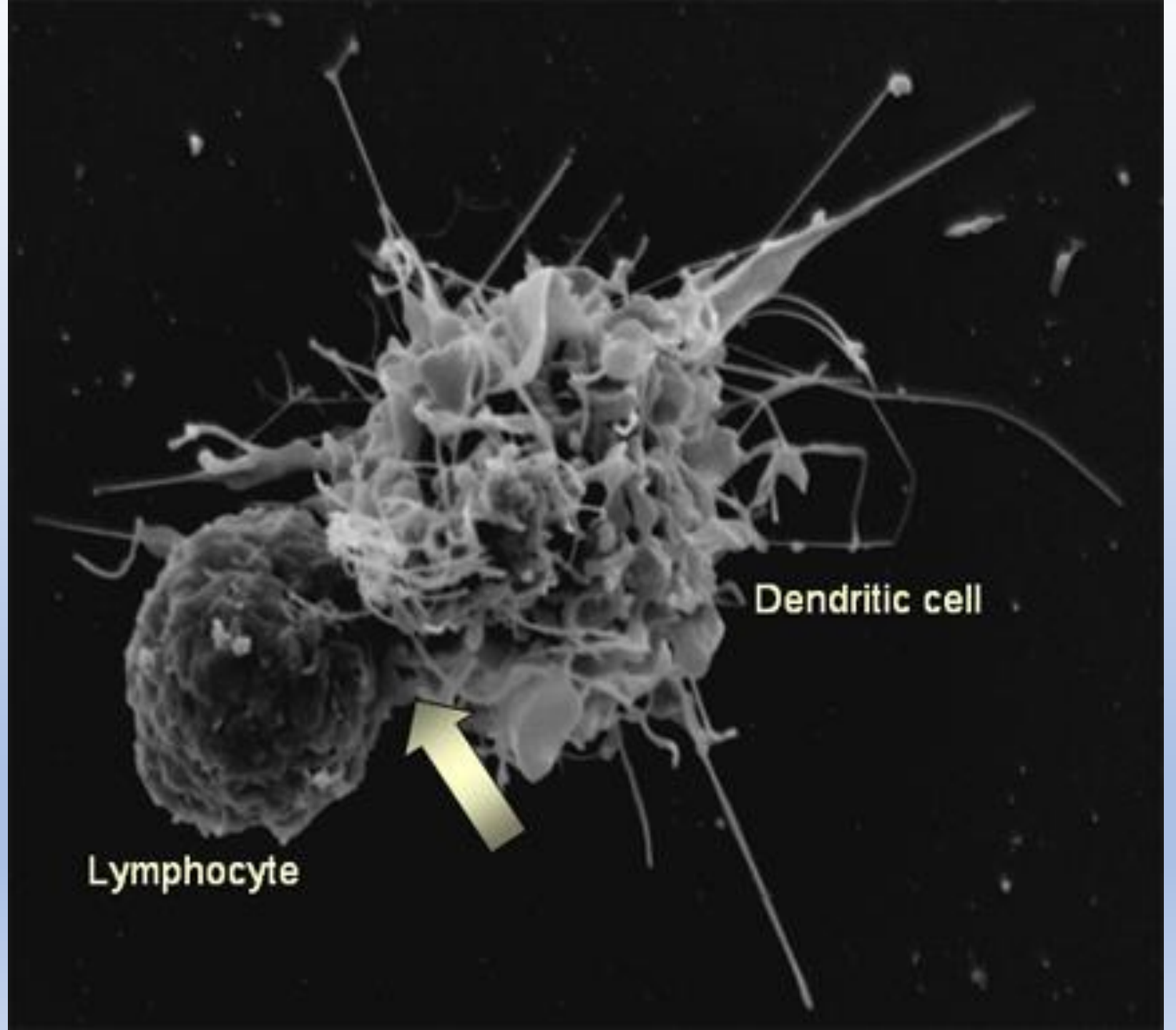
(Polly Matzinger, PhD)

- **Immune system is less concerned with distinguishing self from non-self (strangers) than it is with mounting responses to danger:**
  "entities that do damage"
- **Risk of harm is determined by antigen presenting cells (via induction of costimulatory molecules by alarm signals).**
- **Stranger + danger → inflammation**

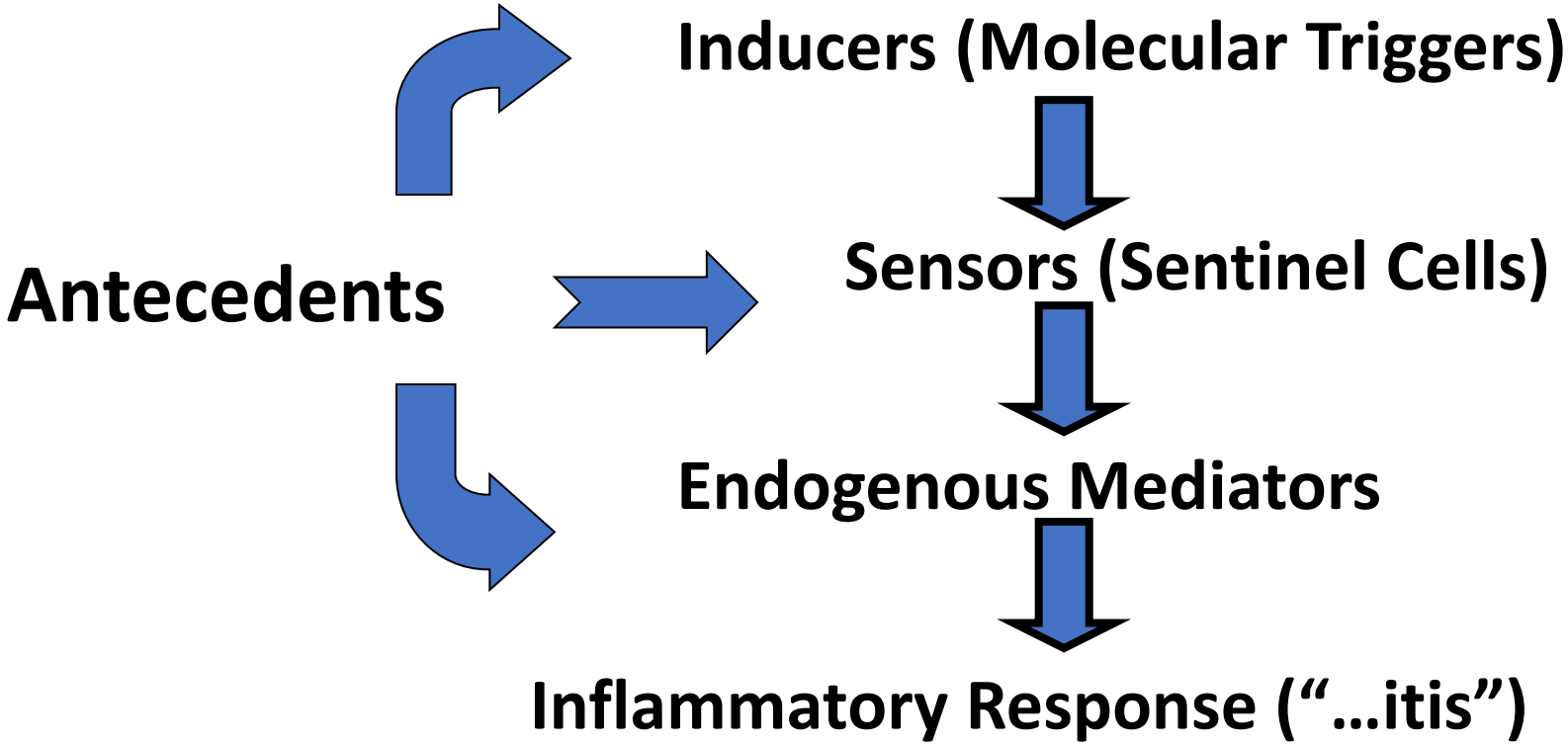


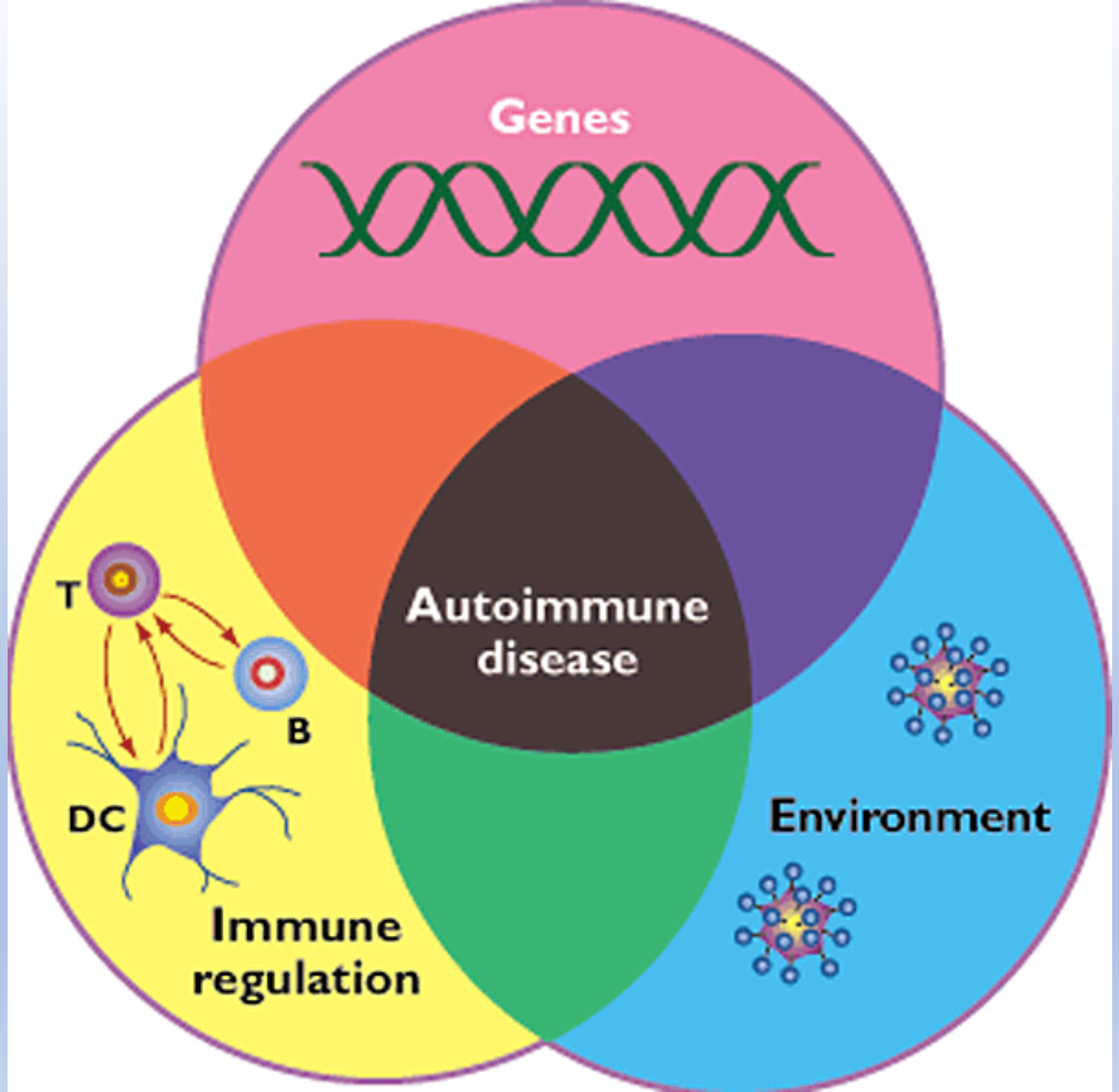
Dendritic Cell

Dendritic cells: innate immune system's barrier sentinels for determining risk information about interactions with the world outside:
Is this molecular pattern a stranger? **(Pathogen associated molecular pattern)**
Is this molecular pattern dangerous?
(Damage/danger associated molecular pattern)


Dendritic cell
Lymphocyte

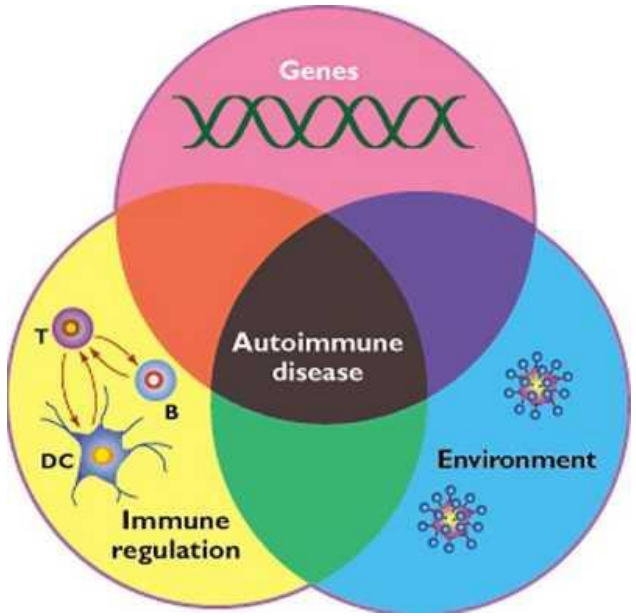
The Inflammatory Process: A Physiologic Algorithm




Genes
T
B
DC
Autoimmune disease
Immune regulation
Environment

Up to 20% of the population has genetic variants (eg, immune SNPs, serotypes: HLA-DR4; haplotypes, etc.) that can predispose them to autoimmune disease. However, only a small fraction go on to develop full-blown autoimmune disorders.

Genes are not destiny. Mitigating factors (triggers & mediators) must be involved…



"Mild forms of the autoimmune response probably occur naturally in most people. ***But, for people with a predisposition to autoimmunity, environmental factors, such as toxic chemicals, drugs, bacteria or viruses, may trigger a full-fledged response."***

Press release: September, 1999. National Institute of Environmental Health Sciences, NIH
www.nih.gov/news/pr/sept99/niehs-28.htm

Systemic Autoimmune Disorders in Celiac Disease

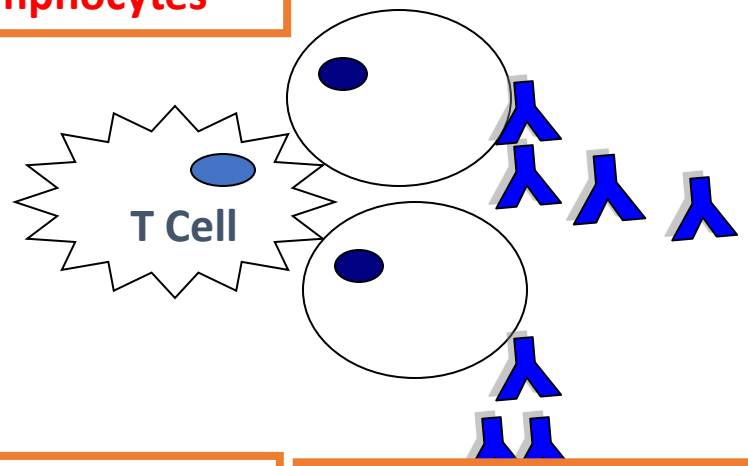
- **Autoimmune diseases involve a miscommunication between innate & adaptive immunity**
- **Molecular mimicry or bystander effects alone may not explain the complex events involved in the pathogenesis of ADs, rather the continuous stimulation by environmental triggers (nonself antigens) appears necessary to perpetuate the process. This implies that the autoimmune response can be theoretically stopped & reversed if the interplay between genes & triggers is prevented**
- **The third element necessary to develop autoimmunity is the loss of protective barrier function**

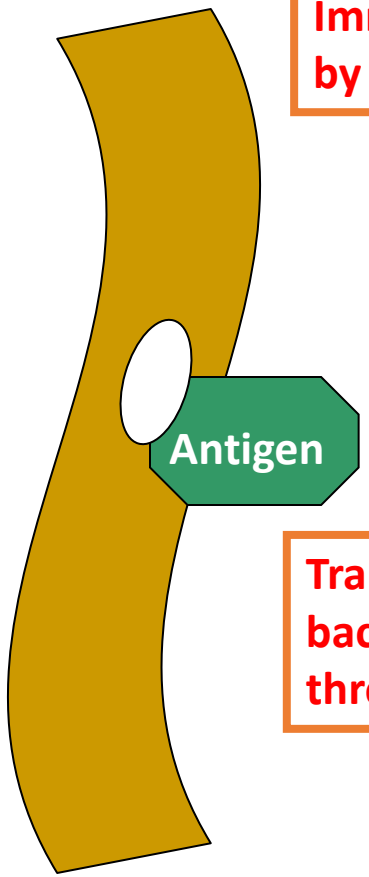
Fasano, A, Clin Opin Gastroenterol, 2006 Vol 22(6): 674-679

‘Leaky Gut’ and Autoimmunity

Immune reaction occurs by T & B lymphocytes

B cells form antibodies

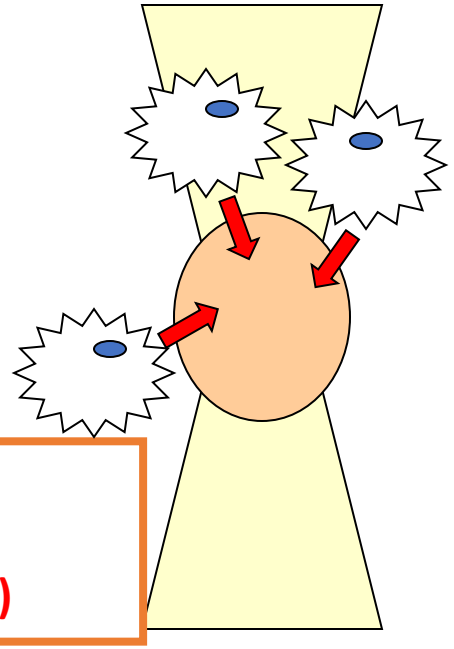




Leaky gut

Transmigration of bacteria or food antigen through leaky gut

Antibodies confuse self (cartilage) with other (bacteria, virus, microbe)



Knee joint

Immune reaction occurs, resulting in pain, swelling, tissue damage

What about leaky lungs?

DO YOU INHALE?

"Everybody's doing it!"

7 out of 10 smokers inhale knowingly—
the other 3 inhale unknowingly

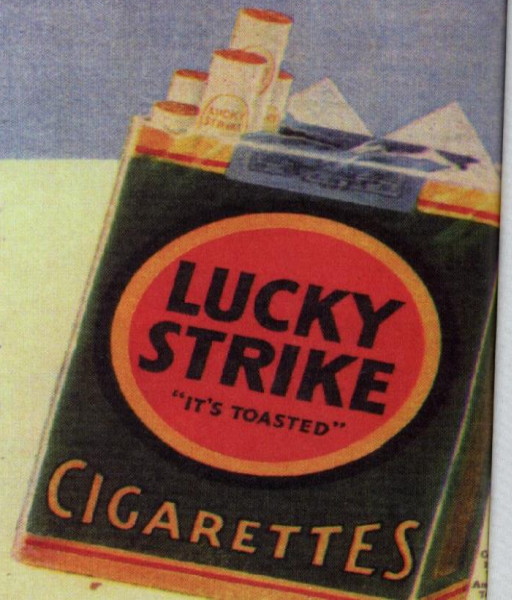
DO you inhale? 7 out of 10 smokers *know* they inhale. The other 3 inhale without realizing it. Every smoker inhales—for every smoker breathes in some part of the smoke he or she draws out of a cigarette.

Do you inhale? Of course you do! Lucky Strike has dared to raise this vital question . . . because certain impurities concealed in even the finest, mildest tobacco leaves are removed by Luckies' famous purifying process. Luckies created that process. Only Luckies have it!

Do you inhale? More than 20,000 physicians, after Luckies had been furnished them for tests, *basing their opinions on their smoking experience,* stated that Luckies are less irritating to the throat than other cigarettes.

"It's toasted"

Your Protection
against irritation—against cough



O. K. AMERICA—TUNE IN ON LUCKY STRIKE—60 modern minutes with the world's finest dance orchestras, and famous Lucky Strike features, every Tuesday, Thursday and Saturday evening over N. B. C. networks.

"More than 20,000 physicians, after Luckies had been furnished them for tests, *basing their opinions on their smoking experience*, stated that Luckies are less irritating than other cigarettes."

Mad Men?

Holy Smokes!!

Cigarette smoking has been strongly linked to numerous autoimmune diseases

Cigarette smoking & autoimmune disease: what can we learn from epidemiology?

- **Rheumatoid arthritis and cigarette smoking:**
  - Risk is highest in men: OR up to 4.4 X
  - Smoking increases risk of *seropositive* RA 2.4X in women
  - Smoking intensity and duration both greatly increase risk
  - Smoking increases severity of symptoms
  - Increased risk remains for 20 yrs after cessation
  - "Cigarette smoking is the most conclusively established environmental risk factor for RA"

Costenbader, KH, Lupus, Vol. 15, No. 11, 737-745 (2006)

Smoking and Air Pollution as Pro-Inflammatory Triggers for the Development of Rheumatoid Arthritis.

- **Smoking initiates chronic inflammatory events in the lungs.**
- **These, in turn, promote the release of the enzymes, peptidylarginine deiminases (PAD) 2 and 4 from smoke-activated, resident and infiltrating pulmonary phagocytes.**
- **Peptidylarginine deiminases mediate conversion of various endogenous proteins to putative citrullinated autoantigens.**
- **In genetically susceptible individuals, these autoantigens trigger the production of autoantibodies to anti-citrullinated peptide, an event which precedes the development of RA.**

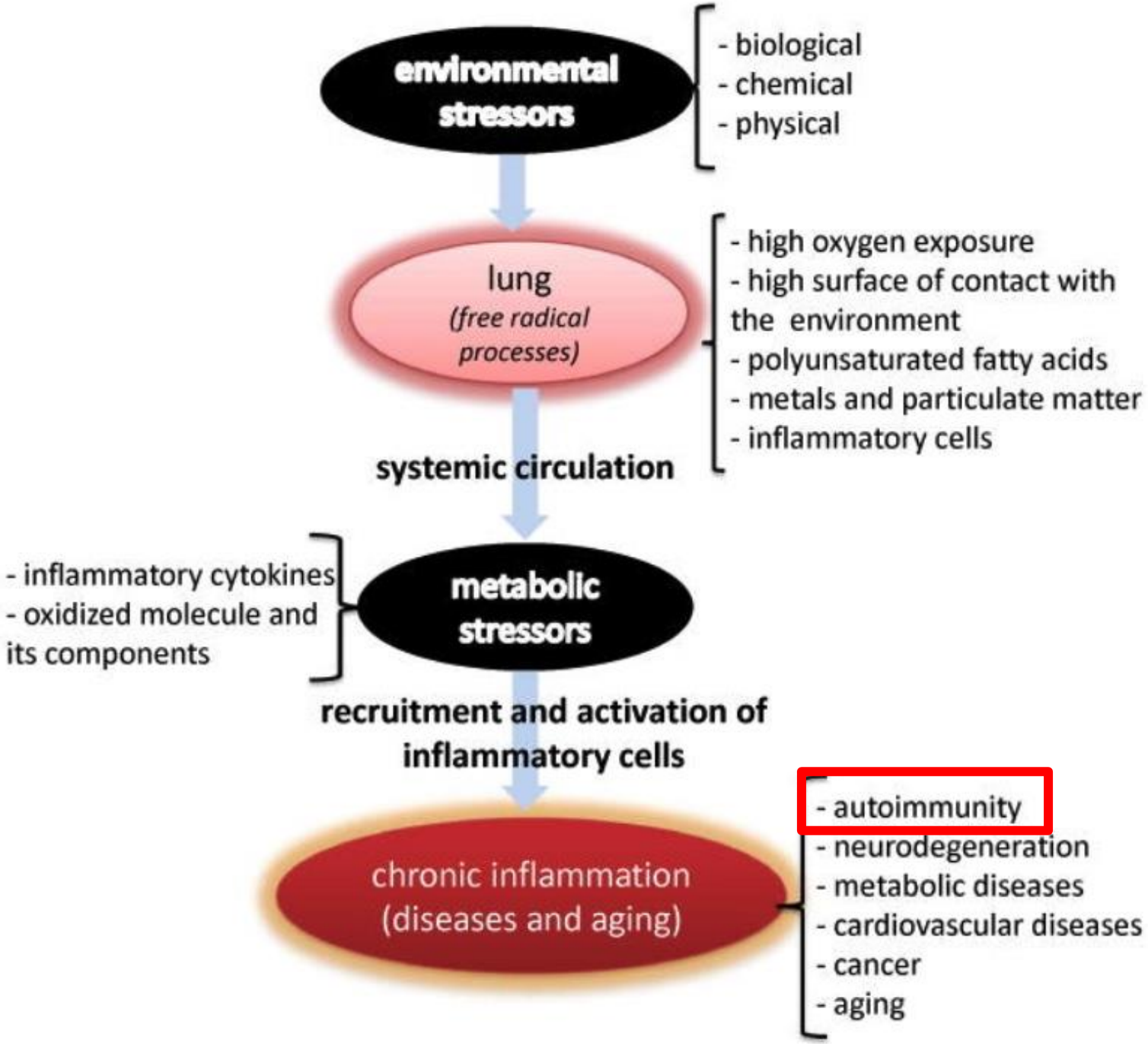
Anderson R, Meyer PW, Ally MM, Tikly M, Nicotine Tob Res. 2016 Jul;18(7):1556-65

Industrial air emissions, and proximity to major industrial emitters, are associated with anti-citrullinated protein antibodies.

- **Randomly sampled 1586 subjects out of 20,000 population from Quebec, Canada**
- **After adjusting for age, sex, smoking, and ethnicity, found**
  - **Positive association between anti-CCPA and annual industrial PM 2.5 and sulfur dioxide emissions (i.e. living closer to emitters increases anti-CCPA)**
  - **Negative association between anti-CCPA and to a major industrial emitter of both PM 2.5 and SO2 (living further away from emitters decreases anti-CCPA)**
- **"These analyses suggest that exposure to industrial emissions of air pollutants is related to ACCPA positivity."**

Bernatsky S, Smargiassi A, Joseph L, et al, Environ Res. 2017 Aug;157:60-63

Does rheumatoid arthritis (and other autoimmune disease) start in the gut, *or in the lungs*?



Gomez-Mejiba SE, Zhai Z, Akram H, et al. Inhalation of Environmental Stressors & Chronic Inflammation: Autoimmunity and Neurodegeneration. *Mutation research*. 2009;674(1-2):62-72.

Citrullination and autoimmunity

- Environmental exposure to cigarette smoke and nanomaterials of air pollution may be able to induce citrullination in lung cells prior to any detectable onset of inflammatory responses, suggesting that protein citrullination could be considered as a sign of early cellular damage
- Citrullination has been reported to be a process present in a wide range of inflammatory tissues. Indeed, citrullinated proteins have been detected also in other inflammatory arthritides and in inflammatory conditions other than arthritides (polymyositis, inflammatory bowel disease and chronic tonsillitis)
- These data support the hypothesis that rather than being a disease-dependent process, citrullination is an inflammatory-dependent condition that plays a central role in autoimmune diseases.

Valesini G, Shoenfeld Y, et al Autoimmun Rev. 2015 Jun;14(6):490-7

Anti-Cyclic Citrullinated Peptide Antibodies

- Current method is 96% specific for RA
- Elevated titers detected >10 years before onset of clinical disease
- Sensitivity (likelihood of positive test) increases from 50% at Dx to >75% over course of disease
- Likely involved in pathogenesis
  - Citrullinated Ags are highly expressed in inflamed joints
  - Positive test predicts joint erosion
  - Antigen-antibody complexes activate complement = inflammatory

Floris van Gaalen et al. J Immunol 2005;175:5575-5580

Autoimmunity to specific citrullinated proteins gives the first clues to the etiology of rheumatoid arthritis

- Four citrullinated whole protein antigens, fibrinogen, vimentin, collagen type II, and alpha-enolase, are now well established, with others awaiting further characterization
- All four proteins are expressed in the joint, and there is evidence that antibodies to citrullinated fibrinogen and collagen type II mediate inflammation by the formation of immune complexes
- Antibodies to citrullinated proteins are associated with HLA 'shared epitope' alleles
- *Porphyromonas gingivalis*, pathogenic bacteria that is a major cause of periodontal disease, expresses endogenous citrullinated proteins
- Thus, both smoking and *Porphyromonas gingivalis* are attractive etiological agents for further investigation into the gene/environment/autoimmunity triad of RA.

Wegner N, Lundberg K, Kinloch A, et al, Immunol Rev. 2010 Jan;233(1):34-54

“Good Fences Make Good Neighbors”

Healthy barriers (gut, lung, skin) promote tolerance

Case Study: recurrent hand & foot pain

- 55 yo white female with CC of recurrent polyarthralgias in fingers, wrists, elbows, and arches of both feet
- HPI: 2-3 months prior to visit developed pain in arches of both feet while walking in urban environment. Consulted podiatrist – X-rays showed bilateral heel spurs and osteoarthritis of right great toe MTP. Tried orthotics and new shoes with little effect.
- Also had recurrent pains in hands and elbows. Consulted with rheumatologist who ran battery of immune labs – all WNL. X-rays of wrists showed erosive changes in ulnar styloids. Consultant recommended adalimumab, told her this was "data-driven." Patient researched the drug extensively and decided against it - concerned about risk vs benefit. Sought 2nd opinion.

Licensed from
NY Times

Case Study: recurrent hand & foot pain

- **PMH**
  - **Synthetic cartilage graft, right great toe MTP for *Hallux Rigidus* (degenerative arthritis)**
  - **Ganglionectomy, right wrist (De Quervain tenosynovitis)**
  - **Osteopenia**
  - **Post-menopausal x 10 years, initially took E2 patch but GYN stopped Rx after positive test for MTHFR variant (+/+ A1298C, -/- C677T) – "could increase risk of blood clots" (???)**

Case Study: recurrent hand & foot pain

- **Lifestyle Hx**
  - **Nonsmoker; lives near large body of water – lots of free air with minimal exposure to air pollution**
  - **Social EtOH: 1-3 drinks / wk**
  - **Tennis: 3-4 x week; Spinning classes: 2x/wk; weight training**
  - **Walks regularly, formerly long-distance runner**
  - **Diet: omnivorous, eats out a lot, minimal refined foods; fish/chicken are main proteins, some dairy, moderate gluten intake**
  - **Dietary supplements: fish oil, curcumin, NAC, vitamin D**

Case Study: recurrent hand & foot pain

- **Physical exam (via telehealth –during pandemic)**
  - **WNWD causasian female, NAD**
  - **No observable joint deformities or limited ROM; no red or swollen joints**
  - **No rashes**
- **Labs**
  - **CBC: WNL; Comprehensive metabolic panel: WNL**
  - **Hemoglobin A1c: 5.3%; TSH: 1.810 uIU/mL**
  - **HLA-B27 antigen: negative**
  - **RF: <14; anti-CCP <16 units (negative); ANA screen: negative**
  - **CRP: 0.7 mg/L**
  - **C3: 106 mg/dL (nl 83-193); C4: 21 mg/dL (nl 15-57)**

Case Study: recurrent hand & foot pain

- Radiology studies
  - DEXA
    - AP L spine L1-L1, T score: -2.4
    - L total hip, T score -1.0
  - X-rays of feet: bilateral bone spurs; left bunion, cartilage implant on right
  - X-rays of wrists: erosive change of ulnar styloids, bilateral with mild overlying soft tissue swelling possible tenosynovitis of extensor carpi ulnaris

Case Study: recurrent hand & foot pain

- **Additional labs**
  - **14.3.3 ETA protein <0.2 ng/mL**
  - **Sjogren's antibody panel (SS-A/SS-B): <1.0 (negative)**
  - **Sm antibody: <1.0; SM/RNA antibody: <1.0**
  - **Vitamin D, 25-OH: 75.3 ng/mL (nl 30-150 ng/mL)**
  - **Oxidized LDL (serum): 38 U/L (nl <60)**
  - **Urinary F2 isoprostane: <0.20 (minimally detectable)**
  - **OmegaCheck (whole blood EPA+DPA+DHA): 9.1% (>5.5%)**

Case Study: recurrent hand & foot pain

Test Name	In Range	Out Of Range	Reference Range
CYTOKINE PANEL 13, SERUM			
TUMOR NECROSIS FACTOR ALPHA, SERUM		**9.8 H**	<=7.2 pg/mL
INTERPRETIVE INFORMATION: Cytokines Results are used to understand the pathophysiology of immune, infectious, or inflammatory disorders, or may be used for research purposes.			
INTERLEUKIN 2, SERUM	<2.1		<=2.1 pg/mL
INTERLEUKIN 2 RECEPTOR, SOLUBLE, SERUM	649.8		175.3-858.2 pg/mL
INTERLEUKIN 12, SERUM	<1.9		<=1.9 pg/mL
INTERFERON GAMMA, SERUM	<4.2		<=4.2 pg/mL
INTERLEUKIN 4, SERUM	<2.2		<=2.2 pg/mL
INTERLEUKIN 5, SERUM	<2.1		<=2.1 pg/mL
INTERLEUKIN 10, SERUM		**3.6 H**	<=2.8 pg/mL
INTERLEUKIN 13, SERUM		**9.5 H**	<=2.3 pg/mL
INTERLEUKIN 17, SERUM	<1.4		<=1.4 pg/mL
INTERLEUKIN 1 BETA, SERUM	<6.5		<=6.7 pg/mL
INTERLEUKIN 6, SERUM		**4.4 H**	<=2.0 pg/mL
INTERLEUKIN 8, SERUM		**6.6 H**	<=3.0 pg/mL

ARTHRITIS & RHEUMATISM
Vol. 62, No. 2, February 2010, pp 383–391
DOI 10.1002/art.27186

Up-Regulation of Cytokines and Chemokines Predates the Onset of Rheumatoid Arthritis

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Objective. **To identify whether cytokines, cytokine-related factors, and chemokines are up-regulated prior to the development of rheumatoid arthritis (RA).**

Methods. **A nested case–control study was performed in 86 individuals who had donated blood samples before experiencing any symptoms of disease (pre-patients) and 256 matched control subjects (1:3 ratio). In 69 of the pre-patients, blood samples were also obtained at the time of the diagnosis of RA. The plasma levels of 30 cytokines, related factors, and chemokines were measured using a multiplex system.**

Results. **The levels of several of the cytokines, cytokine receptors, and chemokines were significantly increased in individuals before disease onset compared with the levels in control subjects; i.e., those representing signs of general immune activation (interleukin-1β [IL-1β], IL-2, IL-6, IL-1 receptor antagonist, and tumor necrosis factor), activation of Th1 cells (interferon-γ, of most of these increased further after disease onset. The concentration of IL-17 in individuals before disease onset was significantly higher than that in patients after disease onset. Individuals in whom RA subsequently developed were discriminated from control subjects mainly by the presence of Th1 cells, Th2 cells, and Treg cell–related cytokines, while chemokines, stromal cell–derived cytokines, and angiogenic-related markers separated patients after the development of RA from individuals before the onset of RA.**

Conclusion. **Individuals in whom RA later developed had significantly increased levels of several cytokines, cytokine-related factors, and chemokines representing the adaptive immune system (Th1, Th2, and Treg cell–related factors); after disease onset, the involvement and activation of the immune system was more general and widespread.**

Up-Regulation of Cytokines and Chemokines Predates the Onset of Rheumatoid Arthritis

- **Study conducted in Northern Sweden**
- **Blood samples collected from general population**
- **86 individuals identified as having donated blood samples before the onset of any symptoms of joint disease**
- **Median period of time predating the onset was 3.3 years**

Kokkonen, H., Söderström, I., Rocklöv, J., Hallmans, G., Lejon, K., & Rantapää Dahlqvist, S. (2010). Up-regulation of cytokines and chemokines predates the onset of rheumatoid arthritis. *Arthritis & Rheumatism, 62*(2), 383-391.

Cytokines as Biomarkers in Rheumatoid Arthritis

- **New biomarkers for RA are still needed for early diagnosis, prognosis, tailoring therapy, management of co-morbidities (CVD), and prediction of relapse.**
- **Numerous cytokines found to be involved in RA pathology and have potential to be biomarkers**
- **Given the complexity and heterogeneous nature of RA, it is unlikely that a single cytokine may provide sufficient discrimination; therefore multiple biomarker signatures may represent more realistic approach for the future of personalised medicine in RA.**

Agata Burska, Marjorie Boissinot, & Frederique Ponchel. (2014). Cytokines as Biomarkers in Rheumatoid Arthritis. *Mediators of Inflammation, 2014*, Mediators of Inflammation, 01 January 2014, Vol.2014.

Where do we go from here?

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Case Study: recurrent hand & foot pain

- Keep diet diary: notice if certain foods exacerbate symptoms; consider elimination diet (esp refined foods, gluten, dairy free)
- Nutraceuticals:
  - EPA-DHA: 2000 mg daily
  - Pro-Resolving mediators: 1200 mcg daily x 1 month, then 600 mcg
  - Curcumin phytosome: 1000 mg bid
  - Boswellia phytosome: 700 mg big
  - Glucosamine sulfate: 1500 mg with chondroiton sulfate: 750 mg
  - Methylsulfonylmethane (MSM): 3 grams bid
- Obtain gut microbiome metagenomic analysis

Case Study: recurrent hand & foot pain

- **Gut microbiome metagenomic analysis:**
  - **Elevated Staphylococcus**
  - **Elevated Streptococci**
  - **Elevated Klebsiella**
  - **Elevated Enterobacteria**
  - **Elevated fungal species**
  - **Low Akkermansia muciniphila**
  - **Low Faecalibacterium praustnitzii**
  - **Low Roseburia**
  - **Low Ruminococcus (no *R gnavus*)**

A Role for the Microbiome in Juvenile Idiopathic Arthritis?

http://www.medpagetoday.com/MeetingCoverage/ACR/48682

- **Findings presented by Daniel Horton, MD, Univ. of PA, at 2014 annual meeting of American College of Rheumatology**
- **After adjusting for potential confounders, any antibiotic use was associated with more than twice the risk of JIA**
- **Risk increased in a dose-dependent manner**

Expansion of intestinal *Prevotella copri* correlates with enhanced susceptibility to arthritis (eLIFE, 2013: e01202)

- 16S sequencing performed on 114 stool samples from RA patients & controls
- *Prevotella copri* more abundant in majority of untreated RA than in controls
- In mouse model, *P copri* dominates the intestinal microbiota, reducing many beneficial species
- Rx of *P copri* in the gut may delay or prevent the onset of RA

Alterations in the gut microbiome implicate key taxa and metabolic pathways across inflammatory arthritis phenotypes

- **The Inflammatory Arthritis Microbiome Consortium investigated 440 stool shotgun metagenomes comprising 221 treatment naiive adults diagnosed with rheumatoid arthritis, ankylosing spondylitis, or psoriatic arthritis and 219 healthy controls and individuals with joint pain without an underlying inflammatory cause.**
- **Results confirm and extend previous findings of increased carriage of typically oral or inflammatory taxa, and decreased abundance and prevalence of several typical gut clades**
- **Enriched bacteria included *E coli*, *Ruminococcus gnavus*, and *Streptococcus species***
- **Elevated levels of *Prevotella copri* were NOT detected in this study!**

Thompson *et al.*, *Sci. Transl. Med.* **15**, eabn4722 (2023)

Case Study: recurrent hand & foot pain

- **Additional GI Recommendations**
  - ***Akkermansia muciniphila*** **probiotic (butyrate producer): 100 million AFUs (Active Fluorescent Units) bid**
  - **Prebiotic powder, 8 gram serving 1-2 x daily, containing**
    - **Resistant potato starch**
    - **Resistant green banana starch**
    - **Oat beta glucan**
    - **Soluble maize fiber**

Case Study: recurrent hand & foot pain

- **Follow-up at four months:**
  - **Arches of feet are much less painful, despite being very active physically: walking frequently, but less on sidewalks**
  - **Pain in wrists much reduced, “at most 2/10,” despite playing tennis 3x/wk, weight training 3x/wk**
  - **Attributes improvement to dietary supplements, which began helping within weeks**

Putting it all together….

Possible Antecedents of Inflammatory Arthritis

- Genetics
  - HLA-DR4
  - Immune SNPs
- Barrier disruptions (leaky gut)
- Chronic dysbiosis
- Nutritional deficiency (vitamins A & D)
- Pro-inflammatory diet (high arachidonic acid, saturated long-chain fats, or trans-fats)
- Oxidative stress (chronic)
- Reproductive hormone imbalances
- Chronic stress

Potential Sources of Molecular Triggers for Inflammatory Arthritis

- Toxins (eg. smoke, air pollution)
- Foods (gluten, dairy products)
- Microbes (gut and lung)
- Trauma (tissue damage)

The “Anti-Inflammatory” Diet

"Never, ever, think outside the box."

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The Role of Integrative, Functional Medicine in the Management of Inflammatory Arthritis

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The Role of Integrative Functional Med icine in the Management of Inflammatory Arthritis