Immunity

When your Friend turns to Foe

Fellowship in Anti-Aging Medicine
Module 4

Did You Know, Immune Dysregulation is Found in:

- Alzheimer's Disease
- Schizophrenia
- Heart Disease
- Spontaneous Abortions
- Depression
- Hyperhomocysteinaemia
And more…

The Gut Regulates Systemic Immunity

- The proper functioning of the gut environment is essential for systemic immunity
- Antigen Presenting Cells (APC) such as M cells, B cells, endothelial cells, macrophages and dendritic cells dictate the immune response in the gut.
- These cells send messages (cytokines) to the systemic immune system, which then dictates its response
- Improving gut flora can normalise immunity.

The Gut Directs Immunity

"First, the cells of the gut itself produce TGF-b, vasoactive intestinal peptide (which controls the secretory piece of IgA), and other immunologically relevant molecules."


The Gut Directs Immunity

"Second, the luminal side of the intestinal epithelium contains a set of specialized Ag (antigen) -handling cells called M (microfold) cells. These cells overlay intestinal lymphoid follicles and Peyer’s patches, sending down long protrusions that form pockets in which T cells, B cells, and macrophages can be found."

The Gut Directs Immunity

“Third, in contrast to other lymph nodes, B cells far outnumber all other lymphoid cells in the Peyer’s patches. They might therefore serve as a specialized set of APCs to induce tolerance or to drive immune responses toward particular effector classes.”


Gut M Cells Passage Antigens

“After the uptake of antigens through M cells, the antigens are processed and presented by professional APCs. A major APC population in the subepithelial (dome) region of PPs is characterised as DCs.”


How The Gut Regulates Immunity

“The gut is believed to be central in the development of counter-regulatory immune function. The gastrointestinal tract and associated mucosal immune system is an IL-10 and TGF dominant environment, promoting mucosal immune responses and systemic immune tolerance.”


Systemic Immunity: Review

“Systemic immune responses and tolerance are regulated by gut associated lymphoid tissues (GALT) or mucosal-associated lymphoid tissues (MALT), which are also thought to be central in the development of counter-regulatory immune function.”

**Review: Leukocytes**

The leukocytes are subdivided into **granulocytes** (containing large granules in the cytoplasm) and **agranulocytes** (without granules). The granulocytes consist of neutrophils (55–70%), eosinophils (1–3%), and basophils (0.5–1.0%). The agranulocytes are **lymphocytes** (consisting of B cells and T cells) and **monocytes**. Lymphocytes circulate in the blood and lymph systems, and make their home in the lymphoid organs.

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**Review: Innate Immunity**

The innate immunity system is what we are born with and it is nonspecific; all antigens are attacked pretty much equally. It is genetically based and we pass it on to our offspring.

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**Review: Innate Immunity**

Each of the cells in the innate immune system bind to antigen using **pattern-recognition receptors**. These receptors are encoded in the germ line of each person. This immunity is passed from generation to generation. Over the course of human development these receptors for pathogen-associated molecular patterns have evolved via natural selection to be specific to certain characteristics of broad classes of infectious organisms.

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**Review: (Innate) Phagocytosis**

A **phagocyte** is a cell that attracts (by chemotaxis), adheres to, engulfs, and ingests foreign bodies. **Promonocytes** are made in the bone marrow, after which they are released into the blood and called circulating **monocytes**, which eventually mature into **macrophages**, meaning "big eaters".

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**Review: Adaptive or Acquired Immunity**

B **cells** are produced in the **stem cells** of the bone marrow; they produce antibody and oversee humoral immunity. **T cells** are nonantibody-producing lymphocytes which are also produced in the bone marrow but sensitized in the **thymus** and constitute the basis of cell-mediated immunity. Parts of the immune system are changeable and can adapt to better attack the invading antigen. There are two fundamental adaptive mechanisms: cell-mediated immunity and humoral immunity.
Review: T-Cells

Cytotoxic or killer T cells (CD8+) do their work by releasing lymphotoxins, which cause cell lysis. Helper T cells (CD4+) serve as managers, directing the immune response. They secrete chemicals called lymphokines that stimulate cytotoxic T cells and B cells to grow and divide, attract neutrophils, and enhance the ability of macrophages to engulf and destroy microbes.

Suppressor T cells inhibit the production of cytotoxic T cells once they are unneeded, lest they cause more damage than necessary. Memory T cells are programmed to recognize and respond to a pathogen once it has invaded and been repelled.

Review: B-Cells

An immunocompetent but as yet immature B-lymphocyte is stimulated to maturity when an antigen binds to its surface receptors and there is a T helper cell nearby (to release a cytokine). Most of the family of clones become plasma cells. These cells, after an initial lag, produce highly specific antibodies at a rate of as many as 2000 molecules per second for four to five days. The other B cells become long-lived memory cells.

Antibodies are soluble proteins secreted by the plasma offspring (clones) of primed B cells. The antibodies inactivate antigens by, (a) complement fixation (proteins attach to antigen surface and cause holes to form, i.e., cell lysis), (b) neutralization (binding to specific sites to prevent attachment—this is the same as taking their parking space), (c) agglutination (clumping), (d) precipitation (forcing insolubility and settling out of solution), and other more arcane methods.

Review: Macrophage

Once a macrophage phagocytizes a cell, it places some of its proteins, called epitopes, on its surface—much like a fighter plane displaying its hits. These surface markers serve as an alarm to other immune cells that then infer the form of the invader. All cells that do this are called antigen presenting cells (APCs).

The non-fixed or wandering macrophages roam the blood vessels and can even leave them to go to an infection site where they destroy dead tissue and pathogens. Emigration by squeezing through the capillary walls to the tissue is called diapedesis or extravasation. The presence of histamines at the infection site attract the cells to their source.
**Review: NK Cells**

Natural killer cells move in the blood and lymph to lyse (cause to burst) cancer cells and virus-infected body cells. They are large granular lymphocytes that attach to the glycoproteins on the surfaces of infected cells and kill them.

**Review: Complement System**

The complement system is a major triggered enzyme plasma system. It coats microbes with molecules that make them more susceptible to engulfment by phagocytes. Vascular permeability mediators increase the permeability of the capillaries to allow more plasma and complement fluid to flow to the site of infection.

**Review: Eosinophils**

Eosinophils are attracted to cells coated with complement C3B, where they release major basic protein (MBP), cationic protein, perforins, and oxygen metabolites, all of which work together to burn holes in cells and helminths (worms). About 13% of the WBCs are eosinophils. Their lifespan is about 8–12 days. Neutrophils, eosinophils, and macrophages are all phagocytes.

**Review: Dendritic cells**

Dendritic cells are covered with a maze of membranous processes that look like nerve cell dendrites. Most of them are highly efficient antigen presenting cells. There are four basic types: Langerhans cells, interstitial dendritic cells, interdigitating dendritic cells, and circulating dendritic cells.

**IL-10 is King!**

"Although initially classified as a Th2 cytokine, IL-10 is produced by a much wider range of cell types (dendritic cells, monocytes, macrophages, CD4+ and CD8+ T cells, natural killer cells, neutrophils and epithelial cells), and is now viewed more as a potent immunoregulatory cytokine. It plays an important role modulating and dampening excessive immune responses across the whole immune system."


"IL-10 is also produced by a recently described T-cell subset; the CD4+ CD25+ regulatory T cell. Interleukin-10 inhibits T-cell activation, immunoglobulin (Ig)E production, eosinophil recruitment and many other aspects of allergic inflammation."

Corticosteroids Increase IL-10

"Of note, inhaled corticosteroids increase IL-10 responses by alveolar macrophages, suggesting that this may contribute to the anti-inflammatory action of these medications."

"Both IL-10 and TGF gene polymorphisms have been noted in association with asthma and atopy."

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Th1/Th2 Paradigm

"In the current research literature Th1 cells (now sometimes called "Type 1 immunity") and Th2 cells ("Type 2 immunity") are invoked to rationalize virtually all the known patterns of immune response."

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Th1/Th2: The Two Generals of Immunity

**Th1**
- IL-1
- IL-2
- IL-8
- IL-12
- INF-g

**Th2**
- IL-4
- IL-5
- IL-13

**Inflammatory**
- IL-1b
- IL-6
- TNF-a

**Anti-inflammatory** (Balancing)
- IL-10
- TGF-b

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Th1/Th2 Beneficial Roles

"Th1 cells are hypothesized to lead the attack against intracellular pathogens such as viruses, raise the classic delayed-type hypersensitivity (DTH) skin response to viral and bacterial antigens, and fight cancer cells. Th2 cells are believed to emphasize protection against extracellular pathogens such as multicellular parasites."

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Th1/Th2 Negative Roles

"On the negative side, the Th1 pathway is often portrayed as being the more aggressive of the two, and apparently, when it is overreactive, can generate organ-specific autoimmune disease (e.g., arthritis, multiple sclerosis, type 1 diabetes). The Th2 pathway is seen as underlying allergy and related IgE-based disease, and predisposing to systemic autoimmune disease."

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Th1/Th2 Paradigm: APCs

"Curiously, published studies on Th1/Th2 dominance often downplay the dendritic cells (DCs), monocyte-macrophages, and other antigen-presenting cells (APCs). Judging from the current body of knowledge, these cells are just as strongly qualified to supervise immunity."  


DC's in the Gut Dictate T-Helper Response

The kinds of immune responses evoked by each DC activation in the gut are distinct:

- The generation of Th2 cells for the induction of an IgA response, the induction of Th3/Tr1 cells for oral tolerance and the generation of Th1 cells for antimicrobial immune responses.


Normal Immune/Gut Relations and Oral Tolerance

Under normal conditions, the gut has several mechanisms that control allergies and immune over reactions to certain foods. At a high dose of foods, the immune system undergoes deletion, which reduces the immune response. When a low dose is introduced, IL-10 and TGF-b is released also down regulating the immune system.

Th1/Th2 Cell Interactions and Oral Tolerance

Building a Th1 Response: Microbe Attack

T-helper Cell Interactions

<table>
<thead>
<tr>
<th>Helper T cells</th>
<th>Production of suppressive cytokines</th>
<th>Th1</th>
<th>Th2</th>
<th>Th3</th>
<th>Th4</th>
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<tbody>
<tr>
<td>IL-4</td>
<td>+ / –</td>
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<td>IL-10</td>
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<tr>
<td>Essential cytokines for the induction of each Th-cell</td>
<td>IL-12</td>
<td>IL-2/IL-4</td>
<td>IL-4/IL-10</td>
<td>IL-10</td>
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Th1 Cell Production

"A DC or related APC exposed to an intracellular pathogen (or perhaps a cell wall antigen or other smaller fragment of the organism) will likely become type-1 biased. It promptly migrates to a nearby lymph node and begins to secrete IL-12."

Th1 Cell Production

"As this cytokine builds in concentration it begins to influence naive T cells to eventually become Th1 cells. Natural killer (NK) cells also respond to the IL-12 environment and proceed to release IFN-gamma, which reinforces the APC’s production of IL-12 and also helps drive the naive T-cell commitment process."

Th1 Cell Production

"As they attain maturity, Th1 cells also produce IFN-gamma, which (together with the NK cells) stimulates the APC and naive T cells to polarize into more Th1 cells, in a self-reinforcing "autocrine" loop."


Building a Th2 Response: Parasite Attack

Th2 Cell Production

“Like the Th1 cells, the emergence of Th2 cells is also dependent on their cytokine environment. Their maturation is likely initiated by the cytokine IL-6 from an APC, but also driving their maturation is IL-4 released by NK cells, mast cells, and eosinophils.”


Th2 Cell Production

“As the Th2 cells mature they also produce IL-4, which together with the other participating cell types generates an autocrine loop to the naive T cells to make more Th2 cells.”


Hormones and Immunity

Oestrogen Increases Th2

“Estrogen appears to play a central role in the immune response and immune-mediated diseases. Clinical observations indicate that some autoimmune diseases, such as rheumatoid arthritis and multiple sclerosis, frequently remit during pregnancy but exacerbate, or have their onset during the postpartum period.”

**Oestrogen Increases Th2**

“Recent evidence indicates that estrogens inhibit the production of TH1 proinflammatory cytokines, such as IL-12, TNF-alpha and IFN-gamma, whereas they stimulate the production of TH2 anti-inflammatory cytokines, such as IL-10, IL-4, and TGF-beta. This can explain why estrogen suppresses and potentiates TH1- and TH2-mediated diseases, respectively.”


**Oestrogen Increases Th2**

“We hypothesize that exacerbation or suppression of inflammatory diseases by estrogen is mediated by skewing TH1-type to TH2-type response. This view represents a novel mechanism for the modulatory effect of estrogen on certain inflammatory diseases that can lead to beneficial or detrimental impacts depending on the type of immune involved.”


**DHEA and Cortisol Increases Th2**

“Of importance may be the finding of a positive correlation between DHEA and IL-4 (TH2 cytokine), together with a relatively high negative correlation between cortisol and IL-10 (also TH2 cytokine).”


**Progesterone Induces a Th2 Shift**

“The pregnancy-related hormone progesterone induces Th2 immunity; on the other hand, relaxin induces Th1 immunity. Preeclamptic placentas produce more progesterone than do normal placentas.”


**7-OH-DHEA Increases Th1**

“On the other hand, 7-OH-DHEA showed a positive correlation with IFN-g (TH1 cytokine), thus confirming the fact that from the point of view of their immunomodulatory role, the 7-hydroxyepimers of DHEA differ markedly in their effects.”


**Low Testosterone/DHEA in RA (Th1 Excess)**

“Low plasma and synovial fluid testosterone concentrations are observed in male RA patients; low plasma DHEAS levels are mainly observed in female RA patients.”

Low Oestrogen/Progesterone Promote RA (Th1 Excess)

"The menopausal peak of RA suggests that estrogens and/or progesterone deficiency also play a role in the disease, and many data indicate that estrogens suppress cellular immunity, but stimulate humoral immunity (i.e., deficiency promotes cellular Th1-type immunity)."


Low Androgens are Observed in RA

"In particular, low levels of gonadal and adrenal androgens (testosterone and DHT, DHEA and DHEAS) and a reduced androgen:estrogen ratio have been detected in body fluids (i.e., blood, synovial fluid, smears, saliva) of male and female RA patients."


Low Androgens are Observed in RA

"Sex hormones might exert their immune-modulating effects, at least in RA synovitis, because synovial macrophages, monocytes, and lymphocytes possess functional androgen and estrogen receptors and may metabolize gonadal hormones."


Low Androgens are Observed in RA

"Recent studies have shown positive effects of androgen replacement therapy at least in male RA patients, particularly as adjuvant treatment."


HRT (E2) Induces a Th1 Shift, Which is Atherogenic

"Surprisingly, E2 induces an inflammatory-immune response towards a T helper cell (Th1) profile with increasing interferon-gamma production that could destabilize atheromatous plaques, and could account for the increase in the frequency of cardiovascular events in women undergoing HRT."

Pregnancy and Immunity

Th2 During Pregnancy

“The first-born child, as opposed to subsequent children, and perhaps male fetuses more so than female fetuses, are foreign to the mother’s innate immune response. To prevent T helper type 1 (Th1)-mediated rejection, the inherent ability of the mother’s and fetus’s immune systems to mount a protective Th2 response promotes successful pregnancy.”


Allergies are Less Common in Premature Infants

“The onset of labor is associated with an increase in cyclo-oxygenase-2 production of prostaglandin [E.sub.2]. Th2 cytokines inhibit cyclooxygenase-2 activity and permit the pregnancy to continue until term. Observations confirm atopy to be less common in premature infants as opposed to infants born at term or later.”


Pregnancy is a Th2 ‘Condition’

“Interleukin (IL)-18 acts in synergy with IL-12 to promote development of T helper 1 (Th1) responses. On the other hand, IL-18 alone has the capacity to induce Th2 responses.”


Pregnancy is a Th2 ‘Condition’

“These results suggest that elevated IL-18 secretion and decreased IL-12 secretion by PBMC may induce Th2 dominance in normal pregnancy, while elevated secretion of both IL-18 and IL-12 by PBMC may cause Th1 dominance in severe pre-eclampsia.”


Pregnancy and Th1/Th2 Balance

“To explain why fetuses are not rejected by the maternal system, Wegnamm et al. proposed that of the cytokines produced by T cells, type-2 T helper (Th2) cytokines predominate during pregnancy and suppress Th-1 type immune reaction by cytotoxic T cells that might attack fetuses and trophoblasts.”

Pregnancy Improves RA

“Pregnancy improves the symptoms of RA in 75 percent of patients, leading to a significant resolution of inflammation and sufficient symptom relief to enable patients to taper off or even stop medications. In fact, the positive effect of pregnancy alone has been deemed greater than the benefit of some of the newer therapeutic agents.”


The Consequence of Th2 Pregnancy

“The consequence of protection of the pregnancy by regulation of maternal Th-1/Th-2 balance is that the fetus is also exposed to a high concentration of Th-2 and T regulatory cytokines. These are present in the placenta, together with maternal IgE and allergens which have reached the amniotic fluid via the maternal circulation, leading to the potential for fetal allergic sensitisation, particularly as a consequence of swallowing and the generation of gut priming of the immune response.”


Allergies Run In the Family

“In addition to differences in IgE levels in amniotic fluid of atopic mothers, there are also higher levels of IL-10. This regulatory cytokine will suppress both Th-1 and Th-2 cells.

**Allergies Run In the Family**

“...a number of factors counter-balance the drive to a fully committed Th-2 response to allergens in the fetus. These include the fetal generation of IFN-g and a maternal supply of soluble CD14 which, in combination with endotoxin, will lead to stimulation of IL-12 and, therefore, IFN-production. Maternal IgG antibody which is actively transported across the placenta may block fetal allergen sensitisation.”


**Infants are Born Th2 Dominant**

“Forty-five healthy term neonates, 25 of the neonates’ mothers and 27 healthy adults (controls) participated in the study. Cytokine concentrations were measured in blood samples from the umbilical cord, from the neonates on the 1st and 5th day after birth, from mothers and from controls.”


**Infants are Born Th2 Dominant**

“IFN-g concentrations were significantly lower in the umbilical cord, compared to concentrations in the controls (p < 0.04), and increased significantly from the umbilical cord to levels in neonates on day 5 (p < 0.03). In mothers and the umbilical cord, IFN-g concentrations were dependent on the mode of delivery, being higher after vaginal delivery than after elective Cesarean section.”


**Infants are Born Th2 Dominant**

“IL-4 concentrations in the umbilical cord for 1-day and 5-day neonates were significantly elevated compared to those in mothers (p < 0.001; p < 0.0007; p < 0.0001, respectively) and controls (p < 0.05; p < 0.01; p < 0.006, respectively).”


**Infants are Born Th2 Dominant**

“These findings promote a role for Th2-mediated responses in the age-dependent reduction of intestinal helminth infections in humans.”

We Needs More Bugs!

The ‘Hygiene Hypothesis’

“Numerous studies have suggested that there is an inverse relation between early exposure to microbial products and a reduced risk of developing allergy and allergic disease. As all babies are born with a weakly Th-2 biased immune response, there must be a rapid down-regulation postnatally.”


The ‘Hygiene Hypothesis’

“Supporting the hygiene hypothesis, Ball et al and Illi et al presented data suggesting that frequent respiratory infections early in life prevent the development of atopy and allergic respiratory disease.”


Infections Reduce Allergy

“Exposure to microbial products has been suggested as one important event achieving this effect. A number of studies have shown an inverse relation between the prevalence of atopy and tuberculin responsiveness, hepatitis A, and measles infection in early childhood.”


RAW Milk Reduces Allergy

“It has been suggested that the much lower prevalence of allergy and asthma among the children of farmers who have been born on farms and have been exposed to raw and sometimes unpasteurised milk, which obviously has a higher microbial load, particularly of lactobacilli, is consistent with the gut flora hypothesis.”


‘Natural’ Diets Reduce Allergy

“The anthroposophic lifestyle, which avoids immunisations and antibiotics but includes consumption of a diet of fermented vegetables rich in lactobacilli, is associated with significantly less atopy and skin test positivity in childhood.”

**Antibiotics, Maternal Allergy and Vaccines Increase Allergy**

"Logistic regression analysis identified three statistically significant predictors of subsequent atopic disease: maternal atopy (1.97, 95% CI 1.46 to 2.66, p<0.0001), immunisation with whole-cell pertussis vaccine (1.76, 95% CI 1.39 to 2.23, p<0.0001), and treatment with oral antibiotics in the first two years of life (2.07, 95% CI 1.64 to 2.60, p<0.0001)."


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**Preeclampsia is Th1 Dominant**

"Recent data demonstrate that up-regulation of Th1 responses occurs not only in peripheral blood but also at the fetomaternal interface in preeclamptic patients."


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**Pregnancy Loss Corresponds With a Th1 Excess**

"Cytokines are critical immunoregulatory molecules, responsible for determining the nature of an immune response. It has been proposed that Th2/Th3 immune reactions support normal pregnancy, while Th1 immunity is considered detrimental to the fetus."


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**Pregnancy Loss Corresponds With a Th1 Excess**

"Our results support the importance of Th2/Th3 immune responses in pregnancy loss, and suggest that an individual's immunogenetic profile indicative of imbalances in Th2/Th3 cytokines is associated with pregnancy loss."


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**Pregnancy Loss Corresponds With a Th1 Excess**

"Previous data on murine abortion indicate that DPP-IV may play a critical role in pregnancy failure by inducing a Th1 local response. This abortive effect may be mediated by enhancing the levels of Th1 abortogenic cytokines locally."

**Exercise and Immunity**

"In conclusion, the postexercise decrease in T lymphocyte number is accompanied by a more pronounced decrease in type 1 T cells, which may be linked to high plasma epinephrine. Furthermore, IL-6 may stimulate type 2 T cells, thereby maintaining a relatively unaltered percentage of these cells in the circulation."


"Exhaustive exercise causes the suppression of T lymphocyte activity while asthmatic and allergic diseases are subclinically more prevalent in athletes. One of the mechanisms behind these observations might be a lower type-1 and higher type-2 cytokine balance, which we previously demonstrated to occur after exhaustive exercise."


"This may be one of the mechanisms behind several phenomena including cellular immunosuppression, an increase in the relative proportion of type-2 cytokines following exhaustive exercise, and the higher incidence of infections and allergic disorders in regularly exercising endurance athletes."


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**TNF, From Th1 Cells Induce Preeclampsia**

"TNF also induces activation of endothelial cells and the induction of glomerular endothelial damage."

"TNF suppresses production of the vasodilator NO."


"The marathon race caused a marked increase in the plasma concentrations of IL-6 and IL-10. Their responses were correlated (r = 0.78, p < 0.01), indicating that IL-6 is an inducer of IL-10, and may partly induce the type-1 < type-2 cytokine balance."

Intense Exercise Improves Rheumatoid Arthritis

“We undertook this randomized, controlled, multicenter trial to compare the effectiveness and safety of a 2-year intensive exercise program (Rheumatoid Arthritis Patients In Training [RAPIT]) with those of physical therapy (termed usual care [UC]).”


Intense Exercise Improves Rheumatoid Arthritis

“CONCLUSION: A long-term high-intensity exercise program is more effective than UC in improving functional ability of RA patients. Intensive exercise does not increase radiographic damage of the large joints.”


Exercise Induces IL-6 Release

“Cytokines such as interleukin (IL)-6 are proteins, which were originally discovered within the immune system. Recent studies, however, demonstrate that IL-6 is produced by, and released from contracting skeletal muscles during exercise.”


Exercise Induces IL-6 Release

“IL-6 can enhance lipolysis in humans and might play a role in glucose metabolism. In addition, muscle-derived IL-6 is likely to initiate many of the exercise associated immune changes, as IL-6 can increase plasma levels of the cytokines IL-1 ra and IL-10, together with cortisol and blood neutrophils.”


Exercise Induces IL-6 Release

“Also, the observed shift towards Th2 lymphocyte dominance during exercise may be mediated by IL-6. Because carbohydrate ingestion during exercise has been demonstrated to blunt the IL-6 and hormonal response, it might also blunt other beneficial adaptations.”


Stress and Immunity
Stress Effects The Immune System

"Previously, a large number of studies reported that psychological stress and psychiatric illness reduces immune responsiveness. However, it turned out that stress reduces immune responsiveness is an oversimplified statement because the interactions between central nervous system, endocrine system and the immune system are undoubtedly complex."


Stress Effects The Immune System

"This review shows evidence that short-time (minutes) or preparation to a written examination, in those students who are stressed, induces the production of proinflammatory cytokines which may be related to Th1 response."


Stress Effects The Immune System

"However, longer mental stress (days) causes dysregulation in the immune function by shifting the cytokine response to Th2 response."


Stress Effects The Immune System

"Recent evidence indicates that glucocorticoids and catecholamines, the major stress hormones, inhibit the production of proinflammatory cytokines, such as interleukin (IL)-12, tumor necrosis factor (TNF)-alpha, and interferon (IFN)-gamma, whereas they stimulate the production of antiinflammatory cytokines, such as IL-10, IL-4, and transforming growth factor (TGF)-beta."


Stress (Catecholamines) Stimulate Bacterial Growth

"The mechanisms of promoting infection in stressful situations have not been defined, but catecholamines could play a role. In the present study gram negative bacteria grown with catecholamines showed enhanced bacterial growth compared to controls."

Stress (Catecholamines) Stimulate Bacterial Growth

"Therefore, stress-induced enhanced bacterial growth and immunosuppression could play a role in suspension-induced enhanced mortality due to infection."


Antibiotics and Immunity

We have shown previously that the b-lactam antibiotic benzylpenicillin (BP) conjugates to IFN- and reduces its activity in a number of in vitro assays. We also showed that BP does not bind to IL-4.


Probiotics Prevent Antibiotic Immune Suppression

"These results suggest that adequate probiotic intervention after antibiotic treatment may improve the intestinal ecosystem, and thereby prevent the Th2-shifted immunity induced by neonatal antibiotic use."


Medications and Immunity

"Although generally nontoxic, b-lactams are one of the classes of drug most frequently associated with IgE-mediated allergy. Our data led us to hypothesize that selective impairment of IFN-gamma activity by b-lactams during the early phase of an immune response may favor the generation of Th2 over Th1 responses, thus leading to IgE production and allergy."


Methotrexate (MTX) Suppressers Th1

"These results indicate that MTX appears to suppress Th1 and, to a lesser extent, Th2 immune responses and its anti-arthritis effect on human rheumatoid arthritis might be at least in part explained by down-regulation of Th1 responses involved in the disease."

**Flu Vaccine Suppresses Th1**

“We confirm that vaccine aggregates deviate the immune response to a greater Th2 cytokine pattern with potential implications for vaccine screening, safety, and efficacy.”


**Vaccines Induce Th2**

“Our results indicate early and persistent Th2 responses to the vaccine, in contrast to a more delayed and transient pattern of IFN-gamma production.”


**Vaccines Induce Asthma**

“Researchers in England note similar results in a survey of 446 children. In a group of 203 children who had not been immunized for pertussis, two percent had a diagnosis of asthma at eight years of age, compared to 11 percent of 243 who had been vaccinated for pertussis (p=0.0005).”

Odent MR, Culijn EE, Kimmel T. Pertussis vaccination and asthma: is there a link? JAMA 1994;272:592-593.

**Th2 Conditions**

**Allergies**

**Common Causes of Th2 Dominance**

- Genetics
- Micro-organisms
- RSV
- Yeast/Fungi
- Chlamydia?

- Pertussis vaccination
- Heavy Metals
- Lead
- Mercury
- Zinc deficiency
- Pollution


**Dust Mites Increase Th2**

“The allergic response to dust mites involves an immediate hypersensitivity response, including increases in specific IgE antibodies and T-cells of the Th2 phenotype. Inhalation challenge of the allergic individual with dust mite antigen produces airway hyper-reactivity and bronchospasm, along with an eosinophil-dominated inflammatory response.”

Cockroaches Increase Th2

"As with dust mites, cockroaches can be a very significant allergen source in the allergic asthmatic. It is thought that cockroach antigens (from the body and feces) pose a significant threat to individuals with asthma, and may be partially responsible for the greatly increased morbidity and mortality from asthma in inner-city residents."


NSAID’s/Asthma Exacerbates Asthma

"Since most NSAIDs block the enzyme cyclooxygenase, it is thought this leaves more arachidonic acid to react with the other arm of the eicosanoid pathway, regulated by activity of lipoxygenase. Downstream metabolites of this pathway include the leukotrienes, very potent stimulators of inflammation and bronchial constriction."


Depression and Asthma are Linked

"In a study of 230 patients with asthma, 45 percent scored high enough on depression ratings scales to be considered depressed. Those with more depressive symptoms reported worse health-related quality of life than asthma patients without depression."


Allergies are Increasing

"The prevalence of allergic respiratory diseases, asthma and allergic rhinoconjunctivitis, has increased dramatically since the advent of industrialization. Many hypotheses exist to explain this phenomena: better hygiene, fewer severe infections early in life due to treatment with antibiotics and vaccinations, the loss of some protective effect found in rural lifestyle, environmental pollution, and changes in dietary habits."

Allergy is a Th2 Dominant Condition

"Compared to non-atopic individuals, atopics have higher Th2 (IL-4, IL-5, IL-13 and IL-9) peripheral blood mononuclear cell (PBMC) responses to allergens and other stimuli. Similar patterns are seen in asthmatics as a reflection of their atopic propensity."


Allergy/Asthma is a Th1 Deficient Condition

"In a long-term follow-up study, persistent asthmatics had reduced Th1 (IFN-g) responses to house dust mite compared to adults with resolved asthma, but both groups had higher IL-5 and IL-13 responses compared to non-atopic controls."


Allergy is a Th2 Dominant Condition

"Strong associations with allergic disease have also provided a strong case for a primary role of T helper type 2 (Th2) cells in the development of asthma."


Allergy is a Th2 Dominant Condition

"There is a substantial body of evidence implicating most 'Th2' cytokines (interleukin (IL)-4, IL-5, IL-9, IL-13) in the expression and development of airways inflammation and hyperactivity (AHR)."


Allergy is a Th2 Dominant Condition

"While all of these cytokines appear to have a role, the recent literature indicates that IL-13 is especially critical and may be 'sufficient and necessary' for the development of reactive airways disease, at least in animal models."

"IL-13 appears to act directly on airways epithelial cells to produce the pathological features of asthma."


Allergy is a Th2 Dominant Condition

"IL-13 and transforming growth factor beta (TGF-b) also act synergistically on human airway fibroblasts to increase production of eotaxin-1, a powerful eosinophil chemoattractant."

Th1 Conditions: Causes

Weet Bix and Milk Anyone?

Diabetes Type I is a Th1 Driven Condition

"Disease pathogenesis is associated with a shift of the cytokine secretion pattern in the pancreas from Th2- (low levels of IFN-g, high levels of IL-10) to Th1- (high levels of IFN-g, low levels of IL-10) type cytokines. Genetic predisposition is a prerequisite for the development of diabetes."


Diabetes Type I is Caused by Grains

"With regard to dietary antigens, it has been shown that cereal-based diets are usually associated with a higher diabetes incidence than the semi-purified diets that lack diabetes-inducing properties."


Grains Increase Th1 Autoimmunity

"The shift towards a pro-inflammatory cytokine milieu in the gut after feeding a cereal-based diet compared to a hypoallergenic semi-purified diet could be demonstrated as an up-regulation of the mRNA for the Th1-associated cytokines IFN and TNF-a, the inflammatory marker iNOS, and an increased ratio of Th1/Th2 cytokines (IFN/IL-10 or IFN/TGF)."


Diabetes Type I is Caused by Grains

"The present study shows that the cytokine mRNA expression in the small intestine of diabetes prone NOD mice fed with a cereal-based diet was shifted towards a pro-inflammatory response compared to the mRNA expression in animals fed with Prosobee or Prosobee supplemented with casein."


Grains Increase Th1 Autoimmunity

"A Th1-based cytokine response has been demonstrated in the intestinal lesions in celiac disease and certain other inflammatory bowel diseases."

Grains Increase Th1 Autoimmunity

“Hence, the strong diabetogenic effects of feeding a cereal-based diet were accompanied by a shift towards Th1-type reactivity in the gut, while this was not the case for the less diabetogenic casein fraction of cow-milk.”


Cows Milk Increases Type I Diabetes

“Oral tolerance reactions are usually dependent on a T-helper (Th) 2–Th3 cytokine secretion profile. Conversely, a pro-inflammatory Th1-biased cytokine profile is related to disturbed oral tolerance mechanisms. In recent years it has become clearer that in patients with type 1 diabetes mellitus there is a systemic bias towards Th1-type immune responses.”


Cows Milk Increases Type I Diabetes

“In several studies the avoidance of intact cow’s milk proteins led to a reduced frequency of diabetes, while the addition of cow’s milk to the rodent’s diet resulted in an increased incidence of the disease.”

Cows Milk Increases Type I Diabetes

"The outcome of such dietary studies is obscured by the fact that cereal-based diets appear to induce an even higher frequency of diabetes."


Cows Milk Increases Type I Diabetes

"Despite these uncertainties an international multi-centre trial has been set up to test the hypothesis that the avoidance of intact cow’s milk proteins after prolonged breast-feeding in the first 9 months in genetically-predisposed infants might prevent the appearance of diabetes-associated autoantibodies or even type 1 diabetes mellitus itself."


Cows Milk Increases Type I Diabetes

"An interim analysis of this primary prevention trial suggests that delayed introduction of cow’s milk products in the infant diet decreases the incidence of islet autoimmunity."


Cows Milk Increases Type I Diabetes: Mechanisms?

"One theoretical mechanism for the link between cow’s milk exposure and autoimmune diabetes could be immunological cross reactivity (molecular mimicry) between cow’s milk proteins and autoantigens of the b-cell. Indeed, sequence homologies between cow’s milk proteins and islet autoantigens have already been identified."


Cows Milk Increases Type I Diabetes: Mechanisms?

"Cow’s milk-based diets have also been implicated in the aetiology of other immune-mediated diseases in human subjects, such as multiple sclerosis, and have been shown to induce mild rheumatoid arthritis in genetically predisposed animals."


Cows Milk Increases Type I Diabetes: Mechanisms?

"Furthermore, the consumption of cow’s milk has also been associated with some other neurological diseases, e.g. autism, some of which have not been proved to be immune mediated."

**Psoriasis is a Th1/IL-10 Deficient Disease**

"IFN-gamma was markedly elevated in all sera from psoriasis patients, 33.8 +/- 1.3 pg/ml (mean +/- standard error) versus 8 +/- 1.5 pg/ml for normal controls (p < 0.01), and positively correlated with all indices of disease severity (Spearman r > 0.6)."


**Crohn's is a Th1 Dominant Disease**

"Crohn's disease (CD) is a chronic inflammatory condition of the gastrointestinal tract, characterized by overactive T-helper (Th)1-mediated responses towards resident bacterial flora in genetically susceptible individuals."


**Psoriasis is a Th1/IL-10 Deficient Disease**

"Also, serum IL-10 levels were below detection levels in psoriatics compared with controls (6.4 +/- 1.3 pg/ml)."


**RA is Antagonised by Allergies**

"These results support the concept that RA and atopy antagonize each other and that a change in the cytokine patterns of Th1 and Th2 cells could provide an indication for curative effects on RA."

RA Sufferers Have Less Allergies

"CONCLUSIONS: Atopic disorders are decreased in RA."


Insomnia is a Th2 Dominant Condition

"The present results showed a link between insomnia unrelated to medical disorders and a shift in the Th1/Th2 balance toward Th2 dominance, indicating that the relationship between sleep quality and the etiology of immune-related diseases should be reconsidered."


Homocysteine? Immunity?

"Moderate hyperhomocysteinemia is associated with an increased risk of atherosclerosis, thrombosis and neurodegenerative diseases. Homocysteine accumulation in the blood can be due to many underlying causes, which may interact with each other, e.g. genetic disposition and B-vitamin status."


Hyperhomocysteinemia Causes Neurodegeneration and Heart Disease

"Deficiency of these B-vitamins in parallel with moderate hyperhomocysteinemia is often found in patients with enhanced activation of the cellular immune system, like Alzheimer's disease, rheumatoid arthritis and also vascular diseases."


Hyperhomocysteinemia: Associations with Th1

"On the one hand proliferation of immunocompetent cells having an enhanced demand for B-vitamins leads to the accumulation of homocysteine. On the other hand macrophages stimulated by TH1-type cytokine interferon-gamma form reactive oxygen species (ROS), which oxidize antioxidants, lipoproteins and oxidation-sensitive B-vitamins."


Th1 Deplete B Vitamins
**Th1 Causes Hyperhomocysteinaemia**

"Thereby Th1-type immune response could contribute importantly to the development of hyperhomocysteinemia, and may also be a major determinant of disease progression."


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**Atherosclerosis: an Immune Disorder?**

"Studies published in 1974 already found that the WBC count was a strong predictor of infarction. The predictive value of the WBC count was similar to that of serum total cholesterol or a single determination of blood pressure."


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**Atherosclerosis: an Immune Disorder?**

"Later on it was found that smokers with WBC counts in excess of 9000 per ml had an increased risk to develop AMI, four times greater than smokers with a leukocyte count below 6000 per ml."


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**Atherosclerosis: an Immune Disorder?**

"Another study demonstrated that a total WBC count in excess of 10000 per l was associated with a risk that was approximately twice that seen when the WBC count was at or below 4000 per l. This excess risk was independent of gender, smoking history, blood pressure, and cholesterol level."


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**Atherosclerosis: an Immune Disorder?**

"Total WBC count was correlated with the risk of thrombotic cerebral infarction; patients suffering thrombotic strokes had a statistically significantly higher antecedent WBC count than did members of the cohort not experiencing ischemic events."

Atherosclerosis: an Immune Disorder?

“Even when tobacco smoking was controlled/corrected for, the WBC count was found to predict coronary heart disease prevalence, risk of nonfatal MI, and risk of sudden cardiac death. In the PARIS-1 study, 2026 patients were examined 2–60 months after suffering a first AMI; the total WBC count obtained at that time was found to correlate strongly with the risk of reinfarction.”


CRP (C-reactive protein) Causes Atherosclerosis

“CRP was shown to possess proatherogenic properties. For example, CRP activates endothelial cells to express adhesion molecules, ICAM-1, vascular cell adhesion molecule 1, selectins, and the chemokines, monocyte chemotactic protein 1.”


Th1 Excess Promotes Atherosclerosis

“Most of the activated T cells in the plaque are T helper 1 subtype (Th1), which secrete interferon-gamma (IFN-gamma), now generally accepted as a proatherogenic cytokine.”

**Tr1 Reduces Atherosclerosis**

“We hypothesized that adoptive transfer of a novel subtype of T lymphocytes called regulatory T cells type 1 (Tr1) would inhibit Th1 responses by inducing a bystander immune suppression and therefore limit the development of atherosclerosis.”


**Tr1 Reduces Atherosclerosis**

“Tr1 cells showed a significant decrease in Th1 responses, as revealed by a decrease in OVA-specific IgG2a serum levels (P<0.0001), a decrease in the production of interferon-gamma (P<0.001), and an increase in interleukin-10 production (P<0.001) by cultured spleen and lymph T cells compared with controls.”


**Tr1 Reduces Atherosclerosis**

“CONCLUSIONS: Tr1-type regulatory immune response reduces the development of experimental atherosclerosis.”


**IL-10 Reduces Th1 and Reduces Atherosclerosis**

“Atherosclerosis has a close relationship to inflammation, particularly T helper type 1 lymphocyte (Th1) response. Interleukin-10 (IL-10), is thought to suppress Th1 response.”


**IL-10 Reduces Th1 and Reduces Atherosclerosis**

“IL-10 gene transfer significantly reduced the atherosclerotic plaque area and the macrophage infiltrated area. IL-12 and IFN-gamma mRNA expressions in spleens and plasma IFN-gamma levels were decreased by IL-10 gene transfer.”


**IL-10 Reduces Th1 and Reduces Atherosclerosis**

“Therefore, IL-10 gene transfer changed the Th1 response and suppressed atherosclerotic lesion formation in apoE-KO mice. IL-10 could be a new target as a therapeutic tool for the treatment of atherosclerosis.”

**IL-10 Reduces Inflammation**

"Interleukin-10 (IL-10) is a potent anti-inflammatory cytokine in Th1 cell-mediated chronic inflammatory diseases such as, e.g. Crohn's disease. Moreover, IL-10 has been shown to limit the progression of atherosclerosis, presumably by influencing endothelial cell function."


**IL-10 Induces NOS-3**

"Subsequent exposure to IL-10 results in an up-regulation of both endothelial nitric-oxide synthase (NOS-3) expression and activity."

"Increased NOS-3 expression may, thus, be one mechanism by which IL-10 exerts its anti-inflammatory effects in Th1 cell-mediated chronic inflammatory diseases."


**IL-10 Deficiency Induces Atherosclerosis**

"Lack of IL-10 led to increased low-density lipoprotein cholesterol whereas very-low-density lipoprotein was reduced. In parallel, T-helper 1 responses and lesion size were dramatically increased in double knockout compared with E-/- controls."


**IL-10 Deficiency Induces Atherosclerosis**

"In parallel, T-helper 1 responses and lesion size were dramatically increased in double knockout compared with E-/- controls. At 48 wk, matrix metalloproteinases and tissue factor activities were increased in lesions of double-knockout mice. Furthermore, markers of systemic coagulation were increased, and vascular thrombosis in response to i.v. thrombin occurred more frequently."


**IL-10 Deficiency Induces Atherosclerosis**

"Our findings suggest that IL-10 deficiency plays a deleterious role in atherosclerosis. The early phase of lesion development was increased, and the proteolytic and procoagulant activity was elevated in advanced lesions. These data show that IL-10 may reduce atherogenesis and improve the stability of plaques."


**Statins are Immunomodulators**

"Statins may also be potent immunomodulatory agents and be beneficial in the treatment of autoimmune diseases. Statins have already been used to reduce the rejection of human heart transplants by the immune system, and there have been reports of a protective effect of injected statins in models of brain autoimmunity similar to experimental autoimmune encephalomyelitis."

Statins are Immunomodulators

“Atorvastatin has been shown to have pleiotropic immunomodulatory effects involving both antigen presenting cells and T cell compartment. Thus, statins may be beneficial for MS, and clinical trials of the effects of statins on MS are now in progress, hopefully in a favorable way.”


Statins Benefit MS

“Number and volume of Gd-enhancing lesions declined by 44%, (p<0.0001) and 41% (p=0.0018), respectively. Treatment was well tolerated. Oral simvastatin might inhibit inflammatory components of multiple sclerosis that lead to neurological disability.”


Alzheimer's and Immunity

There are close relationships between the central nervous system (CNS) and the immune system (IS). Not only has the old paradigm of the immunological privileged site of the CNS been overcome by neuroimmunological research, the field of psychoneuro-endocrino-immunology has also shown that the activity of the immune system is influenced by the CNS and vice versa.


Alzheimer’s Treatment

“Recently, several groups demonstrated that immunization of APP transgenic mouse (APP/Tg) models of AD with human Aβ42 peptide blocks the deposition of Aβ in the central nervous system and can at least partially promote the clearance of established plaque material from the brain.”

David H. Cribbs1, Anaht Ghochkyan2, Vitaly Vasilevko2, Mike Tran1, Irina Petrushina1, Nadya Sadzikava1, Davit Babliyan2, Patrick Kesslak1, Thomas Kebab-Emmons3, Carl W. Colman1 and Michael G. Agadjanyan2 Adjuvant-dependent modulation of Th1 and Th2 responses to immunization with β-amyloid. International Immunology, Vol. 15, No. 4, pp. 505-514, April 2003

Reducing Th1 Benefits Alzheimer’s

“Taken together, these results show enhanced Th2 and down-regulated Th1 immunity following immune challenge with Abeta(1-42).”

Alzheimer’s: a Th1 Condition?

“A marked increase in IFN-g secretion by peripheral mononuclear cells and by NK cells either spontaneously or after IL-2 stimulation was found in AD patients. The release of IFN-g, the principal Th1 cytokine, in both studies appeared to be dependent upon the severity of disease.”


Alzheimer’s: a Th1 Condition?

“Two investigations from Huberman and co-workers explored the link between IL-2 and AD and exhibited similar results. They indicated that IL-2 secretion by peripheral blood mononuclear cells was significantly elevated in AD patients, though solely in the moderately severe stage of the disease.”


Th2 Cytokines Protect Against AD

“In contrast to IFN-g, IL-4 reduces the expression of CD40 on cultivated microglial cells. Moreover, IL-4 reduces the neurotoxicity of microglia through inhibition of IFN-g-mediated microglial activation, resulting in a reduced production of TNF-a and NO (nitrogen monoxide).”


Increasing Th2 May Reduce AD

“IL-10 was found to suppress Ab-induced inflammatory proteins such as IL-1 and TNF-a. Altogether, the Th2-like cytokines IL-4 and IL-10 appear to be potent in reducing the activity and neurotoxicity of microglia. Their activity might be reduced in AD patients.”


Th2 Cytokines Protect Against AD

“The typical Th2 parameters should protect from Ab-induced microglia activation and the typical Th1 cytokines seem to be crucially involved in the pathological mechanism of Alzheimer’s disease.”

Alzheimer’s is Inflammatory

“Several data of altered serum IL-6 levels in AD seem to confirm this finding: Higher IL-6 plasma levels in AD patients than in controls have been reported and another study showed higher levels of IL-6 in severely demented patients compared to those with mild to moderate stage of disease.”


Anti-inflammatory Drugs Benefit Alzheimer’s

“There is strong evidence that conventional nonsteroidal anti-inflammatory drugs delay the onset and slow the progression of AD, suggesting that anti-inflammatory therapy may have a protective effect against AD. These data fit very well with the theory of a Th1-related immune mechanism in the development of the AD pathology.”


Schizophrenia: a Th2 Condition?

“Total serum Immunoglobulin E (IgE)—the characteristic immunoglobulin of allergic/atopic disorders—was shown to be significantly higher in schizophrenic patients with poor therapy response.”


Schizophrenia: a Th2 Condition?

“A similar subgroup of patients, those suffering from more pronounced negative symptoms, was described as expressing higher levels of CSF IgG (Muller & Ackenheil, 1995). McAllister et al. (1989) and Printz and colleagues (1999) reported markedly elevated levels of peripheral CD51 B cells in schizophrenic patients compared to healthy controls.”


Schizophrenia: INF-g

“Those patients who had predominantly positive symptoms of schizophrenia (delusions, hallucinations, bizarre behavior, and thought disorders) had an elevated production of IFN-g, while negative symptoms (asociality or withdrawal, flat affect, attention impairment, avolition, or apathy) were associated with decreased IFN-g production.”


Schizophrenia: a Th2 Condition?

“A significant decrease in the production of IL-2 by peripheral lymphocytes is one of the best replicated immunological findings in schizophrenia. Some data suggested that decreased IL-2 production is associated with acute illness in patients who produce elevated amounts of autoantibodies or in patients with later age at onset.”

**Schizophrenia: a Th2 Condition?**

"Altogether, due to the heterogeneity of schizophrenia, most of the studies describe a subgroup of schizophrenic patients with immunological findings, indicating a shift from Th1-like cellular to Th2-like humoral immune reactivity."


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**Major Depression (MD): a Th1 Condition?**

"The essential amino acid tryptophan is the precursor of two distinct metabolism pathways, leading to the products serotonin or kynurenine. The enzyme indoleamine-2,3-dioxygenase (IDO) metabolizes tryptophan to kynurenine, which is further catabolized to quinolinic acid by the enzyme kynurenine hydroxylase. Both IDO and kynurenine hydroxylase are induced by IFN-g."


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**Tryptophan’s Metabolic Fate During Th1 Excess**

![Tryptophan's Metabolic Fate Diagram]

**Major Depression (MD): a Th1 Condition?**

"An IFN-g-induced, IDO-mediated decrease of central nervous tryptophan availability may lead to a serotoninergic deficiency."

Treatments for Immune Dysfunction

Astragalus Normalises Th1:Th2

"Levels of serum IL-4 and IL-10 in HSK patients were significantly higher and those of IL-2 and gamma-IFN were significantly lower than those in the healthy control (all P < 0.01). These parameters were significantly improved in the patients of the AM group after treatment, but with no change in patients of the ribavirin group."


Astragalus Normalises Th1:Th2 in Cancer Patients: Background

"Th2 cytokine is predominant in tumor patients and was found to be associated with tumor progression. Reversing of Th2 dominant status is thought to be a promising strategy."


Astragalus Normalises Th1:Th2 in Cancer Patients

"Astragalus (AG) was observed to reverse Th2 status of lung cancer. AG enhanced culture supernatant and gene expression levels of Th1 cytokine (IFNgamma and IL-2) and its transcript factor (T-bet), and reduced those of Th2 cytokines in cultured PBMNC of lung cancer patients."


Astragalus Normalises Th1:Th2 in Cancer Patients

"These results demonstrated that traditional Chinese medicine AG might reverse the Th2 predominant status in lung cancer patients, which is a probable alternative therapeutic regime in future."


Golden Seal

- Is Golden Seal Good for Allergies?
- How Does it Work?
Berberine Herbs Increase Th1 via IL-12

"Berberine is an alkaloid that has been isolated from Hydrastis canadensis (goldenseal), Coptis chinensis (Coptis or goldenthread), Berberis aquifolium (Oregon grape), Berberis vulgaris (barberry), and Berberis aristata (tree turmeric)."


Berberine Herbs Increase Th1 via IL-12

"Interleukin-12 (IL-12), a heterodimeric cytokine secreted by macrophages and other antigen-presenting cells (APC), is critical for the development of Th1 cells and the initiation of the cell-mediated immune response."


Berberine Herbs Increase Th1 via IL-12

"Berberine has shown a number of beneficial effects including immunostimulation and macrophage activation. Recently, we reported that berberine induced the production of IL-12p40, a larger subunit of IL-12, in mouse macrophages."


Berberine Herbs Increase Th1 via IL-12

"In this study we have demonstrated that pretreatment with berberine induced IL-12 production in both macrophages and dendritic cells (DCs), and strongly enhanced IL-12 production when subsequently stimulated with either lipopolysaccharide (LPS) or heat-killed Listeria monocytogenes (HKL), two well-known inducers of IL-12 production."


Berberine Herbs Increase Th1 via IL-12

"Importantly, the increased levels of IL-12 production in berberine-treated macrophages deviated CD4+ T cells from the Th2 to the Th1 pathway."


**Berberine Stimulates Th1 Cytokines and Reduces Th2 Cytokines**

![Graph showing the stimulation of Th1 cytokines and reduction of Th2 cytokines by berberine.](image)

**Berberine Containing Herbs Reduce Allergies**

“These findings may point to a possible therapeutic use of berberine or medicinal plants containing berberine in the Th type 2 cell-mediated immune diseases such as allergic diseases.”

**Polypodium leucotomos modulates Th1/Th2 cytokines**

“The percentage of inhibition was 24% for IL-2, 72% for INF-gamma and 53% for TNF-alpha. With regard to Th2 cytokines, the addition of PLE resulted in a significant increase (33%) in IL-10 production. Surprisingly, the production of the inflammatory cytokine IL-6 was completely abolished (100% inhibition) by PLE at all doses tested.”


**Polypodium leucotomos modulates Th1/Th2 cytokines**

“Taken together, these data suggest that PLE works through the induction of suppressive/anti-inflammatory cytokines such as IL-10 and/or TGF-beta which in turn appear to allow the partial deactivation of macrophages or other accessory cells.”


**Polypodium leucotomos modulates Th1/Th2 cytokines**

“These features suggest that PLE could be useful in the treatment of autoaggressive/inflammatory conditions due to an exacerbation of Th1 responses.”


**Ginseng (Rg1) Induces Th2**

“These results show that Rg1 induces a Th2-dominated pattern from naive CD4+ T cells upon stimulation of the CD3 complex.”

Eui-joon Lee a, Eunjung Ko b, Jinwee Lee b, Samwoong Rho b, Seonggyu Ko c, Min-Kyu Shin b, Byung-il Min a, Moo-Chang Hong b, Si-young Kim d and Hyunsu Bae. Ginsenoside Rg1 enhances CD4+ T-cell activities and modulates Th1/Th2 differentiation. International Immunopharmacology. Volume 4, Issue 2, February 2004, Pages 235-244
**Ginseng (Rg1) Induces IL-4**

Eui-joon Lee a, Eunjung Ko b, Jinseo Lee b, Samwoong Rho b, Seonggyu Ko c, Min-Kyu Shin b, Byung-il Min a, Moo-Chang Hong b, Si-young Kim d and Hyunsu Bae. Ginsenoside Rg1 enhances CD4+ T-cell activities and modulates Th1/Th2 differentiation. International Immunopharmacology. Volume 4, Issue 2, February 2004, Pages 235-244.

**Ginseng (Rg1) Induces Th2**

These results strongly suggest that Rg1 induces an immune response change from a Th1 cell-dominated pattern to a Th2 cell-dominated pattern.

**Ginseng (Rg1) Reduces INF-y**

In addition, ginsan induced the endogenous production of cytokines such as IL-1, IL-6, IFN-γ and IL-12, which are required for hematopoietic recovery, and was able to enhance Th1 function while interfering with the Th2 response in irradiated mice.


**Lipoic Acid (a-LA) Normalises Th1/Th2 in the Brain**

T cells from mice treated with a-LA produced significantly less IFN and IL-4 than control mice. In particular, administration of a-LA almost completely abolished the production of IFN compared with animals treated with the vehicle alone ($p=0.0047$).


**Lipoic Acid (a-LA) Normalises Th1/Th2 in the Brain**

Similarly, a remarkable reduction of IL-4 levels was detected in treated animals ($p=0.0331$).

“Overall, a-LA inhibits the production of IFN and IL-4 produced by MOG-specific T cells.”

Lipoic Acid (a-LA) Normalises Th1/Th2 in the Brain

These findings further suggest that a-LA, a drug which has been safely tested in other human disorders, may be effective in the clinical management of neurological autoimmune disorders such as MS.


Vitamin D Reduces Th1

“Vitamin D, a common food additive, has been shown to prevent the induction of experimental autoimmune diseases in mice. A possible immune deviation from T(H)1 to T(H)2 responses has been postulated.”


Vitamin A (RA) Decreases Th1 and Increases Th2

“In both systems, all-trans-RA at > or = 1 nM concentrations suppressed Th1 development, but enhanced Th2 development. 9-cis-RA elicited similar effects.”


Low Vitamin A Reduces Th2

“Previously we reported that vitamin A-deficient (-A) mice had a profound reduction in T helper 2 (Th2) cells, accounting for their depressed T-dependent antibody responses. Providing vitamin A or its active metabolites reversed this defect.”


Vitamin A Increases Th2 via IL-4

“Most importantly, with the Th2 polarizing cytokine IL-4, atRA significantly increased the IL-4 secretion (fivefold) and also increased the Th2 cell frequency twofold.”


Vitamin E Increases Th1 in Cancer Patients

“Short-term supplementation with high doses of dietary vitamin E leads to increased CD4:CD8 ratios and to enhanced capacity by their T cells to produce the T helper 1 cytokines interleukin 2 and IFN-gamma. In 10 of 12 patients, an increase of 10% or more (average, 22%) in the number of T cells producing interleukin 2 was seen after 2 weeks of vitamin E supplementation.”

**PGE2 Decreases Th1 in Elderly Patients**

"T helper 1 (Th1) cytokines, especially interferon-gamma (IFN-gamma), play an important role in defending against influenza infection. However, there is an age-associated loss of Th1 cytokine production. Prostaglandin E2 (PGE2) production, which increases with age, can modulate the T helper cell function by suppressing Th1 cytokine production."


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**Vitamin E Increases Th1 in Elderly Patients**

"Following influenza infection, interleukin (IL)-2 and IFN-gamma production was significantly lower in old mice than in young mice. Vitamin E supplementation increased production of IL-2 and IFN-gamma in old mice; higher IFN-gamma production was associated with lower pulmonary viral titre."


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**Vitamin C Increases Th1**

"In animal studies vitamin C deficiency has been linked to compromised immunocompetence characterized by depressed cell-mediated immunity including leukocyte phagocytosis and microbicidal activity but does not affect antibody production."


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**Vitamin C Decreases Th2**

"Studies of asthmatic children receiving a supplement of ascorbic acid have found that asthmatic children receiving the supplement suffered less severe and fewer attacks of asthma during the study period. Similarly serum total IgE levels but not specific IgE levels were reduced among asthmatic children receiving ascorbate."


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**Vitamin C and E are Low in Asthmatics**

"Significantly decreased levels of vitamin C and vitamin E were found in lung lining fluid of asthmatics in a recent study, even though plasma levels were normal."

Astaxanthin Normalise Th1/Th2 Responses in Infected individuals

"Helicobacter pylori is a gram-negative bacterium affecting about half of the world population, causing chronic gastritis type B dominated by activated phagocytes. In some patients the disease evolves into gastric ulcer, duodenal ulcer, gastric cancer or MALT lymphoma."


Astaxanthin Normalise Th1/Th2 Responses in Infected individuals

"We found that treatment of H. pylori infected mice with an algal cell extract containing the antioxidant astaxanthin reduces bacterial load and gastric inflammation. These changes are associated with a shift of the T-lymphocyte response from a predominant Th1-response dominated by IFN-gamma to a Th1/Th2-response with IFN-gamma and IL-4."


Beta-sitosterol (BSS) and its glycoside (BSSG) Normalise Th1/Th2 Responses

"This phytosterol complex seems to target specific T-helper lymphocytes, the Th1 and Th2 cells, helping normalize their functioning and resulting in improved T-lymphocyte and natural killer cell activity."


Omega 6 Oils Modify Th1/Th2 Balance

"Evidence from in vitro and in vivo studies for a role of AA metabolites in immune cell development and functions shows that they can limit or regulate cellular immune reactions and can induce deviation toward a T helper (Th)2-like immune response."


Omega 6 Oils Modify Th1/Th2 Balance

"In contrast to the effects of the oxidative metabolites of AA, the longer-chain n-6 PUFA produced by gamma-linolenic acid (18:3n-6, GLA) feeding decreases the Th2 cytokine and immunoglobulin (Ig)G1 antibody response."


Omega 6 Oils Modify Th1/Th2 Balance

GLA can also induce T-regulatory cell activity, e.g., transforming growth factor (TGF)-beta-producing T cells; GLA feeding studies also demonstrate reduced proinflammatory interleukin (IL)-1 and tumor necrosis factor (TNF)-alpha production.

Omega 3 Oils Increase Th2, and Decrease Th1

The n-3 PUFA diets decreased production of prostaglandin E2 while increasing oxidative burst and tumour necrosis factor alpha production. In addition adaptive Th1-driven responses (immunoglobulin, Ig)G2a, IgG2b, interferon-gamma:interleukin 4) were decreased, whereas Th2-driven and mucosal immune responses were increased (IgE) or unaffected (IgG1, IgA).


B6 Increases Th1

These studies collectively suggest that a B6 deficiency suppresses Th1-like activity and promotes Th2-like activity whereas its repletion reverses this tendency.


Folate Increases Th1

These findings suggest that folate may promote a Th1-like response.


B12 Suppressers Th1

This results indicates that B12 may suppress a Th1-like response.


Minerals and Immunity

Zinc and Immunity: Background

Zinc plays an important role in cell-mediated immune function. Altered cellular immune response resulting from zinc deficiency leads to frequent microbial infections, thymic atrophy, decreased natural killer activity, decreased thymic hormone activity, and altered cytokine production.

**Zinc Boosts Th1 Cytokines**

"These data demonstrate that zinc mediates positively the gene expression of IL-2 and IFN-gamma in the Th1 cell line and negatively TNF-alpha, IL-1 beta, and IL-8 in the monocyte-macrophage cell line."


**Zinc Boosts Th1 Cytokines**

"Zinc deficiency caused an imbalance between Th1 and Th2 functions, with a subsequent increased production of IL-4, IL-6, and IL-10, and decreased production of IL-2, IFN-[Gamma], and tumor necrosis factor alpha."


**Zinc Reduces Viral Severity**

"Treatment of colds with zinc reduced the mean daily clinical score and this was statistically significant on the fourth and fifth day of medication. Similarly, medication (zinc) also reduced the mean daily nasal secretion weight and total tissue count and these reductions were statistically significant on days two and six for nasal secretion weights and days four to six of medication for tissue counts when compared with placebo."


**Selenium Reduces Viral Severity**

Selenium deficiency is linked to the occurrence, virulence, or disease progression of some viral infections.


**Selenium Reduces Viral Mutations**

"Because flu virus mutations create new virus strains each year, it becomes virtually impossible for the body's immune system to develop a permanent defense. However, taking adequate amounts of selenium can prevent those mutations from occurring."


**Selenium Reduces Viral Mutations**

"Influenza viruses infecting selenium-deficient mice developed 29 mutations, which led to greater virulence. In contrast, selenium-replete mice experienced no mutations in the infecting virus and had milder symptoms."

Copper Enhances Th1

"Some of the recent research showed that interleukin 2 is reduced in copper deficiency and is likely the mechanism by which T cell proliferation is reduced. These results were extended to show that even in marginal deficiency, when common indexes of copper are not affected by the diet, the proliferative response and interleukin concentrations are reduced."


Copper Deficiency Reduces Neutrophils

"The number of neutrophils in human peripheral blood is reduced in cases of severe copper deficiency. Not only are they reduced in number, but their ability to generate superoxide anion and kill ingested microorganisms is also reduced in both overt and marginal copper deficiency."


Micro-organisms and T-helper Balance

Pathogenic Microbes

Klebsiella Induces a Th1 Response

"Thus our results strongly support the concept that differential modulation of DC explains the differences in the immune response to various bacterial strains and indicates that K. pneumoniae induces Th1 immune responses via DC."


Klebsiella Induces AS, a Th1 Disease

"This suggests the involvement of outer membrane proteins of Klebsiella pneumoniae in the pathogenic mechanism of ankylosing spondylitis."


Microbes and Immunity

Friendly Bacteria Reduce Th1
Inflammatory Bowel Disease (IBD)

"In active IBD lesions, there are elevated numbers of activated macrophages and T-lymphocytes in the lamina propria. These cells are activated with an excessive production of interleukin (IL)-1, tumor necrosis factor (TNF)-α and reactive oxygen radicals."


L. Plantarum Normalises Immunity


L. Plantarum Improves IBD

"In rats, (Colitis) attenuated by Lactobacillus plantarum. Treatment with lactobacilli also prevented the development of spontaneous colitis in interleukin (IL)-10-deficient mice and attenuated established colitis in the same knockout model."


L. Plantarum Increases IL-10

"Lactobacillus plantarum demonstrates beneficial immunomodulatory activity by increasing IL-10 synthesis and secretion in macrophages and T-cells derived from the inflamed colon. This may provide a mechanism through which probiotic bacteria ameliorate inappropriate inflammation and induce tolerance."


L. Plantarum Increases IL-10

"Importantly, mononuclear cells derived from an inflamed colon displayed significant increases in IL-10 production after incubation with L. plantarum. This increase was not present with any other bacterial sonicate and demonstrated the ability of this probiotic to induce secretion of a downregulatory cytokine in an environment of excessive inflammation."


L. Plantarum Reduces Colitis

"Interleukin (IL)-10-deficient (IL-10-/-) mice develop colitis under specific pathogen-free (SPF) conditions and remain disease free if kept sterile (germ free [GF])."

L. Plantarum Reduces Colitis

Treating SPF IL-10-/- mice with L. plantarum attenuated previously established colonic inflammation as manifested by decreased mucosal IL-12, IFN-gamma, and immunoglobulin G2a levels.


L. Plantarum Reduces Colitis

These results demonstrate that L. plantarum can attenuate immune-mediated colitis and suggest a potential therapeutic role for this agent in clinical inflammatory bowel diseases.


Lactobacillus rhamnosus GG Normalises Immunity

Lactobacillus rhamnosus GG reduces colitis.

Lactobacillus rhamnosus GG has been used in acute colitis treatment. However, it is unclear whether the LGG prevents chronic colitis. The aim of this study was to examine the prophylactic effect of LGG on animal colitis, cytokine secretion, and mucin gene expression.


LGG Reduces Arthritis

LGG reduces arthritis.

The mean number of tender and swollen joints decreased from 8.3 to 4.6 in the Lactobacillus group and from 5.5 to 4.8 in the placebo group (p = 0.41). According to the global assessment the RA activity was reduced in 71% (LGG group) vs. 30% (controls) (p = 0.15).

LGG Reduces Inflammation

"Additionally, TNF-alpha, IL-6 and in part IFN-gamma cytokine secretion by PB cells following stimulation with whole stool preparations and single members of the flora was significantly decreased, whereas the IL-10 and in part IL-4 cytokine secretion was increased at the end of the study."


LGG Reduces Inflammation: Mechanism of Action

"Lactobacillus species may be capable of producing soluble molecules that inhibit TNF-alpha production in activated macrophages. As overproduction of pro-inflammatory cytokines, especially TNF-alpha, is implicated in pathogenesis of chronic intestinal inflammation."


Bifidobacteria Normalises Immunity

Probiotics Reduces Colitis: Recent Clinical Trial

"Thirty patients received treatment with sulphasalazine (SASP) and glucocorticoid and then were randomly administered bifid triple viable capsule (BIFICO) (1.26 g/d), or an identical placebo (starch) for 8 wk. The patients were evaluated clinically, endoscopically and histologically after 2 mo of treatment or in case of relapse of UC."


Probiotics Reduces Colitis: Recent Clinical Trial

"Three patients (20%) in the BIFICO group had relapses during 2-mo follow-up period, compared with 14 (93.3%) in placebo group (P<0.01). The concentration of fecal lactobacilli, bifidobacteria was significantly increased in BIFICO-treated group only (P<0.01)."


Probiotics Reduces Colitis: Recent Clinical Trial

"The expressions of NF-kappaB p65 and DNA binding activity of NF-kappaB were significantly attenuated in the treatment group than that in control (P<0.05). The mRNA expression of anti-inflammatory cytokines was elevated in comparison with the control group."

Probiotics Reduces Colitis: Recent Clinical Trial

“CONCLUSION: The probiotic could impede the activation of NF-kappaB, decrease the expressions of TNF-alpha and IL-1beta and elevate the expression of IL-10.”

Bifidobacteria Reduces Colitis (Th1)

“Here we show that Bifidobacterium genomic DNA induced secretion of the antiinflammatory interleukin-10 by PBMC. Total bacterial DNA from feces collected after probiotic administration modulated the immune response by a decrease of interleukin-1 beta and an increase of interleukin-10.”

Microbes and Immunity

Friendly Bacteria Reduce Th2

Probiotics Reduces NF-kB

“Probiotics can suppress interleukin-8 secretion in intestinal epithelia when stimulated by proinflammatory cytokines, which is most likely mediated by NF-kappaB.”

Lactobacilli Reduce Th2

“In a subsequent study, perinatal administration of lactobacilli halved the later development of atopic eczema during the first 2 years of life. Specific strains of the healthy gut microbiota have been shown to induce the production of IL-10 and transforming growth factor-beta, which possess an important regulative role in the development of allergic type immune response.”
**Lactobacilli Strengthen Gut Barrier Function**

"Probiotics also strengthen gut defense barrier mechanisms and reduce antigen load in the gut."


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**Acidophilus Yogurt Reduces Th2**

"Cultured PBMC of the group fed with yoghurt released more IFN gamma and less IL-4."

"CONCLUSION: Yoghurt feeding appears to improve or prevent allergic recurrences in rhinopathic patients."


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**Lactobacillus GG Reduces Allergy**

"This has led inevitably to a study employing lactobacillus GG given prenatally to mothers who had at least one first degree relative or partner with atopic disease and to their infants for the first six months of life. Atopic eczema occurred less frequently up to 2 years of age in the actively treated compared with the placebo treated infants."


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**LGG Reduces Eosinophils**

"During active treatment, sECP levels decreased from 17.4 to 12.6 μg/L but remained stable during placebo treatment. A significant difference between the change in sECP levels during active treatment compared with the change observed during placebo treatment was demonstrated. The mean change in sECP was −6.2 μg/L (95% CI, −13.3 to 0.5 μg/L) versus 2.0 μg/L (95% CI, −0.5 to 4.6 μg/L) during placebo treatment (P = .03)."

Lactococci Reduces Th2, Even if Dead

“Six strains induced the production of cytokines (IL-12, IL-6, and TNF-alpha) in macrophage-like cell line J774.1, and the highest induction was observed with Lactococcus lactis subsp. lactis G50. The cytokine induction in the J774.1 cell line was almost entirely sustained after heat-killing of the strain.”


Lactococci Increases Th1

“Spleen cells from BALB/c mice fed G50 culture produced more IL-12 and IFN-gamma and slightly less IL-4 and IL-6 than the control (i.e., without strain G50), indicating that strain G50 can enhance Th1-type immune response in vivo.”


Lactococci Decreases Th2

“These results suggest that strain G50 has an ability to suppress the Th2 response. Thus, Lactococcus lactis subsp. lactis G50 is a potential probiotic strain for the suppression of hypersensitive reactions caused by the Th2 response.”


Probiotics Normalise Immunity and Inflammation

“Lactobacillus acidophilus TMC 0356 significantly induced the production of more IL-6, IL-10, IL-12, and TNF-alpha than the other bacteria tested (p < 0.0001; ANOVA).”


Probiotics Normalise Immunity and Inflammation

“These results suggest that lactobacilli can activate macrophages to secrete both inflammatory and anti-inflammatory cytokines. Selected strains might be used to bring about pro or antiinflammatory immune reactions.”


Probiotics

Friendly Bacteria Reduces Infections
Probiotics Reduce Infections

“Consumption of lactic acid bacteria (LAB) has been suggested to confer a range of health benefits including stimulation of the immune system and increased resistance to malignancy and infectious illness.”


LGG Reduces Nasal Infections

“The results indicate that regular intake of probiotics (LGG) can reduce Staphylococcus aureus, Streptococcus pneumoniae, beta-hemolytic streptococci, and Haemophilus influenzae in the upper respiratory tract. The results also indicate a linkage of the lymphoid tissue between the gut and the upper respiratory tract.”


LGG Reduces Nasal Infections

“The results also indicate a linkage of the lymphoid tissue between the gut and the upper respiratory tract.”


NCFM Acidophilus Benefits Humans

“A blend of probiotic strains containing NCFM decreased the incidence of pediatric diarrhea. NCFM led to a significant decrease in levels of toxic amines in the blood of dialysis patients with small bowel bacterial overgrowth. At adequate daily feeding levels, NCFM may facilitate lactose digestion in lactose-intolerant subjects.”


NCFM Acidophilus Benefits Humans

“NCFM survives gastrointestinal tract transit in both healthy and diseased populations. NCFM inhibits aberrant crypt formation in mutagenized rats, indicative of activity that could decrease the risk of colon cancer.”


Probiotics Increase Interferon-gamma

“Spleen cells from mice given L. rhamnosus, L. acidophilus or B. lactis also produced significantly higher amounts of interferon-gamma in response to stimulation with concanavalin A than cells from the control mice.”

Probiotics Increase Antibodies to Microbes

“Together, these results suggest that supplementation of the diet with L. rhamnosus (HN001), L. acidophilus (HN017) or B. lactis (HN019) is able to enhance several indices of natural and acquired immunity in healthy mice.”


Acidophilus Kills Klebsiela

“It has been shown that introduction of Lactobacillus substantially decreased the level of the gut contamination by Klebsiella, prevented generalization of infection and death of animals. Significant higher levels of IgA in the blood serum, IgA and IgM in the gut content, percentage of splenocytes, expressing surface IgM and IgG were observed on the 7th day as compared with those in animals without Lactobacillus.”


Acidophilus Kills Klebsiela

“A conclusion was made that introduction of Lactobacillus prevents development of the Klebsiella infection and protects the immune system from excessive antigenic action.”