Treating Inflammation Naturally

Inflammation is a Symptom not a Disease

Edited by Desire' Dubounet
Anti-Inflammatory Foods

Foods To Eat

Fats and Oils. (Uncooked - not boiled oil) Omega-3 fatty acids are found in cold-water oily fish, flax seeds, canola oil and pumpkin seeds. Consumption of monounsaturated fatty acids found in olive oil, avocados, and nuts has been linked to reduced risk of cardiovascular disease. Other healthful oils include rice bran oil, grape seed oil, and walnut oil. Use cold processed sunflower and olive oil daily on bread or salads.

Fruits and Vegetables. Whole fruits, berries and vegetables are all rich in vitamins, minerals, fiber, antioxidants and phytochemicals. Choose green and brightly colored vegetables, and whole fruits such as broccoli, chard, strawberries, blueberries, spinach, carrots and squash. You should eat at least five and preferably more) servings of fruits and vegetables each day.

Protein Sources. Possible anti-inflammatory protein sources include lean poultry, fish and seafood (fatty fish offer protein as well as omega-3 fatty acids). Non-GMO Soy and Non-GMO- soy foods such as tofu and tempeh, along with other legumes and nuts and seeds can be used as plant-based protein sources. The best nuts are walnuts, almonds, pecans and Brazil nuts.

Beverages. Your body needs water. Drink tap, sparkling or bottled water, 100-percent fruit juices, herbal tea, low-sodium vegetable juice are all healthful sources of water the can reduce inflammation. 100% pineapple juice and papaya juice will help provide enzymes to treat inflammation. Probiotic yogurt and probiotic drinks will also help.

Foods To Avoid.

Loading up on junk foods, high-fat meats, sugar, and highly processed foods may increase the potential for inflammation in your body. Reduce your consumption of trans-fats and saturated fats by cutting back on highly processed foods, red meats, and high-fat processed meats such as bacon and sausage. Cut back on refined white flours in bread and pasta (look for 100-percent whole-grains instead). Eliminate added sugars by decreasing your consumption of sugary sodas, pastries, candy, rich desserts, and pre-sweetened cereals.

No boiled oil or eat things boiled in oil.

Another possible source of irritation comes from the nightshade family of plants, which includes potatoes, tomatoes, and eggplant. These vegetables contain a chemical alkaloid called solanine, which can trigger pain in some people. While there aren't any formal research findings that back the claim about nightshade plants, some people do believe they get relief from the symptoms of pain and inflammation when they eliminate them.
Avoid High Glycemic Index foods eat the foods in green avoid the foods in red. High glycemic index foods burden the pancreas by switching pancreas function to insulin regulation over enzyme production. The body needs enzyme to break up old, diseased, or toxic tissues. High glycemic foods means a reduced amount of anti-inflammatory enzymes. And this aggravates all inflammation.

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<th><strong>LOW GLYCEMIC FOODS</strong></th>
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<th><strong>HIGH GLYCEMIC FOODS</strong></th>
<th><strong>Not all carbohydrates are created equal</strong></th>
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**The Glycemic Index of Selected Foods**

- Avoid the foods in red.
- Eat the foods in green.

**Not all carbohydrates are created equal**

Carbohydrates with a low GI (55 or less) will make your blood glucose rise slowly and fall gently over a longer time. Carbohydrates with a high GI (70 or more) are digested quickly causing your blood glucose levels to spike and then crash.
### The Glycemic Index of Selected Foods

Dextrose enters the cell too fast and makes High Glycemic Index foods. This makes immune weakness, nervous irritation, and aggravates all diseases. Avoid our exposure to high glycemic foods.

Avoid the foods in Red

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Eat the foods in Green
Anti-inflammatory Diet and LifeStyle Must Dos

Choose fresh foods more often and choose fewer heavily processed foods.

- For breakfast, try oatmeal served with fresh berries and walnuts.
- Snack on whole fruits, nuts, seeds, and fresh vegetables instead of cookies and candy.
- Eat more fish and less fatty red meat.
- Stir fry with small amounts of sunflower, olive oil or safflower. No deep fried foods.
- Try a tofu stir-fry or scramble.
- Have a salad with lots of fresh vegetables as your meal.
- Stay away from deep-fried foods; bake, broil, poach or stir-fry instead.
- Choose dark green or brightly colored vegetables as side dishes -- they should fill half your dinner plate.
- Lifestyle changes will go a long way toward reducing chronic inflammation in your body, so focus on making the following changes:
- Eat foods that are rich in natural enzyme like pineapple (the core has the most Bromelain) and papaya.

Focus on eating a healthy diet. This includes avoiding pro-inflammatory foods like trans fats, fried foods, sugar and grains, foods cooked at high temperatures and oxidized cholesterol (cholesterol that has gone rancid, such as that from overcooked, scrambled eggs).

Get plenty of animal-based omega-3 fats by taking a high-quality krill oil that is chock full of these beneficial omega-3s. My favorite in this area is krill oil.

Optimize your insulin levels. If your fasting insulin level is not lower than three consider limiting or eliminating your intake of grains and sugars until you optimize your insulin level.

Exercise regularly. Exercise is a great way to lower inflammation without any of the side effects associated with medications.

Quit smoking. Smoking hardens your arteries and increases inflammation. But research shows you can reverse all the damaging effects to your arteries within 10 years of quitting. However, be sure you get your diet under control first so you don’t fall into the trap of trading cigarettes for unhealthy junk foods.

Make sure your waist size is normal. If you’re a woman with a waist measurement of over 35 inches or a man with a waist of over 40 inches, you probably have high inflammation and should take steps to lose weight.

Have healthy outlets for stress and other negative emotions. High levels of stress hormones can lead to the release of excess inflammatory chemicals, so be sure you use tools to help deal with your current stress and resolve past emotional challenges as well.
Meditation, prayer and my personal favorite the Meridian Tapping Technique (MTT) are all useful stress management techniques to try out.

**Optimize your vitamin D levels.** Most people are not aware that vitamin D can have a profoundly dramatic impact on your health.

Your best source of vitamin D is through your skin being exposed to the sun or alternatively using a safe tanning bed. In the wintertime, however, you may need to take an oral supplement. Just make sure you’re taking the right form of vitamin D in the appropriate amounts to reap the benefits, and remember to get your vitamin D levels tested regularly.

**Useful Herbs and Supplements to Fight Inflammation**

Finally, although they are not a long-term solution, the herbs that follow are useful for treating the symptoms of inflammation and relieving pain while you work at implementing the lifestyle changes above:

**Boswellia:** Also known as boswellin or “Indian frankincense,” this herb contains specific active anti-inflammatory ingredients, referred to as boswellic acids that animal studies have shown significantly reduce inflammation. This is one of my personal favorites as I have seen it work well with rheumatoid arthritis patients.

**Bromelain:** This enzyme, found in pineapples (mostly the core), is a natural anti-inflammatory. It can be taken in supplement form, but eating fresh pineapple may also be helpful.

**Papain** is an enzyme found in papaya that also helps.

**Resveratrol:** Resveratrol is a potent antioxidant found in certain fruits, vegetables and cocoa that is emerging as a modern-day fountain of youth. It works by preventing your body from creating sphingosine kinase and phospholipase D -- two molecules known to trigger inflammation. The science surrounding this compound is so compelling that it has become one of my all-time favorite antioxidants, and I believe one that shows real promise of health benefits.

**Evening Primrose, Black Currant and Borage Oils:** These contain the essential fatty acid gamma linolenic acid (GLA), which is useful for treating arthritic pain. It is reasonable for many to take these as a supplement, particularly if you struggle with dry skin in the winter, as this is a strong indicator that you are deficient in these fats.

**Turmeric, Tulsi and Rosemary:** The transcription protein Nuclear Factor-kappa Beta (NFκB) is a major inducer of inflammation, and these three herbs are capable of modulating NFκB.

- A powerful natural remedy for inflammation is Ginger. It has been known for centuries to have strong anti-inflammatory properties. According to the National Institutes of
Health in the past 25 years research has proved this. Ginger has pharmacological similarities with NSAID’s non steroidal anti inflammatory drugs. This natural remedy for inflammation is capable of more than NSAID’s and does not have the side effects. Ginger as a natural treatment for inflammation comes either fresh or as an extract. Even ginger snaps if made with Ginger and not made from artificial flavor can be beneficial. Using ginger as a spice in cooking is a great way to use this natural remedy for inflammation.

- Arnica is another natural treatment for inflammation. Arnica is generally used externally and applied to the affected area in the form of a cream, salve, ointment or tincture. According to University of Maryland medical center Arnica has been used medicinally since the 1500’s. It is only taken internally in a much diluted form.
- St. John's Wort is also a natural remedy for inflammation. It is very popular as a natural remedy for mild depression. This natural remedy can be applied externally as cream to reduce inflammation caused by insect bites, cuts and wounds. St. John’s Wort has antibacterial properties which are believed to help in the reduction of inflammation of skin irritation.
- Garlic as a natural remedy for inflammation is very effective. Garlic is great against joint inflammation. Garlic can be used as you would expect simply as an ingredient to your food. Garlic can also be used externally. According to Soul-Guidance.com in 1916 the British government used garlic bulbs to help heal wounded soldiers. It was applied to the soldier’s wounds and not one case of sepsis occurred in those treated this way.
- Cayenne has been used to naturally treat inflammation as well. Cayenne has circulatory improving properties and it is believed these properties are helpful in the natural reduction of inflammation. Cayenne is used generally for throat inflammation and is available as a spray.
- All of these natural remedies for treating inflammation have been effective for hundreds and even thousands of years. The most important thing is to increase omega 3 and reduce omega 6 in the diet. As always, when working with medicine herbal or not consult a physician when in doubt. When having an inflammation episode, stopping the intake of omega 6 is often recommended.

Maintaining a healthy weight also appears to be helpful for reducing pain and inflammation.
Fat cells in an obese mouse have swollen up with stored lipids and become much larger. The purple dots between the cells are inflammatory cells and macrophages that cluster around dead and degenerated cells to engulf and digest them.

Studies in our lab and others have clearly demonstrated that chronic inflammation is a central feature of obesity and the associated metabolic disease cluster. This inflammatory response is distinct, appears to respond to intrinsic cues, and does not resemble the classical inflammatory paradigm. New names have been suggested to describe this phenomenon including “metaflammation” or “paraflammation”.

We examine the molecular mechanisms leading to the emergence of these inflammatory responses and how they are linked to metabolic homeostasis as well as disease. Our effort is targeted to major cell types and organs where inflammatory and metabolic pathways interface, such as adipose and liver tissue as well as macrophages. In these systems and various genetic models, we explore the hormonal and metabolic signals that generate profound effects on systemic endocrine equilibrium.
Obesity-related activation of the serine/threonine kinases, such as JNK, and the consequent inhibition of insulin receptor signaling via phosphorylation of a substrate of insulin receptor, IRS-1 is a central mechanism of insulin resistance. In mice lacking JNK genes, there is dramatic protection from obesity and diabetes. There is also genetic evidence that JNK activation is linked to type 2 diabetes in humans. Currently, we are investigating the detailed molecular mechanisms, target cell types and organs and different JNK isoforms underlying this crosstalk. We also investigate the metabolic signals and stresses that give rise to JNK activation and explore therapeutic and preventive possibilities for diabetes, obesity, and atherosclerosis by blocking JNK function. The ability of nutrients to trigger inflammation raises an important question regarding the control of overt inflammation during physiological fluctuations in nutrient and energy exposure. In search for molecules that prevent such aberrant responses, we recently identified a new class of molecules called STAMP that control nutrient-induced inflammatory responses, particularly in adipocytes. These molecules are nutritionally regulated, particularly in visceral adipose tissue, and their absence results in visceral adipose tissue inflammation, stress responses, and insulin resistance under regular dietary conditions. We are currently investigating the molecular mechanisms of actions of these molecules and studying their target cells and organs.

Stress-sensing response of the ER. Under stress conditions, the three branches of the
**Unfolded protein response (UPR) are activated.**

We are also broadly pursuing the molecular mechanisms of the crosstalk between inflammatory and metabolic pathways or integration of nutrient and pathogen sensing pathways. These studies have recently led us to the discovery of endoplasmic reticulum (ER) stress as a central mechanism linking metabolic stress with insulin resistance and type 2 diabetes. ER is a critical organelle responsible for the synthesis, maturation, folding and transport of all secreted and transmembrane proteins. It is also the site for lipid synthesis and packaging. ER meets the fluctuations in its functional capacity by mounting an adaptive response called “unfolded protein response” or UPR. This system helps adapt ER folding capacity and manages ER stress by regulation of protein synthesis and breakdown and also by activating a transcriptional program to assist ER with the necessary components to establish equilibrium. In addition to proteins, ER is also exquisitely sensitive to energy status, nutrients, and pathogens, hence it can integrate these pathways that are central to metabolic pathways.

Obesity also leads to ER stress in metabolically sensitive tissues such as adipose and liver tissues and pancreatic islets. Through activation of JNK and other stress signaling pathways, ER is linked with regulation of insulin action and glucose and lipid metabolism. Currently, we are exploring the molecular mechanisms leading to ER stress in obesity and investigating the role of different UPR branches in metabolic homeostasis. We are also developing strategies for chemically and genetically targeting these pathways for novel therapeutic opportunities against metabolic diseases.

**Suggested reading from Hotamisligil Lab:**


Here is a part from the interaction of professor Desire’ Dubounet and Novak Djokovic when Novak was at his peak in 2010-2011. These are words spoken for all types of Inflammation.

I will now start with the key element of the game adrenaline. Adrenals are the organ just above your kidney that makes adrenaline. Adrenaline is the key sport hormone.

The chines sport proverb says fall down seven times, get up eight.
It is not the size of the dog in the fight, but the size of fight in the dog.

A man that won’t be beaten can’t be beaten.

These quotes reflect the ability of willpower and willpower is from adrenaline. Every stress can weaken the adrenals. Weak adrenals show as weak legs. When your legs are tired and timing and coordination are off we first think of weak adrenals. I saw your adrenals give out in London. Weak legs, timing off.

**FACTORS AFFECTING THE ADRENALS**

There is a simple medical test for the adrenals I developed over 20 years ago. Get a computer driven blood pressure cuff at any local pharmacy. Measure your blood pressure sitting comfortably. Ideal is 120/80 with 60 to 70 pulse beats for an athlete. Start the blood pressure cuff a second time and stand up as the system is mid cycle inflating the cuff. Now we are measuring the blood pressure just after standing. It should be the same if your adrenals are perfect.

The pressure on a liquid is determined by the height of the liquid. The deeper you go into a pool the more pressure. It does not matter the size of the pool only the depth or height of the liquid. As you stand up it takes more power from your heart to pump the blood liquid the extra height of standing. It is your adrenals sending out adrenaline that keep the blood pressure constant. Weak adrenals then will make the standing blood pressure drop 10 or more points from the systolic or diastolic. If your first blood pressure was 120/80 and the second is 110/80 the adrenals are weak as is 110/75. 5 point drop means very little problem. 10 point drop shows the start of weak adrenals this is called hypo-adrenia. More than 10 point drop shows very weak. More than 20 points is very bad. This is why some people pass out when they stand. If coupled with an increase in pulse over 10 beats a sec say from 70 to 82 then the heart is struggling also.
Potassium is a needed mineral for fine-tuned coordination. When you are deficient in Potassium the nerves of the arms get shaky and small muscle movements get irregular. Liquid you release drag out Potassium. So sweat, urine, diarrhea all leech out Potassium. Potassium makes foods orange, so orange juice is rich in it. I see you using an orange mineral sport liquid during the match but watch out it might be made with glucose, or sucrose. True orange juice has fructose. Apple juice has the most fructose. Natural Fructose (not S I N th et ic Hi F ructose corn syrup) gives the body gentle energy not in up and down spurts. You might want to mix some fresh squeezed orange and apple juice into your sport drink.

If you do this every day as part of your morning routine you will see when your adrenals are getting weak from stress. Well first emotional stress, over training, processed sugar, too much salt, too much coffee, lack of sleep and many things can cause hypo-adrenia. Slight Infections of bacteria, virus, and fungus like the sweet tissues of the adrenals, thymus, brain and they can cause weak adrenals. So what to do?

Coffee has the stimulant caffeine. It is legal for use on tour. But of you take coffee every day you build up a tolerance and the stimulation is negated. If you drink coffee now and quit you will get a withdrawal
symptom of tiredness and slight depression. This withdrawal usually takes a week to do. Then if you use
the caffeine as a stimulant when needed it can help strengthen weak adrenals when you need it.
Everyday use soon dissipates the stimulation as you start to tolerate and need it just to be normal.

If you measure your sitting standing BP on match day and find it weak, a small cup of coffee might be
the answer. But this is just a drug (a natural drug) and does not address the real cause of the weak
adrenals. Emotional searching, prayer, meditation might find the real problem if it is emotional.

Foods to use for adrenal weakness are:

Fruits such as apples, kiwi, oranges, avocados, berries and bananas

Legumes, beans and nuts such as almond, lima beans, sesame seeds,

Sunflower seeds and pumpkin seeds

Bean and alfalfa sprouts

Herbs That Help Adrenal Fatigue: use as teas sparingly

More is not better

- **Rhodiola Rosea** -- It enhances memory and concentration. It has been shown
to reduce stress-induced fatigue and improve mental performance.
- **Ashwagandha** -- It has been shown to have a sedating effect on the body and
helps to rebuild the digestive and nervous system.
- **Eleuthero Root or Siberian Ginseng** -- It has been used traditionally to
stimulate and nourish the adrenal glands and increases mental alertness. Eleuthero is
considered an "adaptogen" which means it can help the body adapt to stress.
- **Cordyceps** -- This is a Chinese mushroom used for supporting the adrenal gland and can also
normalize immune function and support kidney, lung, liver, nervous system and cardiovascular
function.
- **Ginko Bilboa** – for memory and mental functioning
- **Goto Kola used for energy**
- **Liquorice herb** (Glycyrrhiza Glabra), Is possibly the most important herb for helping the adrenal
glands to produce natural steroids and also to help balance the immune system in cases of auto-
immune disorders as well as reduce inflammation via these two routes.

Some vegetables like potatoes, tomatoes, and eggplant may actually make pain
from inflammation worse. These vegetables are part of the nightshade family of
plants and contain a chemical alkaloid called solanine. Solanine can trigger pain
in some people.
Anti-Inflammation After Match Drink

A nice way at the end of a match is the use an Anti-Inflammatory Smoothie. The match stress makes inflammation of the joints and muscles. If we relieve it gently with natural enzymes recovery will speed up. Mix the pineapple core (richest part in Bromelain the anti-inflammation enzyme) with equal parts Papaya, add ginger or mint for taste and dilute with water. One glass of this after a match will speed up the natural inflammation relief process. It tastes good and helps the body recover faster.

Stresses Build up in the body

And sometimes we blame the last stressor not the accumulation. It is like blaming the last straw for breaking the camel’s back.

Try to reduce the whole stress picture with forgiveness, acceptance, and courage. Here is a pic story of stress.
The Desi-astrous Sign of Anxiety

Stress is caused by the desire for things to be different.

**Relax**
- Breathe fully
- Yoga & exercise
- Reduce distraction

**Simplify**
- Plan & organize
- Reduce clutter
- Set limits

**Identify Triggers**
- Thoughts
- Feelings
- Food

**Share**
- Thoughts
- Feelings
- Fears

**Nourish Spirit & Intellect**
- Live in the present
- Journal
- Identify spiritual beliefs

**Avoid**
- Procrastination
- Negative thinking
- Catastrophizing

Learn to accept the things you can’t change & change the things you can...and find the wisdom to know the difference.
AMOEBA and JOINT PAIN

Rheumatoid Arthritis (RA) is called an auto-immune disease, because it attacks the body tissue in and around certain joints to cause swelling and pain. Doctors know that the weak link or the overused joint is effected, the immune system attacks itself, hence the name auto-immune; it is assumed to be an automatic response, possibly caused by long term daily stress, an allergy or infection. In RA the synovial membrane (or joint capsule) is affected and then there can be general degeneration of the joint and deformity. After some years it will often develop into osteo-arthritis. RA generally just attacks the smaller joints of hands, fingers, etc. It can cause serious deterioration to the cartilage around the joint. There are other theories as to the cause of RA, and one of these was put forward by Prof. Wyburn-Mason who was able to see and identify certain amoebae that parasite the joints (1). Certain common minerals in the blood, such as boron, can control these parasites. Others blame stress or allergies. Allergies mean that certain things act as a poison to upset or damage some tissue or other. There are a number of blood tests that will confirm a diagnosis of RA. RA is generally associated with other bodily symptoms such as general malaise, fatigue and muscle pains. There are often nerve problems and blood disorders associated with RA. Novak you are pointing to a place that shows Amoebic infection not rotator cuff. The pain in your shoulder is most likely from amoeba since you are from Serbia.
There is an excess of Amoeba in Serbia and all of my Patients who visit there get this exposure. I need to evaluate this and treat you and put this to rest.

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THE AMOeba AS THE CAUSE OF THE SECOND GREAT TYPE OF CHRONIC ARTHRITIS

Preliminary Note

By LEONARD W. ELY, M.D., Associate Professor of Surgery, San Francisco,
ALFRED C. REED, M.D., Assistant Clinical Professor of Medicine, San Francisco,
And
HARRY A. WYCKOFF, M.D., Clinical Pathologist, Stanford University Medical School, San Francisco.

By the second great type of arthritis we mean that form of arthritis hitherto described by the Germans as arthritis deformans, by the English as osteoarthritis, by Goldthwait as hypertrophic arthritis, by Nichols and Richardson as degenerative arthritis, and by other writers under various titles. This is the senile form of arthritis, the chronic rheumatism of the elderly. For want of a better name some writers have called it metabolic arthritis, a singularly unfortunate and quite meaningless term.

Entamoeba coli and Entamoeba hartmanni

Once in the Synovial Fluid they can propagate in peace and within as little as five years they can multiply enough to cause joint inflammation and thus the beginning state of Rheumatoid Arthritis.

They are difficult to diagnose and to treat.

Synovial Fluids most chosen are Knee, Shoulder, Low Back, and Elbow. Smaller joint infections can happen later.

Bad Food - Bad Water ingestion when stomach acid is weaken from stress or dilution.
Dysentery results, but some Amoeba get into the lymph system thru the Intestinal tract and they migrate to areas of synovial fluid to escape the white blood cells.
Most RA is certainly due to an infection by an amoeba or other parasite. Long term daily low level stress makes this auto-immune inflammation worse, and emotional stress increases can make a flare-up. Some doctors will say there is a virus, but in this case the term virus is just a medical term that means ‘I don’t really know’. Some foods can act as an allergen to cause RA. Some meats contain many parasites, particularly pig meat and some of these parasites can get into the body to cause RA. We all have macrophages circulating in the blood, and their work is to identify any foreign cells in the body. Then killer lymphocytes are called in to attack the foreigner. **These can be bacteria or amoebae or still smaller cells such as a true virus.** Some of these invading cells seem to take shelter in the synovial membrane around a joint, possibly because there is no direct blood supply to the synovium and then many doctors will say that the body’s own lymphocytes are attacking our own tissues. And they call it auto-immune disease. The Jews in Palestine have less than 1% with arthritis of all sorts, and very little RA. They do not eat pig meat and this is an indication that the parasites in pig are dangerous. Europeans eat more pig meat than any other race and this is probably the reason for so much RA. Some researchers say that meat does aggravate arthritis, but none of them have ever sorted out the different kinds of meat. Other sources of infection can be mosquitoes or other insects, especially those found in the tropics. If a person feels they picked up their RA while visiting the tropics then they were probably bitten by something that injected a parasite into them.

Patients with RA also feel tired, exhausted and irritable which indicates that RA is a disease of the whole body and not just a disease of the joints. They often have night sweats and have a slightly higher than normal temperature. Some RA victims also have problems with their eyes, heart, nerves, kidneys and lungs which all seem to be infected by the same whole body disease. RA can start suddenly, just overnight, or it can take weeks to develop, and this all fits the theory that some sort of parasitic infection has caused the problem. These can be introduced a little and often. Or there can be a massive invasion of parasite after, say, a feed of poorly cooked sausage. RA is often worse in the fingers and feet, the joints that are used most of all. If the knees are badly affected do not put a pillow under them at night, as then they may become bent permanently and this is bad.

Over the last 20 years a number of my RA patients have used the mineral boron with a blend of safe Mexican herbs for amoeba. These patients will often experience a Herxheimer reaction which is a worsening of the problem after a day or so, but then when they continue with the therapy they will be relieved of all pain and inflammation. This is because the boron and herbs will kill the amoeba parasites in the body and then when the dead parasites are still floating around the blood we can feel worse for a while. But when the white blood cells can get rid of all the dead parasites, one can end the pain forever.

Boron is needed in trace amounts for healthy bones and for the metabolism of calcium, phosphorus, and magnesium. It's also one of the trace minerals that enhances brain function and promotes alertness.

**Most people are not deficient in this mineral.** However, elderly people usually benefit from taking boron supplements of 2 to 3 milligrams daily because they have a greater problem with calcium absorption.

Boron deficiency accentuates [Vitamin D](#) deficiency.
This trace mineral helps to prevent postmenopausal osteoporosis and build muscle. A study conducted by the U.S. Department of Agriculture indicated that within eight days of taking boron supplements of 3 milligrams in their daily diets, a test group of postmenopausal women lost 40 percent less calcium, one-third less magnesium, and slightly less phosphorus through their urine than they had before beginning boron supplements.

Natural Food Sources of Boron

**Foods high in Boron:**

- apples
- carrots
- grapes
- green leafy vegetables
- nuts
- pears
- grains not containing gluten

Traditional doctors will say that RA cannot be cured and can only be treated by drugs that relieve pain and reduce fever and inflammation. They will use aspirin or a similar non-steroidal anti-inflammatory drug but these have side effects and can cause stomach ulcers and internal bleeding and death. Others will use corticosteroids which are very powerful anti-inflammatory drugs, but they also have powerful side effects affecting the stomach, heart and bone adversely. They can also cause skin problems and cause the face to swell. These often have to be taken for the rest of one’s life, so they say. Some doctors want to have surgery to affected joints, but that does not attack the disease that affects the whole body. Please never use steroids they greatly upset the natural balance and hurt the adrenals.
Amoebas are one-celled protozoa. There are several varieties found in humans that are not considered to be disease producers. However, such virulent strains as *Entamoeba coli* and *Entamoeba hartmanni*, can produce mild diarrhea and dysentery. Most amoeba infestations, however, do not produce clinical symptoms.

Amoebas generally have a two-phase life cycle: the infective dormant cyst and trophozoite, a later form that is motile and active. When cysts are ingested, they are carried to the small intestine, where they are released as trophozoites into the colon. This form dwells mainly inside the bowel lumen, where it grows and multiplies. The incubation period varies from a few days to three months. Changes in the host's immune system, or in the organism's pathogenicity, can lead to tissue invasion. The trophozoite can then penetrate through the intestinal lining and invade the liver, lungs, brain, and heart. Subclinical symptoms include the following: upper-right quadrant pain, cramps, occasional nausea, and loose stools. In more serious cases, pronounced abdominal distention, dysentery, fever, and hepatitis may result. Extreme infection can cause abscesses in the liver, the lungs, and the brain.
Chronic diarrhea, gas, and massive food and environmental allergies have all been reported when amoebas are found in the system. Amoebic hepatitis can be mistaken for viral hepatitis; genital amoebiasis for carcinoma; amoebic colitis for ulcerative colitis; and amoebiasis in the brain for a brain tumor. Only a few cysts are needed to cause infection. Amoebic cysts resist iodine and chlorine if concentration of these chemicals is too low.

Two other amoebas responsible for human infection are from the genus *Naegleria*, which live in freshwater lakes, natural warm water springs, or streams, and can produce encephalitis in swimmers. Although rare, the disease is often fatal. The protozoan *Naegleria fowleri* is often found in natural warm water springs. It causes a very rare form of meningitis. The amoeba is inhaled and burrows inside the nose, travelling to the brain. Once there, fatal meningitis progresses rapidly. Bathing in the Roman Baths in the city of Bath is no longer permitted because of this protozoa, that has contaminated the water source.
Acanthamoeba species live in soil, as well as fresh and stagnant water, but can be found anywhere. Infections often come as a result of contact wearers not cleaning their lenses with proper solutions, but
rinsing them off with tap water. This contamination can lead to eye infections, especially of the cornea, resulting in reduced vision or the removal of the eye (enucleation). The amoeba is also responsible for a severe eye infection called **Acanthamoeba keratitis**, which results in pain and inflammation around the cornea. If the disease progresses to an ulcer, a corneal transplant is often required. Since relatively few cases are reported, it is assumed that, this too, has been misdiagnosed as another condition.

**Endolimax nana** is a relatively new member of the pathogenic group of amoebas. It is the smallest of the intestinal amoebas, causing researchers of the past to overlook its potential virulence. This amoeba lives in the lower bowel, but the larvae can sluggishly travel to other parts of the body. It has been linked as a possible cause of rheumatoid arthritis, as well as a host of other collagen-related diseases. (See *The Causation of Rheumatoid Disease and Many Human Cancers: A New Concept in Medicine*, by Roger Wyburn-Mason, MD, PhD). Typically, other researchers disagree and are looking for another cause.

**Entamoeba histolytica** is the cause of amoebic dysentery after being transmitted in cyst form from fecally contaminated food or water by way of food handlers (usually asymptomatic carriers), flies, cockroaches, etc. and from certain sexual practices. The disease (amoebiasis) produces abdominal pain and cramps and diarrhea, containing blood, pus, and mucous. A milder form of the disease can display alternating diarrhea and constipation. This disease affects more than 400 million people worldwide, causing mortality second only to malaria. The infective cyst stage develops in the small intestine into the trophozoite stage, where it grows and multiplies in the open spaces of the bowel, feeding on bacteria, tissues, and blood cells. Trophozoites readily die once outside the body, but, inside, they release an enzyme that dissolves tissue, allowing them to penetrate into the intestinal mucosa, where lesions develop and can turn into extensive ulcerative areas that cause dysentery with watery stools containing blood. If the disease disseminates to various internal organs, abscesses usually develop on the liver and possibly on the brain, lungs, heart, or other tissues, and death can result. Most cases are of a mild diarrheal nature or no symptoms at all.
In acute amebic dysentery, the contents of the intestinal tract pass rapidly through the system, in which case, the amoeba does not have time to develop into the cyst stage, and only the noninfectious trophozoites are released. When the contents of the intestines start to slow down, this allows time for the development of cysts. Therefore, by the time the person thinks he is getting better, he is really becoming infectious.

If the stool movement is stagnant or sluggish, the organism usually develops into a cyst before leaving the bowel, where it can survive in water and soil until ingestion reactivates it. The cysts are very resistant to certain chemicals, and have been known to survive up to seventy-two hours in chlorine solutions routinely used in public water supplies. They can also survive in water for a month in temperatures up to 50°C (122°F) and, since the 1960's, more and more antibiotic-resistant strains have been emerging.
It is becoming increasingly clear that chronic inflammation is the root cause of many serious illnesses - including heart disease, many cancers, and Alzheimer's disease. We all know inflammation on the surface of the body as local redness, heat, swelling and pain. It is the cornerstone of the body's healing response, bringing more nourishment and more immune activity to a site of injury or infection. But when inflammation persists or serves no purpose, it damages the body and causes illness. Stress, lack of exercise, genetic predisposition, and exposure to toxins (like secondhand tobacco smoke) can all contribute to such chronic inflammation, but dietary choices play a big role as well. Learning how specific foods influence the inflammatory process is the best strategy for containing it and reducing long-term disease risks. (Find more details on the mechanics of the inflammation process and the Anti-Inflammatory Food Pyramid.)
The Anti-Inflammatory Diet is not a diet in the popular sense - it is not intended as a weight-loss program (although people can and do lose weight on it), nor is it an eating plan to stay on for a limited period of time. Rather, it is way of selecting and preparing foods based on scientific knowledge of how they can help your body maintain optimum health. Along with influencing inflammation, this diet will provide steady energy and ample vitamins, minerals, essential fatty acids, dietary fiber, and protective phytonutrients.

You can also adapt your existing recipes according to these anti-inflammatory diet principles:

**General Diet Tips:**

- Aim for variety.
Include as much fresh food as possible.
Minimize your consumption of processed foods and fast food.
Eat an abundance of fruits and vegetables.

**Caloric Intake**

- Most adults need to consume between 2,000 and 3,000 calories a day.
- Women and smaller and less active people need fewer calories.
- Men and bigger and more active people need more calories.
- If you are eating the appropriate number of calories for your level of activity, your weight should not fluctuate greatly.
- The distribution of calories you take in should be as follows: 40 to 50 percent from carbohydrates, 30 percent from fat, and 20 to 30 percent from protein.
- Try to include carbohydrates, fat, and protein at each meal.

**Carbohydrates**

- On a 2,000-calorie-a-day diet, adult women should consume between 160 to 200 grams of carbohydrates a day.
- Adult men should consume between 240 to 300 grams of carbohydrates a day.
- The majority of this should be in the form of less-refined, less-processed foods with a low glycemic load.
- Reduce your consumption of foods made with wheat flour and sugar, especially bread and most packaged snack foods (including chips and pretzels).
- Eat more whole grains such as brown rice and bulgur wheat, in which the grain is intact or in a few large pieces. These are preferable to whole wheat flour products, which have roughly the same glycemic index as white flour products.
- Eat more beans, winter squashes, and sweet potatoes.
- Cook pasta al dente and eat it in moderation.
- Avoid products made with high fructose corn syrup.

**Fat**

- On a 2,000-calorie-a-day diet, 600 calories can come from fat - that is, about 67 grams. This should be in a ratio of 1:2:1 of saturated to monounsaturated to polyunsaturated fat.
- Reduce your intake of saturated fat by eating less butter, cream, high-fat cheese, unskinned chicken and fatty meats, and products made with palm kernel oil.
- Use extra-virgin olive oil as a main cooking oil. If you want a neutral tasting oil, use expeller-pressed, organic canola oil. Organic, high-oleic, expeller pressed versions of sunflower and safflower oil are also acceptable.
- Avoid regular safflower and sunflower oils, corn oil, cottonseed oil, and mixed vegetable oils.
- Strictly avoid margarine, vegetable shortening, and all products listing them as ingredients. Strictly avoid all products made with partially hydrogenated oils of any kind. Include in your diet avocados and nuts, especially walnuts, cashews, almonds, and nut butters made from these nuts.
- For omega-3 fatty acids, eat salmon (preferably fresh or frozen wild or canned sockeye), sardines packed in water or olive oil, herring, and black cod (sablefish, butterfish); omega-3 fortified eggs; hemp seeds and flaxseeds (preferably freshly ground); or take a fish oil supplement (look for products that provide both EPA and DHA, in a convenient daily dosage of two to three grams).

**Protein**

- On a 2,000-calorie-a-day diet, your daily intake of protein should be between 80 and 120 grams. Eat less protein if you have liver or kidney problems, allergies, or autoimmune disease.
- Decrease your consumption of animal protein except for fish and high quality natural cheese and yogurt.
Eat more vegetable protein, especially from beans in general and soybeans in particular. Become familiar with the range of whole-soy foods available and find ones you like.

Fiber

Try to eat 40 grams of fiber a day. You can achieve this by increasing your consumption of fruit, especially berries, vegetables (especially beans), and whole grains.

Ready-made cereals can be good fiber sources, but read labels to make sure they give you at least 4 and preferably 5 grams of bran per one-ounce serving.

Phytonutrients

To get maximum natural protection against age-related diseases (including cardiovascular disease, cancer, and neurodegenerative disease) as well as against environmental toxicity, eat a variety of fruits, vegetables and mushrooms.

Choose fruits and vegetables from all parts of the color spectrum, especially berries, tomatoes, orange and yellow fruits, and dark leafy greens.

Choose organic produce whenever possible. Learn which conventionally grown crops are most likely to carry pesticide residues and avoid them.

Eat cruciferous (cabbage-family) vegetables regularly.

Include soy foods in your diet.

Drink tea instead of coffee, especially good quality white, green or oolong tea.

If you drink alcohol, use red wine preferentially.

Enjoy plain dark chocolate in moderation (with a minimum cocoa content of 70 percent).

Vitamins and Minerals

The best way to obtain all of your daily vitamins, minerals, and micronutrients is by eating a diet high in fresh foods with an abundance of fruits and vegetables. In addition, supplement your diet with the following antioxidant cocktail:

- Vitamin C, 200 milligrams a day.
- Vitamin E, 400 IU of natural mixed tocopherols (d-alpha-tocopherol with other tocopherols, or, better, a minimum of 80 milligrams of natural mixed tocopherols and tocotrienols).
- Selenium, 200 micrograms of an organic (yeast-bound) form.
- Mixed carotenoids, 10,000-15,000 IU daily.
- The antioxidants can be most conveniently taken as part of a daily multivitamin/multimineral supplement that also provides at least 400 micrograms of folic acid and 2,000 IU of vitamin D. It should contain no iron (unless you are a female and having regular menstrual periods) and no preformed vitamin A (retinol). Take these supplements with your largest meal.
- Women should take supplemental calcium, preferably as calcium citrate, 500-700 milligrams a day, depending on their dietary intake of this mineral. Men should avoid supplemental calcium.

Other Dietary Supplements

- If you are not eating oily fish at least twice a week, take supplemental fish oil, in capsule or liquid form (two to three grams a day of a product containing both EPA and DHA). Look for molecularly distilled products certified to be free of heavy metals and other contaminants.
- Talk to your doctor about going on low-dose aspirin therapy, one or two baby aspirins a day (81 or 162 milligrams).
- If you are not regularly eating ginger and turmeric, consider taking these in supplemental form.
- Add coenzyme Q10 (CoQ10) to your daily regimen: 60-100 milligrams of a softgel form taken with your largest meal.
- If you are prone to metabolic syndrome, take alpha-lipoic acid, 100 to 400 milligrams a day.
Water

- Drink pure water, or drinks that are mostly water (tea, very diluted fruit juice, sparkling water with lemon) throughout the day.
- Use bottled water or get a home water purifier if your tap water tastes of chlorine or other contaminants, or if you live in an area where the water is known or suspected to be contaminated.

SIMPLY THE EASIEST METHOD TO DEAL WITH INFLAMMATORY PAIN!

The Health Benefits of Onions

According to Arthritis Today onions have components or flavonoids that fight inflammation in the joints of arthritis sufferers. One in particular, quercetin, “inhibits inflammation causing leukotriens, prostaglandins and histamines in Osteoarthritis and Rheumatoid Arthritis”. In English, quercetin can reduce inflammation. A few extra benefits of quercetin include: lowering bad cholesterol, reducing heart disease and help slow the progression of cancer.

For arthritis sufferers bone loss is of major concern. Onions have a flavonoid that acts much like Fosamax, a bone strengthener, known as GPCS (gamma-L-glutamyl-trans-S-1-propenyl-L-cystein sulfoxide). Fosamax is a very successful drug “however, the beneficial effects gradually disappear when the drug is discontinued”. Unless you want to spend the rest of your life using this drug, it is not a viable solution to maintaining bone density. One must also consider the side effects of such a drug. One contradicting side effect of the drug is that is may cause bone and joint pain. Arthritis sufferers have enough pain to deal with, why use a drug which could continue or increase it? Like most prescribed medications, the lists of side effects are not pleasant; ulcers, nausea, rashes and acid backup are just a few.

Those subjected to routine cortisone injections may also experience a reversal in bone loss and damage with regular meals that include onions. Knowing this, taking a few minutes to slice up an onion to add to your meal doesn’t sound like bad idea.

With low calories and very little fat, onions are a healthy addition to any meal or snack. They are equally healthful raw or cooked. One catch though, not all onions are created equal. A study conducted at the Cornell University in Ithaca showed that some onions have better disease fighting chemicals then others. For example, shallots and yellow or red onions are the most beneficial where as white and sweet onions scored lowest.

Depending on personal taste onions can be added to most meals. Slice some raw onion for a sandwich or salad, or chop and cook them up!

Here is a more thorough explanation and recommendations:
According to the Slone Survey, a study of prescription and nonprescription drug use by Americans, 81% of American adults took medication at least on a weekly basis. Many Americans took more than one medication, and 7% took five or more. Among these medications, the top three drugs were all painkillers – acetaminophen (Tylenol and others), ibuprofen (Advil, Motrin, and others), and aspirin.

The majority of these Americans suffer from common and often chronic conditions such as headache, back pain, and arthritis, or musculoskeletal injuries. In 43% of American households, at least one family member suffers from a chronic pain syndrome. The cost of these conditions is staggering, including not only the medications, but also doctors’ visits, diagnostic tests, the cost of therapies such as physical therapy or chiropractic care, as well as the loss of time and productivity associated with chronic pain.

Side effects and complications from taking these medications are also substantial. Anti-inflammatory drug use results in more than 100,000 hospitalizations and 10,000 to 20,000 deaths in the United States each year. Twenty percent of long-term anti-inflammatory medication users develop stomach ulcers. The number one over-the-counter drug, acetaminophen (Tylenol, Tempra, Pandadol and others), is one of the chief causes of liver failure requiring liver transplant in Great Britain and the U.S. Newer prescription anti-inflammatories such as Celebrex and Vioxx have been associated with increased rates of high blood pressure and even heart attacks.

It seems that people suffering from chronic pain are caught in a bind; either live with the pain, or risk serious complications from taking medications. But new research is providing hope and effective alternatives to chronic medication use. This research is beginning to uncover the basic mechanisms of inflammation and pain in the body, and how we can change this process without medications.

The cycle of pain and inflammation in the body is related to many chemicals produced by our cells. These chemicals include certain enzymes and specific fatty acids. Enzymes are complex protein molecules that act as catalysts, or controllers of the chemical reactions in our bodies. Fatty acids come from fat; there are many different types of fatty acids in our bodies. The levels of different fatty acids in our bodies depend largely on our diet. Because fatty acids are directly related to pain and inflammation, our diet can play a substantial role in the amount of pain and inflammation we experience. There are also specific foods that affect the activity of enzymes involved in pain and inflammation.

The chief fatty acid responsible for inflammation is one called arachidonic acid. A diet rich in arachidonic acid contributes to the cycle of pain and inflammation. Foods that are rich in arachidonic acid include animal meats, egg yolks, and shellfish. One step in stopping inflammation is reducing dietary intake of these foods.

But arachidonic acid (AA) can also be synthesized or produced by our bodies. To reduce the production of AA in our bodies we can increase our intake of “anti-inflammatory fats”
such as EPA (eicosapentanoic acid) from fish, and ALA (alpha-linoleic acid) from sources including flax, pumpkin seeds, walnuts and soybeans.

Research has also shown that certain foods and spices can block the enzymes that fuel the process of pain and inflammation. These anti-inflammatory foods and spices include ginger, cayenne, turmeric, garlic & onion, rosemary, and herbs such as Boswellia (an Ayurvedic herb), wintergreen, licorice root, and black willow. Additional nutrients including Vitamin E and Quercetin (a natural anti-inflammatory found in foods such as citrus fruits, apples, onions, parsley, tea, and red wine) also inhibit enzymes that trigger inflammation.

Just as anti-inflammatory foods can have a profound effect on the cycle of pain and inflammation, so does our immune system. Over one-third of our entire immune system is located in the gastrointestinal tract. Reducing inflammation throughout the body therefore requires a healthy gastrointestinal tract. Inflammatory bowel diseases such as Crohn’s disease and Ulcerative Colitis are also commonly associated with arthritis. We can support the health of our gastrointestinal tracts by eating a healthy diet with adequate fiber intake, avoiding unnecessary antibiotics that upset the balance of bacteria in the gastrointestinal tract, and avoiding foods we may be sensitive or allergic to.

Several studies have also suggested that wheat (or gluten, a chief protein in wheat) allergy has been associated with some forms of arthritis including rheumatoid arthritis, and that a gluten-free diet can improve arthritis symptoms in rheumatoid arthritis patients. Wheat allergy is one of the top 6 food allergies along with eggs, milk, nuts, soy, and shellfish.

There are many physical therapies that can help tremendously to relieve chronic pain. Studies have repeatedly shown that for chronic knee pain from arthritis, the most beneficial therapy is strengthening of the quadriceps (thigh) muscle. Acupuncture can provide substantial relief of pain from many causes. Regular massage, physical and neuromuscular therapy by trained therapists can also be extremely helpful in reducing chronic musculoskeletal pain.

Finally, there is also increasing evidence supporting the benefits of mind-body techniques such as meditation, biofeedback, hypnosis, guided imagery, yoga, relaxation therapy, Tai Chi and Chi Gong in the management of chronic pain. These techniques can be extremely helpful and are free of adverse side effects.

Here is a summary of recommendations to help improve pain without pills:

- Eliminate or reduce your intake of red meats, egg yolks, and shellfish to reduce your arachidonic acid levels;
- Supplement your diet with healthy sources of the essential omega-3 fatty acids EPA and ALA by increasing your intake of:
  - Fish and fish oils (eicosapentanoic acid)
  - Ground flax seeds or flax oil
  - Pumpkin seeds
- Walnuts
- Soybeans
- Hemp oil
- Increase your intake of anti-inflammatory foods and spices such as:
  - Turmeric (and its derivative, curcumin)
  - Ginger
  - Garlic & onions
  - Cayenne
  - Rosemary
  - Boswellia
  - Citrus fruits
  - Parsley
- Increase your fiber intake from foods such as whole grains, fruits & vegetables, nuts, seeds and legumes;
- Exercise including aerobic and muscle strengthening;
- Practice mind-body techniques:
  - Biofeedback
  - Meditation
  - Yoga
  - Hypnosis
  - Tai Chi and Chi Gong
- Use helpful physical therapies:
  - Acupuncture
  - Neuromuscular therapy
  - Regular massage
  - Physical therapy
- For those persons with persistent pain despite these measures, consider a trial of a food allergy elimination diet under the supervision of your physician or nutritionist.
Colitis or inflammatory colitis is a medical term used to denote the inflammation of the colon, which is a part of the large intestine. Characterized by severe abdominal pain, loss of appetite, cramping and bloating of stomach and frequent diarrhea, inflammatory colitis occurs due to various different reasons. It may occur due to certain auto-immune diseases or due to various chronic disorders that affect the gastro-intestinal system.

Treatment of colitis differs from person to person and is largely dependent on the type of colitis one is suffering from. This is due to the fact that there are numerous different types of colitis, each one affecting the body in its own different way. Diagnosis thus becomes really important in order to treat the condition. Along with conservative medicine, you can also opt for using naturopathic methods of healing colitis.

**Naturopathy to Treat Colitis**

With the rise in the acceptance of alternative medicine and healing techniques, many people are now turning to using these methods to treat their disorders along with the general medicine or even alone. Naturopathy is one such branch of alternative medicine that is based on using the healing powers of your own body to treat disorders. Read on about how you can treat colitis by using naturopathy.
**Correction of Diet**

One of the most important steps in naturopathy treatments, diet correction aims at removing those foods from your diet that increase the severity of the symptoms of the disease and also contribute to the development of that disease.

**Modification of Diet**

As per the cause of your inflammatory colitis is done and total abstinence may also be suggested. High fiber diets are almost always suggested to people trying out naturopathy for treating colitis. **Raw fruits and vegetables are the best source of fiber and vitamins and minerals** and also make a great salad.

![Image of fruits and vegetables]

**Limit your intake of processed and artificial foods** like fizzy drinks, beverages, spicy fast foods loaded with sodium and fats. Smaller frequent meals put a lesser load on your stomach and reduce the chances of bloating and flatulence. **Rehydrate with lots of water** especially during summer. 7-8 glasses of pure water a day is essential to calm an aggravated digestive system.

**Reducing Intake of OTC and Other Drugs**

Certain OTC drugs used erratically cause migraine, liver problems and retard gastrointestinal function. Think twice before popping a pill every time you have a headache. Also, many prescription drugs contribute to lowering the efficiency of the intestines. Talk to your doctor about this before swapping with another drug.

**Herb Power**

The effectiveness of the herbs given to us by Mother Nature is well known. Naturopathy uses these **herbs to reduce inflammation of the intestines and calm the digestive**
system by its antibacterial and cooling properties. Herbs such as ginkgo, licorice, cinnamon, garlic, angelica, grapefruits and many others are used in the treatment of this condition. However, the quantities and intake methods can be determined only by a professional and these herbs should not be taken without professional advise as some of the herbs, if not taken in indicated quantities, may lead to development of many other problems and may even harm other systems of the body.

**Vitamin Boost**

With a boom in the number of multivitamins now available in the market, choosing the right one which treats your condition effectively is often difficult. Consult the physician before choosing from among the many options in the market.

Also, try including omega-3 fatty acids, vitamin B12, L-glutamine, Vitamin C, Vitamin E and many others show different benefits to the body, each of them contributing to the well-being of your gastro-intestinal system.

**Lifestyle Changes**

Another basic of naturopathic treatments, removal of faulty lifestyle habits like excessive alcoholism, stressful life, smoking and other forms of nicotine consumptions, staying up late nights, insufficient sleep etc. These lifestyle habits hamper with the healthy functioning of the body and aggravate the already existing disorders of the body. Also, these lifestyle changes may also lead to many fatal diseases including heart and respiratory disorders.
**Exercise**

Moderate exercise is very beneficial to the body in terms of healthy weight loss, control of blood cholesterol, improved digestive mechanism and circulatory functions. Try your hand at **aerobic exercises and cardio workout**. Yoga as a method of exercise provides dual benefits. It gives physical benefits as well as mental peace. Implement all these practices in your life as a part of your daily regimen is bound to show noticeable benefits in controlling and reducing the symptoms of inflammatory colitis. Also, other basic precautions such as **personal hygiene, boiling the water before drinking** should be adopted as a part of the treatment procedure to attain maximum benefits in all treatment methods.

Appendicitis results from worm infestations of the colon, bacteria or from stagnant and putrefying foods lying in the intestines. Here are some ideas of natural treatment
Please note that the appendix is located in the abdominal cavity or part of the intestine that is located on the right lower abdomen. In the lining of the appendix, there are many cells that serve as the body's defenses. Since the appendix is not in inflammation or infection, then it will be fine. But if there is inflammation, especially infection, it can make the walls of the appendix is leaking, so it invites a dangerous germ. When this happens and if it is not promptly treated, it will make the patient suffer pain and can lead to death.

The main factor causing the inflammation of the appendix is lagging the rest of the food in the appendix and can not be excreted, so the dirt gets hardened and cause inflammation. This is usually caused by the habit of a person who likes to eat high fat foods, too spicy foods, and consume high carbonated soft drinks. Other causes could be due to the constriction in the intestine so that the rest of the food intake can not be out until the occurrence of inflammation by bacteria in the intestines.

Inflammation of the appendix that you experienced, IneyaAllah it can be treated with herbal medicine technique, i.e. a combination of several herbal plants. Some herbs have the efficacy as antiflogistic (anti-inflammation and stop the inflammation process), antipyretics (febrifuge), antiseptic, and detoxicant as follows:

1. Centella or Pegagan (Centella asiatica) = 30 grams.
2. Key Lime leaves (Citrus aurantifolia) = 20 grams.
3. King of Bitters or Sambiloto (Andrographis paniculata) = 20 grams.
4. Field Sowthistle leaves or Tempuyung (Sonchus arvensis) = 20 grams.
5. Roots of Snakeroot or Puie Pandak (Rauvolfia serpentina) = 5 units.
6. Rock sugar = 100 grams.
Centella or Pegagan (Centella asiatica)

Key Lime or Jeruk Nipis (Citrus aurantifolia)

Sambiloto or King of bitter (Andrographis paniculata)
Field Sowthistle or Tempuyung
(Sonchus arvensis L.)

Roots of Snakerooot or Pule Pandak
(Rauvolfia serpentina)
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All the above herbal materials are washed and boiled in 2 liters of water over low heat for about two hours. Media used for boiling the herbal material is preferably made of enamel. Let the water boils the herbs until it remains half. Strain the water and drink this herbal concoction three times a day. The right time to drink this herbal decoction is in a state before a meal and in warm condition. In addition, I also recommend that you use other herbs to speed up the healing process such as green bean decoction that is drunk every morning.

Finally, avoid hard foods which are difficult to digest by the intestine, high fat foods, chili, pepper, foods that produce gas, and you should never drink alcohol. Thus, above are the answer and my advice in treating disorders of the appendix with herbal remedies. I hope you are satisfied and get well soon. ***
Inflammation is a Symptom not a Disease
Inflammation is a Symptom not a Disease
Inflammation is a Symptom not a Disease
Inflammation is a Symptom not a Disease
DETOX

YOUR BODY

BLOOD
- garlic
- beans
- tofu
- cayenne pepper
- ginger root
- broccoli
- brussels sprouts

LIVER
- leafy greens
- carrots
- beef
- tomatoes
- strawberries
- asparagus
- fish
- sweet potato
- beets
- greens
- lemon
- avocados
- citrus fruits
- green tea
- cabbage
- artichokes
- grapes
- cherries
- bell peppers
- onions
- cauliflower
- flax seed oil
- probiotics
- oats
- yoghurt
- beans
- sweet potato
- blueberries
- olives
- olive oil
- fish
- cabbage
- fresh fruits & veggies
- grains
- flax seed

PANCREAS
- leafy greens

KIDNEYS
- leafy greens
- cranberries
- olives
- olive oil
- fish
- cabbage

LYMPH
- leafy greens
- carrots
- beef
- tomatoes
- strawberries
- asparagus
- fish
- sweet potato
- beets
- greens
- lemon
- avocados
- citrus fruits
- green tea
- cabbage
- artichokes
- grapes
- cherries
- bell peppers
- onions
- cauliflower
- flax seed oil
- probiotics
- oats
- yoghurt
- beans
- sweet potato
- blueberries
- olives
- olive oil
- fish
- cabbage
- fresh fruits & veggies
- grains
- flax seed
Avoid The Four White Deaths

Slow Poison
No Real Nutrition Here

THE THREE UNHEALTHY WHITES

WHITE RICE  WHITE FLOUR  WHITE SUGAR
What is Inflammation

Inflammation (Latin, *īnflammō*, "I ignite, set alight") is part of the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. Inflammation is a protective attempt by the organism to remove the injurious stimuli and to initiate the healing process. Inflammation is not a synonym for infection, even in cases where inflammation is caused by infection. Although infection is caused by a microorganism, inflammation is one of the responses of the organism to the pathogen.
However, inflammation is a stereotyped response, and therefore it is considered as a mechanism of innate immunity, as compared to adaptive immunity, which is specific for each pathogen.[2]

Without inflammation, wounds and infections would never heal.[citation needed] Similarly, progressive destruction of the tissue would compromise the survival of the organism. However, chronic inflammation can also lead to a host of diseases, such as hay fever, periodontitis, atherosclerosis, rheumatoid arthritis, and even cancer (e.g., gallbladder carcinoma). It is for that reason that inflammation is normally closely regulated by the body.

Inflammation can be classified as either acute or chronic. Acute inflammation is the initial response of the body to harmful stimuli and is achieved by the increased movement of plasma and leukocytes (especially granulocytes) from the blood into the injured tissues. A cascade of biochemical events propagates and matures the inflammatory response, involving the local vascular system, the immune system, and various cells within the injured tissue. Prolonged inflammation, known as chronic inflammation, leads to a progressive shift in the type of cells present at the site of inflammation and is characterized by simultaneous destruction and healing of the tissue from the inflammatory process.

Causes

- **Burns**, fire or Infrared radiation
- **Chemical irritants**, boiled oil consumption, too much high glycemic foods, synthetic compounds
- **Frostbite**, Wind Burn
- **Toxins**, synthetic food additives, industrial toxins, or auto toxins from inadequate personal detox
- **Infection** by pathogens
- **Physical injury**, blunt or penetrating or from over use
- Immune reactions due to **hypersensitivity**- allergy, auto toxicity
- **Ionizing radiation**- x-ray, UV from sunlight,
- Foreign bodies, including splinters, dirt and debris, silicosis, asbestos,
- Stress- long term or short term
- **Trauma**- Injury
- **Alcohol**

Types

- **Appendicitis**
- **Bursitis**
### Colitis
- Cystitis
- Dermatitis
- Meningitis

### Comparison between acute and chronic inflammation:

<table>
<thead>
<tr>
<th>Causative agent</th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bacterial Pathogens, injured tissues</td>
<td>Persistent acute inflammation due to non-degradable pathogens, viral infection, persistent foreign bodies, or autoimmune reactions</td>
</tr>
<tr>
<td>Major cells involved</td>
<td>neutrophils (primarily), basophils (inflammatory response), and eosinophils (response to helminth worms and parasites), mononuclear cells (monocytes, macrophages)</td>
<td>Mononuclear cells (monocytes, macrophages, lymphocytes, plasma cells), fibroblasts</td>
</tr>
<tr>
<td>Primary mediators</td>
<td>Vasoactive amines, eicosanoids</td>
<td>IFN-γ and other cytokines, growth factors, reactive oxygen species, hydrolytic enzymes</td>
</tr>
<tr>
<td>Onset</td>
<td>Immediate</td>
<td>Delayed</td>
</tr>
<tr>
<td>Duration</td>
<td>Few days</td>
<td>Up to many months, or years</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Resolution, abscess formation, chronic inflammation</td>
<td>Tissue destruction, fibrosis, necrosis</td>
</tr>
</tbody>
</table>

### Cardinal signs

<table>
<thead>
<tr>
<th>The classic signs and symptoms of acute inflammation:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>English</strong></td>
</tr>
<tr>
<td>Redness</td>
</tr>
<tr>
<td>Swelling</td>
</tr>
<tr>
<td>Heat</td>
</tr>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>Loss of function</td>
</tr>
</tbody>
</table>

All the above signs may be observed in specific instances, but no single sign must, as a matter of course, be present. These are the original, or "cardinal signs" of inflammation.

*Functio laesa* is an apocryphal notion, as it is not unique to inflammation and is a characteristic of many disease states.

Acute inflammation is a short-term process, usually appearing within a few minutes or hours and ceasing upon the removal of the injurious stimulus. It is characterized by five cardinal signs:

The acronym that may be used for this is "PRISH" for Pain, Redness, Immobility (loss of function), Swelling and Heat.

The traditional names for signs of inflammation come from Latin:

- **Dolor** (pain)
- **Calor** (heat)
- **Rubor** (redness)
- **Tumor** (swelling)
- **Functio laesa** (loss of function)\[2\]

The first four (classical signs) were described by **Celsius** (ca 30 BC–38 AD),\[3\] while *loss of function* was added later by **Galen**\[9\] even though the attribution is disputed and the origination of the fifth sign has also been ascribed to **Thomas Sydenham**\[10\] and **Virchow**\[5\].

Redness and heat are due to increased blood flow at body core temperature to the inflamed site; swelling is caused by accumulation of fluid; **pain** is due to release of chemicals that stimulate nerve endings. Loss of function has multiple causes.\[6\]

These five signs appear when acute inflammation occurs on the body’s surface, whereas acute inflammation of internal organs may not result in the full set. Pain only happens where the appropriate sensory nerve endings exist in the inflamed area—e.g., acute inflammation of the lung (**pneumonia**) does not cause pain unless the inflammation involves the **parietal pleura**, which does have **pain-sensitive nerve endings**.\[6\]
Micrograph showing acute inflammation of the prostate gland with the characteristic neutrophilic infiltrate. H&E stain.

The process of acute inflammation is initiated by cells already present in all tissues, mainly resident macrophages, dendritic cells, histiocytes, Kupffer cells and mastocytes. These cells present on their surfaces certain receptors named pattern recognition receptors (PRRs), which recognize molecules that are broadly shared by pathogens but distinguishable from host molecules, collectively referred to as pathogen-associated molecular patterns (PAMPs). At the onset of an infection, burn, or other injuries, these cells undergo activation (one of their PRRs recognize a PAMP) and release inflammatory mediators responsible for the clinical signs of inflammation. Vasodilation and its resulting increased blood flow causes the redness (rubor) and increased heat (calor). Increased permeability of the blood vessels results in an exudation (leakage) of plasma proteins and fluid into the tissue (edema), which manifests itself as swelling (tumor). Some of the released mediators such as bradykinin increase the sensitivity to pain (hyperalgesia, dolor). The mediator molecules also alter the blood vessels to permit the migration of leukocytes, mainly neutrophils, outside of the blood vessels (extravasation) into the tissue. The neutrophils migrate along a chemotactic gradient created by the local cells to reach the site of injury.\(^5\) The loss of function (functio laesa) is probably the result of a neurological reflex in response to pain.

In addition to cell-derived mediators, several acellular biochemical cascade systems consisting of preformed plasma proteins act in parallel to initiate and propagate the inflammatory response. These include the complement system activated by bacteria, and the coagulation and fibrinolysis systems activated by necrosis, e.g. a burn or a trauma.\(^6\)

The acute inflammatory response requires constant stimulation to be sustained. Inflammatory mediators have short half lives and are quickly degraded in the tissue. Hence, acute inflammation ceases once the stimulus has been removed.\(^5\)

**Exudative component**

The exudative component involves the movement of plasma fluid, containing important proteins such as fibrin and immunoglobulins (antibodies), into inflamed tissue. This movement is achieved via the chemically induced dilation and increased permeability of blood vessels, which results in a net loss of blood plasma. The
increased collection of fluid into the tissue causes it to swell (edema). This extravasated fluid is funneled by lymphatics to the regional lymph nodes, flushing bacteria along to start the recognition and attack phase of the adaptive immune system.

**Vascular changes**

Acute inflammation is characterized by marked vascular changes, including vasodilation, increased permeability and the slowing of blood flow, which are induced by the actions of various inflammatory mediators. Vasodilation occurs first at the arteriole level, progressing to the capillary level, and brings about a net increase in the amount of blood present, causing the redness and heat of inflammation. Increased permeability of the vessels results in the movement of plasma into the tissues, with resultant stasis due to the increase in the concentration of the cells within blood - a condition characterized by enlarged vessels packed with cells. Stasis allows leukocytes to marginate (move) along the endothelium, a process critical to their recruitment into the tissues. Normal flowing blood prevents this, as the shearing force along the periphery of the vessels moves cells in the blood into the middle of the vessel.

**Plasma cascade systems**

- The complement system, when activated, creates a cascade of chemical reactions that promotes opsonization, chemotaxis, and agglutination, and produces the MAC.
- The kinin system generates proteins capable of sustaining vasodilation and other physical inflammatory effects.
- The coagulation system or clotting cascade which forms a protective protein mesh over sites of injury.
- The fibrinolysis system, which acts in opposition to the coagulation system, to counterbalance clotting and generate several other inflammatory mediators.

**Plasma derived mediators**

*non-exhaustive list*

<table>
<thead>
<tr>
<th>Name</th>
<th>Produced by</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradykinin</td>
<td>Kinin system</td>
<td>A vasoactive protein which is able to induce vasodilation, increase vascular permeability, cause smooth muscle contraction, and induce pain.</td>
</tr>
<tr>
<td>C3</td>
<td>Complement system</td>
<td>Cleaves to produce C3a and C3b. C3a stimulates histamine release by mast cells, thereby producing vasodilation. C3b is able to bind to bacterial cell walls and act as an opsonin, which marks the invader as a target for phagocytosis.</td>
</tr>
<tr>
<td><strong>C5a</strong></td>
<td><strong>Complement system</strong></td>
<td>Stimulates histamine release by mast cells, thereby producing vasodilation. It is also able to act as a chemoattractant to direct cells via chemotaxis to the site of inflammation.</td>
</tr>
<tr>
<td><strong>Factor XII (Hageman Factor)</strong></td>
<td><strong>Liver</strong></td>
<td>A protein which circulates inactively, until activated by collagen, platelets, or exposed basement membranes via conformational change. When activated, it in turn is able to activate three plasma systems involved in inflammation: the kinin system, fibrinolysis system, and coagulation system.</td>
</tr>
<tr>
<td><strong>Membrane attack complex</strong></td>
<td><strong>Complement system</strong></td>
<td>A complex of the complement proteins C5b, C6, C7, C8, and multiple units of C9. The combination and activation of this range of complement proteins forms the membrane attack complex, which is able to insert into bacterial cell walls and causes cell lysis with ensuing death.</td>
</tr>
<tr>
<td><strong>Plasmin</strong></td>
<td><strong>Fibrinolysis system</strong></td>
<td>Able to break down fibrin clots, cleave complement protein C3, and activate Factor XII.</td>
</tr>
<tr>
<td><strong>Thrombin</strong></td>
<td><strong>Coagulation system</strong></td>
<td>Cleaves the soluble plasma protein fibrinogen to produce insoluble fibrin, which aggregates to form a blood clot. Thrombin can also bind to cells via the PAR1 receptor to trigger several other inflammatory responses, such as production of chemokines and nitric oxide.</td>
</tr>
</tbody>
</table>

**Cellular component**

The cellular component involves leukocytes, which normally reside in blood and must move into the inflamed tissue via extravasation to aid in inflammation. Some act as phagocytes, ingesting bacteria, viruses, and cellular debris. Others release enzymatic granules which damage pathogenic invaders. Leukocytes also release inflammatory mediators which develop and maintain the inflammatory response. Generally speaking, acute inflammation is mediated by granulocytes, while chronic inflammation is mediated by mononuclear cells such as monocytes and lymphocytes.

**Leukocyte extravasation**
Neutrophils migrate from blood vessels to the inflamed tissue via chemotaxis, where they remove pathogens through phagocytosis and degranulation.

Main article: Leukocyte extravasation

Various leukocytes are critically involved in the initiation and maintenance of inflammation. These cells must be able to get to the site of injury from their usual location in the blood, therefore mechanisms exist to recruit and direct leukocytes to the appropriate place. The process of leukocyte movement from the blood to the tissues through the blood vessels is known as extravasation, and can be divided up into a number of broad steps:

1. **Leukocyte localisation and recruitment to the endothelium local to the site of inflammation – involving margination and adhesion to the endothelial cells:** Recruitment of leukocytes is receptor-mediated. The products of inflammation, such as histamine, promote the immediate expression of P-selectin on endothelial cell surfaces. This receptor binds weakly to carbohydrate ligands on leukocyte surfaces and causes them to “roll” along the endothelial surface as bonds are made and broken. Cytokines from injured cells induce the expression of E-selectin on endothelial cells, which functions similarly to P-selectin. Cytokines also induce the expression of immunoglobulin ligands such as ICAM-1 and VCAM-1 on endothelial cells, which further slow leukocytes down. These weakly bound leukocytes are free to detach if not activated by chemokines produced in injured tissue. Activation increases the affinity of bound integrin receptors for immunoglobulin ligands on the endothelial cell surface, firmly binding the leukocytes to the endothelium.

2. **Migration across the endothelium, known as transmigration, via the process of diapedesis:** Chemokine gradients stimulate the adhered leukocytes to move between endothelial cells and pass the basement membrane into the tissues.
3. **Movement of leukocytes within the tissue via chemotaxis:** Leukocytes reaching the tissue interstitium bind to **extracellular matrix** proteins via expressed integrins and **CD44** to prevent their loss from the site. **Chemoattractants** cause the leukocytes to move along a chemotactic gradient towards the source of inflammation.

### Cell derived mediators

*non-exhaustive list*

<table>
<thead>
<tr>
<th>Name</th>
<th>Type</th>
<th>Source</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lysosome granules</td>
<td>Enzymes</td>
<td>Granulocytes</td>
<td>These cells contain a large variety of enzymes which perform a number of functions. Granules can be classified as either specific or azurophilic depending upon the contents, and are able to break down a number of substances, some of which may be plasma-derived proteins which allow these enzymes to act as inflammatory mediators.</td>
</tr>
<tr>
<td>Histamine</td>
<td>Vasoactive amine</td>
<td>Mast cells, basophils, platelets</td>
<td>Stored in preformed granules, histamine is released in response to a number of stimuli. It causes arteriole dilation and increased venous permeability.</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>Cytokine</td>
<td>T-cells, NK cells</td>
<td>Antiviral, immunoregulatory, and anti-tumour properties. This interferon was originally called macrophage-activating factor, and is especially important in the maintenance of chronic inflammation.</td>
</tr>
<tr>
<td>IL-8</td>
<td>Chemokine</td>
<td>Primarily macrophages</td>
<td>Activation and chemoattraction of neutrophils, with a weak effect on monocytes and eosinophils.</td>
</tr>
<tr>
<td>Leukotriene B4</td>
<td>Eicosanoid</td>
<td>Leukocytes</td>
<td>Able to mediate leukocyte adhesion and activation, allowing them to bind to the endothelium and migrate across it. In neutrophils, it is also a potent chemoattractant, and is able to induce the formation of reactive oxygen species and the release of lysosome enzymes by these cells.</td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>Soluble gas</td>
<td>Macrophages, endothelial cells, some neurons</td>
<td>Potent vasodilator, relaxes smooth muscle, reduces platelet aggregation, aids in leukocyte recruitment, direct antimicrobial activity in high concentrations.</td>
</tr>
</tbody>
</table>
**Prostaglandins** | **Eicosanoid** | **Mast cells** | A group of lipids which can cause vasodilation, fever, and pain.
---|---|---|---
**TNF-α and IL-1** | **Cytokines** | Primarily macrophages | Both affect a wide variety of cells to induce many similar inflammatory reactions: fever, production of cytokines, endothelial gene regulation, chemotaxis, leukocyte adherence, activation of fibroblasts. Responsible for the systemic effects of inflammation, such as loss of appetite and increased heart rate.

### Morphologic patterns

Specific patterns of acute and chronic inflammation are seen during particular situations that arise in the body, such as when inflammation occurs on an epithelial surface, or pyogenic bacteria are involved.

- **Granulomatous inflammation:** Characterised by the formation of granulomas, they are the result of a limited but diverse number of diseases, which include among others tuberculosis, leprosy, sarcoidosis, and syphilis.
- **Fibrinous inflammation:** Inflammation resulting in a large increase in vascular permeability allows fibrin to pass through the blood vessels. If an appropriate procoagulative stimulus is present, such as cancer cells, a fibrinous exudate is deposited. This is commonly seen in serous cavities, where the conversion of fibrinous exudate into a scar can occur between serous membranes, limiting their function.
- **Purulent inflammation:** Inflammation resulting in large amount of pus, which consists of neutrophils, dead cells, and fluid. Infection by pyogenic bacteria such as staphylococci is characteristic of this kind of inflammation. Large, localised collections of pus enclosed by surrounding tissues are called abscesses.
- **Serous inflammation:** Characterised by the copious effusion of non-viscous serous fluid, commonly produced by mesothelial cells of serous membranes, but may be derived from blood plasma. Skin blisters exemplify this pattern of inflammation.
- **Ulcerative inflammation:** Inflammation occurring near an epithelium can result in the necrotic loss of tissue from the surface, exposing lower layers. The subsequent excavation in the epithelium is known as an ulcer.

### Inflammatory disorders

Inflammatory abnormalities are a large group of disorders which underlie a vast variety of human diseases. The immune system is often involved with inflammatory disorders, demonstrated in both allergic reactions and some myopathies, with many immune system disorders resulting in abnormal inflammation. Non-immune diseases with etiological origins in inflammatory processes include cancer, atherosclerosis, and ischaemic heart disease.
A large variety of proteins are involved in inflammation, and any one of them is open to a genetic mutation which impairs or otherwise dysregulates the normal function and expression of that protein.

Examples of disorders associated with inflammation include:

- Acne vulgaris
- Asthma
- Autoimmune diseases
- Celiac disease
- Chronic prostatitis
- Glomerulonephritis
- Hypersensitivities
- Inflammatory bowel diseases
- Pelvic inflammatory disease
- Reperfusion injury
- Rheumatoid arthritis
- Sarcoidosis
- Transplant rejection
- Vasculitis
- Interstitial cystitis

**Atherosclerosis**

*Main article: Atherosclerosis*

Atherosclerosis, formerly considered a bland lipid storage disease, actually involves an ongoing inflammatory response. Recent advances in basic science have established a fundamental role for inflammation in mediating all stages of this disease from initiation through progression and, ultimately, the thrombotic complications of atherosclerosis. These new findings provide important links between risk factors and the mechanisms of atherogenesis. Clinical studies have shown that this emerging biology of inflammation in atherosclerosis applies directly to human patients. Elevation in markers of inflammation predicts outcomes of patients with acute coronary syndromes, independently of myocardial damage. In addition, low-grade chronic inflammation, as indicated by levels of the inflammatory marker C-reactive protein, prospectively defines risk of atherosclerotic complications, thus adding to prognostic information provided by traditional risk factors. Moreover, certain treatments that reduce coronary risk also limit inflammation. In the case of lipid lowering with statins, this anti-inflammatory effect does not appear to correlate with reduction in low-density lipoprotein levels. These new insights into inflammation in atherosclerosis not only increase our understanding of this disease, but
also have practical clinical applications in risk stratification and targeting of therapy for this scourge of growing worldwide importance. Clinical Cardiology: New Frontiers (Inflammation and Atherosclerosis)

Allergies

An allergic reaction, formally known as type 1 hypersensitivity, is the result of an inappropriate immune response triggering inflammation. A common example is hay fever, which is caused by a hypersensitive response by skin mast cells to allergens. Pre-sensitised mast cells respond by degranulating, releasing vasoactive chemicals such as histamine. These chemicals propagate an excessive inflammatory response characterised by blood vessel dilation, production of pro-inflammatory molecules, cytokine release, and recruitment of leukocytes. Severe inflammatory response may mature into a systemic response known as anaphylaxis.

Other hypersensitivity reactions (type 2 and type 3) are mediated by antibody reactions and induce inflammation by attracting leukocytes which damage surrounding tissue.

Myopathies

Inflammatory myopathies are caused by the immune system inappropriately attacking components of muscle, leading to signs of muscle inflammation. They may occur in conjunction with other immune disorders, such as systemic sclerosis, and include dermatomyositis, polymyositis, and inclusion body myositis.

Leukocyte defects

Due to the central role of leukocytes in the development and propagation of inflammation, defects in leukocyte function often result in a decreased capacity for inflammatory defense with subsequent vulnerability to infection. Dysfunctional leukocytes may be unable to correctly bind to blood vessels due to surface receptor mutations, digest bacteria (Chediak-Higashi syndrome), or produce microbicides (chronic granulomatous disease). Additionally, diseases affecting the bone marrow may result in abnormal or few leukocytes.

Pharmacological

Certain drugs or exogenic chemical compounds are known to affect inflammation. Vitamin A deficiency causes an increase in inflammatory responses, and anti-inflammatory drugs work specifically by inhibiting normal inflammatory components. Certain illicit drugs such as cocaine and ecstasy may exert some of their detrimental effects by activating transcription factors intimately involved with inflammation (e.g. NF-κB).

Cancer

Inflammation orchestrates the microenvironment around tumours, contributing to proliferation, survival and migration. Cancer cells use selectins, chemokines and their receptors for invasion, migration and metastasis. On the other hand, many cells of the immune system contribute to cancer immunology, suppressing cancer. Molecular intersection between receptors of steroid hormones, which have important
effects on cellular development, and transcription factors that play key roles in inflammation, such as NF-kB, may mediate some of the most critical effects of inflammatory stimuli on cancer cells.[16]
Resolution of inflammation

The inflammatory response must be actively terminated when no longer needed to prevent unnecessary "bystander" damage to tissues. Failure to do so results in chronic inflammation, and cellular destruction. Resolution of inflammation occurs by different mechanisms in different tissues. Mechanisms which serve to terminate inflammation include:

- Short half-life of inflammatory mediators in vivo.
- Production and release of Transforming growth factor (TGF) beta from macrophages.
- Production and release of Interleukin 10 (IL-10).
- Production of anti-inflammatory lipoxins.
- Downregulation of pro-inflammatory molecules, such as leukotrienes.
- Upregulation of anti-inflammatory molecules such as the Interleukin 1 receptor antagonist or the soluble tumor necrosis factor receptor (TNFR).
- Apoptosis of pro-inflammatory cells.
- Desensitization of receptors.
- Increased survival of cells in regions of inflammation due to their interaction with the extracellular matrix (ECM).
- Downregulation of receptor activity by high concentrations of ligands.
- Cleavage of chemokines by matrix metalloproteinases (MMPs) might lead to production of anti-inflammatory factors.
- Production of resolvins, protectins or maresins.

Acute inflammation normally resolves by mechanisms that have remained somewhat elusive. Emerging evidence now suggests that an active, coordinated program of resolution initiates in the first few hours after an inflammatory response begins. After entering tissues, granulocytes promote the switch of arachidonic acid–derived prostaglandins and leukotrienes to lipoxins, which initiate the termination sequence. Neutrophil recruitment thus ceases and programmed death by apoptosis is engaged. These events coincide with the biosynthesis, from omega-3 polyunsaturated fatty acids, of resolvins and protectins, which critically shorten the period of neutrophil infiltration by initiating apoptosis. Consequently, apoptotic neutrophils undergo phagocytosis by macrophages, leading to neutrophil clearance and release of anti-inflammatory and reparative cytokines such as transforming growth factor-β1. The anti-inflammatory program ends with the departure of macrophages through the lymphatics.

—Charles Serhan
Systemic effects

An *infectious organism* can escape the confines of the immediate tissue via the *circulatory system* or *lymphatic system*, where it may spread to other parts of the body. If an organism is not contained by the actions of acute inflammation it may gain access to the lymphatic system via nearby *lymph vessels*. An infection of the lymph vessels is known as *lymphangitis*, and infection of a lymph node is known as *lymphadenitis*. A pathogen can gain access to the bloodstream through lymphatic drainage into the circulatory system.

When inflammation overwhelms the host, *systemic inflammatory response syndrome* is diagnosed. When it is due to *infection*, the term *sepsis* is applied, with the terms *bacteremia* being applied specifically for bacterial sepsis and *viremia* specifically to viral sepsis. *Vasodilation* and organ dysfunction are serious problems associated with widespread infection that may lead to *septic shock* and death.

**Acute-phase proteins**

Inflammation also induces high systemic levels of *acute-phase proteins*. In acute inflammation, these proteins prove beneficial, however in chronic inflammation they can contribute to *amyloidosis*. These proteins...
include C-reactive protein, serum amyloid A, and serum amyloid P, which cause a range of systemic effects including:\[5\]:

- Fever
- Increased blood pressure
- Decreased sweating
- Malaise
- Loss of appetite
- Somnolence

**Leukocyte numbers**

Inflammation often affects the numbers of leukocytes present in the body:

- **Leukocytosis** is often seen during inflammation induced by infection, where it results in a large increase in the amount of leukocytes in the blood, especially immature cells. Leukocyte numbers usually increase to between 15 000 and 20 000 cells per microliter, but extreme cases can see it approach 100 000 cells per microliter.\[5\] Bacterial infection usually results in an increase of neutrophils, creating neutrophilia, whereas diseases such as asthma, hay fever, and parasite infestation result in an increase in eosinophils, creating eosinophilia.\[5\]

- **Leukopenia** can be induced by certain infections and diseases, including viral infection, Rickettsia infection, some protozoa, tuberculosis, and some cancers.\[5\]
Systemic inflammation and obesity

With the discovery of interleukins (IL), the concept of systemic inflammation developed. Although the processes involved are identical to tissue inflammation, systemic inflammation is not confined to a particular tissue but involves the endothelium and other organ systems.

Chronic inflammation is widely observed in obesity. The obese commonly have many elevated markers of inflammation, including:

- IL-6 (Interleukin-6)
- IL-8 (Interleukin-8)
- IL-18 (Interleukin-18)
- **TNF-α (Tumor necrosis factor-alpha)**[^31][^32]
- **CRP (C-reactive protein)**[^31][^32]
- **Insulin[^31][^32]***
- **Blood glucose[^31][^32]**
- **Leptin[^31][^32]**

Low-grade chronic inflammation is characterized by a two- to threefold increase in the systemic concentrations of cytokines such as TNF-α, IL-6, and CRP.[^33] Waist circumference correlates significantly with systemic inflammatory response.[^44] A predominant factor in this correlation is due to the autoimmune response triggered by adiposity, whereby immune cells may mistake fatty deposits for intruders. The body attacks fat similar to bacteria and fungi. When expanded fat cells leak or break open, macrophages mobilize to clean up and embed into the adipose tissue. Then macrophages release inflammatory chemicals, including TNF-α and (IL-6). TNF’s primary role is to regulate the immune cells and induce inflammation. White blood cells then assist by releasing more cytokines. This link between adiposity and inflammation has been shown to produce 10-35% of IL-6 in a resting individual, and this production increases with increasing adiposity.[^45]

During clinical studies, inflammatory-related molecule levels were reduced and increased levels of anti-inflammatory molecules were seen within four weeks after patients began a very low calorie diet.[^46] The association of systemic inflammation with insulin resistance and atherosclerosis is the subject of intense research.[^37]

In the obese mouse models, inflammation and macrophage-specific genes are upregulated in white adipose tissue (WAT). There were also signs of dramatic increase in circulating insulin level, adipocyte lipolysis and formation of multinucleate giant cells.[^48] The fat-derived protein called angiopoietin-like protein 2 (Angptl2) elevates in fat tissues. Higher than normal Angptl2 level in fat tissues develop inflammation as well as insulin and leptin resistance. Stored fat secretes leptin to signal satiety. Leptin resistance plays a role in the process where appetite overrules the message of satiety. Angptl2 then starts an inflammatory cascade causing blood vessels to remodel and attract macrophages. Angptl2 is an adipocyte-derived inflammatory mediator linking obesity to systemic insulin resistance.[^citation needed] It is possible that, as an inflammatory marker, leptin responds specifically to adipose-derived inflammatory cytokines.

**C-reactive protein** (CRP) is generated at a higher level in obese people. It raises when there is inflammation throughout the body. Mild elevation in CRP increase risk of heart attacks, strokes, high blood pressure, muscle weakness and fragility.[^citation needed]
Systemic inflammation and overeating

Hyperglycemia from high glycemic foods induces IL-6 production from endothelial cells and macrophages. \(^{[39]}\) Meals high in saturated fat, as well as meals high in calories have been associated with increases in inflammatory markers. \(^{[40][41]}\) While the inflammatory responses are acute and arise in response to overeating, the response may become chronic if the overeating is chronic.

Outcomes

Scars present on the skin, evidence of fibrosis and healing of a wound
The outcome in a particular circumstance will be determined by the tissue in which the injury has occurred and the injurious agent that is causing it. Here are the possible outcomes to inflammation:

1. **Resolution**
   The complete restoration of the inflamed tissue back to a normal status. Inflammatory measures such as vasodilation, chemical production, and leukocyte infiltration cease, and damaged parenchymal cells regenerate. In situations where limited or short lived inflammation has occurred this is usually the outcome.

2. **Fibrosis**
   Large amounts of tissue destruction, or damage in tissues unable to regenerate, can not be regenerated completely by the body. Fibrous scarring occurs in these areas of damage, forming a scar composed primarily of collagen. The scar will not contain any specialized structures, such as parenchymal cells, hence functional impairment may occur.

3. **Abscess Formation**
   A cavity is formed containing pus, an opaque liquid containing dead white blood cells and bacteria with general debris from destroyed cells.

4. **Chronic inflammation**
   In acute inflammation, if the injurious agent persists then chronic inflammation will ensue. This process, marked by inflammation lasting many days, months or even years, may lead to the formation of a chronic wound. Chronic inflammation is characterised by the dominating presence of macrophages in the injured tissue. These cells are powerful defensive agents of the body, but the toxins they release (including reactive oxygen species) are injurious to the organism's own tissues as well as invading agents. Consequently, chronic inflammation is almost always accompanied by tissue destruction.

**Examples**

Inflammation is usually indicated by adding the suffix "-itis", as shown below. However, some conditions such as asthma and pneumonia do not follow this convention. More examples are available at list of types of inflammation.

* Acute appendicitis
Exercise and Inflammation

**Exercise-induced acute inflammation**

Acute inflammation of the muscle cells, as understood in exercise physiology,\(^\text{[43]}\) can result after induced eccentric and concentric muscle training. Participation in eccentric training and conditioning, including resistance training and activities that emphasize eccentric lengthening of the muscle including downhill running on a moderate to high incline can result in considerable soreness within 24 to 48 hours, even though blood lactate levels, previously thought to cause muscle soreness, were much higher with level running. This delayed onset muscle soreness (DOMS) results from structural damage to the contractile filaments and Z-disks, which has been noted especially in marathon runners whose muscle fibers revealed remarkable damage to the muscle fibers after both training and marathon competition. The onset and timing of this gradient damage to the muscle parallels the degree of muscle soreness experienced by the runners.

Z-disks are the point of contact for the contractile proteins. They provide structural support for the transmission of force when the muscle fibers are activated to shorten. However, in marathon runners and those who
subscribe to the overload principle to enhance their muscles, show moderate Z-disk streaming and major disruption of the thick and thin filaments in parallel groups of sarcomeres as a result of the force of eccentric actions or stretching of the tightened muscle fibers.

This disruption of the muscle fibers triggers white blood cells to increase following the induced muscle soreness, leading to the inflammatory response observation from the induced muscle soreness. Elevations in plasma enzymes, myoglobinemia, and abnormal muscle histology and ultrastructure are concluded to be associated with the inflammatory response. High tension in the contractile-elastic system of muscle results in structural damage to the muscle fiber and plasmalemma and its epimysium, perimysium, and/or endomysium. The myosium damage disrupts calcium homeostasis in the injured fiber and fiber bundles, resulting in necrosis that peaks about 48 hours after exercise. The products of the macrophage activity and intracellular contents (such as histamines, kinins, and $K^+$) accumulate outside the cells. These substances then stimulate the free nerve endings in the muscle; a process that appears accentuated by eccentric exercise, in which large forces are distributed over a relatively small cross-sectional area of the muscle.

**Post-inflammatory muscle growth and repair**

There is a known relationship between inflammation and muscle growth.\[^{43}\] For instance, high doses of anti-inflammatory medicines (e.g., NSAIDs) are able to blunt muscle growth.\[^{44}[^{45}]\]

It has been further theorized that the acute localized inflammatory responses to muscular contraction during exercise, as described above, are a necessary precursor to muscle growth.\[^{46}\] As a response to muscular contractions, the acute inflammatory response initiates the breakdown and removal of damaged muscle tissue.\[^{47}\] Muscles can synthesize cytokines in response to contractions,\[^{48}[^{49}[^{50}]\] such that the cytokines *Interleukin-1 beta (IL-1β)*, TNF-α, and IL-6 are expressed in skeletal muscle up to 5 days after exercise.\[^{51}\]

In particular, the increase in levels of IL-6 can reach up to one hundred times that of resting levels.\[^{52}\] Depending on volume, intensity, and other training factors, the IL-6 increase associated with training initiates about 4 hours after resistance training and remains elevated for up to 24 hours.\[^{53}[^{54}[^{55}]\]

These acute increases in cytokines, as a response to muscle contractions, help initiate the process of muscle repair and growth by activating satellite cells within the inflamed muscle. Satellite cells are crucial for skeletal muscle adaption to exercise.\[^{56}\] They contribute to hypertrophy by providing new myonuclei and repair damaged segments of mature myofibers for successful regeneration following injury- or exercise-induced muscle damage;\[^{55}[^{56}[^{57}]\] high-level powerlifters can have up to 100% more satellite cells than untrained controls.\[^{58}[^{59}[^{60}]\]

A rapid and transient localization of the IL-6 receptor and increased IL-6 expression occurs in satellite cells following contractions.\[^{61}\] IL-6 has been shown to mediate hypertrophic muscle growth both *in vitro* and *in*
Unaccustomed exercise can increase IL-6 by up to sixfold at 5 hours post-exercise and threefold 8 days after exercise. Also telling is the fact that NSAIDs can decrease satellite cell response to exercise, thereby reducing exercise-induced protein synthesis.

The increase in cytokines after resistance exercise coincides with the decrease in levels of myostatin, a protein that inhibits muscle differentiation and growth. The cytokine response to resistance exercise and moderate-intensity running occur differently, with the latter causing a more prolonged response, especially at the 12-24 hour mark.

### Chronic inflammation and muscle loss

Both chronic and extreme inflammation are associated with disruptions of anabolic signals initiating muscle growth. Chronic inflammation has been implicated as part of the cause of the muscle loss that occurs with aging. Increased protein levels of myostatin have been described in patients with diseases characterized by chronic low-grade inflammation. Increased levels of TNF-α can suppress the AKT/mTOR pathway, a crucial pathway for regulating skeletal muscle hypertrophy, thereby increasing muscle catabolism. Cytokines may antagonize the anabolic effects of Insulin-like growth factor 1 (IGF-1). In the case of sepsis, an extreme whole body inflammatory state, the synthesis of both myofibrillar and sarcoplasmic proteins is inhibited, with the inhibition taking place preferentially in fast-twitch muscle fibers. Sepsis is also able to prevent leucine from stimulating muscle protein synthesis. In animal models, when inflammation is created, mTOR loses its ability to be stimulated by muscle growth.

### Exercise as a treatment for inflammation

Regular physical activity is reported to decrease markers of inflammation, although the correlation is imperfect and seems to reveal differing results contingent upon training intensity. For instance, while baseline measurements of circulating inflammatory markers do not seem to differ greatly between healthy trained and untrained adults, long-term chronic training may help reduce chronic low-grade inflammation. On the other hand, levels of inflammatory markers (IL-6) remained elevated longer into the recovery period following an acute bout of exercise in patients with inflammatory diseases, relative to the recovery of healthy controls. It may well be that low-intensity training can reduce resting pro-inflammatory markers (CRP, IL-6), while moderate-intensity training has milder and less-established anti-inflammatory benefits. There is a strong relationship between exhaustive exercise and chronic low-grade inflammation. Marathon running may enhance IL-6 levels as much as 100 times over normal and increases total leucocyte count and neutrophil mobilization. As such, individuals pursuing exercise as a means to treat the other factors behind chronic inflammation may wish to balance their exercise protocol with bouts of low-intensity training, while striving to avoid chronic over-exertion.
Signal-to-noise theory

Given that localized acute inflammation is a necessary component for muscle growth, and that chronic low-grade inflammation is associated with a disruption of anabolic signals initiating muscle growth, it has been theorized that a signal-to-noise model may best describe the relationship between inflammation and muscle growth. By keeping the "noise" of chronic inflammation to a minimum, the localized acute inflammatory response signals a stronger anabolic response than could be achieved with higher levels of chronic inflammation.

See also

- Anaphylatoxin
- Anti-inflammatories
Djokovic on a roll since cutting out pizza, bread

By Associated Press on 23 Sep 2011 11:09

LONDON - Ever since eliminating pizza from his diet and being on the SCIO, Novak Djokovic has been on an incredible roll.

Djokovic has been boasting all season about how he has more energy on the tennis court since starting a gluten-free diet, cutting out pizza and bread from his daily life. But the top-ranked Serb has been reluctant to discuss his new regimen in any detail, preferring to let his game do the talking.

The man with the answers is Igor Cetojevic, a Serbian doctor, medical professor with the International Medical University of Natural Education and nutritionist who began working with Djokovic at the end of last year.

"I checked him with the SCIO to see what is going on, gave some advice and therapy," Cetojevic told The Associated Press in a telephone interview."He started to follow them. He started to sleep properly for the first time in his life."

It actually seems as if it was as easy as that. Djokovic had won only one Grand Slam title heading into 2011. He now has four after winning the Australian Open, Wimbledon and the U.S. Open, while
For the past couple of years, Djokovic had been firmly entrenched as the No. 3 player in the world behind Roger Federer and Rafael Nadal. Although he was consistently going deep into the majors, Djokovic’s lone big title came at the 2008 Australian Open. Otherwise, he was losing early or even pulling out of matches because he wasn't in good enough shape.

When things started to change, Djokovic hushed up, declining to talk about his new training routine.

"I can't talk about it," Djokovic said at the French Open, "because it's private." Last month, about two weeks before the start of the U.S. Open, Djokovic again demurred when asked about the diet.

"I cannot tell you everything," said Djokovic, who grew up at his parents' pizza parlor on Mt. Kopaonik in southern Serbia. "There are things that I keep for myself."  

But the science behind the decision to essentially cut wheat, barley and rye out of Djokovic's diet isn't all that secret. Cetojevic said he used a SCIO bio-feedback machine (developed by Desire' Dubounet) - basically attaching some wires to a person and connecting them to a computer - to study the effects that food has on Djokovic's body. He saw that the gluten was "through the roof," and knew he needed to do something about it.

"We can see most reactions in the body so we can eliminate the bad guys and put good guys in," Cetojevic, a medical Professor for the International Medical University, explained, keeping it as simple as can be. Cetojevic said the details behind the program can be complicated and he isn't surprised when Djokovic evades questions about the diet and the electrical treatment.

"Novak's not a medical doctor," said Cetojevic, adding that even he found it difficult to explain to people what was going on. "He cannot talk about that." The idea of working with Djokovic came about two years ago, long before Cetojevic had ever met the tennis star. And it started because of his wife, a holistic therapist from the United States.

"I saw Nole playing some match against (Jo-Wilfried) Tsonga in Australia," Cetojevic said. "My wife told me, 'This guy has some allergy.' I said, 'I don't think so. Something else is there.' "She told me, 'Help him. He's your countryman,'" Cetojevic said with a laugh. Cetojevic made some calls to people who knew Djokovic and left the message that he might be able to help. "Time passed, and one day they called me," said Cetojevic, who flew to Split, Croatia, to meet Djokovic for the first time as he played in the Davis Cup quarterfinals against Croatia in July 2010.

It was there that the lessons started, and they involved more than just nutrition. "I started teaching Nole simple things, like avoid talking on the telephone and eating because you're ignoring your food," said Cetojevic, who also studied traditional Chinese medicine, Quantum energetic medicine and
magnetotherapy. "He started responding very well. Started to kind of eat well, not have weak stomach, vomiting after meals. "Slowly, slowly he started to build up. I started to observe how he behaves."

The new ideas, including blessing his food before eating in order to have an "emotional, spiritual connection with food," were not completely accepted by some in Djokovic's camp, Cetojevic said, especially after the player started losing weight. But once the results started coming and the weight came back, Cetojevic was hired full time. "In Chinese medicine, confidence is in the stomach," Cetojevic said.

Even Federer, a 16-time Grand Slam champion and former No. 1, said he doesn't really understand what it is about the gluten-free diet that has made Djokovic so tough to beat. "I don't even know what that all means," Federer said last month at the U.S. Open."I eat healthy, and I think that's what people should do, too, if they have the options." But believing in it, and putting it into effect, is really what matters. And Djokovic has done just that.

Cetojevic sat in the players' box at Rod Laver Arena as Djokovic beat Andy Murray to win his second Grand Slam title at the Australian Open. Djokovic then ran his winning streak to 43 straight matches before losing to Federer in the French Open semifinals. A few weeks later, Djokovic beat defending champion Nadal to win his first Wimbledon title. It was Djokovic's desire to win Wimbledon that initially endeared him to Cetojevic.

"When he was a very small boy, he played at home with this little empty pot and on a little chair he stepped on it and said, 'Novak Djokovic, Wimbledon champion.' He was already visualizing what he wants to be," Cetojevic said. "That pure will to succeed touched me." And after that Wimbledon win and right after Djokovic pulled a few blades of grass from the manicured lawn at the All England Club to physically taste his victory, Cetojevic knew his job was complete. "I stopped after Wimbledon because that was our goal," said Cetojevic, who returned to his practice in Cyprus. "We had our target."

**The last two losses of Novak came while NOT being on the SCIO. Showing just how powerful the SCIO is.**

By CHRIS LEHOURITES AP Sports Writer

**As a note now Desire' Dubounet has become Novak’s personal medical doctor and she treats him daily. After defending the Australian open in2012, Novak seems impossible to beat with Desire’s help.**
Dr. Desi and Novak working together in Monaco. But after 3-15-2012 Desi would resign to help others.
Neural immune pathways and their connection to inflammatory diseases

Farideh Eskandari, Jeanette I Webster and Esther M Sternberg

Section on Neuroendocrine Immunology and Behavior, NIMH/NIH, Bethesda, MD, USA

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Abstract

Inflammation and inflammatory responses are modulated by a bidirectional communication between the neuroendocrine and immune system. Many lines of research have established the numerous routes by which the immune system and the central nervous system (CNS) communicate. The CNS signals the immune system through hormonal pathways, including the hypothalamic–pituitary–adrenal axis and the hormones of the neuroendocrine stress response, and through neuronal pathways, including the autonomic nervous system. The hypothalamic–pituitary–gonadal axis and sex hormones also have an important immunoregulatory role. The immune system signals the CNS through immune mediators and cytokines that can cross the blood–brain barrier, or signal indirectly through the vagus nerve or second messengers. Neuroendocrine regulation of immune function is essential for survival during stress or infection and to modulate immune responses in inflammatory disease. This review discusses neuroimmune interactions and evidence for the role of such neural immune regulation of inflammation, rather than a discussion of the individual inflammatory mediators, in rheumatoid arthritis.

Introduction

The inflammatory response is modulated in part by a bidirectional communication between the brain and the immune systems. This involves hormonal and neuronal mechanisms by which the brain regulates the function of the immune system and, in the reverse, cytokines, which allow the immune system to regulate the brain. In a healthy individual this bidirectional regulatory system forms a negative feedback loop, which keeps the immune system and central nervous system (CNS) in balance. Perturbations of these regulatory systems could potentially lead to either overactivation of immune responses and inflammatory disease, or oversuppression of the immune system and increased susceptibility to infectious disease. Many lines of research have recently established the numerous routes by which the immune system and the CNS communicate. This review will focus on these regulatory systems and their involvement in the pathogenesis of inflammatory diseases such as rheumatoid arthritis (RA). For other reviews on the involvement of these regulatory pathways in RA and other inflammatory diseases, see reviews by Eijsbouts and Murphy [1], Crofford [2], and Imrich [3].

There are two major pathways by which the CNS regulates the immune system: the first
is the hormonal response, mainly through the hypothalamic–pituitary–adrenal (HPA) axis, as well as the hypothalamic–pituitary–gonadal (HPG), the hypothalamic–pituitary–thyroid (HPT) and the hypothalamic–growth-hormone axes; the second is the autonomic nervous system, through the release of norepinephrine (noradrenaline) and acetylcholine from sympathetic and parasympathetic nerves. In turn, the immune system can also regulate the CNS through cytokines.

Conversely, cytokines released in the periphery change brain function, whereas cytokines produced within the CNS act more like growth factors. Thus, cytokines produced at inflammatory sites signal the brain to produce sickness-related behavior including depression and other symptoms such as fever [4-7]. In addition, cytokines produced locally exert paracrine/autocrine effects on hormone secretion and cell proliferation [8,9].

The interactions between the neuroendocrine and immune systems provide a finely tuned regulatory system required for health. Disturbances at any level can lead to changes in susceptibility to or severity of infectious, inflammatory or autoimmune diseases.

**Regulation of the immune system by the CNS**

**Hormonal pathways**

**HPA axis**

On stimulation, corticotropin-releasing hormone (CRH) is secreted from the paraventricular nucleus of the hypothalamus into the hypophyseal portal blood supply. CRH then stimulates the expression and release of adrenocorticotropin (ACTH) from the anterior pituitary gland. Arginine vasopressin (AVP) synergistically enhances CRH-stimulated ACTH release [10,11]. ACTH in turn induces the expression and release of glucocorticoids from the adrenal glands.

Glucocorticoids regulate a wide variety of immune-related genes and immune cell expression and function. For example, glucocorticoids modulate the expression of cytokines, adhesion molecules, chemoattractants and other inflammatory mediators and molecules and affect immune cell trafficking, migration, maturation, and differentiation [12,13]. Glucocorticoids cause a Th1 (cellular immunity) to Th2 (humoral immunity) shift in the immune response, from a proinflammatory cytokine pattern with increased interleukin (IL)-1 and tumor necrosis factor (TNF)-α to an anti-inflammatory cytokine pattern with increased IL-10 and IL-4 [14,15]. Pharmacological doses and preparations of glucocorticoids cause a general suppression of the immune system, whereas physiological doses and preparations of glucocorticoids are not completely immunosuppressive but can enhance and specifically regulate the immune response under certain circumstances. For example, physiological concentrations of natural glucocorticoids (i.e. corticosterone) stimulate delayed-type hypersensitivity reactions acutely, whereas pharmacological preparations (i.e. dexamethasone) are immunosuppressive [16].

Glucocorticoids exert these immunomodulatory effects through a cytosolic receptor, the glucocorticoid receptor (GR). This is a ligand-dependent transcription factor that, after
binding of the ligand, dissociates from a protein complex, dimerizes, and translocates to the nucleus, where it binds to specific DNA sequences (glucocorticoid response elements) to regulate gene transcription [17]. GR can also interfere with other signaling pathways, such as nuclear factor (NF)-κB and activator protein-1 (AP-1), to repress gene transcription; it is through these mechanisms that most of the anti-inflammatory actions are mediated [18-21]. A splice variant of GR, GRβ, that is unable to bind ligand but is able to bind to DNA and cannot activate gene transcription [22] (although this is still under some dispute), has been suggested to be able to act as a dominant repressor of GR [23,24]. Increased GRβ expression has been shown in several inflammatory diseases including asthma [25-28], inflammatory bowel disease/ulcerative colitis [29,30], and RA [31].

**HPG axis**

In addition to the HPA axis, other central hormonal systems, such as the HPG axis and in particular estrogen, also modulate the immune system [32]. In general, physiological concentrations of estrogen enhance immune responses [33,34] whereas physiological concentrations of androgens, such as testosterone and dehydroepiandrosterone (DHEA), are immunosuppressive [34]. Females of all species exhibit a greater risk of developing many autoimmune/inflammatory diseases, such as systemic lupus erythematosus, RA and multiple sclerosis, ranging from a 2-fold to a 10-fold higher risk compared with males [35,36]. Animal models have provided evidence for the importance of in vivo modulation of the immune system by the estrogen receptors [37,38]. Knockout mouse models indicate that both estrogen receptors α and β are important for thymus development and atrophy in a gender-specific manner [39].

In contrast, immune stress, such as occurs during inflammation, has an inhibitory effect on the HPG axis and thus gonadal function is reduced in conditions associated with severe inflammation such as sepsis and trauma. This effect is mediated either through a direct cytokine effect on hypothalamic neurons secreting luteinizing hormone releasing hormone [40,41] or through other factors such as CRH [42,43] and endogenous opioids [44]. Cytokines also affect gonadal sex steroid production by acting directly on the gonads [45].

**Hypothalamic–growth-hormone axis**

Growth hormone (GH) is a modulator of the immune system [46,47]. The effects of GH are mediated primarily through insulin-like growth factor-1 (IGF-1). GH and IGF-1 have been shown to modulate the immune system by inducing the survival and proliferation of lymphoid cells [48], leading some to suggest that GH functions as a cytokine [49]. Thus, immune cells including T and B lymphocytes [50] and mononuclear cells [51] express IGF-1 receptor. After binding to these receptors, GH activates the phosphoinositide 3-kinase/Akt and NF-κB signal transduction pathways, leading to the expression of genes involved in the cell cycle. The NF-κB pathway is also important in immunity, and therefore some of the GH effects on the immune system might be mediated through this signal transduction pathway [49]. However, the role of GH in regulation of the immune system is somewhat controversial. Studies in GH knockout animals have shown that this hormone is only minimally required for immune function [52], leading to an alternative hypothesis in which the primary role of GH is proposed to be protection from the immunosuppressive effects of glucocorticoids during stress [53].
GH might also modulate immune function indirectly by interacting with other hormonal systems. Thus, short-term increases in glucocorticoids increase GH production [54], whereas long-term high doses result in a decrease in the hypothalamic–GH axis and even growth impairment [55]. Conversely, prolonged HPA axis activation and resultant excessive glucocorticoid production, as occurs during chronic stress, also inhibits the hypothalamic–GH axis [56-58]. Consistent with this is the observation that children with chronic inflammatory disease exhibit growth retardation. During the early phase of inflammatory reactions, the concentration of GH is increased. In spite of an initial rise in GH secretion, GH action is reduced because of GH and IGF-1 resistance induced by inflammation. IL-1α initially stimulates GH [59], but subsequently inhibits its secretion [60].

**HPT axis**

As with the interaction between the HPA axis and the immune system, there is a bidirectional interaction between the HPT axis and immune system [61]. The HPT axis has an immunomodulatory effect on most aspects of the immune system. Thyrotropin-releasing hormone (TRH), thyroid-stimulating hormone (TSH), and the thyroid hormones triiodothyronine (T3) and thyroxine (T4) all have stimulatory effects on immune cells [62-64]. As for GH, the role of thyroid hormones in the regulation of immunity is somewhat controversial, and for the same reasons the alternative hypothesis of protection from the immunosuppressive effects of glucocorticoids has also been suggested for thyroid hormones [53]. Inflammation inhibits TSH secretion because of the inhibitory effect of cytokines on TRH [62]. IL-1 has been shown to suppress TSH secretion [59], whereas IL-2 has been shown to stimulate the pituitary–thyroid axis [65]. IL-6 and its receptor have been shown to be involved in developing euthyroid sick syndrome in patients with acute myocardial infarction [66].

In addition to direct effects of thyroid hormones on immune response, there is also interaction between the HPA and HPT axes. Hyperthyroid and hypothyroid states in rats have been shown to alter responses of the HPA axis, with hypothyroidism resulting in a reduced HPA axis response and hyperthyroidism resulting in an increased HPA axis response [67]. In agreement with this, administration of thyroxine, inducing a hyperthyroid state, has been shown to activate the HPA axis and be protective against an inflammatory challenge in rats [68], and hypothyroidism has been shown to cause a reduction in CRH gene expression [69]. Chronic HPA axis activation also represses TSH production and inhibits the conversion of inactive T4 to the active T3 [70].

**Neural pathways**

**Sympathetic nervous system**

The sympathetic nervous system regulates the immune system at regional, local, and systemic levels. Immune organs including thymus, spleen, and lymph nodes are innervated by sympathetic nerves [71-73]. Immune cells also express neurotransmitter receptors, such as adrenergic receptors on lymphocytes, that allow them to respond to neurotransmitters released from these nerves.

Catecholamines inhibit production of proinflammatory cytokines, such as IL-12, TNF-α, and interferon-γ, and stimulate the production of anti-inflammatory cytokines, such as IL-10 and transforming growth factor-β [15]. Through this mechanism, systemic
catecholamines can cause a selective suppression of Th1 responses and enhance Th2 responses [15,74]. However, in certain local responses and under certain conditions, catecholamines can enhance regional immune responses by inducing the production of IL-1, TNF-α, and IL-8 [75]. Interruption of sympathetic innervation of immune organs has been shown to modulate the outcome of, and susceptibility to, inflammatory and infectious disease. Denervation of lymph node noradrenergic fibers is associated with exacerbation of inflammation [76,77], whereas systemic sympathectomy or denervation of joints is associated with decreased severity of inflammation [77]. However, mice lacking β2-adrenergic receptor from early development (β2AR−/− mice) maintain their immune homeostasis [78]. Therefore, dual activation of the sympathetic nervous system and HPA axis is required for full modulation of host defenses to infection [16,79].

Opioids

Opioids suppress many aspects of immune responses, including antimicrobial resistance, antibody production, and delayed-type hypersensitivity. This occurs in part through the desensitization of chemokine receptors on neutrophils, monocytes, and lymphocytes [80,81]. Morphine decreases mitogen responsiveness and natural killer cell activity [82-86]. In addition to these direct effects, morphine could also affect immune responses indirectly through adrenergic effects, because it increases concentrations of catecholamines in the plasma [87].

Parasympathetic nervous system

Activation of the parasympathetic nervous system results in the activation of cholinergic nerve fibers of the efferent vagus nerve and the release of acetylcholine at the synapses. Together with the inflammation-activated sensory nerve fibers of the vagus nerve (discussed below) this forms the so-called 'inflammatory reflex'. This is a rapid mechanism by which inflammatory signals reach the brain; the brain responds with a rapid anti-inflammatory action through cholinergic nerve fibers [88].

Acetylcholine attenuates the release of proinflammatory cytokines (TNF, IL-1β, IL-6, and IL-18) but not the anti-inflammatory cytokine IL-10, in lipopolysaccharide-stimulated human macrophage cultures through the post-transcriptional suppression of protein synthesis. This effect seems, at least in part, to be independent of the HPA axis, because direct electrical stimulation of the peripheral vagus nerve does not stimulate the HPA axis but decreases hepatic lipopolysaccharide-stimulated TNF synthesis and the development of shock during lethal endotoxemia [89].

Peripheral nervous system

The peripheral nervous system regulates immunity locally, at sites of inflammation, through neuropeptides such as substance P, peripherally released CRH, and vasoactive intestinal polypeptide. These molecules are released from nerve endings or synapses, or they may be synthesized and released by immune cells and have immunomodulatory and generally proinflammatory effects [90-92].

Neuropeptides

The HPA axis is also subject to regulation by both neurotransmitters and neuropeptides from within the CNS. CRH is positively regulated by serotonergic [93-95], cholinergic [96,97], and catecholaminergic [98] systems. Other neuropeptides, such as γ-
aminobutyric acid/benzodiazepines (GABA/BZD) have been shown to inhibit the serotonin-induced secretion of CRH [99].

**Regulation of the CNS by the immune system**

**Cytokines**

Cytokines are important factors connecting and modulating the immune and neuroendocrine systems. Cytokines and their receptors are expressed in the neuroendocrine system and exert their effects both centrally and peripherally [100-102]. Systemic cytokines can affect the brain through several mechanisms, including active transport across the blood–brain barrier [103], through leaky areas in the blood–brain barrier in the circumventricular organs [104] or through the activation of neural pathways such as the vagal nerve [105]. The blood–brain barrier is absent or imperfect in several small areas of the brain, the so-called circumventricular organs, which are located at various sites within the walls of the cerebral ventricles. These include the median eminence, the organum vasculosum of the laminae terminalis (OVLT), the subfornical organ, the choroid plexus, the neural lobe of the pituitary, and the area postrema. In addition, in the presence of inflammation, the permeability of the blood–brain barrier might be generally altered [106-108]. Moreover, circulating IL-1 can interact with IL-1 receptors on endothelial cells of the vasculature and thereby stimulate signaling molecules such as nitric oxide or prostaglandins, which can locally influence neurons [109].

Cytokines signal the brain not only to activate the HPA axis but also to facilitate pain and induce a series of mood and behavioral responses generally termed sickness behavior [110,111]. Cytokines, such as IL-1, IL-6, and TNF-α, are also produced in the brain [112-114]. Thus, these brain-derived cytokines can stimulate the HPA axis. For example, IL-1 stimulates the expression of the gene encoding CRH and thereby the release of the hormone from the hypothalamus [115], the release of AVP from the hypothalamus [116], and the release of ACTH from the anterior pituitary [117]. IL-2 stimulates AVP secretion from the hypothalamus [118]. IL-6 [119] and TNF-α [120] also stimulate ACTH secretion. In chronic inflammation there seems to be a shift from CRH-driven to AVP-driven HPA axis response [121].

However, in contrast to these effects of peripheral cytokines on neuroendocrine responses in the CNS, cytokines produced within the brain by resident glia or invading immune cells act more like growth factors protecting from or enhancing neuronal cell death. Cytokines might therefore have a pathological consequence, because cytokine-mediated neuronal cell death is thought to be important in several neurodegenerative diseases such as neuroAIDS, Alzheimer's disease, multiple sclerosis, stroke, and nerve trauma [100-102]. In contrast, activated immune cells and cytokines might also protect neuronal survival after trauma and contribute to neural repair [122].

**Vagus nerve**

The vagus nerve is involved in signaling of the CNS to the immune system. The vagus innervates most visceral structures such as the lung and the gastrointestinal tract, where there may be frequent contact with pathogens. Immune stimuli activate vagal
sensory neurons, possibly after binding to receptors in cells in paraganglial structures [123-126]. Administration of endotoxins and IL-1 has been shown to induce Fos expression in the vagal sensory ganglia, and vagotomy abolishes this early activation gene response [124-126]. Vagal afferents terminate in the dorsal vagal complex of the caudal medulla, which consists of the area postrema, the nucleus of the solitary tract, and the dorsal motor nucleus of the vagus. These nuclei integrate sensory signals and control visceral reflexes, and also relay visceral sensory information to the central autonomic network [127]. Subdiaphragmatic vagotomy inhibits activation of the paraventricular nucleus and subsequent secretion of ACTH in response to lipopolysaccharides and IL-1 [128,129].

Correlation between blunted HPA axis and disease
A blunted HPA axis has been associated with increased susceptibility to autoimmune/inflammatory disease in a variety of animal models and human studies. In general, at the baseline the HPA axis parameters do not differ in individuals susceptible and resistant to inflammatory disease. However, differences become apparent with stimulation of the axis.

Animal models
A blunted HPA axis has been associated with susceptibility to autoimmune/inflammatory diseases in several animal models. These include the Obese strain (OS) chickens, a model for thyroiditis [130]; MRL mice, which develop lupus [131]; and Lewis (LEW/N) rats. A region on rat chromosome 10 that links to the innate carrageenan inflammation [132] is syntenic with a region on human chromosome 17 that is known to link to susceptibility to a variety of autoimmune diseases [133] and is also syntenic with one of the 20 different regions on 15 different chromosomes shown to link to inflammatory arthritis in other linkage studies [134-136]. Several candidate genes within the rat chromosome 10 linkage region are known to have a role in hypothalamic CRH regulation as well as inflammation, including the CRH R1 receptor, angiotensin-converting enzyme, and STAT3 and STAT5a/5b [132]. However, these candidate genes either show no mutation in the coding region and no differences in regulation between susceptible and resistant strains, or show a mutation in the coding region that does not seem to have a role in expression of the inflammatory trait [137]. As in most complex illnesses and traits, the genotypic contribution to variance in the trait is small: about 35%, which is consistent with such multigenic and polygenic conditions.

Inbred rat strains provide a genetically uniform system that can be systemically manipulated to test the role of neuro-endocrine regulation of various aspects of immunity. Lewis (LEW/N) rats are highly susceptible to the development of a wide range of autoimmune diseases in response to a variety of proinflammatory/antigenic stimuli. Fischer (F344/N) rats are relatively resistant to development of these illnesses after exposure to the same dose of antigens or proinflammatory stimuli. These two strains also show related differences in HPA axis responsiveness. The inflammatory-susceptible LEW/N rats exhibit a blunted HPA axis response, compared with inflammatory-resistant F344/N rats with an exaggerated HPA axis response [138-140]. Differences in the expression of hypothalamic CRH [141], pro-opiomelanocortin,
corticosterone-binding globulin [142] and glucocorticoid expression and activation [143,144] have been shown in these two rat strains.

Disruptions of the HPA axis in inflammatory resistant animals, through genetic, surgical, or pharmacological interventions, have been shown to be associated with enhanced susceptibility to, or increased severity of, inflammatory disease [139,145-148]. Reconstitution of the HPA axis in these inflammatory-susceptible animals, either pharmacologically with glucocorticoids or surgically by intracerebral fetal hypothalamic tissue transplantation, has been shown to attenuate inflammatory disease [139,149].

**Animal models of arthritis**

Several animal models exist for RA in rodents. Lewis rats develop arthritis in response to streptococcal cell walls [138,139], heterologous (but not homologous) type II collagen in incomplete Freund's adjuvant (IFA) [150], and various adjuvant oils – including mycobacteria (MTB-AIA) [109], pristine [151], and avridine, but not IFA alone [152]. Inbred dark Agouti (DA) rats develop arthritis in response to heterologous and homologous type II collagen in IFA [153-156], cartilage oligomeric matrix protein [109], MTB-AIA [152], pristine, avridine [157], and ovalbumin-induced arthritis. DBA mice develop arthritis in response to type II collagen in complete Freund's adjuvant [158,159]. For specific reviews on animal models for RA, refer to reviews by Morand and Leech [160] and Joe and Wilder [161].

A premorbid blunting of normal diurnal corticosterone levels in both Lewis and DA rats has been shown in animals susceptible to experimentally induced arthritis [162]. In adjuvant-induced arthritis, chronic activation of the HPA axis is seen 7–21 days after adjuvant injection, together with loss of circadian rhythm [163]. This chronic activation of the HPA axis was shown to be due to increased corticosterone secretion due to an increase in the pulse frequency of secretion in adjuvant-induced arthritis [164]. During this chronic activation of the HPA axis, rats with adjuvant-induced arthritis are incapable of mounting an HPA axis response to acute stress (such as noise) but are still able to respond to an acute immunological stress [165]. Adrenalectomy or glucocorticoid receptor blockade exacerbates the disease state and results in death or disease expression in surviving animals [139,166,167]. It has been suggested that mortality from such shock-like responses is due to the increased cytokine production that occurs in adrenalectomized animals exposed to proinflammatory stimuli [166,168].

In addition to the role of HPA axis dysregulation, a dual role for the sympathetic nervous system in animal models of RA has been suggested. Activation of β-adrenoceptors or A2 receptors by high concentrations of norepinephrine or adenosine results in increased intracellular concentrations of cAMP and anti-inflammatory responses, whereas activation of α2-adrenoceptors and A1 receptors by low concentrations of norepinephrine or adenosine results in proinflammatory events, such as the release of substance P [169]. Consistent with this is the observation that β-adrenergic agonists attenuate RA in animal models [170,171]. Rolipram, an inhibitor of the PDE-IV phosphodiesterase, an enzyme that degrades cAMP, has been shown reduce inflammation in several rodent models [170,172-174]. The effects of rolipram have also been suggested to be mediated by catecholamines [175] or by the stimulation of the adrenal and HPA axis [176,177]. There is also a loss of sympathetic nerve fibers during adjuvant-induced arthritis [178]. The peripheral natural anti-inflammatory agent,
vasoactive intestinal peptide, has been shown to reduce the severity of arthritis symptoms in the mouse model of collagen-induced arthritis \[179,180\].

In addition to the sympathetic nervous system, the parasympathetic nervous system is also important in immune regulation. A role of the cholinergic parasympathetic nervous system in an animal model of RA was suggested because direct stimulation of the vagus nerve was shown to inhibit the inflammatory response \[181\]. Impairment of the cholinergic regulation also exacerbates an inflammatory response to adjuvant in the knees of rats \[182\].

**Summary of animal model studies and therapeutic correlates**

Thus, animal models for arthritis have shown a role for the HPA axis, sympathetic, parasympathetic, and peripheral nervous systems. They have shown the necessity of endogenous glucocorticoids in regulating the immune response after exposure to antigenic or proinflammatory stimuli, and severity of inflammatory/autoimmune disease or mortality after removal of these endogenous glucocorticoids by adrenalectomy or GR blockade. Animal models have enabled genetic linkage studies, which have demonstrated the multigenic, polygenic nature of such inflammatory diseases with genes on more than 20 different chromosomes being linked to inflammatory arthritis. Finally, animal models have shown defects in the sympathetic and parasympathetic nervous system in arthritis. These findings have led to the development and testing of novel therapies (see the penultimate section, ‘New therapies’).

**Human studies**

In humans, ovine CRH, hypoglycemia, or psychological stresses have been used to stimulate the HPA axis. In such studies, blunted HPA axis responses have been shown in a variety of autoimmune/inflammatory or allergic diseases such as allergic asthma and atopic dermatitis \[183-186\], fibromyalgia \[187-190\], chronic fatigue syndrome \[188,189,191,192\], Sjögren’s syndrome \[2,193\], systemic lupus erythematosus \[2,194\], multiple sclerosis \[195,196\], and RA \[1,197-202\]. Conversely, chronic stimulation of the stress hormone response, such as experienced by caregivers of Alzheimer’s patients, students taking examinations, couples during marital conflict, and Army Rangers undergoing extreme exercise, results in chronically elevated glucocorticoids, causing a shift from Th1 to Th2 immune response, and is associated with an enhanced susceptibility to viral infection, prolonged wound healing, or decreased antibody production in response to vaccination \[203-206\].

**Rheumatoid arthritis**

RA is more common in women than in men, with onset usually occurring between menarche and menopause \[207,208\]. However, the incidence of RA becomes much less gender specific in elderly men and women \[207\]. In women, RA activity is reduced during pregnancy but returns postpartum, suggesting a role for the hormones that are fluctuating at this time (cortisol, progesterone, and estrogen) in the regulation of RA activity \[33,209-212\].

Glucocorticoids have been used for therapy for RA since the 1950s \[213,214\], when the Nobel Prize was awarded for the discovery of this effect. They are effective because of their anti-inflammatory actions in the suppression of many inflammatory immune molecules and cells. In patients with RA, administration of glucocorticoids decreases the
release of TNF-α into the bloodstream [215]; however, there are many debilitating side effects including weight gain, bone loss, and mood changes.

**The HPA axis in RA**

Human clinical studies are much more difficult to perform than animal models. However, some evidence exists supporting the involvement of the HPA axis in RA. Alterations in the diurnal rhythm of cortisol secretion have been documented in patients with RA [216,217]. An association between the cortisol diurnal cycle and diurnal variations in RA activity has been made, although it still remains to be determined whether this is cause or effect [218]. One of the most pertinent observations for the regulation of RA by endogenous cortisol comes from a study in which RA was exacerbated by inhibition of adrenal glucocorticoid synthesis by the 11β-hydroxylase inhibitor metyrapone [219].

Several studies have looked for abnormalities in the HPA axis of patients with RA. In general, these point to an inappropriately low cortisol response. Subtle changes in cortisol responses have been reported in response to insulin-induced hypoglycemia [201]. However, another study, also using insulin-induced hypoglycemia, described a blunted HPA axis in patients with RA [220]. In one study, lower cortisol responses to surgical stress were shown in patients with RA compared with healthy controls and an inflammatory control group, whereas normal responses of ACTH and cortisol to ovine CRH were seen in the same patients [198]; however, these results are complicated by the steroid therapy that these patients were taking. Other studies have shown increased peripheral ACTH levels in patients with RA without increases in cortisol [221-223], whereas other studies have shown a normal HPA axis in patients with RA [200]. Some studies have suggested that, given the inflammatory state of RA, a normal cortisol response is in fact indicative of an under-responsive HPA axis [224,225]. It has become generally accepted that lower than normal cortisol responses to stimulation are characteristic of RA [169,197,201,216,221,223,225-227]. Most recently Straub and colleagues have shown that the most sensitive indicator of blunted HPA axis responsiveness in early, untreated PA is an inappropriately low ratio of cortisol to IL-6 in these subjects [228].

Such defects in the stress response system are in agreement with patients' descriptions of RA 'flare up' during stress [229], which are likely to be caused by imbalances of the neuroendocrine and immune systems induced by psychosocial stressors [230]. It is worth noting that psychosocial stress is important in RA disease activity [231-233]. However, this will not be reviewed here and readers are referred to reviews by Walker and colleagues [234] and Herrmann and colleagues [235].

**Glucocorticoid receptors in RA**

Quantification of the numbers of GRs by ligand binding studies has produced contrasting results. In one study, normal or even slightly elevated numbers of GRs in peripheral blood mononuclear cells (PBMCs) were seen in untreated patients with RA [236], whereas other studies have shown a decrease in the number of GR molecules in the lymphocytes of patients with RA in comparison with controls [237]. Others have also shown a downregulation of GR during early RA [238,239]. Recently, Neeck and colleagues, evaluating the expression of GR by immunoblot analysis, showed a higher expression of GR in untreated patients with RA in comparison with controls but a
decreased GR expression in glucocorticoid-treated patients with RA in comparison with controls [202]. This has been confirmed by others [240]. A polymorphism in the 5’ untranslated region of exon 9 of the GR gene, which is associated with enhanced stability of the dominant-negative splice variant, GRβ, has been shown in patients with RA [31]. Enhanced expression of GRβ has also been shown in the PBMCs of steroid-resistant patients with RA [241]. A polymorphism in the CRH gene has also been described as a susceptibility marker for RA in an indigenous South African population [242-244].

Other hormone measures in RA

Patients with RA also show abnormalities in other endocrine hormones. Like other inflammatory diseases, they have been shown to have low serum androgen levels but unchanged serum estrogen levels [245-252]. Growth retardation is a phenomenon seen in juvenile RA [253], and an impairment of the GH axis has been shown in patients with active and remitted RA [220,225]. An increased expression of IGF-1-binding protein, resulting in a decreased concentration of free IGF-1, was also observed in patients with RA [254-256]. However, another study has attributed this difference in IGF-binding proteins to physical activity rather than inflammation [257].

An association between thyroid and rheumatoid disorders, such as RA and autoimmune thyroiditis, has been known for many years [258] although little is known about the thyroid involvement in RA. One study has shown that patients with RA have increased free T₄ levels, and consequently lower free T₃, than normal controls [259], although other studies were unable to confirm low levels in T₃ patients with RA [260]. However, a higher incidence of thyroid dysfunction has been shown in women with RA [261,262].

Sympathetic nervous system in RA

The extent to which the sympathetic nervous system is involved in human RA is unclear. In one study, a decreased number of β-adrenoceptors in the PBMCs and synovial lymphocytes of patients with RA was described, suggesting a shift to a proinflammatory state [263,264]. Regional blockade of the sympathetic nervous system in patients with RA has been described to attenuate some of features of RA [265]. Others were unable to confirm this result but found defects in other aspects of this signaling pathway [266]. However, as in animal models, β-adrenergic agonists have been shown to attenuate RA in humans [267].

For the sympathetic nervous system to be able to modulate inflammation in RA it is necessary for the synovial tissue to be innervated by sympathetic nerve fibers. In patients with long-term RA there is a significant decrease in sympathetic nerve fibers but an increase in substance P-producing sensory nerve fibers [268,269], suggesting a decrease in the anti-inflammatory effects of the sympathetic nervous system and an increase in the proinflammatory effects of the peripheral nervous system.

Peripheral neuropeptides in RA

Consistent with these changes in peripheral and autonomic innervation in RA are findings of altered peripheral neuropeptides in RA. proinflamatory CRH is locally secreted in the synovium of patients with RA and at a lower level than in osteoarthritis [199,270]. Human T lymphocytes have been shown to synthesize and secrete CRH [271]. Inflammation in chronic RA has also been shown to be attenuated with the μ-
opioid-specific agonist morphine [272]. In animal models, infusion of substance P into the knee exacerbated RA [273].

Summary of hormonal findings in RA

Studies of patients with RA are difficult to interpret and some might be tainted by a prior use of glucocorticoids used generally in the treatment of RA. However, these studies have generally shown a defect in cortisol secretion after HPA axis stimulation, decreased androgen levels, a blunted GH response, and dysregulation of the thyroid response. In addition there is evidence of an impaired response of the sympathetic nervous system and enhanced levels of the peripheral proinflammatory neuropeptides CRH and substance P. In some cases, a decrease in the number of GRs has been shown in RA, or reduced glucocorticoid sensitivity has been observed due to GRβ overexpression, which is consistent with relative glucocorticoid resistance in some patients. Furthermore, a polymorphism of the GRβ associated with the enhanced stability of that receptor has also been shown in RA [31]. It still remains to be fully determined whether these alterations in neuroendocrine pathways and receptors are involved in the pathogenesis of RA or whether they are a result of the inflammatory status of the disease.

Conclusion

The CNS and immune system communicate through multiple neuroanatomical and hormonal routes and molecular mechanisms. The interactions between the neuroendocrine and immune systems provide a finely tuned regulatory system required for health. Disturbances at any level can lead to changes in susceptibility to, and severity of, autoimmune/inflammatory disease. A thorough understanding of the mechanisms by which the CNS and immune systems communicate at all levels will provide many new insights into the bidirectional regulation of these systems and the disruptions in these communications that lead to disease, and ultimately will inform new avenues of therapy for autoimmune/inflammatory disease. Animal models of arthritis have shown changes in both the HPA axis and the sympathetic nervous system during inflammation. More importantly, these models have demonstrated the importance of endogenous glucocorticoids in the regulation of immunity and the prevention of lethality from an uncontrolled immune response. Furthermore, in both animals and humans, RA is associated with dysregulation of the HPA, HPT, HPG, and GH axes. There is also evidence of an impaired regulation of immunity by the sympathetic nervous system and of defects in glucocorticoid signaling. These principles are now being used to test novel therapies for RA based on addressing and correcting the dysregulation of these neural and neuroendocrine pathways.


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OF COURSE I'M STRESSED, I'M MARRIED WITH THREE TEENAGE DAUGHTERS AND ONE BATHROOM!

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"STRESSED" IS "DESSERTS" SPelled Backwards
Science News
... from universities, journals, and other research organizations

Yoga Reduces Cytokine Levels Known to Promote Inflammation, Study Shows

ScienceDaily (Jan. 14, 2010) — Regularly practicing yoga exercises may lower a number of compounds in the blood and reduce the level of inflammation that normally rises because of both normal aging and stress, a new study has shown.

The study, done by Ohio State University researchers and just reported in the journal *Psychosomatic Medicine*, showed that women who routinely practiced yoga had lower amounts of the cytokine interleukin-6 (IL-6) in their blood. The women also showed smaller increases in IL-6 after stressful experiences than did women who were the same age and weight but who were not yoga practitioners. IL-6 is an important part of the body’s inflammatory response and has been implicated in heart disease, stroke, type-2 diabetes, arthritis and a host of other age-related debilitating diseases. Reducing inflammation may provide substantial short- and long-term health benefits, the researchers suggest.
"In addition to having lower levels of inflammation before they were stressed, we also saw lower inflammatory responses to stress among the expert yoga practitioners in the study," explained Janice Kiecolt-Glaser, professor of psychiatry and psychology and lead author of the study.

"Hopefully, this means that people can eventually learn to respond less strongly to stressors in their everyday lives by using yoga and other stress-reducing modalities."

For the study, the researchers assembled a group of 50 women, age 41 on average. They were divided into two groups -- "novices," who had either taken yoga classes or who practiced at home with yoga videos for no more than 6 to 12 sessions, and "experts," who had practiced yoga one of two times weekly for at least two years and at least twice weekly for the last year.

Each of the women was asked to attend three sessions in the university's Clinical Research Center at two-week intervals. Each session began with participants filling out questionnaires and completing several psychological tests to gauge mood and anxiety levels.

Each woman also was fitted with a catheter in one arm through which blood samples could be taken several times during the research tasks for later evaluation.

Participants then performed several tasks during each visit designed to increase their stress levels including immersing their foot into extremely cold water for a minute, after which they were asked to solve a series of successively more difficult mathematics problems without paper or pencil.

Following these "stressors," participants would either participate in a yoga session, walk on treadmill set at a slow pace (.5 miles per hour) designed to mirror the metabolic demands of the yoga session or watch neutral, rather boring videos. The treadmill and video tasks were designed as contrast conditions to the yoga session.
New research shows that regularly practicing yoga exercises may lower a number of compounds in the blood and reduce the level of inflammation that normally rises because of both normal aging and stress.

Once the blood samples were analyzed after the study, researchers saw that the women labeled as "novices" had levels of the pro-inflammatory cytokine IL-6 that were 41 percent higher than those in the study's "experts."

"In essence, the experts walked into the study with lower levels of inflammation than the novices, and the experts were also better able to limit their stress responses than were the novices," Kiecolt-Glaser explained.

The researchers did not find the differences they had expected between the novices and experts in their physiological responses to the yoga session.

Co-author Lisa Christian, an assistant professor of psychology, psychiatry and obstetrics and gynecology, suggested one possible reason:

"The yoga poses we used were chosen from those thought to be restorative or relaxing. We had to limit the movements to those novices could perform as well as experts.

"Part of the problem with sorting out exactly what makes yoga effective in reducing stress is that if you try to break it down into its components, like the movements or the breathing, it's hard to say what particular
thing is causing the effect,” said Christian, herself a yoga instructor. “That research simply hasn’t been
done yet.”
Ron Glaser, a co-author and a professor of molecular virology, immunology and medical genetics, said
that the study has some fairly clear implications for health.
"We know that inflammation plays a major role in many diseases. Yoga appears to be a simple and
enjoyable way to add an intervention that might reduce risks for developing heart disease, diabetes and
other age-related diseases" he said.
"This is an easy thing people can do to help reduce their risks of illness."
Bill Malarkey, an professor of internal medicine and co-author on the study, pointed to the inflexibility that
routinely comes with aging.
"Muscles shorten and tighten over time, mainly because of inactivity," he said. "The stretching and
exercise that comes with yoga actually increases a person's flexibility and that, in turn, allows relaxation
which can lower stress."
Malarkey sees the people's adoption of yoga or other regular exercise as one of the key solutions to our
current health care crisis. "People need to be educated about this. They need to be taking responsibility
for their health and how they live. Doing yoga and similar activities can make a difference."
As a clinician, he says, "Much of my time is being spent simply trying to get people to slow down."
The researchers' next step is a clinical trial to see if yoga can improve the health and reduce inflammation
that has been linked to debilitating fatigue among breast cancer survivors. They're seeking 200 women to
volunteer for the study that's funded by the National Cancer Institute.
Researchers Heather Preston, Carrie Houts and Charles Emery were also part of the research team
which was supported in part by a grant from the National Center for Complementary and Alternative
Medicine, part of the National Institutes of Health.
I always knew there was a good, scientific reason I should get back into yoga. Not just because it’s a darn
good workout that’ll make you sweat and shake. Not because it stretches out too-tight muscles. And not
because it makes you lean and lithe like Gwyneth Paltrow. Those don’t hurt.

But there’s another incentive. A study published in the most recent issue of the journal *Psychosomatic
Medicine* found that regular yoga practice may reduce blood levels of a compound that causes
inflammation. Let me back up...
IL-6 (or cytokine interleukin-6 if you really want to get specific) is found in the body as a response to
inflammation. It’s been linked in previous studies to type 2 diabetes, heart disease, arthritis, and other
age-related diseases. In the current study, the researchers measured the levels of this compound in the
blood of 50 yoga gurus and novices.
Blood levels of IL-6 were measured after participants experienced a stressful event then either did some
yoga poses or walked on a treadmill. The findings were pretty interesting: Novices had levels of IL-6 that
were more than 40 percent higher than the experts. Which means those who had practiced yoga for some
time went into the study with lower levels of inflammation. What’s more, the researchers say **expert
yogis were better able to limit their body’s response to stress than novices were.**
The researchers don’t know exactly what about yoga lowers this inflammatory response, but they say it’s
an important discovery since inflammation plays a major role in disease. One explanation: “The stretching
and exercise that comes with yoga actually increases a person’s flexibility and that, in turn, allows
relaxation which can lower stress,” says William Malarkey, MD, a professor in internal medicine at Ohio
State University and one of the study’s authors.

“Part of the problem with sorting out exactly what makes yoga effective in reducing stress is that if you try
to break it down into its components, like the movements or the breathing, it’s hard to say what particular
thing is causing the effect,” says study co-author Lisa Christian, an assistant professor of psychiatry at Ohio State University and a yoga instructor.

It's been a while since I actually did a full-on yoga workout. Back in the day—when my knees didn’t go crunch, pop, ouch during exercise—I took yoga a couple times a week. I even sweated through Bikram yoga (for someone as chronically cold as me, working out in a 100-degree room isn’t so bad). I loved the way it made my body feel: strong, stretchy, and powerful. And I loved the way it built muscle. Now I'm too nervous about possibly hurting my knees to do a full yoga class, though I'll do some PT-approved poses now and then. Of course, as my knees are getting stronger, I’m feeling the yoga itch once again. I’d spring for a private lesson so that I can be sure the poses are all safe for injured knees,
but I'm not made of money. Drat. I think I'll have to hold off on the whole yoga thing until my knees are really

I Must do my Kundalini Yoga
Each and Everyday
Aging and Inflammation

*Causes of Age-Related Inflammation*

Chronic systemic inflammation is an underlying cause of many seemingly unrelated, age-related diseases. As humans grow older, systemic inflammation can inflict devastating degenerative effects throughout the body (Ward 1995; McCarty 1999; Brod 2000). This fact is often overlooked by the medical establishment, yet persuasive scientific evidence exists that correcting a chronic inflammatory disorder will enable many of the infirmities of aging to be prevented or reversed.

The pathological consequences of inflammation are well-documented in the medical literature (Willard et al. 1999; Hogan et al. 2001). Regrettably, the dangers of systemic inflammation continue to be ignored, even though proven ways exist to reverse this process. By following specific prevention protocols suggested by the Life Extension Foundation, the inflammatory cascade can be significantly reduced.

The Causes of Age-Related Inflammation

Aging results in an increase of inflammatory cytokines (destructive cell-signaling chemicals) that
contribute to the progression of many degenerative diseases (Van der Meide et al. 1996; Licinio et al. 1999). Rheumatoid arthritis is a classic autoimmune disorder in which excess levels of cytokines such as tumor necrosis factor-alpha (TNF-a), interleukin-6 (IL-6), interleukin 1b [IL-1(b)], and/or interleukin-8 (IL-8) are known to cause or contribute to the inflammatory syndrome (Deon et al. 2001).

Chronic inflammation is also involved in diseases as diverse as atherosclerosis, cancer, heart valve dysfunction, obesity, diabetes, congestive heart failure, digestive system diseases, and Alzheimer's disease (Brouqui et al. 1994; Devaux et al. 1997; De Keyser et al. 1998). In aged people with multiple degenerative diseases, the inflammatory marker, C-reactive protein, is often sharply elevated, indicating the presence of an underlying inflammatory disorder (Invitti 2002; Lee et al. 2002; Santoro et al. 2002; Sitzer et al. 2002). When a cytokine blood profile is conducted on people in a weakened condition, an excess level of one or more of the inflammatory cytokines, e.g., TNF-a, IL-6, IL-1(b), or IL-8, is usually found (Santoro et al. 2002). (See the Suggested Reading reference list for additional citations.)

Protecting Against Inflammatory-Related Disease

The New England Journal of Medicine published several studies in the year 2000 showing that the blood indicators of inflammation are strong predictive factors for determining who will suffer a heart attack (Lindahl et al. 2000; Packard et al. 2000; Rader 2000). The January 2001 issue of Life Extension Magazine described these studies and explained how individuals could protect themselves against these inflammatory markers (such as C-reactive protein, homocysteine, and fibrinogen).

A growing consensus among scientists is that common disorders such as atherosclerosis, colon cancer, and Alzheimer's disease are all caused in part by a chronic inflammatory syndrome. Seemingly unrelated diseases have a common link. People who have multiple degenerative disorders often exhibit excess levels of pro-inflammatory markers in their blood. Here is a partial list of common medical conditions that are associated with chronic inflammation:

<table>
<thead>
<tr>
<th>Disease Related To Chronic Inflammation</th>
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<tr>
<td>Disease</td>
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<td>Allergy</td>
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<td>Lupus</td>
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<td>Pancreatitis</td>
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Psoriasis
Inflammatory cytokines induce dermatitis

Stroke
Chronic inflammation promoted thromboembolic events

Surgical complications
Inflammatory cytokines prevent healing

A critical inflammatory marker is C-reactive protein. This marker indicates an increased risk for destabilized atherosclerotic plaque and abnormal arterial clotting. When arterial plaque becomes destabilized, it can burst open and block the flow of blood through a coronary artery, resulting in an acute heart attack. One of the New England Journal of Medicine studies showed that people with high levels of C-reactive protein were almost three times as likely to die from a heart attack (Ridker et al. 1997).

The Life Extension Foundation long ago advised members to have an annual C-reactive protein blood test to detect systemic inflammation that could increase the risk of heart attack, stroke, cancer and a host of age-related diseases. In fact, on January 28, 2003, the American Heart Association and Centers for Disease Control & Prevention (CDC) jointly endorsed the C-reactive protein test to screen for coronary-artery inflammation to identify those at risk for heart attack.

What Causes Elevated C-reactive Protein?

- Elevated C-Reactive Protein and Interleukin-6 Predict Type II Diabetes

While some doctors are finally catching on to the fact that elevated C-reactive protein increases heart attack and stroke risk, they still know little about its other dangers. Even fewer practicing physicians understand that pro-inflammatory cytokines are an underlying cause of systemic inflammation that is indicated by excess C-reactive protein in the blood.

In an abstract published in the March 6, 2002 issue of the Journal of the American College of Cardiology (JACC), tumor necrosis factor-alpha (TNF-a) levels were measured in a group of people with high blood pressure and a group with normal blood pressure (Verdecchia et al. 2002). The objective of this study was to ascertain if arterial flow mediated dilation was affected by hypertension and chronic inflammation as evidenced by high levels of the pro-inflammatory cytokine TNF-a.

The hypertensive subjects taking anti-hypertensive medications had about the same blood pressure as the healthy test subjects. Arterial flow medicated dilation, however, was significantly impaired in the hypertensives and this group also showed higher levels of TNF-a, indicating persistent inflammation despite blood pressure control. This study showed that even when blood pressure is under control, hypertensives still suffer from continuous damage to the inner lining of the arterial wall (endothelial dysfunction) caused by a chronic inflammatory insult. The doctors who conducted this study concluded by stating:

"Antihypertensive therapy alone may be insufficient to improve endothelial dysfunction in hypertensives with high plasma levels of inflammatory markers. Additional therapy to target inflammation may be necessary to improve endothelial function and to prevent progression of coronary atherosclerosis in high-risk hypertensives with subclinical inflammations."

A sensitive index to evaluate how much endothelial damage is occurring is the measurement of TPA (tissue-type plasminogen activator), a clot-dissolving enzyme found in the blood. This same study showed elevated TPA levels in hypertensives, indicating continued endothelial damage despite blood pressure reduction. These findings indicate that hypertensives should have their blood tested for both TNF-a and TPA to assess how much inner wall (endothelial) arterial
damage is occurring (Vardecchia et al. 2002). If TNF-a and/or TPA levels are high, aggressive therapies to suppress the inflammatory cascade should be considered.

Elevated C-Reactive Protein and Interleukin-6 Predict Type II Diabetes
In a study published in the July 18, 2001 issue of the Journal of the American Medical Association, a group from the famous Women's Health Study was evaluated to ascertain what risk factors could predict future development of Type II diabetes (Pradhan et al. 2001). The findings showed that baseline levels of C-reactive protein and interleukin-6 (IL-6) were significantly higher among those who subsequently developed diabetes compared to those who did not.

When comparing the highest versus lowest quartile, women with the higher IL-6 levels were 7.5 times more likely to develop diabetes while those in the higher C-reactive protein ranges were 15.7 times more likely to become diabetic. After adjusting for all other known risk factors, women with the highest IL-6 levels were 2.3 times at greater risk, while those with the highest C-reactive protein levels were 4.2 times more likely to become diabetic. It should be noted that these other diabetic risk factors (such as obesity, estrogen replacement therapy and smoking) all sharply increase inflammatory markers in the blood. The doctors who conducted this study concluded by stating:
"Elevated C-reactive protein and IL-6 predict the development of Type II diabetes mellitus. These data support a possible role for inflammation in diabetogenesis."

C-Reactive Protein and IL-6 Predict Death
• Frailty in Elderly Linked to Inflammation
It is well established the elevated C-reactive protein, IL-6 and other inflammatory cytokines indicate significantly greater risks of contracting or dying from specific diseases (heart attack, stroke, Alzheimer's disease, etc.).

A group of doctors wanted to ascertain if C-reactive protein and IL-6 could also predict the risks of all-cause mortality. In a study published in the American Journal of Medicine, a sample of 1,293 healthy elderly people were was followed for a period of 4.6 years (Harris et al. 1999). Higher IL-6 levels were associated with a twofold greater risk of death. Higher C-reactive protein was also associated with a greater risk of death, but to a lesser extent than elevated IL-6. Subjects with both high C-reactive protein and IL-6 were 2.6 times more likely to die during follow up than those with low levels of both of these measurements of inflammation. These results were independent of all other mortality risk factors. The doctors concluded by stating:
"These measurements (C-reactive protein and IL-6) may be useful for identification of high-risk subgroups for anti-inflammatory interventions."

Frailty in Elderly Linked to Inflammation
In a study of almost 5,000 elderly people, scientists discovered that frail seniors were more likely to have signs of increased inflammation than their more active counterparts. This study was published in the Archives of Internal Medicine (Walston et al. 2002) and showed that these frail seniors with elevated blood inflammatory markers also tended to show more clotting activity, muscle weakness, fatigue and disability than active elderly people.
Findings from these studies should motivate every health conscious individual to have their blood tested for C-reactive protein. If it is elevated, then the Inflammatory Cytokine Test Panel is highly recommended. Those who suffer from any type of chronic disease may also consider the Inflammatory Cytokine Test Panel in order to identify the specific inflammatory mediator that is causing or contributing to their problem.

Glycation's Role in Inflammation

- **Cooking and Aging Have Similar Biological Properties**

Eating high temperature cooked food is another contributor in the production of inflammatory cytokines. In fact, it has been shown that eating high temperature cooked food leads to the formation of advanced glycation end (AGE) products. Glycation can be described as the binding of a protein molecule to a glucose molecule resulting in the formation of damaged protein structures. Many age-related diseases such as arterial stiffening, cataract and neurological impairment are at least partially attributable to glycation. These destructive glycation reactions render proteins in the body cross-linked and barely functional. As these degraded proteins accumulate, they cause cells to emit signals that induce the production of inflammatory cytokines.

The glycation process is presently irreversible, though an important study indicates a drug in clinical trials may be partially effective. According to a Proceedings of the National Academy of Sciences study, consuming foods cooked at high temperature accelerates the glycation process, and the subsequent formation of advanced glycation end products.

A more succinct descriptive term for "advanced glycation end products" is "glycotoxin," since "advanced glycation end products" are toxic to the body. We will use the word "glycotoxin" from here on to describe the term "advanced glycation end products."

**Inflammation: Chronic**

**Cooking and Aging Have Similar Biological Properties**

Cooking foods at high temperatures results in a "browning" effect, where sugars and certain oxidized fats react with proteins to form glycotoxins in the food. Normal aging can also be regarded as a slow cooking process, since these same glycotoxins form in the skin, arteries, eye lenses, joints, cartilage, etc. of our body.

The Proceedings of the National Academy of Sciences study shows that consuming foods high in glycotoxins might be responsible for the induction of a low-grade, but chronic state of inflammation. In addition, the glycotoxins in food cooked at high temperatures also promote the formation of glycotoxins in our living tissues. The implication of these findings is profound.

What one eats plays a major role in chronic inflammatory processes. Consuming low glycemic foods prevents the insulin surge that contributes to chronic inflammatory processes. It is also important to avoid over consumption of foods high in arachidonic acid (beef, egg yolk, dairy, etc.).

We now know that eating too much over-cooked food causes an increase in inflammatory cytokines. Since most "junk" foods are cooked at extremely high temperatures, it makes sense to avoid French fries, hamburgers, potato chips, fried food and other snacks. These
foods not only contain lots of glycotoxins, they also create other metabolic disorders that can induce degenerative disease.

Consuming at least 1000 mg a day of carnosine, and/or 300 mg of the European drug aminoguanidine can inhibit pathological glycation reactions in the body. Eating high temperature cooked foods also induces the formation of glycotoxins. Avoiding foods cooked at high temperature not only reduces pathological glycation processes, but also prevents the formation of numerous gene-mutating toxins that are known carcinogens.

Food is cooked to destroy bacteria and other pathogens that could cause a serious illness. It is important not to eat undercooked food, but avoiding food unnecessarily cooked at higher temperatures is desirable. Certain foods (like fried foods) have to cook at high temperatures. Health conscious people are increasingly avoiding fried foods because they are associated with many health risks.

With the availability of cytokine blood profile tests, it is now possible to ascertain the underlying cause of chronic inflammatory disease. The appropriate drugs, nutrients, dietary change(s) and/or hormones can then be used to suppress the specific cytokines (such as IL-6 or TNF-a) that are promoting the inflammatory cascade.

The Detrimental Effects of Sleep Deprivation

On June 22, 2002, researchers at the annual meeting of the Endocrine Society held in San Francisco reported that sleep deprivation markedly increases inflammatory cytokines. This finding helps explain why pain flare-up occurs in response to lack of sleep in a variety of disorders. According to the researchers, even modest sleep restriction adversely affects hormone and cytokine levels. In this carefully controlled study, sleep deprivation caused a 40% to 60% average increase in the inflammatory marker IL-6 in men and women, while men alone showed a 20% to 30% increase in TNF-a. Both IL-6 and TNF are potent pro-inflammatory cytokines that induce systemic inflammation (Vgontzas et al. 1999; Vgontzas et al. 2001).

The study results were presented by Dr. Alexandros Vgontzas, professor of psychiatry at The Pennsylvania State University in Hershey. Dr. Vgontzas stated that the findings indicate that getting a full night's rest of eight hours is not just a nice bonus, but a necessity. He stated that people who are missing even two to three hours of sleep function poorly the next day.

Dr. Vgontzas added that the finding that lack of sleep may stimulate an increase in chronic inflammatory response is worrisome because inflammation has been linked to the most common lethal conditions affecting humans today. Vgontzas warned: "Restriction of sleep a few hours is a major risk for public safety."

This study has significant implications for the treatment of chronic pain and inflammatory disorders. For many, following the recommendations in Life Extension's Insomnia Protocol could provide considerable relief from pain and other disorders by preventing the increase of pro-inflammatory cytokines.

The Dangerous Pro-Inflammatory Cytokines

- Reducing Inflammation
The following acronyms represent the most dangerous pro-inflammatory cytokines. Health-conscious persons should become familiar with these terms because excess levels of these cytokines cause or contribute to many diseases states:

- TNF-a tumor necrosis factor-alpha
- IL-6 interleukin-6
- IL-1(b) interleukin-1 beta
- IL-8 interleukin-6

Reducing Inflammation

Scientists have identified dietary supplements and prescription drugs that can reduce levels of the pro-inflammatory cytokines. The docosahexaenoic acid (DHA) fraction of fish oil is the best documented supplement to suppress TNF-a, IL-6, IL-1(b), and IL-8 (Jeyarajah et al. 1999; James et al. 2000; Watanabe et al. 2000; Yano et al. 2000). A study on healthy humans and those with rheumatoid disease shows that fish oil suppresses these dangerous cytokines by up to 90% (James et al. 2000).

Other cytokine-lowering supplements are DHEA (Casson et al. 1993), vitamin K (Reddi et al. 1995; Weber 1997), GLA (gamma linolenic acid) (Purasiri et al. 1994), and nettle leaf extract (Teucher et al. 1996). Antioxidants, such as vitamin E (Devaraj et al. 2000) and N-acetyl-cysteine (Gosset et al. 1999), may also lower pro-inflammatory cytokines and protect against their toxic effects.

Prescription drugs like Enbrel ($10,000 a year) directly bind to TNF-a and block its interaction with TNF cell surface receptors. Enbrel has demonstrated significant clinical improvement in rheumatoid arthritis patients, as have high-dose fish oil supplements (Kremer 2000). High levels of TNF-a may persist even in people receiving Enbrel drug therapy. Even if Enbrel brings TNF-a down to a safe range, other inflammatory cytokines such as IL-6 and IL-1(b) may continue to wreak havoc throughout the body. High levels of tumor necrosis factor (TNF-a) are destructive to many vital tissues such as joint cartilage (e.g., rheumatoid arthritis) and heart muscle (e.g., congestive heart failure).

Excess IL-6 and other inflammatory cytokines attack bone and promote the formation of fibrinogen that can induce a heart attack or stroke (di Minno et al. 1992). To prevent and treat the multiple diseases of aging, it is critical to keep these destructive immune chemicals (cytokines) in safe ranges.

Methods of Lowering Elevated C-Reactive Protein

Those who are in relative good health, but have elevated C-reactive protein, can try to lower it using a variety of diet modifications, supplements and/or drugs. Supplements
such as vitamin E, borage oil, fish oil, DHEA, vitamin K and nettle leaf extract can lower C-reactive protein. Diets low in arachidonic acid, omega-6 fatty acids, saturated fats, high-glycemic food and overcooked food can suppress inflammatory factors in the body.

If diet and supplements fail, drugs such as ibuprofen, aspirin, pentoxifylline or one of the statins (such as Pravachol®) should be tried. If the modified diet, nutrients and/or drugs lower C-reactive protein to below 1.3 (mg/L) of blood, then this is an indication that the underlying inflammatory fire has been extinguished. (The high-sensitivity C-reactive protein blood test is recommended to measure this indicator.)

For those whose blood tests reveal persistently high inflammatory cytokine levels despite taking the supplements mentioned above, a low-cost prescription drug may be of enormous benefit.

The generic name of this low-cost prescription drug is pentoxifylline (PTX); the brand name is Trental. This drug was first used in Europe in 1972 and long ago was removed from patent status (meaning it is not cost-prohibitive). PTX is prescribed to improve blood flow properties by decreasing its viscosity. It works by improving red blood cell flexibility, decreasing platelet aggregation, and reducing fibrinogen levels (de la Cruz et al 1993; Gara 1993; Gaur et al. 1993). PTX has fallen from favor because no drug company has the economic incentive to market it to physicians. PTX is primarily prescribed to patients with peripheral artery disease, although it may have potential efficacy in treating a wide range of diseases relating to chronic inflammation.

Numerous studies show that pentoxifylline (PTX) is a potent inhibitor of TNF-a, IL-1(b), IL-6, and other pro-inflammatory cytokines (Neuner et al. 1994; Noel et al. 2000; Pollice et al. 2001; Ventura et al. 2001). Similarly, studies also show that DHA fish oil suppresses these same cytokines (Das 2000; Yano et al. 2000). In people who have a chronic disease involving elevated levels of the inflammatory cytokines, the daily administration of 400-800 mg of PTX and/or 1000-2000 mg of DHA fish oil could be of enormous benefit.

Individuals with chronic disease sometimes find it difficult to suppress C-reactive protein. In these cases, it is important to identify the specific inflammatory cytokines that are responsible for the destructive inflammatory processes that is causing or contributing to the underlying disease state. This enables a custom tailored program to be implemented, and its success measured by suppressing the pro-inflammatory cytokine culprits. For instance, if levels of TNF-a levels are elevated, and natural approaches fail to lower it, the prescription drug Enbrel should be considered.

**Inflammatory Cytokine Blood Testing**

People suffering from chronic disease often have elevated levels of C-reactive protein in their blood. C-reactive protein indicates an inflammatory process is going on in the body, but does not identify the specific pro-inflammatory cytokine that may be the underlying cause.

Testing for pro-inflammatory cytokines has been prohibitively expensive because there has been so little demand for it. The Life Extension Foundation offers an inflammatory cytokine profile at an affordable price. Below is the cytokine panel for this test along with the optimal anti-inflammatory ranges:
As stated earlier in this chapter, an inexpensive C-reactive protein (high-sensitivity) blood test (CRP-hs) can help reveal if you have systemic inflammation. If your C-reactive protein level is over 1.3 (mg/L), this is an indication that you have an inflammatory event occurring in your body. Those with elevated CRP-hs levels (and who have a disease associated with chronic inflammation) should consider using a supplement protocol and/or prescription drugs known to suppress elevated pro-inflammatory cytokines.

**The Importance of Cytokine Testing for Those Suffering From Chronic Illness**

There are many chronic disease states that can now be managed by the proper utilization of the Inflammatory Cytokine Blood Panel. If you are elderly, or suffer from any serious disorder, these cytokine tests can enable your doctor to prescribe therapies that specifically target the inflammatory cytokine responsible for your poor state of health.

From a practical standpoint, if you suffer from congestive heart failure, and your levels of TNF-a remain persistently high, you may ask your doctor to prescribe the drug Enbrel®, which specifically counteracts the destructive effects of TNF-a.

If you suffer from cancer and your levels of IL-6 remain persistently high, you may consider high dose DHEA or asking your doctor to prescribe a bisphosphonate drug (such as Zometa® that protects against bone destruction that releases excess IL-6 into the body. Those with prostate, certain types of breast cancer, and other hormonally driven cancer should consider other IL-6 lowering therapies (such as high dose DHA fish oil extract) in lieu of DHEA.

Some cancer and patients display elevated levels of IL-8, which induces cancer cells to express growth factors that fuel their propagation. In hepatitis C, elevated IL-8 signals interferon drug resistance. An IL-8 suppressing therapy will soon be available to Americans (it is already used in Japan).

Those with systemic inflammatory disease often manifest high levels of IL-1b. If diet, the anti-inflammatory supplements (fish oil, borage oil, DHEA, etc.) and cytokine-suppressing drugs (pentoxifylline, 400 mg twice a day) fail to suppress this destructive cytokine, then ask your doctor to prescribe the drug Arava (leflunomide), starting at the low dose of 10 mg a day.

**Diet and Inflammation**

In addition to toxic cytokines, there are other inflammatory pathways that can be mediated via diet modification. A common problem involves overproduction of pro-inflammatory hormone-like "messengers" (such as prostaglandin E2) and underproduction of anti-inflammatory "messengers" (such
The good news is that omega-3 fatty acids found in fish oil help to suppress the formation of undesirable prostaglandin E2 and promote synthesis of beneficial prostaglandin E3 (Kelley et al. 1985; Watanabe et al. 2000). Gamma-linolenic acid (GLA) induces production of the anti-inflammatory prostaglandin E1 (Das et al. 1989; Fan et al. 1997). What you eat can significantly affect whether you have more of the beneficial prostaglandins (E1 and E3) as opposed to the pro-inflammatory prostaglandin E2.

Because prostaglandin E2 is a culprit in inflammation, reducing the consumption of foods that are high in omega-6 fatty acids and increasing the consumption of omega-3 rich foods, such as salmon and other fish, can be beneficial. Limiting foods that convert to arachidonic acid can help reduce inflammation. Arachidonic acid is a precursor to both prostaglandin E2 and the pro-inflammatory cytokine leukotriene B(4) (Brock et al. 1999). Another dietary factor that can lead to high levels of arachidonic acid is the overconsumption of high-glycemic index carbohydrates that cause excess production of insulin (Kreisberg et al. 1983). These quickly digestible foods include fruit juices or rice cakes. Food heavy in polyunsaturated fats or saturated fats can also increase prostaglandin E2.

Additionally, a study of elderly patients with heart disease requiring elective surgery (Tepaske et al. 2001) found that nutritional supplements containing omega-3 polyunsaturated fatty acids (as well as yeast and L-arginine) improved the outlook for high-risk patients when given a minimum of 5 days prior to surgery.

The number of inflammatory-related diseases that could be successfully treated with cytokine-lowering therapy is staggering. PTX and supplements such as fish oil, nettle leaf, DHEA, and vitamin K possess mechanisms of suppressing inflammatory cytokines. Unfortunately, there are no side-by-side comparisons to enable us to categorically state whether PTX or natural agents (such as DHA fish oil) work better.

Foods cooked at high temperatures can produce a browning effect in which glycotoxins are formed from the reaction of sugars and oxidized fats with protein. Glycotoxins may contribute to low-grade chronic inflammation. High glycemic foods may also contribute to the inflammatory process. Dietary modifications to reduce inflammation should include elimination of foods and cooking processes that contribute to a chronic state.

For those who have multiple degenerative diseases, the cytokine profile blood test and the C-reactive protein blood test are highly recommended. This may be done through your own physician or the Life Extension Foundation. If your cytokine test reveals excess levels of cytokines such as TNF-a, IL-1(b), or both, nutritional supplementation, dietary modifications, and low-cost prescription medications such as PTX are advised.

The following supplements are suggested:

- The docosahexaenoic acid (DHA) fraction of fish oil may be the most effective nonprescription supplement to suppress pro-inflammatory cytokines. Gamma-linolenic acid (GLA) is a precursor of PGE1, a potent anti-inflammatory agent. A product called Super EPA/DHA provides 1400 mg of EPA and 1000 mg of DHA in 4 capsules.

- DHEA is a hormone that decreases with age. DHEA has been shown to suppress IL-6, an inflammatory cytokine that often increases as people age. Typical doses of DHEA are 25-50 mg daily, although some people take 100 mg daily. Refer to the DHEA Replacement protocol for suggested blood tests to safely and optimally use DHEA.

- Nettle leaf (Urtica) has been shown to suppress the proinflammatory cytokine TNF-a. Take 1000 mg daily.

- Vitamin E, richest in sunflower oil, and N-acetyl-cysteine (NAC) are protective antioxidants with anti-inflammatory properties. Vitamin E that contains gamma-tocopherol and tocotrienols provides the most broad-spectrum protection. Take 1 capsule daily of Gamma E Tocopherols with Sesame Lignans and Tocotrienols with Sesame Lignans. NAC is an amino acid with antiviral and liver protectant properties. One 600 mg capsule daily is recommended.

- Vitamin K, rich in cabbage juice, helps reduce levels of IL-6, a pro-inflammatory messenger. Vitamin K also helps in the treatment of osteoporosis by regulating calcium and promoting bone calcification. One 10 mg capsule daily is recommended for prevention purposes. Do not take
vitamin K if you are taking Coumadin or some other type of anticoagulant medicine.

- Consuming at least 1000 mg per day of carnosine can inhibit pathological glycation reactions in the body.

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Stress, Inflammation, and Yoga Practice


Abstract

Objective

To address the mechanisms underlying hatha yoga's potential stress-reduction benefits, we compared inflammatory and endocrine responses of novice and expert yoga practitioners before, during, and after a restorative hatha yoga session, as well as in two control
conditions. Stressors before each of the three conditions provided data on the extent to which yoga speeded an individual's physiological recovery.

Methods

50 healthy women (mean age=41.32, range=30–65), 25 novices and 25 experts, were exposed to each of the conditions (yoga, movement control, and passive-video control) during three separate visits.

Results

The yoga session boosted participants’ positive affect compared to the control conditions, but no overall differences in inflammatory or endocrine responses were unique to the yoga session. Importantly, even though novices and experts did not differ on key dimensions including age, abdominal adiposity, and cardiorespiratory fitness, novices’ serum IL-6 levels were 41% higher than those of experts across sessions, and the odds of a novice having detectable CRP were 4.75 times as high as that of an expert. Differences in stress responses between experts and novices provided one plausible mechanism for their divergent serum IL-6 data; experts produced less LPS-stimulated IL-6 in response to the stressor than novices, and IL-6 promotes CRP production.

Conclusion

The ability to minimize inflammatory responses to stressful encounters influences the burden that stressors place on an individual. If yoga dampens or limits stress-related changes, then regular practice could have substantial health benefits.

Keywords: yoga, inflammation, psychoneuroimmunology, complementary medicine, IL-6, CRP

Inflammation is a robust and reliable predictor of all-cause mortality in older adults (1). Proinflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) play a role in cardiovascular disease, type II diabetes, arthritis, osteoporosis, Alzheimer's disease, periodontal disease, and frailty and functional decline (2–3). In addition, inflammation is now regarded as a risk factor for most cancers because of the evidence that inflammation influences tumor promotion, survival, proliferation, invasion, angiogenesis, and metastases (4). Behavioral lifestyle factors can substantially influence inflammation. Obesity has been characterized as a state of chronic inflammation because of the elevated plasma levels of IL-6, TNF-α, and CRP (5). One obvious mechanism is provided by the fact that adipocytes (fat cells) are capable of producing and secreting IL-6 and TNF-α; in fact, up to 30% of IL-6 may be derived from adipose tissue (6). Physical activity is also an important behavioral cofactor; people who describe themselves as active have lower levels of inflammatory biomarkers than their sedentary counterparts (7). Indeed, when physical or cardiorespiratory fitness is assessed rigorously and objectively by maximal exercise testing, fitness is inversely associated with inflammation, even after adjusting for confounds including age, smoking, medications, and visceral fat (8–11). Although regular physical activity is associated with lower levels of IL-6 and other proinflammatory cytokines, acute exercise transiently boosts production and release of IL-6 from skeletal muscles; the IL-6 that is released during physical activity inhibits TNF-α
production and can induce IL-10 production, one mechanism underlying exercise’s anti-inflammatory function (1). Lower levels of circulating IL-6 at rest as well as following exercise appear to be the normal adaptation to training (12).

In addition to exercise and obesity, behavior affects inflammation through other pathways; even relatively modest levels of anxiety and depressive symptoms can raise proinflammatory cytokine production (13). Additionally, psychological stressors can directly provoke transient increases in proinflammatory cytokines (14–15), and chronic stressors have been linked to sustained overproduction of IL-6 (16–17).

Yoga’s reputation for stress reduction and mental health benefits has bolstered its popularity in recent years, and data from randomized trials suggest that yoga reduces symptoms of anxiety and depression (18–19). Hatha yoga, the most common form practiced in the western world, combines body postures or asanas, breath control or pranayama, and meditation (20). Mechanistic explanations for yoga’s potential mental and physical health benefits have highlighted reductions in sympathetic nervous system tone (21–22), and increases in vagal activity (22), both of which could have favorable endocrine and immune consequences, including lower inflammation.

In fact, one recent randomized trial suggested that yoga might have positive benefits for inflammation; 9 heart failure patients randomized to a two-month hatha yoga intervention showed a 22% reduction in IL-6 and a 20% reduction in CRP compared to minimal change in the 10 patients who received standard medical care (23). In contrast, CRP did not change following a 6-week nonrandomized trial in 33 individuals both with and without established coronary artery disease, but the group did show significant reductions in blood pressure, heart rate, and body mass index (BMI) (24). Surprisingly few studies have attempted to relate endocrine or immune function to yoga practice, even though some hatha yoga postures are characterized as immune enhancing or restorative (25).

We assessed cardiovascular, inflammatory, and endocrine responses in novice and expert yoga practitioners before, during, and after a hatha yoga session, as well as in two control conditions. To test yoga’s restorative potential, stressors preceded each of the three conditions, providing data on the extent to which yoga speeded an individual’s physiological recovery. In addition, tape stripping a small area of forearm skin before each of the conditions provided data on the course of skin barrier repair, a stress-sensitive process modulated by both cortisol and cytokine production (26–27).

The ability to minimize autonomic and inflammatory responses in stressful situations undoubtedly influences the burden that stressors place on an individual. Thus, we designed this study to assess yoga’s ability to promote recovery from a stressor. We elected to conduct the yoga session after the stressor, rather than prior to the stressor, for several reasons. First, anticipation of a stressor following the yoga session could reduce participants’ ability to fully relax and concentrate during the yoga session, particularly among novices; completing the stressor prior to the yoga session could allow for a more relaxing yoga experience, providing greater power to detect effects of yoga. In addition, our ability to track changes in physiological markers of interest during the yoga session was improved by eliciting a physiological response prior to the session. Finally, using a stressor prior to the yoga session allowed us to examine whether regular yoga practice resulted in differential magnitude of reactivity to the stressor, independent of the effects of a recent yoga session.

We hypothesized that: (1) experienced yoga practitioners would have lower levels of inflammation, and smaller autonomic, endocrine, and inflammatory responses to the stressors than novices. (2) During and following the yoga session, subjects would demonstrate more rapid declines (recovery) in stress hormones and proinflammatory...
cytokine production, and better skin barrier repair than evidenced following either of the control conditions. Mood measures would reflect greater positive change following yoga compared to the control conditions.

METHOD

Participants

Women were recruited through online ads and notices posted in yoga studios. All women participated in some form of hatha yoga. We excluded women who were taking medications with obvious immunological or endocrinological consequences, as well as individuals who had chronic health problems with implications for these systems (e.g., cancer, recent surgeries, diabetes, etc.). Additional exclusion criteria included smoking, use of statins, beta blockers, psychoactive drugs, excessive alcohol use, convulsive disorders, or a BMI ≥ 30.

The average age of the final sample of 50 women who completed all 3 visits was 41.32 (SD=10.33, range=30–65); 44 were white, 3 were African American, 2 were Native American, 1 was Asian, and all had at least some college education. One expert and one novice dropped out after one session because of time constraints. Data were collected between August, 2005 and October, 2008.

Screening Session

Participants were screened and classified as novices versus experts using a two-step process. First, participants completed an online screening questionnaire assessing the type, frequency, and duration of yoga practice over the past year and over their lifetimes. Women were classified as novices if they had participated in yoga classes or home practice with yoga videos for 6–12 sessions. Experts had practiced yoga regularly 1–2 times per week (75–90 min sessions) for at least 2 years, and at least 2 times per week for the past year. Others were rated as intermediate and deemed not eligible for further participation. Each participant was classified by two raters. Raters conferred when classifications were discrepant, obtaining additional information as needed to reach consensus.

The screening session was used to assess yoga skills, flexibility, and cardiovascular fitness. Participants performed 8 selected poses under the guidance of an experienced instructor, blind to their reported experience, who evaluated their form to assure that novices and experts had skills commensurate with their self-reports. Each pose was rated on a 1–5 scale, focusing on 5–7 indicators of form specific to the pose, with higher ratings indicating better form. Four women were excluded because their self-report indicated expert practice, but they showed lack of familiarity and/or limited ability to perform poses during the screening session. To further objectively characterize hamstring and low back elasticity, participants completed the sit-and-reach test, a common flexibility test (28). Sagittal abdominal diameter (SAD) measurements provided data on the total amount of abdominal fat. Validational studies using computerized axial tomography and dual-energy X-ray absorptiometry have demonstrated its utility as a noninvasive central adiposity measure (29).

Cardiopulmonary endurance was evaluated during a maximal graded cycle ergometry exercise test, starting at 25 watts and increasing by 25 watts every two minutes, with continuous monitoring via 12-lead EKG (MedGraphics Cardio2, Cardio Perfect). Maximum
oxygen consumption (VO₂max) was calculated from 10-second averages of breath-by-breath expired air (MedGraphics Cardio2, Breeze Suite).

Three Clinical Research Center (CRC) Visits

Each participant completed three CRC sessions (yoga and two control conditions), scheduled at least 2 weeks apart. The order of the three conditions was randomly assigned. Each visit followed the timeline, illustrated in Figure 1, differing only in the condition randomized for that visit; participants returned for a 30 minute follow-up the morning after each session. On arrival, participants completed questionnaires and ate a standardized breakfast after fasting since midnight. A heparin well was placed in one arm for subsequent serial blood draws, and remained in place until the end of each 6-hour session. Next they rested in a hospital bed for a 20-minute relaxation period, and then provided baseline blood and saliva samples.

Figure 1
Timeline for experimental participation during each of the three CRC sessions.

A tape-stripping session followed the baseline blood samples (26, 30). Skin barrier disruption was evaluated by measuring transepidermal water loss (TEWL), as described under skin barrier studies. During the next 12–14 minutes subjects participated in a Stroop task which served both as a mild stressor and an unobtrusive mood measure. Two additional stressors (a cold pressor test and mental arithmetic), described below, preceded each of the three conditions. Catecholamine samples were drawn from the catheter twice during each of the conditions and again at the end, as shown in Figure 1; we had successfully piloted catheter placement so that we could obtain blood samples during the conditions without disturbing the subjects or the condition routine. To control for the known positional effects in stimulating catecholamine release, subjects spent the same amount of time lying down in the movement and video conditions before each of these blood draws as they did in the yoga session (in the hospital bed for the former, on the yoga mat for the latter).

Following the hour and 15-minute intervention and blood draws, participants completed another Stroop task. Subjects remained in the CRC until approximately 1:30 PM, with additional TEWL measurements of the tape-stripped sites, as well as regular salivary cortisol sampling and a standardized lunch. Participants returned at 7:30 AM the following morning for a final blood draw.

Hatha yoga condition

Iyengar yoga, the form of hatha yoga used in this study, emphasizes the use of props to help students achieve precise postures safely and comfortably according to their particular body types and needs. The screening sessions and the yoga condition sessions were directed by four experienced yoga teachers following a script. The poses were chosen based on their purported relationship to immune function and/or restorative effects (25). A restorative session was selected rather than a vigorous sequence in order to best promote recovery from the stressor. In addition, we wanted poses that could be performed without undue strain by
both novice and experienced practitioners so we could compare endocrine and inflammatory changes in the two groups.

The poses used were (in order) Supta Baddha Konasana (Reclining Bound Angle Pose), Adho Mukha Svanasana (Downward Facing Dog), Supported Uttanasana (Intense Forward Stretch), Parsvotanasana (Intense Side Stretch Pose), Prasarita Padottanansana (Wide-Legged Forward Bend), Janu Sirsasana (Head to Knee Pose), Bharadvajasana (Simple Seated Twist Pose), Viparita Karani (Restful Inversion), Supported Setu Bandha Sarvanagasana (Bridge Pose), and Savasana (Corpse Pose). Blood draws occurred during the last two minutes of Supta Baddha Konasana (pose held 10 minutes), Viparita Karani (10 minutes), and Savasana (15 minutes).

Control conditions

Walking on a treadmill at .5 miles per hour was used to control for general physical movement/cardiovascular expenditure because it best approximated the heart rates during the restorative yoga session. To match the lower heart rate, women also rested supine on a bed for several minutes after walking, before and after getting their blood drawn.

The second control condition, a neutral video that did not include any music, allowed us to contrast the effects of yoga with no activity. It included a sequence on how to design physics experiments for a high school classroom, as well as segments from two lectures on polymers and quantum mechanics.

Self-Report Measures

During the screening session participants completed the version of the Food Frequency Questionnaire (FFQ) validated for the Women’s Health Initiative (31). Participants reported the type, frequency, and quantity of foods and beverages consumed in the past 90 days. The Pittsburgh Sleep Quality Index assessed sleep quality and disturbances over a one-month interval; it has good diagnostic sensitivity and specificity in distinguishing good and poor sleepers (32). Completed during the screening session, we also assessed sleep prior to and following each visit.

Evidence suggests that the scales of the Mood and Anxiety Symptom Questionnaire (MASQ) measure anxiety and depression well, with limited overlap, compared with other self-report measures (33–34). The MASQ was administered during the screening session and at the beginning of each of the three admissions.

The Positive and Negative Affect Schedule (PANAS) includes two 10-item mood scales (35). The positive and negative scales are largely uncorrelated, and show good convergent and discriminant validity when related to state mood scales and other variables (35). Several additional words were added to better capture low positive affect: happy, satisfied, disappointed, discouraged, low, sad (36). The PANAS was administered during the screening session, as well as three times during each CRC visit (at baseline, after the intervention, and at the session's end).

Stressors

For the emotional Stroop, participants name the color in which negative or threatening words are printed. Following work by Mogg et al. (37), we used 60 words (divided into three sets) from their lists in each of the following categories: anxiety- and depression-relevant
negative words, positive words, and neutral household words. Interference scores were calculated as previously described (30).

Widely used in behavioral and psychophysiological research, the cold pressor provides a reliable and safe way to induce mild acute pain and provoke endocrine and inflammatory changes (15, 30). After sitting for a 15-minute adaptation period, participants immersed their right foot for 2 minutes in warm (37° C) water, and then immersed their foot in a pan of 4° C water for 1 minute (38).

After the cold pressor, the participant performed mental arithmetic serial subtraction tasks for 5 minutes. To maintain a high level of task difficulty and involvement, the subtrahend was reset each minute based on performance in the preceding minute, such that better performance led to more demanding subtraction (39). When participants made a mistake, the experimenter administering the task said “error,” and gave them the correct number.

**Endocrine Data**

All cortisol and catecholamine samples for a subject were frozen after collection and analyzed within the same assay run after the participant had completed the study. Assay methods are described in prior publications (30, 39).

**Skin Barrier Assessment**

Cellophane tape stripping, a common dermatological paradigm for studying restoration of the skin barrier, was used to examine whether the time necessary for recovery from minor physical insults varied by condition or yoga expertise. Measurement of the rate of transepidermal water loss (TEWL) through human skin provides a noninvasive method to monitor changes in the skin’s barrier function as previously described (30). TEWL was measured twice during the session using a computerized evaporimetry instrument, the DermaLab® (CyberDERM, Media, PA), and barrier recovery was calculated (26).

**Cardiovascular Data**

Participants wore a Polar™ heart rate monitor which sampled beat by beat intervals. Heart rate was monitored throughout the yoga and activity control exercise sessions.

**Immunological Data**

We assayed IL-6, the soluble IL-6 receptor (sIL-6r), TNF-α, CRP, as well as LPS-stimulated production of IL-6 and TNF-α. Elevated levels of these cytokines, including the sIL-6r, are associated with an activated inflammatory response. Serum levels of TNF-α, IL-6, and the sIL-6r were assayed using Quantikine High Sensitivity Immunoassay kits (R&D), per kit instructions (16, 40).

In addition, supernatants from PBLs stimulated with 5µg/ml lipopolysaccharide (LPS) for 72 h were assayed for IL-6 and TNF-α using ELISA kits (B–D Pharmingen). Unstimulated cells incubated in media were used as a control. The assay was run according to kit instructions. Blood samples were obtained prior to each condition in the morning, immediately following the two stressors, after the condition, and at the end of the day for stimulated cytokine production. Because the time course for stress-induced changes in serum cytokine levels is slower than for stimulated cytokine production (15), we omitted the immediate post-stressor sample for serum cytokines.
The high sensitivity C-reactive protein (hsCRP) assay was performed using chemiluminescence methodology with the Immulite 1000 (Siemens Medical Solutions, Los Angeles, Ca.) The lowest level of detection is .3 mg/dL. Intra-assay coefficient of variation is 5.1% and inter-assay coefficient variation is 7.3%.

**Statistical Analyses**

Mixed models from SAS 9.1 (SAS Institute Inc, Cary, NC) were used to analyze differences between novices and experts in the repeated measures across the three visits, and differences between time points within visits. The three-way interaction of expertise by condition by time, as well as all lower order interactions and main effects were considered; visit order number was included as a possible confounding variable. For all cytokine analyses, the MASQ depression score from each visit and the participant’s age, VO₂max, and SAD were included as additional possible confounding variables. A heterogeneous Toeplitz covariance structure was used to account for the unequal distance between time points and allow for some flexibility in the estimation of variances/covariances parameters without reducing power by allowing for unnecessary complexity. Application of the Kenward-Roger correction (41) to the degrees of freedom brought Type I errors rates back to the nominal level (42), sometimes resulting in noninteger values for degrees of freedom. Log (base 10) transformations were used for serum IL-6 and TNF-α, LPS-stimulated TNF-α production, epinephrine, and norepinephrine to correct for nonnormality. The hsCRP values and the PANAS negative mood scale could not be normalized and thus were dichotomized and analyzed with logistic regression. All tests used a 2-sided, α = .0.5 significance level; when necessary, p-values for unplanned multiple comparisons were adjusted using the Tukey-Kramer procedure (43). For planned comparisons with multiple tests, the family-wise Type I error rate was set at α = .15 and a Bonferroni adjustment was used to determine critical p-values for individual tests.

**Results**

As shown in Table 1, novice and expert practitioners did not differ on key variables that have been associated with inflammation. Seven women in each of the groups were postmenopausal. As a consequence of our stringent exclusion criteria, overall medication use was low; novices and experts did not differ in the proportion reporting use of aspirin, ibuprofen, or other over-the-counter analgesics, ps > .39, birth control pills, hormone replacement therapy, omega-3 supplements, or a daily multivitamin, ps > .23.

![Table 1](image)

**Table 1**

Mean (SD) demographic, physiological, dietary, and behavioral data for novice and expert yoga practitioners
Mean ratings of novices’ (21.92, SD=4.93) and experts’ (31.86, SD=4.83) ability to perform common yoga poses, assessed during the screening session, were clearly different, \( F(1,48) = 51.82, P < .000 \). Similarly, novices \((M=31.88, SD=7.77)\) had substantially less hamstring and low back flexibility than experts \((M=41.81, SD=5.19)\), producing the expected differences on the sit-and-reach test, \( F(1,49) = 27.91, P < .001 \).

**Self-Report and Behavioral Data**

There was a significant time by condition interaction for PANAS positive affect, \( F(4, 198) = 14.49, P < .001 \) (**Figure 2**). Participants’ positive mood scores increased following yoga, decreased following the video, and were unchanged following movement.

**Figure 2**
Mean (± SEM) changes in self-reported positive affect on the PANAS as a function of time and condition. Experts and novices did not differ.

Due to a lack of variability in PANAS negative affect scores, values were dichotomized as “at the minimum” \((n = 280, 62.36\%)\) and “above the minimum” \((n = 169, 37.64\%)\). Logistic regression on the transformed values was conducted with Generalized Estimating Equations (GEEs) using an unstructured covariance matrix to account for the repeated visits. Results revealed a significant time main effect, \( X^2(1) = 14.35, P < .001 \), and a significant time by yoga expertise interaction, \( X^2(2) = 5.45, P < .02 \). Experts were more apt to report negative affect above the minimum at the end of the conditions than novices. Stroop interference scores showed no differences for either the positive or negative emotion words as a function of time, expertise, condition, or their interactions, all \( P_s > .24 \). However, as illustrated by the heart rate increase (**Figure 3**), the Stroop did function as a mild stressor.

**Figure 3**
Mean (± SEM) heart rate throughout the admissions as a function of novice vs. expert yoga practitioner status. * denotes \( P = .03 \).

**Sleep**

Novices and experts did not differ in hours of sleep the night before the CRC visits, \( F(1,47.8) = 0.63, p = .43 \). However, after controlling for the previous night’s sleep, novices \((M = 6.75, SD = .93)\) reported significantly fewer hours of sleep than experts \((M = 7.24, SD =1.00)\) following the 6-hour days in the CRC, \( F(1,46) = 5.94, P = .02 \).

**Skin Barrier Repair**

The speed of skin barrier repair following tape stripping did not differ as a function of expertise, condition, time, or their interactions, all \( P_s > .08 \).
Heart Rate

Analysis of participants’ heart rates revealed significant main effects for time and condition, as well as significant interactions between time and yoga expertise, $F(7, 247) = 3.97, P < .001$, and time and condition, $F(14, 359) = 15.47, P < .001$. Comparisons were planned between novices and experts for heart rate during the stressor, as well as three values collected well into the condition. Using a critical $p$-value of .038, experts had lower heart rates than novices during the stressor, $t = 2.30, P = .025$ (Figure 3); no other tested time points reached even an uncorrected level of significance, all $P$’s > .08. Additionally, the degree of change from the Stroop to the stressors differed between the expertise levels, $t=2.16, P = .035$, with novices exhibiting larger responses to the stressors than experts. For the time by condition interaction, a critical $P$-value of .025 was used to compare yoga to the other two activities at time points during and after the condition. Participants’ heart rate during the yoga condition was higher than when in the video condition 10 minutes into the intervention, $t=9.61, P < .001$, and lower than the video condition at the end of the intervention, $t=3.05, P = .004$; similarly, yoga was higher than movement 10 minutes into the condition, $t=2.41, P = .02$, and lower post-condition, $t=4.96, P < .001$. However, as planned in the experimental design, the overall mean heart rate during the yoga condition did not differ from that in the movement condition, $P = .17$.

Cortisol and Catecholamines

The significant time effect for cortisol reflected the normal diurnal fall across the morning as well as the usual post-lunch increase, $F(6, 371) = 80.21, P < .001$. There were no significant group or condition effects or interactions. There was a significant condition by time interaction for norepinephrine, $F(10, 318) = 8.08, P < .001$. Similar to the heart rate data, participants’ norepinephrine response after 10 minutes of the yoga was significantly higher than the same interval in either the video, $F(1,121) = 27.42, P < .001$, or the movement condition, $F(1,121) = 12.77, P < .001$. Novices and experts did not differ in norepinephrine production, $F(1, 46.1) = .34, P = .56$. The significant time effect for epinephrine reflected a post-stressor peak value for the session, followed by a decrease through the conditions, $F(5,341) = 12.62, P < .001$. In addition, experts had higher overall levels of epinephrine than novices, $F(1,48.5) = 8.26, P = .006$, a surprising finding in view of the norepinephrine and heart rate data. Examination of raw data showed that 4 experts and 1 novice were outliers across time; comparisons between these individuals and the remainder of the sample showed significantly fewer hours of sleep prior to the three visits, $F(1,49)=9.52,P=.003$, but no differences in affect, other health behaviors, or inflammation.

Serum Cytokines and hsCRP

Experts had lower overall IL-6 serum levels than novices, $F(1,45.7) = 4.98, P = .03$. Indeed, novices’ average IL-6 values were 41% higher than those of experts (Figure 4). Additionally, although the group effect did not reach traditional significance levels for either sIL-6r, $F(1,43.5)=3.55, P = .07$, or TNF-$\alpha$, $F(1,45.3)=2.25, P = .14$, both were in the expected direction, with lower levels of inflammation in yoga experts compared to novices.
Figure 4
Mean (± SEM) serum IL-6 as a function of novice vs. expert yoga practitioner status also reflect significantly elevated levels of IL-6 post-intervention.

Significant time effects were observed for all serum cytokines, all F(8,268) > 16, all Ps < .001. Specifically, we observed elevations in IL-6 at the sessions’ end compared to the following morning, t=12.40, adj. P < .001 (Figure 4). For sIL-6r, levels were higher at the sessions’ end, \( t=4.90, \) adj. P < .001, and the next morning, \( t=6.11, \) adj. P < .001, compared to baseline. Although TNF-α did not increase at the sessions’ end, it did rise the following morning, \( t=4.76, \) adj. P < .001.

We assessed hsCRP once at baseline at each of the three visits; 43% of the values (\( n = 65 \)) were below the assay’s detectable lower bound of .3 mg/dL, and thus hsCRP was dichotomized as undetectable/detectable. The logistic regression with GEEs analysis showed that the odds of a novice having a detectable hsCRP level were 4.75 times that of experts (\( \beta = -1.55, \) P = .009).

LPS-Stimulated Cytokine Production

The expertise by time interaction for stimulated IL-6 production, \( F(4,275) = 2.57, \) P < .04, is shown in Figure 5. A planned comparison showed that experts produced less IL-6 in response to the stressors than novices (\( M_{\text{diff}} = 26076, \) SE\(_{\text{diff}} = 13104), F(1,53.1) = 3.96, P = .05. No other time points approached significance (all Ps > .14). Stress-induced LPS-reactivity was significantly correlated with total serum IL-6, \( r=.33, \) P =.02.

Figure 5
Mean (± SEM) LPS-stimulated IL-6 production throughout the admissions as a function of novice vs. expert yoga practitioner status. * denotes P = .05.

In the condition by time interaction for TNF-α, \( F(8,268) = 2.03, \) P = .04, values obtained immediately following the stressor were lower in the yoga condition, compared to the video and movement conditions combined (\( M_{\text{diff}} = .09, \) SE\(_{\text{diff}} = .04), F(1,133) = 2.29, P = .02. Values obtained immediately following the stressor were lower in the yoga condition, compared to the video and movement conditions combined (\( M_{\text{diff}} = .09, \) SD\(_{\text{diff}} = .36), F(1,137) = 4.90, P = .03.

To identify individuals producing high vs. low levels of inflammatory markers across the assay battery, median splits were applied to the average baseline values of our six markers: serum IL-6, TNF-α, sIL-6r, and hsCRP, and LPS-stimulated IL-6 and TNF-α production. Individuals falling into the low or high category on each marker were given a score of 0 or 1, respectively, and the summed values were grouped into low (0 or 1), medium (2 or 3) or high (4–6). Novices and experts showed very different patterns, \( \chi^2(2)=13.91, \) P < .001 (Figure 6); 60% of the novices were high producers compared to only 24% of experts, while 40% of experts were low producers and 0% of the novices.
**Figure 6**
The numbers of novices and experts falling into low, medium, or high inflammatory groups based on the number of assays on which they were above the baseline median values for serum IL-6, TNF-α, sIL-6r, and hsCRP, and LPS-stimulated IL-6 and TNF-α (more ...)

**Discussion**

Emotional and physical stressors activate immune and endocrine pathways that can enhance proinflammatory cytokine production. This study, designed as an initial investigation to address the mechanisms underlying yoga’s potential stress-reduction benefits, revealed substantial differences between novices and experts. Novices’ average serum IL-6 levels were 41% higher than those of experts, and the odds of a novice having detectable hsCRP were 4.75 times as high as that of an expert.

The differences in stress responses between experts and novices provided one plausible mechanism for their divergent serum IL-6 data. Experts produced less LPS-stimulated IL-6 in response to the stressor than novices. Monocytes/macrophages are a major source for serum IL-6, and thus greater stress-related IL-6 production by these cells would contribute to the larger downstream IL-6 pool; moreover, IL-6 has a central role in promoting CRP production (9). Furthermore, across the battery of inflammatory assays, 60% of novices were high producers compared to only 24% of experts, and 40% of experts were low producers compared to 0% of novices. These data suggest that regular yoga practice may reduce inflammation below levels predicted by such key risk factors as age, abdominal adiposity, cardiorespiratory fitness, and depressive symptoms.

In spite of these notable baseline group differences in inflammation, there were no significant differences between expert and novice practitioners in stress-induced LPS-stimulated production of TNF-α, and the groups did not differ in their stress-induced or baseline levels of cortisol and catecholamines, or in serum cytokine responses to the sessions. There are several explanations for these discrepancies. For example, a meta-analysis of cytokine responses to laboratory stressors suggested that while IL-6 is responsive to acute psychological stressors, TNF-α is not (15), and we are unaware of any data demonstrating reliable acute stress-related changes in sIL-6r. Similarly, although exercise reliably induces increases in IL-6, TNF-α does not increase with exercise; furthermore, IL-6 can inhibit LPS-induced TNF-α production (1), consistent with the declines observed in LPS-induced TNF-α production following the interventions.

Our sessions began early, when cortisol is falling from its diurnal peak, and an intervention would have had to substantially accelerate the rate of decline to show efficacy; indeed, given its half-life, change within an hour or two would require that our intervention had substantially accelerated cortisol’s metabolic breakdown. Furthermore, cortisol adversely affects skin barrier homeostasis (27), and thus our morning session’s timing was problematic for both of these secondary measures.

Despite the fact that novices’ serum IL-6 levels were 41% higher than those of experts, the magnitude of the serum IL-6 change from baseline to post-intervention did not differ between experts and novices. Exercise-related IL-6 increases are strongly predicted by mode, intensity, and duration of exercise; in addition, more fit individuals have lower basal IL-6 and smaller responses to exercise (12). The fact that novices and experts did not differ in terms of their VO₂ max and both were subjected to exactly the same intensity and duration
in exercise in the yoga and movement conditions meant that any differential change would be very difficult to detect, particularly against the background of the typical morning rise from IL-6’s diurnal nadir (44). The yoga session boosted participants’ positive affect compared to decreases in the movement and video control conditions, but we did not find differences in inflammatory or endocrine responses that were unique to the yoga session. The modest changes produced by our low intensity stressor may not have provided an optimal test of yoga’s potential restorative benefits, a limitation of the study. In addition, by designing the yoga portion of the study to be appropriate for novices and experts, we were unable to include some more advanced and purportedly more powerful poses such as full inversions (25).

A central tenet of yoga, meditation, and related practices is the idea that training can reduce stress responses, and several studies have provided supportive data. For example, participants in a compassion meditation randomized trial who practiced more frequently had a smaller rise in IL-6 in response to a laboratory stressor than those who practiced less (45). Performance of 20 minutes of Tai Chi Chih, described as “meditation through movement,” acutely diminished preejection period, an index of sympathetic activity, compared to a passive rest control (46). Individuals who had long-term training in elicitation of the relaxation response differed from novices in patterns of gene expression, and pre-post comparisons following 8 weeks of training produced some of the same differences in novices, including the NF-κB cascade, a key pathway for proinflammatory cytokine production (47). Our selection criteria required that our expert practitioners had practiced yoga for at least two years; it is possible that some of the benefits of yoga may only become evident after years of regular practice.

The ability to minimize autonomic and inflammatory responses to stressful encounters influences the total burden that stressors place on an individual. Larger, more frequent, or more persistent stress-related changes in inflammation would have negative consequences for health. Accordingly, our data provide a window on the pathways through which yoga or related practices may affect physiological functioning and health. If yoga dampens or limits stress-related immunological, endocrinological, and cardiovascular changes, then regular practice could have substantial health benefits.

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**Acronyms**

BMI

body mass index
CRC
Clinical Research Center

CRP
C-reactive protein

FFQ
Food Frequency Questionnaire

GEEs
Generalized Estimating Equations

HR
heart rate

hsCRP
high sensitivity C-reactive protein

IL-6
interleukin 6

LPS
lipopolysaccharide

MASQ
Mood and Anxiety Symptom Questionnaire

PANAS
Positive and Negative Affect Scale

PBLs
peripheral blood leukocytes

SAD
sagittal abdominal diameter

sIL-6r
soluble IL-6 receptor
TEWL
transepidermal water loss

TNF-α
tumor necrosis factor-alpha

VO₂max
maximum oxygen consumption

Footnotes

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