

Starting Strength

Stopping the Spread of Misinflammation

by

Jonathon Sullivan

INTRODUCTION: LOTS OF HEAT, LITTLE LIGHT

There's an idea floating around out there, in that ill-defined nebula that we could call the Fitness Community, that seems to be picking up steam. It's an idea whose proponents pride themselves on being iconoclastic and cutting edge, on slaying sacred cows, on bashing the longstanding conventional wisdom of clueless doctors and fuddy-duddy ironheads of the Old Guard. A recent and apparently virulent exposition of the idea can be found in [this video](#), a presentation that will allegedly "blow your mind."

As expounded in this video and other sources (see, for example, [here](#), [here](#), [here](#), and [here](#)) the idea is this: inflammation is how we heal, how we get huge, and how we get strong. Therefore, things that suppress inflammation are bad for you. From which it follows directly that acetaminophen, aspirin, nonsteroidal anti-inflammatory drugs and cryotherapy (cold therapy; ice and other such interventions) are no-nos. *We Were Wrong* about ice and NSAIDs, the daring iconoclasts tell us, charitably including themselves among those who once cleaved to superstition, and thereby underscoring the difference between themselves and those benighted souls who still won't see the light. *So Wrong*.

To be fair, the idea that interfering with the inflammation of injury or training would slow your healing or hold back your gains is not new. For example, Abadjiev and other exponents of the [Bulgarian method](#) seem to think so.¹ Questions about the effect of anti-inflammatory interventions on healing, hypertrophy and adaptation have been bandied about in the biomedical literature for quite a while, as we'll see. What seems to have changed, at least from where I'm standing, is how confident and vociferous the proponents of these ideas have become. Watching the video (which racked up about 35,000 hits on YouTube inside of ten days), you'd think the question was settled: ice and NSAIDs will screw up your training. The science says so. At 11:05, Kelly Starrett and Gary Reinl suggest that the literature offers us a scientific consensus on this issue. So it must be true.

Right?

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Well...let's put a pin in that. Let's step back, and take a look at where all this is coming from. From where I sit, the *anti-anti-inflammation* (AAI) guys seem to be coalescing around the following arguments:

1. **Inflammation is the body's natural—and therefore correct—response to injury.** Your body knows what it's doing, so interfering with the inflammatory response is ill-considered from the git-go.
2. **Without inflammation, the body would never heal.** You want to heal, don't you? So why in the world would you intervene in the inflammatory process?
3. **Without inflammation, muscles cannot adapt to training stress with protein synthesis and hypertrophy.** Therefore, interfering with training-induced inflammation (i.e., delayed-onset muscle soreness (DOMS)) will stunt your gains.
4. **The scientific literature overwhelmingly supports all of these contentions,** and the issue is essentially settled for Those In The Know. In particular, many AAI exponents point to the literature review on cryotherapy published in the *Emergency Medicine Journal* by Collins in 2008²; a 2001 study by Trappe showing that ibuprofen and acetaminophen dampen post-exercise muscle protein synthesis,³ a study by Mikkelsen published in 2008⁴ concluding that anti-inflammatories block the activation of satellite cells in skeletal muscle after injury, and Novak's 2009 study of skeletal muscle hypertrophy in mice.⁵

This isn't Tinfoil Hat stuff. Right or wrong, these claims are not irrational, and they deserve to be considered. So... let's consider them, shall we?

I hope you're Getting Your Nerd On.

INFLAMMATION: A GEEKY REVIEW FOR INTERESTED ATHLETES

Inflammation is an ancient, primitive and nevertheless highly elaborate response to insult or injury—just about *any* insult or injury.⁶ Inflammation is involved when you sprain an ankle, sustain a burn, catch pneumonia, go into anaphylactic shock from a bee sting, deteriorate from a wheezing fit to status asthmaticus,^{7,8} do a high volume of heavy squats, get appendicitis, have an ischemic stroke,⁹ go into septic shock,¹⁰ or start raising antibodies against yourself, as in the autoimmune diseases. Inflammation is horribly complex in the particulars—it remains a vibrant field of investigation. But the broad scope of the process is well-understood and easily apprehended, even by doctors and fuddy-duddies.

Inflammation begins when injury, infection or some other insult exposes the tissue to pro-inflammatory substances. Such substances constitute a diverse range of biomolecules and toxins, including environmental irritants and antigens, bacterial and viral products, and inflammatory mediators produced by our own cells. These substances engage in a complex web of interactions with tissue and the immune system to trigger profound changes in the injured area, which manifest as the classic clinical signs of inflammation: *tumor*, *dolor*, *rubor* and *calor*. That's swelling, pain, redness and heat, for those of you who, like me, are a bit rusty on your Latin.

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That's the big picture. Let's fill it in by doing what people like me always do when confronted with the task of explaining complex physiology: put up some geeky cartoons with lots of arrows and tell a story.

First, let's introduce the major players:

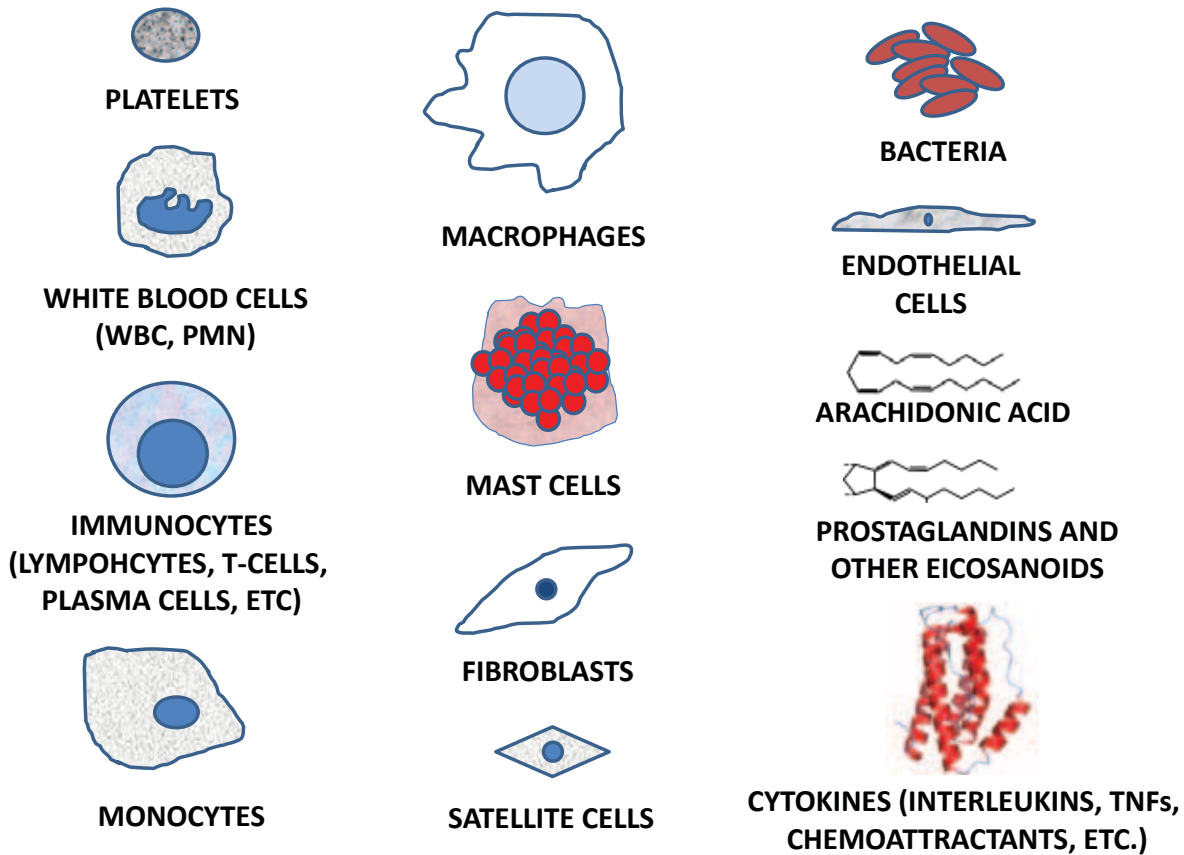


Figure 1. The major players.

Our story has a cast of thousands¹¹, but some of the major players are pictured above. **Platelets** are tiny, non-nucleated cell fragments that, as I'm sure you know, play an important role in hemostasis (suppressing bleeding). But their role in inflammation is also crucial, and there are important interactions between the hemostatic and inflammatory cascades. Platelets catalyze a number of relevant biochemical reactions on their surface membranes.^{12,13} **White blood cells** (WBCs, neutrophils, polymorphonuclear leukocytes (PMNs), granulocytes) normally hang out in the vascular space, like shock troops playing poker in the barracks, until an insult puts them on alert. Their granules are filled with digestive enzymes and other antibiotic goodies.¹¹ **Immunocytes** (L) are a large and diverse family of immune system cells with complex interactions and functions that participate in cell-mediated immunity, antibody production, and inflammatory responses. **Monocytes** (Mo) are a class of immune cells which, under the right circumstances, grow up to be macrophages. **Macrophages** (Mp) are, like WBCs, *phagocytic* cells, meaning they gobble up bacteria, foreign matter and cellular debris. But they also elaborate an array of signaling molecules, including cytokines and growth factors, important in inflammation and healing.¹¹ Like neutrophils, **mast cells** (MC) and other specialized granulocytes

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contain packets of enzymes and signaling substances. Mast cell granules are stuffed with histamine, serotonin, and proteases (enzymes that eat protein). Granule release is triggered by antibody-antigen interactions. Mast cells hang out in tissue, close to neurovascular structures, waiting for something to piss them off so they can spill their guts and Unleash Hell.¹¹ **Fibroblasts** (F) are the progenitors of scar tissue, and critical to wound healing. **Satellite cells** (S) are specialized stem cells that reside within muscle fibers and, when activated, participate directly in the repair of damaged muscle tissue.¹⁴ **Bacteria** are...well, *nasty*, and we have given them an appropriately fecal hue in our little cartoon. Depending on the species, they exude specific toxins and immunogens that can trigger a range of immune responses from local inflammation to full-blown systemic syndromes...some of them quite colorful and devastating.^{11,15} **Endothelial cells** (E) and their basement membrane form the lining of blood vessels. Capillaries are little more than a single layer of epithelium surrounded by the basement membrane.¹⁶

Molecular players include **arachidonic acid** (AA), a product of damage to cell membrane lipid. Arachidonate is rapidly converted to various species of signaling molecules called **eicosanoids**, the most important for our discussion being **prostaglandins** (PG) but also including prostacyclins, leukotrienes, thromboxanes, and other potent chemical messengers, with diverse physiologic effects in both health and disease.^{11,17} A vast array of peptide molecules also participate in inflammation and repair, including an entire bestiary of **cytokines** (interleukins, interferons, and other immunomodulators), cell adhesion molecules, enzymes, growth factors, and antibodies.¹¹

Now, as in any good story, let's put the players in a setting; namely, the tissue.

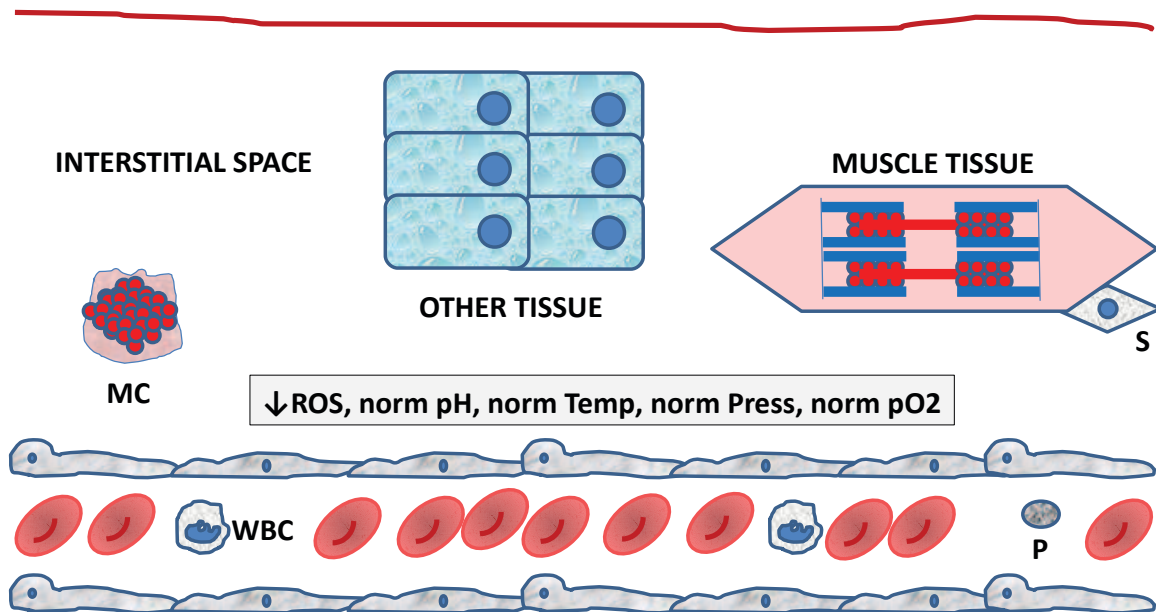


Figure 2. Normal tissue in homeostasis.

In this idyllic tableau, there's a place for everything, and everything in its place. White cells are in their barracks, in the vascular space. Blood vessel integrity is high, blood cells and plasma are in the bloodstream where they belong, mast cells keep it in their pants, lymphocytes and monocytes are garrisoned away in the bone marrow and lymphatic system, and the tissue is sterile (no bacteria around). Tissue pressure and pH are normal, and the molecular environment is stable. Everything is... kind of boring, really.

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The stage is set. Let's introduce a conflict, and watch as Hijinks Ensurue. This is where the story really gets underway.

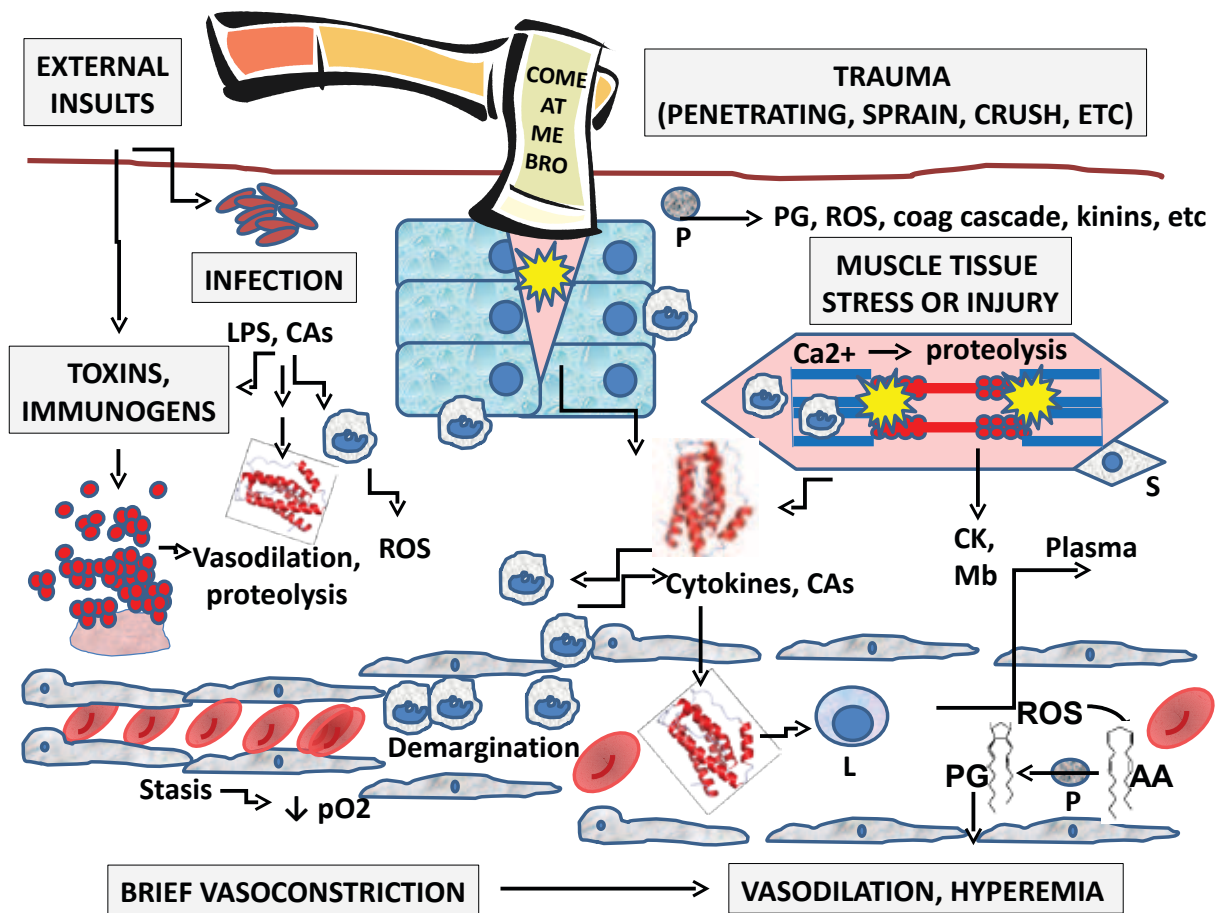


Figure 3. Insult and early inflammatory processes.

Looks like a war zone, doesn't it? Virtually any insult to the tissue can *quickly* set off a goat rodeo like the one pictured here. A very early response to the insult is vasoconstriction, which rapidly diminishes blood flow to the area, followed soon by vasodilation, which leads to tissue congestion, redness and heat.

Bacteria elaborate secreted toxins, or substances from their cell walls such as **lipopolysaccharide** (LPS), which trigger an inflammatory response. Some of these substances act as **chemoattractants** (CA) that draw WBCs to the action, as a silent alarm attracts SWAT to a bank robbery. Bacteria and their vile products can also attract the attention of antibodies. Binding of these *immunoglobulins* to bacterial surfaces act as additional triggers to the complex inflammatory cascade, including activation of the *complement* system (not pictured).¹¹

Any kind of trauma, from penetrating to crush to your basic sprain, disrupts tissue and vascular integrity, resulting in the exposure of tissue factors, the activation of platelets, and the release of arachidonate and free fatty acids. These are converted by enzymes called *cyclooxygenases* and *lipoxygenases* to prostaglandins, leukotrienes and other eicosanoids, sending powerful signals to the immune system, vascular structures, nerve endings, white blood cells, you name it. Some of these

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signals are pro-inflammatory, *while others are anti-inflammatory*, a good point to keep in mind.^{18,19} Among other things, pro-inflammatory prostaglandins can attract white blood cells to the area and profoundly affect cellular functions.¹¹ All of these processes result in the elaboration of more cytokines, which further drive and modulate the inflammatory response,²⁰ and induce many more white blood cells to storm into the tissue,²¹ a process called **demargination**.¹¹ White blood cells release digestive enzymes and reactive oxygen species (“free radicals”), all of which promote the degradation of damaged tissue—and, alas, some undamaged tissue, too. Here we see a recurring theme: inflammation is an aggressive, scorched-earth, shock-and-awe response to injury. There’s always collateral damage.²¹

The unique stress imposed on skeletal muscle by eccentric exercise is not yet completely understood. One model holds that eccentric contractions result in the overstretching of some sarcomeres, leading to actomyosin dissociation, direct damage to myofilaments, tearing of the sarcoplasmic reticulum (SR, the muscle cell membrane) and connective tissue, and the release of calcium from the SR.^{18,22} This calcium release triggers the activation of calcium-dependent **lipases**, which eat membrane lipids and produce arachidonate, and of calcium-dependent proteases (**calpains**) which indiscriminately chew up structural proteins, ribosome-associated proteins, enzymes and the like.²³ Damaged muscle probably releases some **cytokines** (“myokines”),^{24,25} and within a short time after injury or strain the muscle tissue is invaded by WBCs.¹⁸ Damaged muscle leaks the pigment myoglobin (Mb) and the enzyme creatine kinase (CK) into the serum, which is why the latter is the most commonly used laboratory marker of rhabdomyolysis. This kind of “myositis” almost always precedes recovery and adaptation... but is it the *cause* of that adaptation? Most exercise scientists assume it is, but this belief has not gone unquestioned.²⁶

In all of these inflammatory scenarios, cytokines are released into the bloodstream and the tissue, driving the inflammatory process and attracting the attention of various breeds of immunocytes. Lymphocytes, T cells, killer cells, monocytes and their kin normally hang in the Rear with Gear, but now they deploy to the Front with the Grunts. The capillaries get leaky, and plasma fluid leaks into the interstitium, causing the tissue to swell (**edema**). In some cases, this swelling can cause the tissue hydrostatic pressure to exceed capillary perfusion pressure, resulting in a total loss of blood flow to the affected tissue (**ischemia**). The resultant **muscle compartment syndrome** may lead to muscle necrosis (death) and permanent loss of function. This phenomenon is well-described in the setting of severe rhabdomyolysis and other forms of acute muscle injury.²⁷

The foregoing is a gross oversimplification of the inflammatory response, but a serviceable one for our purposes. The picture that emerges is like what you’d see downtown after Jason Bourne blows up a CIA office and trashes a city block. Flashing lights and sirens everywhere. Local cops, sheriffs, state troopers, feds, spooks, reporters, EMS, fire department, local cops, helicopters, SWAT, gawkers, looters, barricades, smoke, broken glass, body parts, martial law, who’s-in-charge-here, civil rights violations, and all the screaming and the running and the biting and the scratching. As the late, great Lewis Thomas says in his indispensable book, *The Lives of a Cell*,²⁸ it is a shambles. Inflammation is the best first step to getting back to normal that evolution has come up with *so far*, and there is an awful, implacable, sledgehammer logic to it. But it’s also a Hot Mess, and, from the perspective of the whole city (i.e., *you*, the suffering athlete), it’s damn inconvenient.

By 12-24 hours, we find that the situation is getting a bit more orderly. Gross or capillary bleeding has been dealt with by hemostasis and the formation of platelet plugs and fibrin clots. WBCs continue to eat up invading pathogens, foreign matter and cellular debris. Immunocytes have begun to populate the area, and the complex signaling milieu (cytokines, eicosanoids, stress hormones) spurs the

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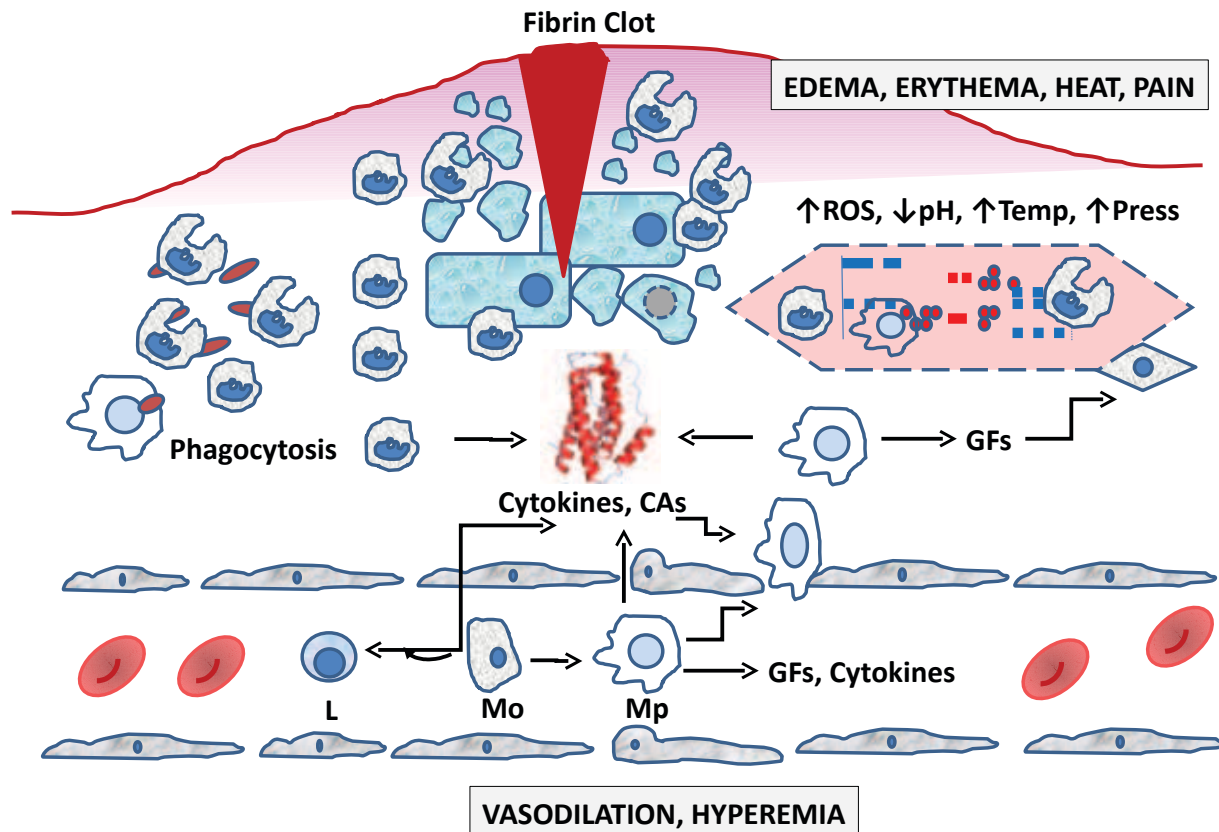


Figure 4. Developed inflammatory response (12-24 hours).

transformation of some of these cells to macrophages, who will presently climb out of the vasculature to assume jurisdiction over the crisis. Like white blood cells, they engage in avid phagocytosis, but they also release growth factors, an early step in the process of rebuilding and repair.^{18,20,21} But it's still a disaster area. Nerve endings are sensitized and screaming, tissue pH and oxygen tension may still be decreased, tissue oxidative stress is high, and tissue temperature and hydrostatic pressure are still way up. *Tumor, dolor, rubor, calor.*

Like all good stories, the tale of inflammation needs a resolution. Later in inflammation (about 24 hours and out, to weeks or even months later), macrophages have supplanted the WBC shock troops. Macrophages continue to mop up the area, gobbling die-hard pathogens and removing debris. They continue to release growth factors and participate in immunomodulation. The cytokine milieu has attracted stem cells and/or fibroblasts, to replace or reconstruct damaged tissue or fill in the craters with scar. Growth factors trigger the activation of muscle satellite cells,¹⁸ which in turn participate in the repair, regeneration and adaptation of muscle fibers. Vascular integrity returns, and tissue hydrostatic pressure, temperature, redox state, oxygenation, and pH gradually normalize. Depending on the initial insult and extent of damage—including damage induced by the inflammatory response itself—this healing process can be brief or it can take a very long time indeed. And the potential outcomes of this process (again, depending on the particulars) are legion, ranging from complete healing to functional or dysfunctional scarring to chronic inflammation, abscess, tissue loss, anaphylaxis, septic shock, cardiovascular collapse, and even death.^{6,29,30}

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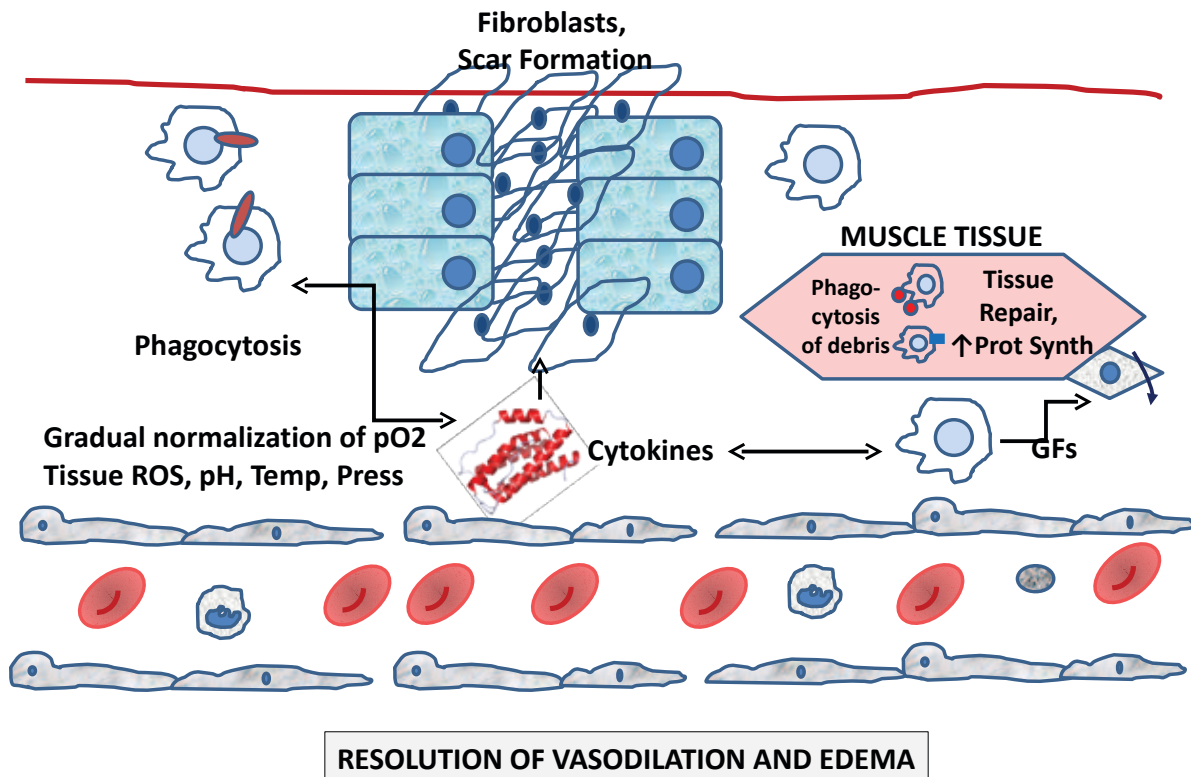


Figure 5. Late inflammation (24+ hours).

ANTI-INFLAMMATORY INTERVENTIONS & EXERCISE: BLINDING US WITH SCIENCE

The one thing everybody knows about inflammation, even your dog, is that it *sucks*. Your injured paw (or whatever) is hot, swollen, tender, and throbbing, and it doesn't work so well. Chasing that squirrel just isn't as interesting as it was a minute ago. Inflammation is nature's way of saying: "You just f*cked up. Maybe you should stop and limp on home."

Because inflammation is both ubiquitous and uncomfortable, the relief of its more unpleasant effects has been a prime focus of medicine for millennia. Compression, cooling, elevation and rest are venerable approaches to relieving the discomfort of inflammation, reinforced in the late 19th century by the advent of modern anti-inflammatory drugs. The AAI guys seem to reserve their ire for ice and NSAIDs, so that's what we'll focus on here.

NSAIDs – Nonsteroidal anti-inflammatory drugs have, as the name implies, a mechanism of action that is distinct from corticosteroids. Most steroid receptors are transcription factors that interact directly with DNA and effect gene expression. NSAIDs, by contrast, influence the activity of cellular enzymes to suppress the release of signaling molecules.

The NSAID class of drugs is fairly broad, and includes salicylates like aspirin, propionic acid derivatives or "profens" such as ibuprofen, ketoprofen and naproxen, acetate derivatives like indomethacin and ketoralac, and the coxibs, which includes celecoxib (Celebrex®) and a plethora of withdrawn and discontinued medications. If we consider the mechanism of action, we can extend

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the NSAID classification to the very common analgesic and antipyretic acetaminophen (Tylenol®), although doing so elicits much brow-furrowing among pharmacologists.³¹

These drugs exert their anti-inflammatory effect by inhibiting cyclooxygenase (COX), a family of enzymes found in most mammalian cells, including platelets and endothelium.³² We have seen that arachidonic acid is released from cell membranes early after injury or insult. Cyclooxygenase converts arachidonic acid into prostaglandins and other eicosanoid signaling molecules, which in turn signal a wide range of pro-inflammatory, anti-inflammatory, vasoactive and cellular processes.³³ COX is thought to come in 3 flavors, or isoforms, although the role of COX3 is as yet unclear. “Classical” NSAIDs target both COX1 and COX2 indiscriminately, with the potential for side effects, particularly gastrointestinal problems. Renal and cardiovascular effects have also been described for NSAIDs, as well as a number of drug interactions.^{34, 35, 36} The coxib NSAIDs target only COX2. This reduces the instance of GI side effects, but may increase the potential for other problems, including pro-thrombotic complications. Much has been made of the side effects of NSAIDs and acetaminophen, which are very real—and often overblown. The human/clinical experience with these medicines encompasses literally billions of doses every year and a low incidence of adverse events. In general they are well-tolerated when used as directed in OTC doses.³¹ Acetaminophen, in particular, has an excellent safety profile.³⁷ Prophylactic use of these medications (i.e., before injury or soreness occur) is probably to be discouraged.³⁸

Now, if you have any experience with NSAIDs, and/or you have meditated upon Figure 3 above, you may have made the following observation: *NSAIDs can antagonize inflammation, but they cannot and do not obliterate it.* Although direct action of NSAIDs on targets beside COX have not been ruled out, their primary mechanism is clearly the suppression of prostaglandin synthesis. And while prostaglandin production is certainly both upstream and important, we’ve seen that it’s nevertheless just one component of this intricate biological clusterfuck. For example, while NSAIDs can inhibit COX production of prostaglandins, they have little or no effect on the production of leukotrienes by lipoxygenase,³² which is also an important pro-inflammatory process. Such observations comport nicely with the common experience that an NSAID can *relieve* pain and swelling, but it doesn’t *eliminate* them, nor does it cause our boo-boos to persist and “never heal.”

Even so, many have put forward the hypothesis that NSAIDs, by moderating the all-out urban warfare response of inflammation, might somehow delay the return to peace and prosperity—i.e., healing and adaptation. As noted earlier, the AAI crowd has seized on some studies that have addressed this hypothesis. Three of the most frequently cited are studies by Novak, Mikkelsen, and Trappe, which we will consider now.

In 2009, Novak published a study of the effect of a COX2 inhibitor on skeletal muscle hypertrophy in mice.⁵ Since it’s tough to get mice to do their squats, the investigator used a **synergist ablation** technique to induce muscular stress and adaptation. And what, you might ask, is synergist ablation? Simple: you completely resect (i.e., *cut out*) the soleus and gastrocnemius muscles at surgery, leaving only the plantaris intact to perform the function of the calf. The idea is that, left all alone in the mangled leg, those plantaris muscles will have to get big and strong. A COX2 inhibitor, NS-398, was administered to these hobbled mice intraperitoneally (i.e., they were shot up with the drug in the abdominal cavity) just before the surgery (when they presumably were neither inflamed nor sore, not having “worked out” yet) and every day thereafter until tissue collection. After two weeks, the mice were sacrificed, the plantaris muscles removed, and the tissue weighed and assayed. The investigators report blunted compensatory hypertrophy and muscle protein synthesis in NSAID-treated mice compared to untreated mice, along with decreased macrophage accumulation and cell proliferation. Interestingly,

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the drug had no impact on expression of IGF-1 or phosphorylation of Akt, mTOR, or p70S6k, which appear to be *critical* events in growth factor signaling and hypertrophy.^{39,40}

The study is well-done as far as it goes, and must be of considerable interest to those working on the role of cyclooxygenase in tissue repair and healing. The investigators conclude—correctly, in my opinion—that their results *suggest* a requirement of COX2 activity for skeletal muscle hypertrophy. They wave their hands about exactly why this is so, and go on to issue concerns about the use of NSAIDs for exercise-induced muscle pain. One should certainly take these misgivings to heart—if one is a mutilated, quasi-amputated rodent who takes abdominal injections of experimental COX2 inhibitors, even before he gets sore, eats rodent chow, and hobbles around a cage full of wood shavings and mouse turds. The scientific implications of this paper may be quite important. The clinical and practical implications of this paper are exactly zippo, because it demonstrates absolutely nothing about the chronic effect of commercially available NSAIDs taken *per os* by intact human athletes engaged in programmed strength training.

The Mikkelsen paper is a small study, in which 8 young men were fitted for microdialysis infusion of the vastus lateralis of each leg prior to the onset of the experiment.⁴ One side (chosen at random) was infused with a placebo, while the other was infused with indomethacin. In other words, these poor bros had a nonsteroidal delivered directly into their muscle by a catheter. And the medication was started before exercise—again, *before they had even evoked an inflammatory response* (aside from the local inflammatory response of having a foreign body rammed into their thigh). Muscle biopsies were collected before and eight days after exercise. Satellite cells were assayed by immunohistochemistry. The methods section does not tell us who counted the cells, whether the cells were counted by more than one investigator or, if so, the magnitude of agreement between counters. Such [methodological controls](#) are crucial to a study like this, and their absence undermines our confidence in the results. Be that as it may, the study reports a decreased number of muscle satellite cells in tissue biopsies from treated muscles.

This is indeed interesting. Also interesting is that the *number of inflammatory cells was unaffected by the infusion*. This finding raises pesky questions which I leave the reader to ponder. The effect of the infusion on soreness was minimal at best, and there was no impact of NSAIDs on maximal isometric strength immediately after exercise. Finally, the investigators undertook no assay of the effect of their strange intramuscular infusions on adaptation—no measurements of strength, power, function or hypertrophy are reported. Even so, these authors, like those of the previous study, felt free to issue grave warnings about the use of NSAIDs. But again, *the clinical relevance of this paper, if any, is entirely speculative*.

Finally, the paper by Trappe³ looked at the effect of acetaminophen and ibuprofen on muscle protein synthesis in 24 men after 10-14 sets of 10 eccentric knee extensor repetitions at 120% of concentric 1RM. Let's set aside the finer points of the methodology and take the results at face value. Muscle protein fractional synthetic rate (FSR) appeared to increase in *all three groups* (placebo, acetaminophen, ibuprofen), but only reached *statistical* significance in the placebo group (who seemed to have a slightly lower FSR at baseline). The *clinical* significance of these increases is unclear at best, and the experiment *did not identify changes in particular proteins*, which immediately raises the question of whether the decreased FSR in the NSAID group was due to *decreased production of inflammatory proteins in muscle* (cytokines and other inflammatory cell products) *rather than decreased production of structural proteins*. Most importantly, the paper undertakes *no assay of practical outcome*—there is no data here on adaptation, strength, power, hypertrophy or any other training-associated measure. So once again, the practical implications of this work to trainees and coaches is...*bupkis*. In fact,

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Trappe went on to conduct a clinical study showing that acetaminophen and ibuprofen *enhanced* hypertrophy and strength gains in older adults.⁴¹

My forays into the literature reveal no shortage of basic science papers like these on the role of the inflammatory system in healing and adaptation. They all have one thing in common: *they're basic science papers*, and we make assumptions about the translation of their findings from the lab bench to the bar at our peril.

A number of studies in humans have addressed more practical outcomes, including some systematic reviews and meta-analyses. They are of varying clinical relevance, and most of them are not what I would call high quality. I have presented a selection of such papers from the last twenty years in Table 1 (appendix below). A cursory look at this table will reveal that the conclusions of these studies are all over the map. In other words, for any study that says NSAIDs will stunt your growth, you can find another that says they don't, or even that they help.

So much for a scientific consensus.

CRYOTHERAPY – The mechanism of cryotherapy as an anti-inflammatory is not as straightforward as that of the NSAIDs. Cryotherapy certainly seems to prolong the vasoconstriction that occurs after injury, delaying (but not ablating) the development of vasodilation and increased capillary permeability. Cryotherapy decreases the rate of biochemical reactions, blunts the elaboration of reactive oxygen species, and slows cell migration into the injured area. And of course cryotherapy decreases pain, probably through multiple pathways, including pain gating, suppression of substance P and bradykinin release, and inhibition of pain fiber transmission.

There's no shortage of basic science data on cryotherapy, healing and hypertrophy.^{42,43,44} Again, some such studies could be fodder for the anti-icing, anti-anti-inflammation crowd. Others would suggest that icing is salutary. But again, they all have one thing in common: they're basic science studies, and their relevance to actual training practice is unclear at best.

Clinical studies also abound, and as with NSAIDs, they are generally of middling-to-low quality. But a meta-analysis of such studies, published in 2007 by Collins² in the *Emergency Medicine Journal*, has drawn the attention of [anti-icing](#) exponents. Let's look at it.

This paper is not a true meta-analysis, and I'm not sure it even meets the threshold for a systematic review. It seems rather to be an implicit literature review. The author included both human studies and animal studies, which is a bit odd, and his review excluded studies of exercise-induced injury (see page 2 of the paper, Methods section).

Let me say that again: *this review, a major data point cited by the AAI guys, excluded study of exercise-induced injury.*

The author identified four animal studies, all of which suggested that “excessive or prolonged cooling is damaging.” As is usually the case with animal studies, the clinical relevance of such data is unclear. The author reports that, after applying his exclusion criteria, he identified four human studies worthy of his consideration. Two of these were randomized controlled clinical trials. *One showed a positive effect of cryotherapy (cooling gel) and the other did not.* Two systematic reviews of human data were reviewed. *One was inconclusive and the other suggested that ice may hasten return to participation.*

So far, so what? Except the author then concludes that “*there is insufficient evidence to suggest that cryotherapy improves clinical outcome in the management of soft tissue injuries.*” But the author's *own results* show that at least two papers meeting his inclusion criteria *do* suggest that cryotherapy has a positive clinical effect. This is an example of a frequently-encountered phenomenon in the literature: conclusions that do not reflect, or even contradict, the findings of the study.

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The study was criticized—in the same journal in which it was published—for important methodological flaws, including the omission of several studies that met the author’s inclusion criteria, serious issues with the author’s quality scores, a lack of structured assessment of the two included systematic reviews, subjective evaluation of included studies, and the inevitable heterogeneity of incorporating data from both human and animal studies.

In short, Collins’ paper is not a particularly comprehensive, well-done, or revealing analysis of the available data. But that’s not really the point I want to make right now, because, although this paper is brandished by the anti-icing crowd, it’s really just one study. (Less charitably, it may be considered an implicit review of cherry-picked studies. And an irrelevant one, at that.) And so, again, I have prepared a table presenting the results of many investigations of cryotherapy in humans over the last twenty years (Table 2, appen). And again, we find that the literature is...how shall we put it? *Discordant*. The much ballyhooed scientific consensus on ice seems to be just as elusive as the one for NSAIDs.

Of course, the inconsistency of clinical studies of anti-inflammatory interventions (both ice and NSAIDs) shouldn’t surprise us. Nor should the failure of clinical studies to consistently bear out the concerns raised by basic science research on cryotherapy and nonsteroidals. Again, icing and nonsteroidals can’t obliterate inflammation, they can only inhibit certain parts of the inflammatory response. And their long-term clinical effect on healing and adaptation in people who train seriously will inevitably be confounded—and diluted—by diverse other factors: programming, diet, training compliance, mood, motivation, pain threshold, genetics, training history, return to function, nature and extent of injury, coaching, and a plethora of other variables that could never be definitively controlled. Here we have an example of the critical distinction between physiologic outcome measures and practical, “patient-oriented” outcome measures. The real question isn’t what happens to your satellite cells or your prostaglandins when you pop a pill or rub an ice pack on your throbbing knee. The real question is how the use of anti-inflammatory therapies affect your performance and health over a training career. *We just don’t have good data on that yet*. And I wouldn’t hold my breath waiting for it.

BACK TO THE ARGUMENT

So, with all of the foregoing in mind, let’s circle around and get to cases. If you can remember back that far, I told you that the AAI guys seem to be making the following arguments:

1. **Inflammation is the body’s natural—and therefore correct—response to injury. Your body knows what it’s doing, and interfering with the inflammatory response is therefore ill-considered.** This is the easiest argument to dispense with, because it’s just silly—not to mention selectively applied. For example, in the video it is made clear that ice and NSAIDs are bad because they interfere with inflammation, but compression, which suppresses post-inflammatory edema, is not. In any event, this argument proceeds from the assumption that pristine natural processes are always optimal to the realization of human ends, which is clearly not the case; and that the human body is a “perfect machine,” which is just so much bullshit.

Here’s a reality check: Mother Nature doesn’t give a rat’s ass about your program, your WOD time, your 1RM bench press, or even your survival as an individual.⁴⁵ She designed you to make new primate gene replicators, and then croak. Let’s not even talk about the design of the low back, the exquisite suicidal sensitivity of neural and cardiac

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tissue to brief ischemia, or the deplorable shortcomings of cartilage. Inflammation is *not* an ideal adaptation just because it's the "natural" response to insult. Pain, scarring, functional impairment, tissue loss and cancer are also natural responses to insult—and all can result from inflammation. On the logic of the AAI crowd, analgesia, wound repair by primary intention, tissue debridement, abscess drainage and tissue salvage are also bad ideas. If that's what you *really think*, it's unlikely we're going to have a meeting of the minds. God help you if you ever get anaphylaxis or appendicitis.

2. **Without inflammation, the body would never heal. You want to heal, don't you? So why in the world would you intervene in the inflammatory process?** As we have seen, inflammation is indeed the *de facto* initial stage of healing. But we've also seen that neither ice nor NSAIDs are capable of obliterating the inflammatory response, and that there is no scientific consensus that anti-inflammatory interventions retard wound healing, stunt adaptation, or delay return to function to any practically relevant degree. Next!
3. **Without inflammation, muscles and other tissues cannot respond to training stress with protein synthesis and hypertrophy. Therefore, interfering with training-induced inflammation (eg, DOMS) will stunt your gains.** Again, there is no consensus in the clinical literature, such as it is, to support this contention. There is data suggesting that you can screw up muscle protein synthesis or satellite cell activation or hypertrophy if you pump NSAIDs into mutilated mice or infuse them directly into the thigh muscles of bros doing leg presses. That's just not the same thing as regular human beings popping ibuprofen for DOMS, and tells us nothing about the actual practical impact of such therapy on performance, healing or adaptation.
4. **The scientific literature overwhelmingly supports all of these contentions, and the issue is essentially settled.** I think we all know by now that this *simply isn't true*.^{46,47} Despite decades of work and dozens of clinical studies and systematic reviews, the issue remains most decidedly *unsettled*.

STOP SPREADING MISINFLAMMATION

Point # 4 above deserves a little extra unpacking, because it raises two important issues.

The first is this: in one sense, the anti-anti-inflammatory guys might be right. If we had an infallible window into Truth (which, by the way, would *not* be called Science), we might very well observe that athletes who ice or pop ibuprofens are *slightly* stunting their gains or *slightly* delaying their healing. Or we might find that the AAI guys are wrong, and that athletes who keep inflammation on a short leash actually heal *a bit* faster and/or get back under the bar *a little* sooner.

But either way, the AAI guys wouldn't be *very* right or *very* wrong. By which I mean that if anti-inflammatory interventions delay healing or blunt gains, *they don't do it by very damn much*. Conversely, if they aid return to function or actually promote gains, again, it's not by very damn much. Because the one thing we can take from the available evidence is that the effect size of anti-inflammatory medications on healing and adaptation is probably small. If NSAIDs or cryotherapy had a robust effect on healing or adaptation, I believe we'd know it by now, because these issues have drawn considerable scientific attention, and large, robust effect sizes are easy to detect, easy to replicate, and

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hard to argue with. When it comes to healing and hypertrophy in the setting of anti-inflammatory treatment, we're probably making a mountain out of a molehill.

From a practical perspective, this means that the critical deciding factor in whether to take NSAIDs or cryotherapy for training-associated pain is *whether they make you feel better*. And that's good news, because when it comes to the science of *you*, an N=1 observation is practical and relevant. It's difficult if not impossible to tell whether NSAIDs reduce *your* time to heal. (Unless you're willing to inflict exactly the same injury on yourself at least twice. Please don't.) You can't tell whether icing your aching hamstrings after squats or a sprain changes *your* muscle protein synthesis or impacts *your* strength gains over time. (Trust me. You can't.) But you *can* tell, to a reasonable and practical extent, whether cryotherapy or NSAIDs make *you* feel better when *you're* hurting.

And if they make you feel better, and if you're hurting, and if you have no contraindications, *then for heaven's sake just use them*. Life is painful enough without suffering through a bad case of DOMS or a jacked-up knee because some grad student in a lab cut up a premedicated mouse, or because some Big Name Coach has decreed that Icing Ain't Natural. Use medicines as directed, use ice judiciously, use compression and elevation if they make you feel better. Take care of your pain and keep your inflammation shock troops under civilian control. Get some rest, maintain mobility, use good judgment, and recover, so you can get on with your life and ease back into your training.

The second and larger point raised by #4 above is the unfortunate human propensity to seize on a piece of scientific data that aligns with our own world view and take that as an indication that Science is On Our Side. It demonstrates a complete misapprehension of the way science works, a lack of critical thinking, and a woeful ignorance of the fact that even peer-reviewed scientific literature is, on average, about 95% shit by weight.

This has wider implications than one might imagine, because **BroScience**, like any other toxin, can extravasate into the wider culture, with untoward results. In particular, misinformation about NSAIDs has the potential to do real harm. These are inexpensive, well-tolerated and effective drugs, indispensable not only as anti-inflammatories but as antipyretics, analgesics, and antithrombotic agents.^{36,37} Their use relieves untold suffering and can even save lives. It's a Big Deal. Some of you may think I've been a bit contentious in this article. But the first time one of my patients with chronic pain, acute trauma or coronary syndrome looks at me like I'm a monster for giving her Tylenol®, Motrin™ or aspirin because Crystal The Crossfit Coach or Brendan the Bodybuilder told her they were poison...well. Then I'll *really* go all Braveheart on somebody.

BroScience, like poverty and taxes, will always be with us, but we can suppress it by learning and teaching the proper approach to the literature, cool it down by avoiding rigid, categorical or premature conclusions based on minimal data, and limit the damage and suffering with judicious doses of both skepticism and curiosity toward all ideas, old and new.

So, to the AAI guys I say this: anti-inflammatory therapy may slow adaptation and healing. Or it may not. I really just don't know. ***And neither do you.*** You certainly don't have enough good scientific data or consensus backing you up to be as categorical in your opinions about ice and NSAIDs as you are, nor to withhold them from athletes in pain. When and if convincing evidence demonstrates a meaningful negative effect of these interventions on our training, I'll be the first to say you guys were right. But for now, if the science tells us anything at all, it's that the minimal practical effect of this therapy on our healing and adaptation just doesn't justify getting all inflamed about it.

Maybe you guys should take a chill pill.

Jonathon Sullivan MD, PhD, FACEP, SSC is Attending Physician at Detroit Receiving Hospital Emergency Department, and Associate Director of the Cerebral Resuscitation Laboratory at Wayne State University. His research is focused on molecular mechanisms of brain injury and repair after cardiac arrest. He is a Starting Strength Coach, a *Krav Maga* Practitioner, and a 3d *Dan* and certified instructor of *Tang Soo Do*. He's old and creaky, but he's still trying to get stronger, and buys his acetaminophen and aspirin by the crate. He can be contacted at GreySteel.org.

Dr. Sullivan has no commercial relationships with drug manufacturers, cryotherapy device manufactures, the Ice Fairy, or any other conflict of interest to disclose. People with medical questions or issues should see their doctor. This article is offered for educational purposes only, does not represent the opinions of the Detroit Medical Center or Wayne State University, and does not constitute medical advice for any specific patient, disease, injury or condition. So don't get any big ideas.

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Illustrations were prepared by the author.

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APPENDIX: HUMAN STUDIES OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS, ACETAMINOPHEN AND CRYOTHERAPY.

A note on the tables: Papers were identified by multiple-iteration searches of relevant terms (“cryotherapy,” “NSAIDs,” “DOMS,” “hypertrophy,” “soft tissue injury,” etc), on Pub Med and Google Scholar, followed by searches of related and referenced articles. Basic science and animal studies were not tabulated, nor were clearly irrelevant studies. I reviewed and included papers only if the full text was reasonably accessible and they were published in the last 20 years. (I have a life and a job and everything.) I made no attempt to grade the quality of the studies. The purpose of the exercise was not to conduct an exhaustive survey nor to rate the evidence, but rather to evaluate the claim that the literature has reached a consensus on the use of NSAIDs and cryotherapy in the setting of training injury and soreness.

To this end, I include a summary column indicating whether the paper could be reasonably interpreted as supporting the use of the therapy. This was an *entirely implicit assignment*, based on my own understanding of the paper, and made solely by me, without the use of any objective decision instrument or scoring system. *The assignment was guided based on the assumption that the reader derives some relief from the therapy in question, unless the paper substantially challenged the palliative efficacy of that therapy.* For example, if the paper offered strong evidence of a robust maladaptive impact of the therapy, this would override the palliative assumption, and the recommendation assigned would be No (N). If the paper offered no evidence of maladaptive impact, or evidence of a positive impact, the palliative assumption would take precedence, and the recommendation assigned would be Yes (Y). If the paper offered weak evidence of adaptive or maladaptive impact, the assignment would be Maybe (M), Maybe Yes (MY), or Maybe No (MN), depending on my own implicit evaluation of the paper and the reliability of its findings. If the paper substantially challenged the palliative efficacy of the the therapy and identified no other robust adaptive benefit, this overrode the palliative assumption, and the recommendation was No. (The reader may obviously have different ideas if she gets relief from the therapy, but this assignment decision was made to *err on the side of the AAI argument*).

Just be perfectly clear: this is all *very presumptuous on my part*; this “scoring” was completely implicit, unscientific and loosey-goosey; and it was done *only* to highlight the diverse conclusions and lack of consensus in the literature, while making the tables more accessible to the truncated attention span of North American readers. The reader is strongly advised to take all of this with a shaker of salt, and is invited to read the articles tabulated here and *make his or her own conclusions...*always a Good Idea.

TABLE 1: HUMAN STUDIES OF NSAIDs AND RELATED DRUGS FOR SOFT-TISSUE INJURIES AND MUSCLE SORENESS. DB=double blind. R=randomized. PC=placebo-controlled. RCT=randomized controlled trial. CxT= crossover trial. MA = meta-analysis. For information on the recommendation assignments in the right-hand column, see the Appendix Notes.

CITATION	STUDY TYPE	CONCLUSIONS	NSAIDs: Y,N,M
1990s			
Various treatment techniques on signs and symptoms of delayed onset muscle soreness. Gulick DT et al. <i>J Athlet Train</i> 1996;31(2):145-52.	RCT	The authors report no benefit of an NSAID (oxaprozin), ice, stretching, high velocity concentric exercise, or sublingual or topical <i>A. montana</i> extract on DOMS induced by eccentric forearm contractions. In fact, NSAID and <i>A. montana</i> “appeared” to impede recovery. No long-term practically relevant outcomes were assessed.	N
Anti-inflammatory doses of ibuprofen: effect on neutrophils and exercise-induced muscle injury. Pizza FX, Cavendar D, Stockard A. <i>Int J Sports Med</i> 1999; 20(2): 98-102.	RPCT	“Anti-inflammatory doses of ibuprofen reduced CK activity but not the neutrophil response or other indirect markers of muscle injury during recovery from eccentric arm exercise.” There was no impact on isometric strength or soreness. No long-term variables were studied.	Y
2000s			
Effect of ketoprofen on muscle function and sEMG activity after eccentric exercise. Sayers SP, Knight CA, Clarkson PM, et al. <i>Med Sci Sports Exerc</i> 2001; 33(5): 702-10.	RT	Ketoprofen had no impact on reducing post-exercise increases in myoelectric activity. It improved soreness compared with placebo.	Y
Managing delayed-onset muscle soreness: Lack of effect of selected oral systemic analgesis. Barlas et al, <i>PhysMedRehabil</i> 2000;81:966-72.	DBPCRT	No beneficial effect of aspirin, codeine (?) or paracetamol in reducing DOMS induced in nondominant elbow flexors by repeated eccentric contractions. No study of impact on adaptation or healing.	N
Nonsteroidal anti-inflammatory therapy after eccentric exercise in healthy older individuals. Baldwin AC. <i>J Gerontol Med Sci</i> 2001;56A(8)M510-13.	DBCT	Naproxen sodium decreased muscle injury, strength loss and soreness after eccentric knee extensions in 15 elderly (aged approx 60 years) men and women. The authors conclude that this therapy may be beneficial in older patients during the early stages of increased physical activity. No assays of long-term adaptation were undertaken.	Y

CITATION	STUDY TYPE	CONCLUSIONS	NSAIDs: Y,N,M
The effects of ibuprofen on delayed onset muscle soreness and muscular performance after eccentric exercise. Tokmakidis SP,et al. <i>JSCR</i> 2003;17(1):53-59.	RPCT	Nineteen subjects performed eccentric leg curls and got sore hamstrings. They were randomized to ibuprofen or placebo. The ibuprofen group had less soreness and lower CK release and peripheral WBC count, but no differences in maximal strength, vertical jump performance, or knee ROM. "The results of this study reveal that intake of ibuprofen can decrease muscle soreness induced after eccentric exercise but cannot assist in restoring muscle function."	Y
2010s			
The effect of nonsteroidal anti-inflammatory drug administration on acute-phase fracture-healing: a review. Kurmis et al. <i>J Bone Joint Surg</i> 2012;94:815-23.	SR	The authors conducted a review of 316 relevant studies. The available clinical evidence does not substantiate the concern raised by animal studies, and suggests that NSAIDs are safe and effective for pain control after fracture, without an adverse effect on fracture healing. "Although increasing evidence from animal studies suggests that COX-2 inhibition suppresses early fracture healing, in vivo studies involving human subjects have not substantiated this concern....balance of evidence in the available literature appears to suggest that...NSAID(s are)... safe and effective supplement to post-fracture pain control, without...increased risk of...disrupted healing."	Y
Effect of ibuprofen and acetaminophen on post-exercise muscle protein synthesis. Trappe et al. <i>Am J Physiol Endocrinol Metab</i> 2001; 282:E551-6.	RPCT	24 males received a <i>maximal dose</i> of medicine or placebo after 10 eccentric reps at 120% 1RM. Postexercise fractional synthesis rate appeared to be increased in all three groups, but reached statistical significance only in the placebo group. Differences were of unclear practical significance. Muscle breakdown was not effected by any regimen. <i>The authors did not investigate which proteins were affected</i> (i.e., muscle protein, inflammatory protein, etc), and no functional assessments (strength, pain control, time to return to function etc) were undertaken. "The long-term influence of this acute response after resistance exercise for individuals who chronically consume these (or similar) drugs cannot be determined from this study."	MN
Influence of acetaminophen and ibuprofen on skeletal muscle adaptations to resistance exercise in older adults. Trappe et al. <i>Am J Physiol Regul Integr Comp Physiol</i> 2011;300:R655-62.	RDBPCT	"Drug consumption unexpectedly increased muscle volume and muscle strength to a greater extent than placebo." No change in muscle protein content, water content or myosin heavy chain distributions were observed on muscle biopsy. Medication did not inhibit, and in fact appeared to <i>enhance</i> , muscle hypertrophy and strength gains in older adults.	Y

CITATION	STUDY TYPE	CONCLUSIONS	NSAIDs: Y,N,M
Ingestion of low-dose ibuprofen following resistance exercise in postmenopausal women. Candow et al. <i>J Cachexia Sarcopenia Muscle</i> 2012 DOI 10.1007/s13539-012-0077-3	RCT	Postmenopausal women demonstrated no significant difference in strength gain or lean body mass whether they took ibuprofen or placebo after resistance exercise. Analgesic efficacy was not assessed.	M
The effect of nonsteroidal anti-inflammatory drugs on tissue healing. Chen and Dragoo. <i>Knee Surg Sports Traumatol Arthrosc</i> 2012; DOI 10.1007/s00167-012-2095-2	SR	"Short-term, low-dose use of NSAIDs and COX-2 inhibitors does not appear to have a detrimental effect following soft tissue injury, but is inhibitory in cases involving bony healing....Clinically, the prudent use of anti-inflammatory medications following sports medicine injuries and surgeries appears to be a reasonable option in clinical practice unless bone healing is required."	MY
The effects of ibuprofen on muscle hypertrophy, strength, and soreness during resistance training. Krentz et al. <i>Appl Physiol Nutr Metab</i> 2008;33:470-75.	RDBPCT	Ibuprofen did not impair muscle hypertrophy or strength in young men and women after resistance training.	Y
A COX-2 inhibitor reduces muscle soreness, but does not influence recovery and adaptation after eccentric exercise. Paulsen et al. <i>Scan J Med Sci Sports</i> 2010;20:e195-207.	DBPCT	Subjects who took celecoxib had less soreness than the placebo group, but no difference in serum creatine kinase levels or tissue levels of radiolabeled leukocytes (WBCs), monocytes, macrophages or satellite cells.	Y
Influence of acetaminophen and ibuprofen on in vivo patellar tendon adaptations to knee extensor resistance exercise in older adults. Carroll CC et al. <i>J Appl Physiol</i> 2011;111:508-15.	RDBPCT	Patellar tendon anatomical and biophysical properties were assessed with MRI and ultrasound coupled with force measurements before and after training in older adults training with knee extensor exercises. Patellar cross-sectional area (CSA) was unchanged in the placebo and ibuprofen groups and increased in the acetaminophen group. However, tendon deformation and strain, while unaffected except in the placebo and ibuprofen groups, increased in the acetaminophen group. No long-term practical outcome measures were assessed.	MY (Ibuprofen) MN (Acet)

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CITATION	STUDY TYPE	CONCLUSIONS	NSAIDs: Y,N,M
Nonsteroidal anti-inflammatory drug or glucosamine reduced pain and improved muscle strength with resistance training in a randomized controlled trial of knee osteoarthritis patients. Peterson SG et al. <i>Arch Phys Med Rehabil</i> 2011;92:1185-93.	DBRCT	36 men and women with knee osteoarthritis, 50-70 yo, were randomly assigned to ibuprofen, glucosamine or placebo during 12 weeks of quad training. The authors report that "In patients with knee OA, NSAID or glucosamine administration during a 12-week strength-training program did not improve muscle mass gain, but improved maximal muscle strength gain in comparison with treatment with placebo. However, we do not find that the benefits are large enough to justify taking NSAIDs or glucosamine."	MY

TABLE 2: HUMAN STUDIES OF CRYOTHERAPY. DB=double blind. R=randomized. PC=placebo-controlled. RCT=randomized controlled trial. CxT= crossover trial. MA = meta-analysis. For information on the recommendation assignments in the right-hand column, see the Appendix Notes.

CITATION	STUDY TYPE	CONCLUSIONS	LOCAL CRYOTX: Y,N,M
1990s			
Various treatment techniques on signs and symptoms of delayed onset muscle soreness. Gulick DT et al. <i>J Athlet Train</i> 1996;31(2):145-52.	RCT	The authors report no benefit of an NSAID (oxaprozin), ice, stretching, high velocity concentric exercise, or sublingual or topical <i>A. montana</i> extract on DOMS induced by eccentric forearm contractions. No long-term practically relevant outcomes were assessed.	N
Effect of cryotherapy on muscle soreness and strength following eccentric exercise. Paddon-Jones DJ, Quigly BM. <i>Int J Sports Med</i> 1997; 18(8): 588-93.	CT	After performing 64 eccentric elbow flexions with each arm, 8 resistance trained males did five 20 minute immersions in a cold-water bath (1 deg C) interspersed with 60 minute rests. No significant difference between cryo-treated or control arms were noted for soreness, limb volume, isometric torque, isokinetic torque, or any other variable. No long-term assay of adaptive response was undertaken.	MN
2000s			
The use of ice in the treatment of acute soft-tissue injury: a systematic review of randomized controlled trials. Bleakley et al. <i>Am J Sports Med</i> 2004; 32(1)251-61	MA	Analysis of twenty-two studies meeting inclusion criteria yielded marginal evidence that ice plus exercise was most effective after acute ankle injury or surgery. Ice appeared to add little to compression, but this finding was restricted to hospitalized (post-operative) patients. Data on ice after closed soft-tissue injury was sparse. "Many more high-quality trials are needed."	MY
Ice-water immersion and delayed-onset muscle soreness: a randomised controlled trial. Sellwood et al. <i>Br J Sports Med</i> 2007;41:392-7.	DBPCRT	"The protocol of <i>ice-water immersion</i> * used in this study was ineffectual in minimising markers of DOMS in untrained individuals. This study challenges the use of this intervention as a recovery strategy by athletes." <i>The study did not address local cryotherapy for injury or DOMS.</i>	MN*
Efficacy of cold gel for soft tissue injuries: a prospective randomized double-blinded trial. Airaksinen, et al. <i>Am J Sports Med</i> 2003;31(5)680-4.	DBPCRT	Cold gel therapy was safe and effective at reducing pain, compared to placebo, when applied to patients with sports-related soft-tissue injuries.	Y
Does cryotherapy improve outcomes with soft tissue injury? Hubbard and Denegar. <i>J Athlet Training</i> 2004;39(3):278-79.	SR	A systematic review of 22 RCTs, all of relatively low quality, suggested that cryotherapy was effective in reducing pain. Its effectiveness relative to other therapies and its impact on patient-oriented outcomes remains somewhat unclear.	MY

CITATION	STUDY TYPE	CONCLUSIONS	LOCAL CRYOTX: Y,N,M
Ice therapy: how good is the evidence? MacAuley DC. <i>Int J Sports Med</i> 2001; 22(5):379-84.	SR	This systematic review suggests that intermittent application of ice is effective, but notes decreased motor function and reflex activity after ice is applied.	M
The efficacy of ice massage in the treatment of exercise-induced muscle damage. Howatson G, et al. <i>Scand J. Med Sci Sports</i> 2005;15:416-422.	PCCT	Compared to a sham ultrasound therapy (the placebo) ice demonstrated no difference in reduction of discomfort, indirect serum markers of muscle damage (CK, Mb), or enhancement of function. No long-term outcome variables were assessed.	MY
Is ice right? Does cryotherapy improve outcome for acute soft tissue injury. Collins NC, <i>Emerg Med Journal</i> 2008;25:65-68.	SR, sorta.	This implicit review of both human and animal studies concluded—contrary to its own findings—that the literature contains insufficient evidence to suggest that cryotherapy is useful. See detailed analysis in the main body of the article.	N
The effects of various therapeutic measures on shoulder strength and muscle soreness after baseball pitching. Yanagisawa O, Miyanaga Y, Shiraki H et al. <i>J Sports Med Phys Fitness</i> 2003; 43(2):189-201.	RCT	Participants were randomized to one of 4 groups after throwing 98 pitches: ice (IT), light exercise (LSE), ice + light exercise (ILSE), and control (CON). The investigators report that both IT and ILSE had a positive effect, and that ILSE (ice + light exercise) was the optimal therapy.	Y
2010s			
A comparison of topical menthol to ice on pain, evoked tetanic and voluntary force during delayed onset muscle soreness. Johar et al. <i>Int J Sports Phys Ther</i> 2012;7(3):314-22.	RT	A topical menthol preparation displayed better analgesia and permitted greater force generation than ice. No placebo (non-treatment) group was incorporated into the study, so we know nothing about how these two therapies compared with no therapy at all. Investigators were blinded, but obviously patients could not be. No long-term end-points were studied.	M

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