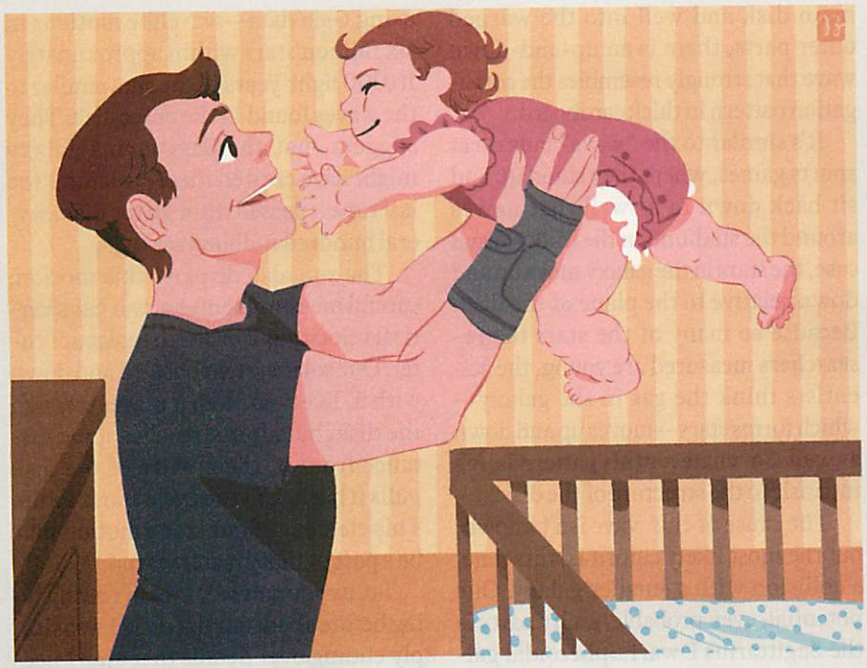
Oregon Intro

2026



Heal Injuries Faster

Toss out the old advice that rest is the best recovery strategy

BY LYDIA DENWORTH

AFTER A SLIP ON THE ICE, a sports injury, even surgery, most people's instinct is to rest what hurts. "When you have an acute injury, your body is sending signals through the peripheral and central nervous systems and the immune system to say, hold on, I need to stop doing this so we can allow the tissue to heal," says Ericka Merriwether, a physical therapist and pain researcher at New York University. Rest, after all, is the first part of the familiar RICE therapy, which stands for "rest, ice, compression and elevation."

But experts no longer believe RICE is the best strategy for recovery. They especially quibble with the first step: rest. Even Gabe Mirkin, the sports medicine physician who coined the RICE acronym in 1978, has acknowledged that newer evidence suggests other approaches are more effective.

Resting an injury can alleviate pain and may be necessary in the short term, especially for injuries such as muscle tears, which might be exacerbated by movement. In most cases, however, limiting movement does not promote healing. In fact, immobilization causes muscles to weaken and lose stability. An injured body part that is immobilized for too long is more likely to move from acute to chronic pain (that is, pain that lasts more than three months).

Instead of rest, "motion is the potion," experts say. And it is important to move far sooner than many imagine. Once a physician determines that movement is safe and that there's no biological reason not to engage in it, it's a case of "use it or lose it," says Rianne van Boekel, a nurse and associate professor at the Radboud University Medical Center in the Netherlands whose research focuses on acute and transitional pain.

Studies bear out the early-movement idea. In a controlled trial of athletes with serious soft-tissue injuries, researchers found that those who started rehabilitation two days after an injury instead of nine days later were able to return to sports 20 days sooner (in 63 days rather than 83). In a separate study, those who engaged in progressive agility training rather than static stretching were less likely to reinjure themselves. And in people with low back pain, consistent movement and exercise can improve pain levels, range of motion, strength and tissue repair.

That helps to explain why a popular acronym to emerge as a replacement for RICE is POLICE, in which the O and L stand for "optimal loading," or putting stress on tissues to induce the cellular changes that optimize recovery. (The other letters stand for "protection," "ice," "compression" and "elevation," so some parts of the RICE approach still hold.)

Putting stress on injured tissues does hurt, and the relation between pain and movement is complex. A person's responses to pain strongly influence their recovery from injury, researchers say, because the perception of pain has social and psychological elements as well as biological ones.

Injured tissue sends signals to the brain, which is where we perceive pain. "People say pain is in your head, and yes, it is," Merriwether says. There are also descending pain pathways from the brain back to the periphery of the body that inhibit and modulate the perception of pain.

That is why social environments and psychology play roles. Studies indicate that family caregivers might delay recovery if they do too much for an injured loved one, says anesthesiologist and pain researcher Esther Pogatzki-Zahn of the University of Münster in Germany. And, she says, people who must carry on with their lives—taking care of children or re-

Continued on page 81

Lydia Denworth is an award-winning science journalist and contributing editor for *Scientific American*. She is author of *Friendship* (W. W. Norton, 2020).

Illustration by Jay Bendt

Continued from page 78

turning to work—often report lower levels of pain than people who don't. On the psychological front, anxiety is a major risk factor for developing chronic pain after an injury. The more someone fears pain, and the more they avoid moving because of it, the worse they usually become.

To encourage movement and the healing it can bring, pain experts are working to educate people. "Pain reduction is the goal," Pogatzki-Zahn says. In a 2025 randomized controlled trial of 150 people, nurses delivered one two-hour virtual lesson on pain and nonpharmacological ways to relieve it. Such approaches can include distraction, mindfulness and virtual-reality exercises. Patients who received the pain intervention scored significantly lower on measures of pain catastrophizing after eight weeks than those who were put on a wait list for the class. The first group also had better scores on pain intensity, depression, pain self-efficacy, fatigue and satisfaction with social roles. "The best way to deal with pain is to accept that you are in pain," van Boekel says.

Painkillers can also help, although the goal should be to take the least amount of medicine for the shortest time possible, van Boekel notes—"enough to be able to move, not to get rid of all the pain." And she advises taking acetaminophen (Tylenol) rather than ibuprofen (Advil) because it has no side effects at correct dosages.

Researchers are also paying closer attention to how pain is assessed. For instance, the latest studies suggest that clinical evaluations should more carefully distinguish between pain at rest and movement-evoked pain because it turns out patient outcomes can vary according to which type of pain they experience.

There is far more to understand about the role of pain and movement in recovery, but for now it seems fair to call on another familiar saying: no pain, no gain. ●

$E = mc^2$

I have no faith, but I do believe
in mass–energy equivalence
    I light its candle
    say its prayer
    press my head against its Western Wall

because there is something holy
about an equation
    its insistence on fairness
    on symmetry
    on equal distribution

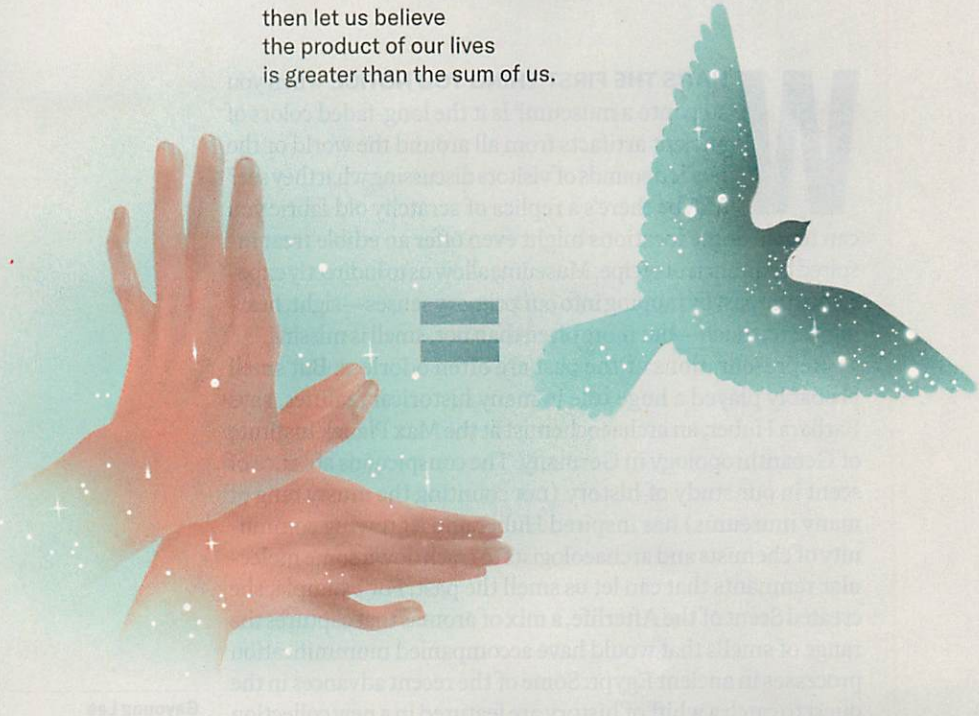
so when I consider after-life
    when my spirit is cleaved
    from its form

it gives me comfort to think:
    if the constant is not me
    it is, at least, the square
    of the speed of light

    that all parts are accounted for

and when I forget who I am
and when I forget thee
and you forget me
    when the currents of our bodies halt
    when the oceans rest in their beds
    and the great winds give way to calm

then let us believe
the product of our lives
is greater than the sum of us.



Elaine Mintzer is a southern California poet and retired high school teacher who finds scientific vocabulary a useful anchor for feelings and philosophy. Her two poetry collections are *Natural Selections* (Bombshelter Press, 2004) and *Drink from the River* (coming soon from Moontide Press).

Illustration by Masha Foya

Immunology

The effect of tattoos on the body is more than skin deep

Christa Lesté-Lasserre

TATTOO ink collects in lymph nodes and interferes with the immune system, causing potentially lifelong changes to the body's disease-fighting mechanisms.

That is the conclusion of a study in mice, in which tattooed animals showed chronic inflammation in their lymph nodes – which were pigmented with the ink – and had altered antibody responses to vaccines. Human lymph nodes from tattooed individuals had similar inflammation and colouring.

"When you're tattooing, you're actually injecting ink into your body," says Santiago González at the University of Lugano in Switzerland. "It's not just a cosmetic effect... there are effects on the immune system as well."

Tattooing has become a global trend. Between 30 and 40 per cent of people in Europe and the US under the age of 40 have at least one tattoo.

González says he and his colleagues were working on an unrelated research project on inflammation in mice when they realised the animals developed "crazy inflammatory reactions" after being given small tattoos for identification.

To find out more, they used standard commercial inks in black, red and green to tattoo a 25-square-millimetre patch of skin on the hind feet of dozens of mice. With specialised imaging equipment, they watched the ink travel along the lymphatic vessels inside the leg up to the nearby lymph nodes almost immediately.

There, the team saw that macrophages – immune cells that clean up debris, pathogens and dead cells – captured the ink, tinting the nodes and provoking acute inflammation. Within about 24 hours, those macrophages died, releasing the ink, which then got captured by other macrophages. Those, too, would die and release ink, which would get taken up by yet other macrophages – creating a cycle of chronic inflammation that lasted well after the tattoo site had healed (*PNAS*, doi.org/qhd9).

EDEN BREITZ/ALAMY

By the end of the experiment, two months after tattooing, the mice's lymph nodes still had levels of inflammatory markers up to five times higher than normal, says González.

"Tattooing is not just cosmetic, there are effects on the immune system as well"

To investigate whether this inflammation affected immune function, they injected vaccines directly into the tattooed skin. The tattooed mice's antibody response to a covid-19 mRNA vaccine was noticeably weaker than in control mice, but their response to an influenza vaccine was stronger.

Tattooing has now become a global trend

Further analyses showed the lymph node macrophages of tattooed mice were so full of ink, they captured less of the covid-19 vaccine – which, as an mRNA vaccine, needs processing by macrophages to be functional. For the protein-based influenza vaccine, however, inflammation boosted the antibody response, perhaps because there were more immune cells recruited to the tattooed site.

Finally, they examined a small set of lymph node biopsies from people who had been tattooed in regions near the nodes. Even two years after tattooing, the nodes still contained visible pigment, packed into the same kinds of macrophages as seen in the mouse study.

Michael Giulbudagian at the German Federal Institute for Risk Assessment in Berlin says "the relevance for human health, in particular after the complete healing of the wound, must be further investigated".

Mental health

Exercise may match antidepressants

We're learning more about the benefits of exercise for treating depression, even if the exact reasons why remain unclear, reports **Carissa Wong**

MANY of us experience a mood boost after exercise, and now an updated review has revealed just how powerful it can be. Even light exercise, like walking or gardening, may ease the symptoms of depression as effectively as talking therapies or antidepressants.

"It really reiterates that exercise provides an option for people who have depressive symptoms, and confirms that exercise may be as effective as psychotherapy and antidepressants," says Andrew Clegg at the University of Lancashire in the UK.

Prior studies, including a key review published by the Cochrane Library in 2013, have found exercise may ease symptoms of depression as effectively as standard therapies, including antidepressants and cognitive behavioural therapy (CBT), where a therapist helps people change their thoughts, feelings and behaviour.

This has prompted healthcare organisations to recommend regular exercise for managing depression. For instance, the UK's National Institute for Health and Care Excellence (NICE) recommends weekly aerobic exercise, such as jogging, for 10 weeks – usually in combination with other therapies, which, on their own, don't benefit everyone.

But since the 2013 review, dozens more trials have been conducted, so the Cochrane Library is now publishing an updated review. "This latest review [almost] doubles the evidence base that was in the previous one," says Clegg, one of the authors.

He and his colleagues analysed results from 69 randomised controlled trials involving nearly 5000 adults who were either clinically diagnosed with mild, moderate or severe depression, or who had a score on a depression symptom scale that is generally considered indicative of the condition. First, the researchers focused on 57 of the trials, in which participants were randomly assigned either to a group that exercised regularly or to a control group that was offered no treatment or that was placed on a waiting list for treatment.

Feeling the difference

The trials varied in design, but they usually involved asking participants to exercise on a weekly basis for a few weeks to months, with the style of exercise ranging from low- or moderate-intensity activities such as gardening and brisk walking, respectively, to vigorous activities such as sprinting or playing football. Trials involving yoga or stretching weren't included as these often involve meditation and breath work, and the team wanted to focus more on the effects of physical activity alone, says Clegg.

The researchers found that exercise seems to moderately reduce the severity of depressive symptoms, such as often feeling sad, or losing interest in other people. "They found a clinically meaningful change – people will feel the difference from that," says Brendon Stubbs at King's College London.

Next, the team focused on 10 trials among the 59 that compared exercise to CBT, and five trials in which some participants took antidepressants but there was no exercise component at all. This revealed that, on average, regular exercise worked as well as the two other therapies (*Cochrane Library*, doi.org/hbh4x9). "There wasn't a difference between them," says Emily Hird at University College London.

TON MOLINA/NURPHOTO VIA GETTY IMAGES

Jogging has previously been recommended for managing depression

By taking a closer look, the team found that light and moderate exercise seem to be more effective than vigorous kinds, which may simply be because they are easier to stick with, says Stubbs.

How exactly exercise brings its benefits is unclear, but it probably works in several ways, says Stubbs.

"It really reiterates that exercise provides an option for people who have depressive symptoms"

Group exercise, for instance, can boost people's social well-being.

Studies have also shown that, during exercise, chemicals released from muscles called myokines help mop up inflammation that is thought to contribute to depressive symptoms, says Stubbs. One particular myokine called brain-derived neurotrophic factor also spurs the growth of new brain cells, which could help the brain rewire itself and break free of negative thought patterns, says Stubbs. In line with this idea, Clegg and his colleagues found that resistance training – which leads to a greater release of myokines versus other forms of exercise – was more effective than aerobic exercise alone, says Stubbs.

Together, the findings support guidelines that recommend exercise for treating depression. However, in all the studies reviewed, participants knew whether they were in a treatment group or control group. This raises the possibility that at least some of the exercise-related improvements could be down to the placebo effect, says Hird.

Larger studies are needed to better understand which types of exercise – including those not included in the review – are best, for whom, and why, says Hird. ▮

By Bernadine Healy, M.D.

The Dangerous Art of the Tattoo

TATTOOS ARE FAST BECOMING A MARK of the 21st century, with one quarter or more of those under the age of 30 adorning their skin with at least one. Whether driven by the urge for personal expression or just plain youthful impulsiveness, most people get tattooed without a clue about the health implications of this invasive skin-puncturing procedure. I'd suggest that all tattooing require a signed consent form outlining risks—the most obvious one being a major case of remorse.

Upwards of 50 percent of those who get tattoos later wish they hadn't. Their regrets become medical when they visit a dermatologist to have the tattoos removed, which is both painful and expensive. In the July issue of the *Archives of Dermatology*, researchers at Texas Tech University Health Sciences Center report on what's behind the change of heart: moving on from the past, problems wearing clothes, embarrassment, and concerns that tattoos could adversely affect job or career.

But tattooing is designed to last forever, delivering permanent ink deep under the epidermis. The skin reacts by protectively encapsulating the alien clumps of pigment in dense fibrous tissue while a few nearby lymph nodes collect what migrates out. For a long time, removal meant surgical excision or deep abrasion of the skin, invariably causing scarring and sometimes the need for skin grafting. In the preferred approach now, the tattoo gradually fades away under many months of laser treatments tailored to the wavelength of the pigments. Sounds easy. But with disruption, the fading tattoo becomes more like a toxic chemical dump.

Chemists from several laboratories, including the government's National Center for Toxicological Research, have identified low levels of carcinogens in tattoo ink. But the laser removal process, which demolishes the pigment by scorching it with heat, triggers chemical reactions that generate carcinogenic and mutation-inducing breakdown products, which are then absorbed by the body. Recently, German scientists reported that concentrations of toxic molecules from red and yellow pigments increased up to 70-fold after laser irradiation. And the bigger the tattoo, the greater the toxic release. This can only make one wonder whether it's better to let the sleeping paint lie, walled off by the body's own protective devices. Only time and a lot more study will tell.

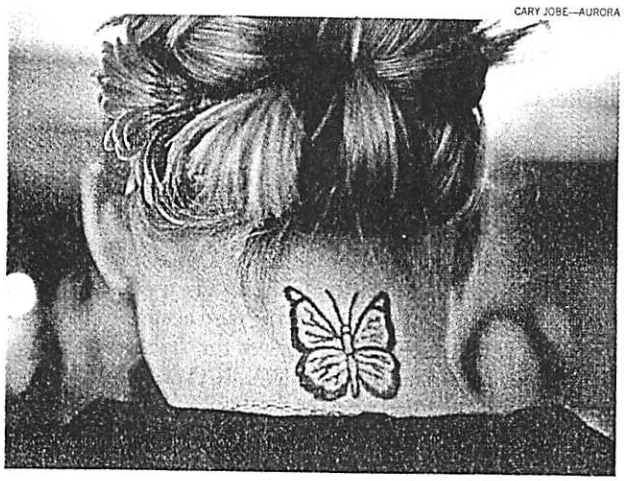
We know so woefully little about tattoos. The Food and Drug Administration, which goes after cosmetics with a vengeance, does not regulate the tattoo industry. In fact, no one really knows exactly what's in the numerous commercial and homemade inks. But they do contain solvents and metals like lead and mercury and a range of impurities acceptable for computer printers or car paint—but not for human injection.

Allergic reactions and skin infections can occur after tattooing. And though they may be coincidental, skin cancers, including melanomas, have been reported within tattoo sites, bearing very close watching. The FDA warns about the risk of tattoo parlors transmitting viruses like HIV and the cancer-causing hepatitis C. Because of this, blood banks typically ban donations from people who have been tattooed in the previous 12 months. The FDA also warns patients that if they have an MRI scan, their tattoos can swell or burn, presumably related to the metal in some inks.

Stigma. Once mainly a guy thing, tattoos now decorate men and women equally, and increasingly they are a women's health issue. It should be obvious that getting or removing tattoos during pregnancy is not a good idea. And some anesthesiologists have expressed concerns about performing epidurals, used during labor, through those symmetrically designed female lower-back tattoos because of the slim possibility that the needle might carry pigment into the spinal canal. Perhaps not surprisingly, most patients seeking removal are women, prompted by a disproportionate level of psychological distress and even tattoo stigma. Witness the tasteless moniker used to describe those lower-back tattoos: "tramp stamp."

Laser removal, which demolishes tattoo pigment, may sound easy. But it opens up a toxic chemical dump.

CARY JOBE—AURORA



I asked a few of my *U.S. News* colleagues about their take on women and tattoos. One said there was something trendy if not sexy about them—but maybe not for his fiancée. Another said he'd date a girl with one if it were not too obvious. A third saw only harmless self-expression. I'm with one young reporter who visited a tattoo parlor for a piece she was writing. She's down on tattoos because of the murky risks—and the idea of looking at the deeds of her youth for 80 years. ●

Immunology

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Christa Lesté-Lasserre

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EDEN BREITZ/ALAMY

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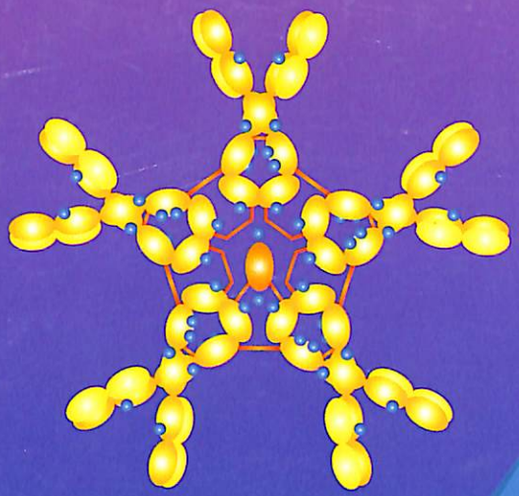

SECOND EDITION

Medical Immunology

made memorable

J. H. L. Playfair
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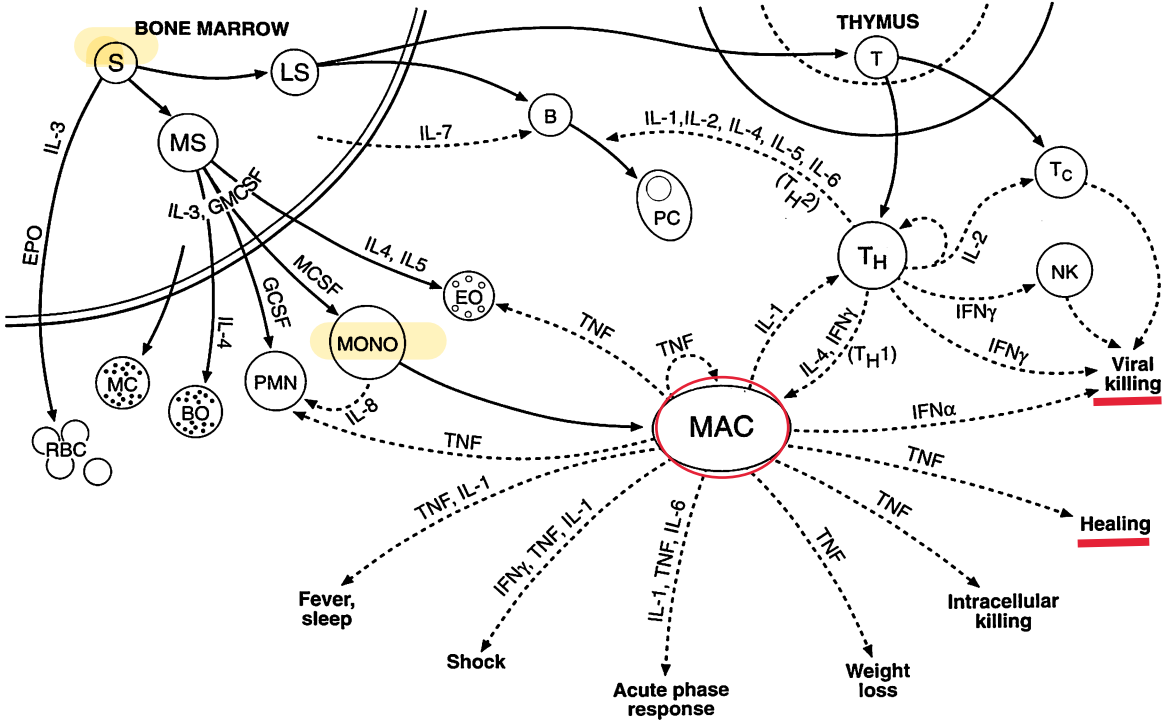
CHURCHILL LIVINGSTONE


BONE MARROW
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IL-8
IFNα
Viral killing
Healing
TNF, IL-1
IFNγ, TNF, IL-1
IL-1, TNF, IL-6
Fever, sleep
Shock
Acute phase response
Weight loss
Intracellular killing

Natural immunity: the rapid defence system

This includes a variety of cells and molecules whose presence can be literally life-saving; we shall see just how important they are when we consider conditions in which they are deficient. There is, however, a price to be paid for such rapid activity, which is that it is fairly vague in its aim. Indeed in the early stages of infection, the precise target may not yet have been identified beyond the recognition that it is, for example, probably a virus or a bacterium. Thus, in police terms, natural immunity responds somewhat on the 'alert all officers' principle. In immunological jargon, this lack of precision is referred to as **non-specific**, by contrast with the very high specificity of later responses (p. 3) but, as will be seen, specificity is relative and a better term for natural immunity might be **low specificity**. Another name sometimes used is **innate**, which reflects the fact that most natural immune mechanisms are present at birth, and indeed before it, and do not change greatly with age. Thus natural, non-specific and innate immunity all refer to essentially the same thing.

The importance of the macrophage

The main cells and molecules responsible for natural immunity are shown in Figure 2, in which the central role of the **macrophage** is emphasized. Indeed, macrophages are probably the single most important cell type in immunity and a complete absence of macrophages would almost certainly be incompatible with survival. Together with the **polymorphonuclear (PMN) neutrophils** they are responsible for recognizing and removing unwanted particulate matter by a process known as **phagocytosis** (see p. 6); they secrete a huge variety of molecules including the antiviral **interferon**, the

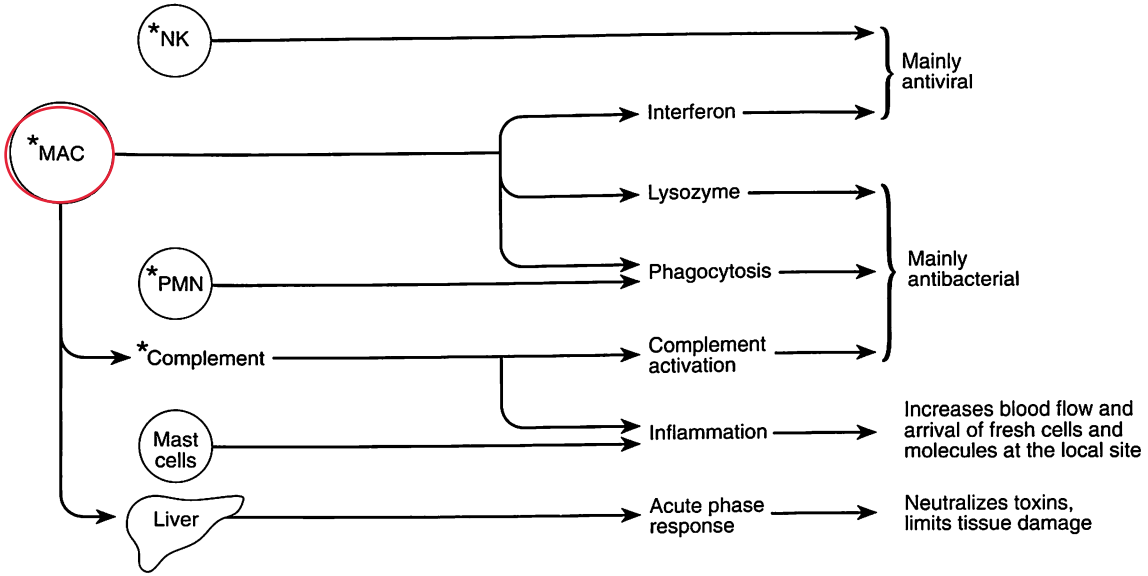


Fig. 2 Natural immune mechanisms form a general purpose, early defence system. They come into action within minutes or hours of infection and/or tissue damage. Note that all these components are relatively non-specific in terms of both recognition and disposal, but some (*) do have the ability to recognize foreign material. However, unlike adaptive mechanisms (p. 3), they do not retain any memory of their encounter with infectious organisms but simply return to 'baseline'. NK, natural killer cells; MAC, macrophage; PMN, polymorphonuclear leucocyte (neutrophil).

Monocyte-derived IL-10 Drives Sex Differences in Pain Duration

Science Immunology
February 20, 2026; Vol. 11; epub
[published by the American Association for the Advancement of Science]

Jaewon Sim, Elizabeth O'Guin, Chiho Sugimoto, Sophie Laumet, and 15 more; From Michigan State University, the University of North Carolina at Chapel Hill, the University of Kansas Medical Center, and the University Hospital Regensburg, Germany. This study cites 100 references.

The assessment in this study used both mouse and human subjects. The human arm of this study used 245 subjects. The objective of this study was to investigate whether IL-10 mediates the relationship between monocytes and chronic posttraumatic pain.

This study used preclinical and human approaches to define the role of IL-10–producing monocytes in pain resolution and to determine whether this mechanism contributes to sex differences.

The human subjects suffered from whiplash injuries. Their musculoskeletal pain severity was assessed in the immediate aftermath of traumatic collision exposure and at 8 weeks and 3 months by asking participants to rate their pain severity in the past week via a 0 to 10 numeric rating scale.

BACKGROUND FROM DAN MURPHY:

Classically, the **monocyte** is located in the blood where it travels to tissues where it differentiates into the **macrophage**, the primary cell of innate immune response.

Cytokines are proteins that are made by immune system cells.

Pro-inflammatory **cytokines** (TNF-alpha, IL-1beta; IL-6, IL-8) *increase* pain.

Anti-inflammatory **cytokines** *reduce* pain. The primary *anti-inflammatory* **cytokine** is *interleukin-10 (IL-10)*. IL-10's antinociceptive role in animals and humans is well established.

The production of *IL-10* is dependent upon a molecule called **resolvins series D**.

Resolvins series D are made from the essential omega-3 fatty acid *docosahexaenoic acid (DHA)*: See these Article Reviews:

28-20: **Inflammation Resolution: A Dual-Pronged Approach to Averting Cytokine Storms in COVID-19**

- "The antinociceptive role of androgens [testosterone] has been reported in preclinical models and human studies of inflammatory pain and musculoskeletal pain."

- The greater abundance of IL-10 and monocytes in males is driven by androgen [testosterone] signaling.

- Cutaneous topical application of testosterone can alleviate musculoskeletal pain.

- "Androgen signaling promoted IL-10 production by monocytes, driving sex differences in IL-10 and monocyte abundance."

- In humans experiencing traumatic injury, males resolve pain faster than females, which is driven by androgen [testosterone] signaling that enhances IL-10 levels in males.

- "Androgen signaling in monocytes facilitates IL-10 production to drive pain resolution." **[Important]**

- "Loss of androgen signaling in males reduces IL-10 monocytes and delays pain resolution."

- "Androgen signaling in monocytes enhances IL-10 production, thereby facilitating pain resolution."

- "We found that IL-10 production is driven by androgen [testosterone] signaling in monocytes."

14) Conclusions:

- Monocytes and IL-10 levels are associated with sex-biased pain resolution of traumatic injury in human patients. **[Important]**

- "These results highlight an important role for cross-talk between IL-10 and immune cells in resolving inflammatory pain."

- IL-10 and monocytes are required to resolve inflammatory pain.

- "IL-10 exerts anti-inflammatory effects by suppressing the transcription of proinflammatory cytokines." **[Key Point]**

- "Emerging evidence reveals an underappreciated role for immune cells in pain resolution."

- "Sex differences in pain resolution are driven by differing levels of IL-10."

- Monocyte-derived IL-10 is a critical mediator of communication between infiltrating immune cells and sensory neurons during pain resolution.

- "Our work demonstrates a role for these monocytes' regulation of pain duration and sex differences."

15) Editor's Summary:

- "Women experience slower pain resolution and are more susceptible to developing chronic pain."

- "IL-10–producing monocytes signal to sensory neurons to drive faster pain resolution in males."

- Androgen [testosterone] signaling promotes accumulation of IL-10 and monocytes for pain resolution, and the effects are elicited by the [omega-3] lipid mediator resolvin series D.

- "In humans experiencing traumatic injury, pain resolved faster in men than women and was associated with higher IL-10 levels."

- "These findings identify a role for monocytes in contributing to sex differences in pain resolution."

COMMENTS FROM DAN MURPHY:

Inflammation alters the threshold of the pain afferent. See *Article Review 29-09*: **The Origin of all Pain is Inflammation and the Inflammatory Response**

Inflammatory proteins called cytokines increase pain. The primary inflammatory cytokines are TNF-alpha, IL-1beta; IL-6, IL-8. See books Younger Next Year and The Great Nerve, (below).

From the same references, the primary anti-inflammatory cytokine is *interleukin-10 (IL-10)*.

Most Importantly, the following study (not yet reviewed) indicates meaningful increases of IL-10 following joint adjusting:

Attenuation Effect of Spinal Manipulation on Neuropathic Pain and Postoperative Pain Through Activating Endogenous Anti-inflammatory Cytokine Interleukin-10;
Journal of Manipulative and Physiological Therapeutics; January 2016; Vol. 39; No. 1; pp. 42-53.

Perhaps that is one of the explanations for why joint adjusting helps people with pain. And we should **all** be taking our **omega-3s to** optimize **resolvins**.

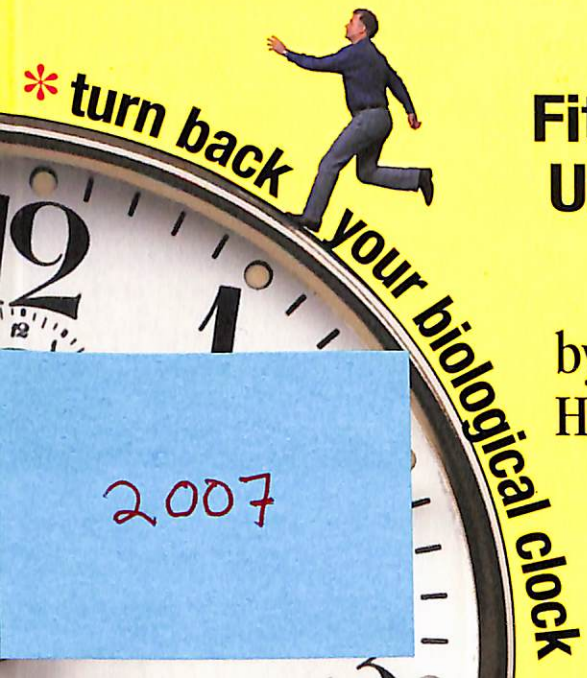
The New York Times Bestseller

"Harry's Rules will change your life."
MEHMET OZ, M.D., coauthor, *YOU: The Owner's Manual*

Younger Next Year*

"Brain-rattling, irresistible, hilarious. If you're up for it... "[this book] could change your life."
THE WASHINGTON POST

Take the Next Step!
Includes Preview Chapter of
THINNER THIS YEAR



Live Strong, Fit, and Sexy—Until You're 80 and Beyond

by Chris Crowley & Henry S. Lodge, M.D.

The New Science of the *Vagus Nerve* and How to Harness Its *Healing Reflexes*

THE GREAT NERVE

2025

KEVIN J. TRACEY, MD

The Great Nerve
The New Science of the *Vagus Nerve* and How to Harness Its *Healing Reflexes*

Kevin Tracey MD
Avery, 2025

"Your vagus nerve is great because it reaches into so many life and health-giving systems in your body and keeps them all in balance."

"The vagus nerve can regulate your body's vital systems and heal a wide variety of medical conditions."

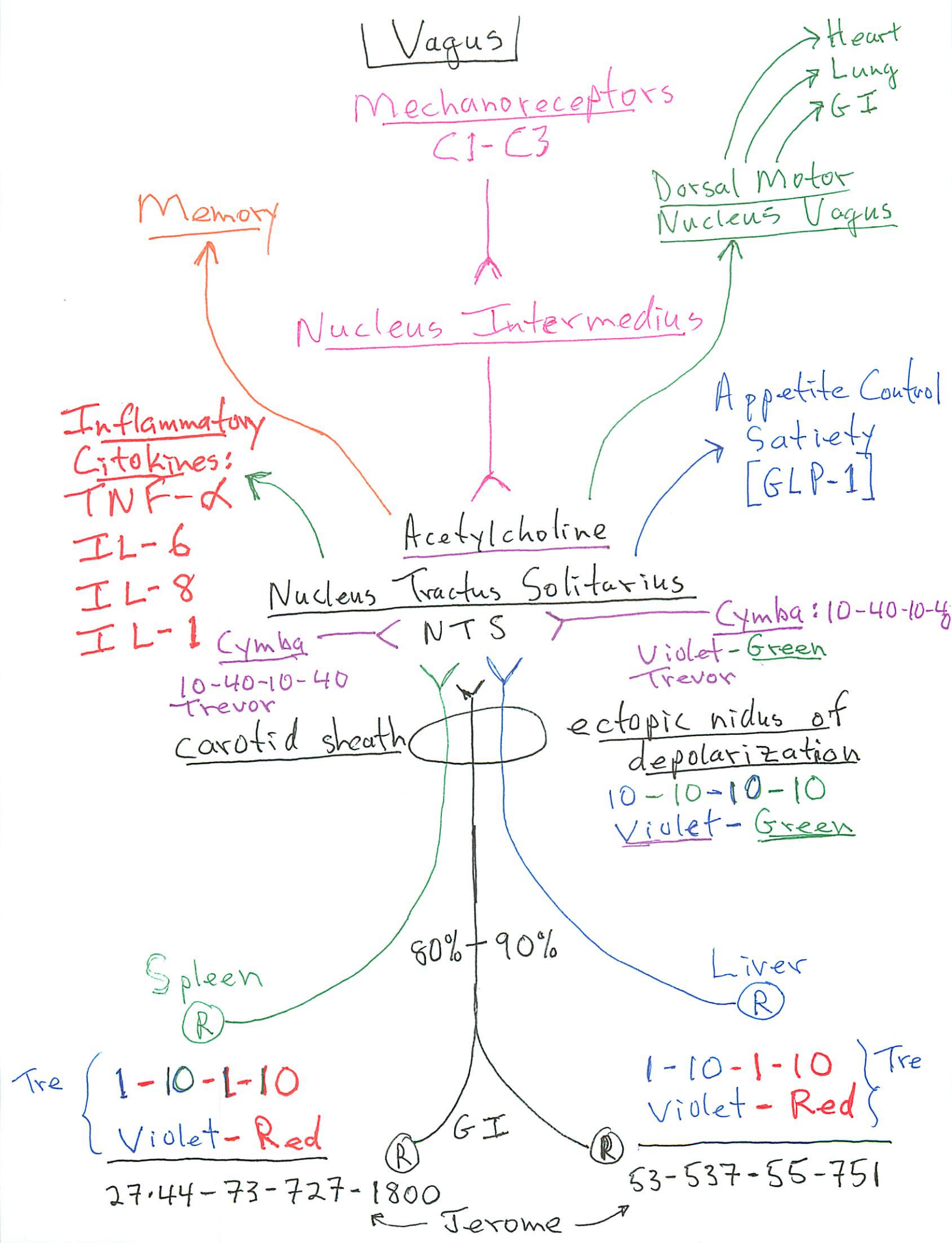
"The vagus nerve is fundamental to our health and vitality…"

"The previously unknown power of the vagus nerve to reverse inflammation, balance the immune system, treat chronic illness…"

"Inflammation has replaced infection as the greatest threat to healthful human longevity."

"A functioning vagus nerve is truly a life-or-death matter; it is the only nerve we have that when cut on both sides, we die."

"How do you know if your vagus nerve is being stimulated? A simple answer is that you know it is being stimulated when your pulse goes down?


Vagus
Mechanoreceptors
C1-C3
Heart
Lung
GI
Dorsal Motor Nucleus Vagus
Memory
Nucleus Intermedius
Inflammatory Cytokines:
TNF-α
IL-6
IL-8
IL-1
Appetite Control
Satiety
[GLP-1]
Acetylcholine
Nucleus Tractus Solitarius
NTS
Cymba
10-40-10-40
Trevor
Cymba: 10-40-10-40
Violet-Green
Trevor
carotid sheath
ectopic nidus of depolarization
10-10-10-10
Violet-Green
80%-90%
Spleen
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Optimal Nutritional Status for a Well-Functioning Immune System Is an Important Factor to Protect against Viral Infections

Nutrients
April 23, 2020; Vol. 12; No. 4; Article 1181

Philip C. Calder, Anitra C. Carr, Adrian F. Gombart, Manfred Eggersdorfer; from the University of Southampton, UK; the University of Otago, New Zealand; Oregon State University; the University Medical Center Groningen, The Netherlands. This study cites 83 references.

BACKGROUND:

To convert European vitamin D serum levels (nmol/L) to US serum levels (ng/ml), divide by 2.5: **50–75 nmol/L / 2.5 = 20-30 ng/ml**

SPMs = *specialized pro-resolving mediators* **resolvins**, **protectins**, **maresins**

KEY POINTS FROM THIS ARTICLE:

1) The Infection Problem

- The global burden of infection is high.
- Acute respiratory tract infections are a major cause of morbidity and mortality across the globe, including seasonal influenza, and COVID-19.
- Acute respiratory tract infections were responsible for approximately 2.38 million deaths worldwide in 2016.
- "New strains of influenza continuously emerge, necessitating development of new vaccines with varying efficacy, and outbreaks of novel viruses can be enormously difficult to contain."
- Severe lower respiratory tract infections are the most common cause of sepsis-related death globally.
- "Additional safe and cost-effective strategies are needed to support the immune system and further protect individuals and populations from harm." **[Key Point]**

2) Nutritional Deficiencies

- "Micronutrient and omega-3 inadequacies or deficiencies are prevalent around the globe."

- Deficiencies and even suboptimal status of these nutrients can impair immune functions, including "decreases in the numbers of lymphocytes, impairment of phagocytosis and microbial killing by innate immune cells, altered production of cytokines, reduced antibody responses, and even impairments in wound healing."

3) Immune System Function

- "The immune system is comprised of both the innate (fast, non-antigen specific) and adaptive (slower, antigen-specific) responses."

- The innate immune system has a variety of phagocytic cells (neutrophils, macrophages, natural killer cells) that recognize the presence of pathogens.

- "The innate system moves quickly to recognize and destroy 'non-self' threats, typically via inflammatory processes, and then resolve the inflammation and repair the damage caused by these events." **[Key Point]**

- The adaptive response includes antigen-specific cells (T lymphocytes and B lymphocytes), which are activated to secrete antibodies specific to the infecting pathogen.

- "Slower to respond than the innate system, the adaptive system is responsible for generating immunological 'memory', whereby a repeated infection with the same pathogen will generate a vigorous, fast antigen-specific response."

- Ideally, vaccines provide protection against subsequent pathogen exposure by the induction of immunological memory.

- "Influenza is caused by a single-stranded RNA virus, and as such exhibits high mutation rates and rapid evolution, which may allow these viruses to escape from pre-existing neutralizing antibodies in the host."

    - Vaccination programs therefore must make predictions each year as to which strains to vaccinate against; in the US, the CDC estimates the influenza vaccine averages to be about 45% effective, with a range from 19%–54%.

4) Nutritional Impact on Immunity

- "[A] compelling strategy is to provide sufficient nutritional support for the immune system."

- "Often missing in public health discussions around immunity and infection are nutritional strategies to support optimal function of the immune system." **[Important]**

- The importance that nutrition plays in immune function is well established.

- "Deficiencies or suboptimal status in micronutrients negatively affect immune function and can decrease resistance to infections." **[Key Point]**

- "A wealth of mechanistic and clinical data show that vitamins, including vitamins A, B6, B12, C, D, E, and folate; trace elements, including zinc, iron, selenium, magnesium, and copper; and the omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid play important and complementary roles in supporting the immune system." **[Key Point]**

    - "Inadequate intake and status of these nutrients are widespread, leading to a decrease in resistance to infections and as a consequence an increase in disease burden."

- "Most micronutrients exhibit pleiotropic [production of additional beneficial effects] roles in supporting immune function."

- "With respect to innate immunity, the vitamins and minerals listed above collectively function to support the development and maintenance of physical barriers; production and activity of antimicrobial proteins; growth, differentiation and motility/chemotaxis of innate cells; phagocytic and killing (e.g., oxidative burst) activities of neutrophils and macrophages; and promotion of and recovery from inflammation (e.g., cytokine production and antioxidant activity)."

- "These data suggest that suboptimal nutrient status in the host population could lead to the emergence of more pathogenic strains of viral diseases, thereby increasing the risks and burdens associated with these illnesses."

- "[These vitamins and minerals] support adaptive immunity, via lymphocyte differentiation, proliferation and homing; cytokine production; antibody production; and the generation of memory cells."

5) "Inflammation is a key component of the immune response." **[Key Point]**

- This inflammation functions to "eliminate the infection."

    - "Inflammation typically resolves quickly at the end of the immune response, due to activation of specific negative-feedback mechanisms."

    - "The omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) present at the site of inflammation are enzymatically converted to specialized pro-resolving mediators (SPMs) known as resolvins, protectins, and maresins." **[Key Point]**

- "Vitamin D metabolites appear to regulate production of specific antimicrobial proteins that directly kill pathogens and thus are likely to help reduce infection including in the lungs."

- Vitamin D levels below 50 nmol/L [20 ng/ml] are inadequate.

    •• Concentrations between 50–75 nmol/L [20-30 ng/ml] are considered sufficient.

- "Vitamin D supplementation reduces the risk of respiratory tract infections in both children and adults."

- "Daily supplementation of vitamin D reduces the risk of acute respiratory tract infections."

- "Vitamin D supplementation can reduce the risk of respiratory tract infections in both children and adults."

- The authors recommend daily intake of 2000 IU/day.

13) Omega-3 fatty acids EPA and DHA:

- A global survey of EPA + DHA status in the blood "found 'low' or 'very low' status of EPA + DHA in most of the countries assessed."

- "Omega-3 fatty acids support an effective immune system, specifically by helping to resolve the inflammatory response." **[Resolvins, Important]**

- "An adequate intake supports the resolution of inflammation via the production of anti-inflammatory metabolites of these fatty acids, including in the respiratory tract."

- "Nutritional deficiencies in these essential fatty acids can result in delayed or suboptimal resolution of inflammation."

14) Conclusions

- Vitamins and trace elements (micronutrients) "play important roles in supporting the cells and tissues of the immune system."

- Supplementation with micronutrients and omega-3 fatty acids is a safe, effective, and low-cost strategy to help support optimal immune function. **[Key Point]**

- "Supplementation above the Recommended Dietary Allowance (RDA), but within recommended upper safety limits, for specific nutrients such as vitamins C and D is warranted."

Homocysteine Status Modifies the Treatment Effect of Omega-3 Fatty Acids on Cognition in a Randomized Clinical Trial in Mild to Moderate Alzheimer's Disease: The OmegAD Study

Journal of Alzheimer's Disease
2019; Vol. 69; No. 1; pp. 189–197

Fredrik Jernerena, Tommy Cederholm, Helga Refsum, A. David Smithe, Cheryl Turnere, Jan Palmbladf, Maria Eriksdotter, Erik Hjorth, Gerd Faxen-Irving, Lars-Olof Wahlund, Marianne Schultzbergg, Hans Basunb, Yvonne Freund-Levig; from Uppsala University, Sweden; Karolinska University Hospital, Sweden; University of Oslo, Norway; University of Oxford, United Kingdom; Orebro County and School of Medicine, Sweden; King's College, UK. This study cites 30 references.

CDR	=	Clinical Dementia Rating
MMSE	=	Mini Mental State Examination (attached at end of review)
ApoE	=	apolipoprotein E
DHA	=	docosahexaenoic acid omega-3 fatty acid
EPA	=	eicosapentaenoic acid omega-3 fatty acid
tHcy	=	total homocysteine
PC	=	phosphatidylcholine

"OmegAD is an RCT investigating the effect of supplemental Omega-3-FAs in patients with mild to moderate AD on cognitive outcomes, primarily the Mini-Mental State Examination (MMSE)." [the MMSE form is attached at end of review] Higher scores indicate better cognitive function.

These authors investigated whether baseline levels of plasma total homocysteine (tHcy), a marker of B vitamin status, modify the effects of omega-3-FAs supplementation on cognitive performance in moderate Alzheimer's Disease (AD).

This study included 171 patients with AD with MMSE ≥15:
88 in the omega-3-FA group; 83 in the placebo group.

Patients received daily doses of 1.7 g docosahexaenoic acid (DHA) and 0.6 g eicosapentaenoic acid (EPA) for 6 months.

The outcomes comparing the omega-3-FA and placebo groups were assessed after the initial 6 months of treatment. Treatment outcome on cognition was analyzed according to baseline levels of tHcy.

"The main objective of this post hoc study is to investigate interactions between baseline levels of total Hcy (tHcy), as a marker of B vitamin status, and supplementation with omega-3-FAs on cognitive and functional assessments in patients with mild to moderate AD, with the hypothesis that the potential positive effects of supplementation with omega-3-FA on the cognitive and functional outcome is related to the baseline levels of tHcy."

- "Without sufficient intake of B vitamins, formation of the relevant forms of PC could be impaired, and the brain may not obtain enough omega-3-FAs."

- "DHA is heavily enriched in the brain, and forms a major component of neuronal membranes, particularly in synapses."

- "There is evidence of an interaction between B vitamin status and omega-3-FAs in relation to brain atrophy and cognitive decline." **[Important]**

4) Prior Studies

- A randomized, double-blind, placebo-controlled study (RCT) evaluating the effect of high dose B vitamin treatment (folic acid, 0.8 mg; vitamin B6, 20 mg; vitamin B12, 0.5 mg) in elderly with mild cognitive impairment (MCI) showed that the protective effect of the B vitamin treatment on brain atrophy rates was dependent on the plasma concentrations of DHA and EPA.

- In subjects with high concentration of Omega-3-FA at baseline, B vitamin treatment slowed the brain atrophy rate by 40% compared with placebo.

  - "Significant interaction effects were also observed in relation to cognitive functions."

- Prior study findings suggest that the protective effect of omega-3-FA supplementation may be dependent on sufficient B vitamin levels. **[Key]**

- "Fish oil plus a multivitamin supplementation that included B vitamin, increased the incorporation of omega-3-FAs into erythrocyte membranes."

5) Findings

- "We found significant interactions between omega-3-FA supplementation and tHcy on cognition and clinical stage assessed by MMSE, [and the] CDR."

- "In patients with tHcy levels <11.7 micromol/L, omega-3-FA supplementation improved cognitive performance as measured by MMSE (+7.1%) and clinical status as measured by CDR (–22.3%) compared with placebo."

  - "Subjects with better B vitamin status benefited more from the omega-3s." **[Key Point]**

- There are significant effects of omega-3-FA treatment on MMSE (7.1% higher) in subjects with low baseline tHcy (<11.7 micromol/L). **[Key Point]**

- "The effect of omega-3-FA treatment on MMSE was modified by baseline tHcy levels."

- The effect of the omega-3-FA treatment on CDR was modified by tHcy levels.

- "Compared with the placebo group, MMSE scores were 7.1% higher and CDR scores 22.3% lower in the omega-3-FA group, indicating better cognitive performance and improved clinical status." **[Key Point]**

- "In this post hoc analysis of the OmegAD study, an RCT investigating the effects of omega-3-FA supplementation on cognitive measurements in patients with mild to moderate AD, we demonstrate significant interactions between omega-3-FA treatment and baseline levels of tHcy on MMSE and CDR score after six months of treatment."

6) Conclusions

- "The effect of omega-3-FA supplementation on cognitive and clinical outcomes is related to baseline tHcy levels, which implies that functional B-vitamin status is a potentially important factor to consider when evaluating the effect of omega-3-FA supplementation". **[Key Point]**

- "Future randomized clinical trials with omega-3-FAs should consider the relationships between omega-3-FAs, Hcy, and B vitamins on cognitive as well as neuropsychiatric symptoms."

- A limitation to this study is the duration of the omega 3-FA intervention was only 6 months.

- "Lower tHcy concentration (<11.7 micromol/L), indicating a better B vitamin status, was associated with a beneficial effect of omega-3-FA supplementation on both cognitive and clinical outcomes."

7) "[It is] apparent that subjects with established AD may not be the ideal target population for nutritional supplements." **[Important]**

- "It is now clear that the underlying processes behind AD may start several decades before the onset of cognitive symptoms." **[Very Important]**

We have reviewed these studies that support this study, that increased omega-3 fatty acids reduce cognitive decline:

Article Review 15-12:
Dietary Fatty Acids and the Aging Brain

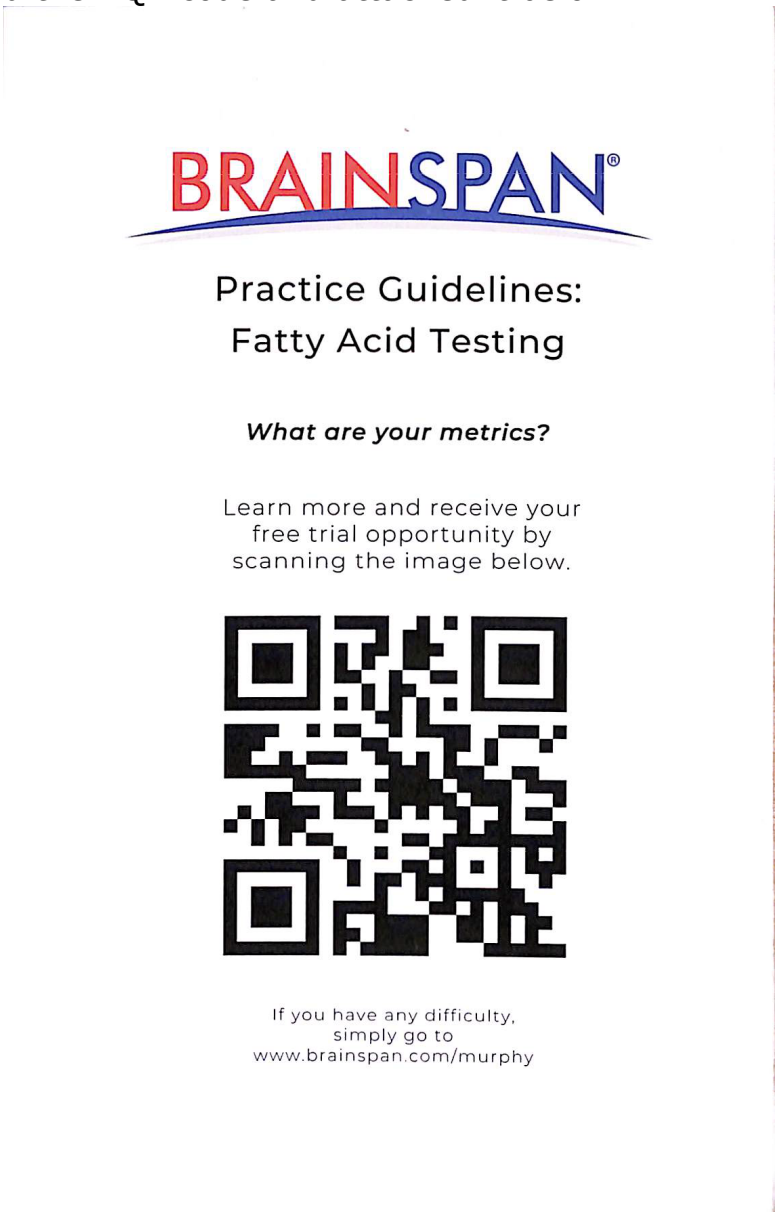
Article Review 13-13:
Nutrient Intake and Plasma Beta-Amyloid

Article Review 2-15:
Association of Fish Oil Supplement Use with Preservation of Brain Volume and Cognitive Function

Article Review 51-18:
Serial Circulating Omega-3 Polyunsaturated Fatty Acids and Healthy Ageing Among Older Adults in the Cardiovascular Health Study

Article Review 46-22:
Red Blood Cell DHA Is Inversely Associated with Risk of Incident Alzheimer's Disease and All-Cause Dementia

The company we use for RBC Fatty Acid assessment is www.brainspan.com/murphy and I have scanned their QR code and attached it below:



Blood-brain Barrier Disruption, Traumatic Encephalopathy, and Cognitive Decline in Retired Athletes

Science Translational Medicine
March 18, 2026; Vol. 18(841)

Chris Greene, Declan Brennan, Sheida Mirloo, Matthew Campbell, and 13 more, from Trinity College Dublin, Ireland; RCSI University of Medicine and Health Sciences, Dublin, Ireland; Dalhousie University, Halifax, Canada; Ben-Gurion University of the Negev, Israel; this study cites 73 references.

A *monocyte* is an immature *macrophage*.

BBB = Blood-Brain Barrier

CTE = Chronic Traumatic Encephalopathy (diagnosed *only* at autopsy)

DCE-MRI = Dynamic Contrast–Enhanced Magnetic Resonance Imaging

MoCA = Montreal Cognitive Assessment (attached)

TES = Traumatic Encephalopathy Syndrome (diagnosed *prior* to death)

BBB permeability was established by Dynamic contrast–enhanced magnetic resonance imaging (DCE-MRI).

"This study included 47 retired contact sport athletes and 15 non–contact sport control participants." [rugby, soccer, American football, boxers]

Subjects underwent blood testing and assessment by DCE-MRI an average of 12.1 years after retirement; subjects had competed for an average of 19.3 years.

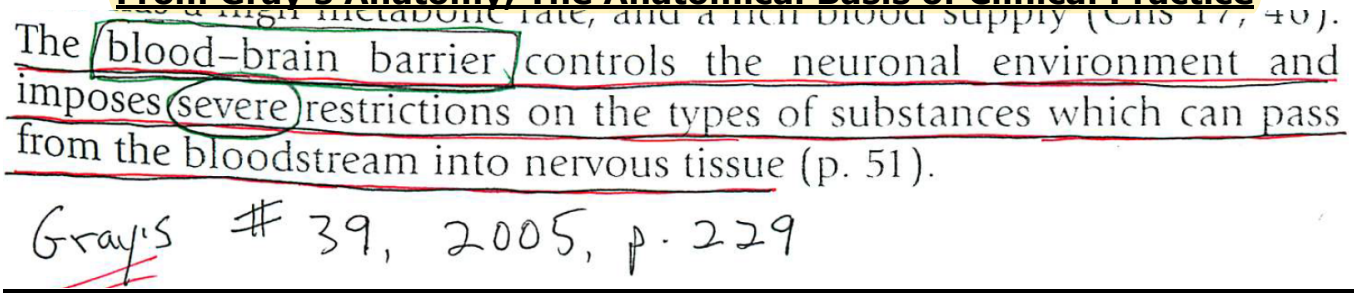
From Textbook of Medical Physiology by Arthur Guyton, MD

Physiological Importance of the Blood-Brain Barrier, and Importance of the Special Composition of the Cerebrospinal Fluid

The neurons of the brain require a very exactly controlled environment, or else their function becomes abnormal and so also does the function of the entire brain. The blood-brain barrier protects the cerebral tissue from detrimental substances in the blood, and the transport processes of the choroid plexuses

Guyton, 6th edition, p. 386

From Gray's Anatomy, The Anatomical Basis of Clinical Practice



KEY POINTS FROM THIS ARTICLE:

1) "Cerebrovascular disruption has been implicated in the pathophysiology of head trauma and chronic traumatic encephalopathy (CTE)."

2) "Sport-related concussion and subconcussive injuries are a matter of growing public health concern worldwide."

3) "In the US, the incidence of sport-related concussion is estimated to be between 1.6 and 3.8 million people per year."

4) "Subconcussive injuries are impacts that exert a force on the brain below the threshold needed to induce concussion." **[Very Important]**

- "Subconcussive injuries occur at rates much higher than those of sport-related concussion."

- "There is mounting evidence that it is the cumulative subconcussive injury burden, rather than the number of distinct concussions, that drives the development of chronic traumatic encephalopathy (CTE)." **[Key Point]**

5) "CTE is a neurodegenerative tauopathy associated with repetitive head injuries."

- CTE can only be definitively diagnosed at autopsy. **[Important]**

- "Efforts to identify antemortem cases of CTE are known as traumatic encephalopathy syndrome (TES)."

6) Diagnosis of **Traumatic Encephalopathy Syndrome (TES)** is based on:
- Substantial exposure to repetitive head injuries
- Cognitive impairment
- Behavioral dysregulation
- The absence of another unifying diagnosis

7) "TBI has long been identified as a risk factor for dementia, cognitive impairment, mood disorders, and suicidality."

- "A MoCA score was used to determine the presence of episodic memory and executive functioning impairment."

- "The MoCA is a 10-min cognitive screening tool that was originally developed to detect mild cognitive impairment and Alzheimer's disease. It has since been validated for several conditions, including TBI."

- "The test assesses seven cognitive domains including executive function, visuospatial ability, language, attention, working memory, short-term memory, and orientation."

- "There is a total possible score of 30, and ≤25 of 30 is considered abnormal and has been shown to be sensitive and specific for mild cognitive impairment detection."

15) Beck's Depression Inventory screening

- "Beck's Depression Inventory is a 5-min self-administered questionnaire that consists of 21 items that participants are asked to rate from 0 to 3 depending on the severity of their subjective symptoms relating to each item."

- "A score of ≤10 is considered normal, with scores ≥11 indicating some level of mood disturbance."

16) Findings

- "BBB disruption persists years after repetitive head trauma." **[Key Point]**

- "Individuals with extensive BBB disruption displayed worse cognitive decline compared with those with less extensive BBB disruption."

- "A greater systemic inflammatory burden with a higher proportion of circulating monocytes was associated with cognitive decline in the retired athletes." **[Important]**

- "Separating the cohort into those with a normal (≥26) or abnormal MoCA score (≤25) revealed greater BBB disruption in the low MoCA score cohort."

- There was a "strong association between the extent of BBB disruption and cognitive decline." **[Important]**

- "The extensive BBB disruption group consisted solely of retired players, and these players were more likely to be diagnosed with TES compared with the non-extensive BBB disruption group." **[Key Point]**

- "The extent of BBB disruption was associated with worse performance on cognitive tests."

- "Our study shows that BBB disruption can be detected many years after retirement in individuals who have been exposed to repetitive head injuries through a lifetime of collision sports activity." **[Very Important]**

    •• "This suggests that ongoing BBB disruption may be involved in the symptomatology of TES, potentially predisposing to the development of CTE."

- Disruption of the BBB are coupled with the release of pro-inflammatory cytokines and immune cell infiltration.

    •• "Our data in postmortem brains from individuals with CTE show abundant immune cell infiltration at regions with CTE pathology."

- Damage to the central nervous system leads to the development of auto-antibodies.

    •• Retired players have elevated amounts of several markers associated with autoimmune disorders. **[Important]**

- "TBI can trigger an autoimmune-like response because of BBB disruption, causing neural proteins to leak into circulation and elicit auto-antibodies."

- "Results strongly associate contact/collision sports with an increased risk of BBB pathology and subsequent cognitive decline in the years after retiring." **[Key Point]**

- "Our results showed that lower scores on MoCA directly correlated with the extent of BBB disruption."

17) "The hypothalamus and circumventricular organs, have a more permeable vasculature, lacking BBB properties, because of the need for these areas to interact directly with the bloodstream."

18) Conclusions:

- "Sustained systemic inflammation and persistent BBB disruption are associated with the long-term outcome of repetitive head trauma."

- The DCE-MRI on 47 retired athletes show that "BBB disruption was evident in players years after retirement." **[Key Point]**

- "BBB disruption is associated with cognitive decline in retired athletes."

- "Extensive BBB disruption is associated with TES."

- "Findings suggest that prolonged and repetitive head trauma exposure over years can increase the likelihood of long-term BBB disruption as well as systemic inflammation characterized by increased monocytes and induction of complement receptor expression."

- "We suggest that long-lasting BBB disruption after brain trauma could trigger a cascade of local and systemic molecular events that lead to white matter change, neuropsychiatric symptoms, and cognitive deficits experienced by retired contact/collision sport athletes." **[Important]**

- "TES was also associated with extensive BBB disruption, suggesting that this should be added to the diagnostic criteria for TES and, subsequently, a heightened predictive diagnosis of CTE."

- BBB disruption may be a pathognomonic marker across all sports, especially in those individuals diagnosed with TES.

Editor's Summary
Orla Smith

- "Athletes who play collision and combat sports with exposure to repetitive head trauma are at increased risk for cognitive decline." **[Key Point]**

- In retired athletes, dynamic contrast–enhanced MRI (DCE-MRI) imaging showed blood-brain barrier (BBB) disruption was present years after exposure to repetitive head impacts.

- Greater leakage of the BBB was associated with poorer cognition in the retired athletes compared with a control group.

- Athletes with extensive BBB leakage showed worse cognitive performance, lower brain volumes, and an increase in monocytes and immunological dysregulation.

- "These findings suggest that persistent BBB disruption and systemic inflammation after sport-related head trauma remain in athletes long after they have retired."

Below is a review of the above study, published in the journal *Nature*:

CONTACT SPORTS LEAVE BRAIN BARRIER LEAKY FOR YEARS
Damage to the Blood–Brain Barrier is Linked to Immune Changes and Cognitive Decline

Nature
March 26, 2026; Vol. 651 (8107); pp. 863-864
Max Kozlov

The blood–brain barrier is a "dense layer of cells lining the blood vessels that supply the brain." "This layer usually keeps harmful substances from leaking out of the blood and into brain tissue."

The researchers scanned the brains of 47 athletes who had retired from playing contact sports with a high risk of concussion and repetitive head impact, such as rugby and boxing, and compared them to a control group of non-athletes and athletes who had played non-contact sports.

KEY POINTS FROM THIS REVIEW in *NATURE*:

1) "Part of the difficulty in studying the long-term effects of head trauma is that some neurodegenerative conditions, such as chronic traumatic encephalopathy (CTE), can be diagnosed only by examining neuronal tissue after death."

2) "Repeated blows to the head over years of contact sports can lead to chronic brain damage."

3) "For decades, scientists have struggled to understand exactly how years of taking hits to the head while playing sports can translate into severe memory loss and dementia later in life."

4) "[The above study] reveals that the protective shield known as the blood–brain barrier can be damaged and leaky decades after an athlete retires from sport." **[Key Point]**

- "This persistent leakiness seems to trigger a long-lasting immune response that is closely tied to cognitive decline."

- The disruption of the blood–brain barrier persists for many years after head trauma.

5) "The brain scans showed that the blood–brain barriers of the contact-sport athletes were significantly leakier than were those of people in the control group, even though the athletes had been retired for an average of 12 years at the time of the study."

- "People with the most extensive barrier damage performed worse than did those with less extensive leakiness on memory and cognitive tests."

6) "This was the first evidence in the living human brain that the blood–brain barrier is disrupted in individuals likely to have CTE."

7) Leaky Blood Brain Barrier is Difficult to Diagnose

- Standard blood tests to spot brain damage are not very effective at identifying those experiencing cognitive decline.

- The warning signs became visible only after examining the athletes' immune systems: "the blood of people with the most barrier damage and greatest cognitive decline contained a higher proportion of inflammatory white blood cells and other biomarkers of immune activation than did the blood of those with less-extensive damage." **[Key Point]**

- "It looked like the athletes were living systemically in a hyper-inflamed state."

8) "The discovery suggests that brain scans detecting leaky vessels could one day serve as a tool for identifying living people at high risk of severe brain diseases." **[Very Important]**

9) "This type of damage we see is from prolonged exposure—it's the cumulative nature of head trauma that is worrying." **[Key Point]**

•••••

Review of this Same Article by *New Scientists*

Boosting the Blood-Brain Barrier Could Avert Brain Damage in Athletes

New Scientists
March 28, 2026
Alice Klein

"Repeated head knocks cause long-term damage in the delicate blood-brain barrier, potentially driving chronic traumatic encephalopathy, a neurodegenerative condition that affect some former footballers, rugby players and boxers."

"[The authors] scanned the brains of 47 former footballers, rugby players and boxers who had retired an average of 12 years earlier."

- "The contrast agent could be seen leaking into many parts of their brains in MRI scans suggesting that their blood-brain barriers were badly damaged."

- "Among the participants who hadn't played contact sports, the contrast agent barely showed up."

"Repeated collisions and whiplash movements of the head during sport damage the blood-brain barrier via mechanical forces."

Incidental Rotator Cuff Abnormalities on Magnetic Resonance Imaging

JAMA Internal Medicine
April 1, 2026; Vol. 186; No. 4; pp. 406-414

Thomas Ibounig, MD; Simo Taimela, MD, PhD; and 16 more: from the University of Helsinki, Finland and Monash University, Australia. This study cites 38 references.

RC = rotator cuff
FTT = full-thickness tear
PTT = partial-thickness tear

The objective of this study was to determine the prevalence of rotator cuff (RC) abnormalities in a population sample and their association with shoulder symptoms.

602 subjects were 41 to 76 years who underwent bilateral 3-Tesla magnetic resonance imaging (MRI) of the shoulders.

The prevalence of RC abnormalities was compared across age groups and between symptomatic and asymptomatic shoulders, adjusting for demographic factors, concurrent MRI findings, and clinical examination.

RC tendon status was classified on MRI as normal, tendinopathic, partial-thickness tear (PTT), or full-thickness tear (FTT).

Among 602 participants (median age, 58 [range, 41-76] years; 52% female), RC abnormalities on MRI were found in 595 (98.7%):
- 11% FTT
- 25% tendinopathy
- 62% PTT

KRY POINTS FROM THIS STUDY:

1) "Shoulder pain is a common musculoskeletal complaint often attributed to rotator cuff (RC) abnormalities."

2) "Shoulder pain affects approximately 18% to 31% of the general population globally each month and ranks as the third most common musculoskeletal complaint in primary care."

- "Rotator cuff (RC) abnormalities account for up to 85% of cases."

3) Prior Studies

- "Imaging frequently reveals RC abnormalities, such as tendinopathy or partial-thickness tears (PTTs) and full-thickness tears (FTTs)."

7) "These findings have important implications for test interpretation in routine clinical care."

- "In middle-aged and older adults, the extremely high pretest probability of MRI detected RC changes—approaching 100% in individuals over age 50—means that the mere presence of an abnormality has limited diagnostic value." **[Key Point]**

8) "RC abnormalities were detected in nearly all shoulders of participants older than age 40 years, challenging the use of traditional terms such as tear."

- These findings "likely represent normal age-related changes rather than clinically relevant structural changes."

9) Conclusions

- "MRI examination of the shoulder found that RC abnormalities are present in nearly all individuals over 40 years of age, irrespective of symptoms."

- "RC abnormalities were nearly universal after age 40 years and showed poor concordance with shoulder symptoms."

- "These findings suggest that RC abnormalities often represent normal age-related changes rather than disease and call into question the clinical value of routine imaging for atraumatic shoulder pain." **[Key Point]**

- Tendinopathy, PTTs, and FTTs may be incidental findings because they have a high population prevalence.

- "Reframing many of these findings as normal age-related changes rather than disease may help guide more appropriate care and reduce unnecessary interventions." **[Important]**

- "We are currently unable to distinguish clinically meaningful MRI abnormalities from incidental findings." **[Key Point]**

- "A positive MRI result does not confirm causality unless features such as a clear traumatic event, acute strength loss, or persistent functional deficit increase the pretest probability."

10) Key Points from Authors:

- "In this cross-sectional study of 602 Finnish adults aged 41 to 76 years who underwent bilateral 3-Tesla shoulder magnetic resonance imaging and clinical assessment, 99% had at least 1 RC abnormality."

- "RC abnormalities were present in both asymptomatic (96%) and symptomatic (98%) shoulders."

- "The findings of this study suggest that RC abnormalities are nearly universal after age 40 years and that routine imaging should not guide diagnosis or treatment of atraumatic shoulder pain." **[Key Point]**

Invited Commentary
LESS IS MORE

Magnetic Resonance Imaging Abnormalities and Incidental Age-Related Changes

JAMA Internal Medicine

Edgar Garcia-Lopez, MD; Brian T. Feeley, MD

1) "Most structural findings in the rotator cuff: tendinopathy, partial thickness tears, and full-thickness tears are overwhelmingly degenerative and commonly present in people even without any shoulder symptomology." **[Key Point]**

2) "These insights matter now more than ever, as radiology reports are released directly to patients through electronic portals; language such as tear or degeneration, while technically accurate, can easily provoke fear and drive unnecessary referrals or procedures when viewed without context."

3) This sample of 602 adults aged 41 to 76 years completed interviews, standardized questionnaires, clinical shoulder examinations, and bilateral 3-Tesla shoulder MRIs.

- 99% of all participants had at least 1 abnormality (tendinopathy, partial-thickness tears, and full-thickness tears) in at least 1 shoulder and 96% of asymptomatic shoulders showed degenerative changes.

4) "Prevalence of rotator cuff pathology in this study was similar to prior ultrasound and MRI studies of asymptomatic shoulders."

5) "Most importantly, imaging findings did not distinguish symptomatic from asymptomatic shoulders." **[Key Point]**

6) "Most full thickness tears occurred in people without symptoms and many participants had bilateral full thickness tears but remained asymptomatic."

7) "This study and similar prior studies call into question our ability to distinguish clinically meaningful MRI abnormalities from incidental age-related degenerative changes that are present in patients older than 40 years."

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Drug that clears Alzheimer's...

Treatment that strengthens the brain's ability to clean itself could delay the onset of Alzheimer's disease by up to seven years, finds **Carissa Wong**

A DUO of drugs that boost our brain's waste-disposal system so it can better remove proteins associated with Alzheimer's disease have been identified for the first time. The combination of a therapy that is commonly used as a sedative with a medicine that prevents dangerously low blood pressure seems to safely and effectively remove proteins linked to the disease, which could delay its onset by seven years.

"This is a significant step forward. Even for healthy people, maybe it could maximise brain function"

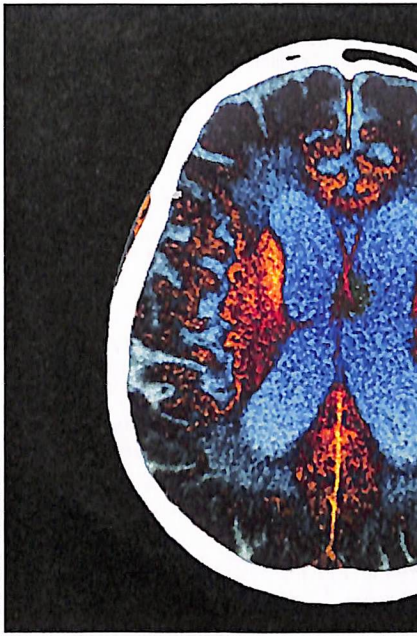
"This is a significant step forward," says Shiju Gu at Harvard University, who wasn't involved in the research. "It could benefit people with neurodegenerative disease, but even for healthy people, maybe you could use it to maximise the function of the brain."

Our brain removes metabolic waste via the glymphatic system, a network of channels surrounding the blood vessels that pump waste fluid to the lymphatic system, where it is carried to the blood for disposal.

The glymphatic system is most active during deeper phases of sleep, when slow brain waves help push along waste fluid after it has been released from brain cells. But it becomes impaired with age, and especially during Alzheimer's disease.

Researchers have previously found that dexmedetomidine, a drug commonly used as a sedative during medical procedures, boosts these brain waves in mice. It also improved the brain's ability to clear waste fluid and slowed cognitive decline in mouse models of Alzheimer's disease.

To explore dexmedetomidine's effects in people, Paul Dagum at pharmaceutical company Applied Cognition in Redwood City, California, and his colleagues recruited 19 adults – aged 60, on average – who were deprived of sleep for one night in a lab. The morning after, the participants – who had no chronic medical



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In Alzheimer's disease, the build-up of misfolded proteins in the brain leads to atrophy

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Arthroscopic Meniscal Surgery vs Non-operative Treatment for Degenerative Tears with Mechanical Symptoms: 5-year Outcomes Systematic Review and Meta-analysis of RCTs

Journal of Orthopaedic Reports
November 3, 2025; epub

Nafisa Zilani, Janice Tan, Siddarth Raj, Alexandros Maris, Angelo V. Vasiliadis, Akash Patel; from Queen Mary University of London and King's College London. This study cites 31 references.

"This systematic review compares long-term outcomes of arthroscopic meniscal surgery (AMS) versus non-operative management."

These authors identified RCTs (2000–2024) with ≥5 years follow-up. Primary outcomes were patient-reported outcome measures for knee function. Secondary outcomes included general health, pain measures, and knee osteoarthritis.

"This systematic review and meta-analysis aims to provide up-to-date evidence available to compare five-year long term effects of AMS to non-operative management in patients with advanced degenerative meniscal tears using only randomized controlled trials (RCTs)."

The patients had degenerative meniscal tear presenting with mechanical symptoms (i.e. pain, swelling, clicking, catching, and locking).

Six studies assessing 1,157 subjects met the inclusion criteria:
- 585 underwent AMS
- 572 underwent non-operative treatment

Arthroscopic meniscal surgery included arthroscopic partial meniscectomy and arthroscopic debridement.

Non-operative management included any non-surgical intervention to manage degeneration of the knee, such as exercise therapy or physiotherapy.

"This systematic review and meta-analysis is the first to investigate compared five-year long-term outcomes between AMS and non-operative management for degenerative meniscal tears with mechanical symptoms."

AMS = arthroscopic meniscal surgery
PROMs = patient reported outcome measures

KEY POINTS FROM THIS ARTICLE:

1) "Degenerative meniscal tears are highly prevalent in orthopaedic practice and commonly occur in both young, physically active individuals and elderly patients, demonstrating a bimodal age distribution."

- "The choice of treatment should be based on patient preferences, specific symptoms and activity levels."

- "The data indicates that AMS may be associated with a higher rate of osteoarthritic progression compared to non-operative treatment, suggesting that surgery could accelerate the degenerative process within the knee joint." **[Very Important]**

    - "This finding has significant clinical implications, as it underscores the need for clinicians to carefully consider the long-term impact of surgical interventions, particularly in patients with pre-existing osteoarthritis." **[Key Point]**

- "The intriguing trend perceived of heightened risk of osteoarthritis progression within the surgical group indicates the necessity for extended probe and refined clinical direction of treatment choice should be based on this factor." **[Key Point]**

- "Research should investigate the potential link between surgical techniques in AMS and the biomechanics contributing to osteoarthritic progression." **[Important]**

9) "The underlying degeneration and inflammation of the joint can cause ongoing symptoms irrespective of whether the torn meniscal tissue is removed or repaired." **[Important]**

10) "As surgery introduces new trauma to the knee, this can cause additional inflammation and delay recovery." **[Important]**

We have reviewed these studies that have questioned the value of arthroscopic knee surgery.

Article Review 19-02:
A Controlled Trial of Arthroscopic Surgery for Osteoarthritis of the Knee

This study is particularly relevant as it suggests that the pain and dysfunction of the osteoarthritic knee may not be from the tears, debris, and inflammation, but rather from common chiropractic management problems: malalignment, muscle weakness, instability, poor proprioception, and obesity.

Article Review 29-14:
Arthroscopic Partial Meniscectomy versus Sham Surgery for a Degenerative Meniscal Tear

Article Review 16-18:
Arthroscopic Surgery for Degenerative Knee Arthritis and Meniscal Tears