

**Subluxation Neurology  
Simplified  
Bridging the Gap  
Between Spinal Health  
and Nervous System  
Function**

**Utah Chiropractic  
Physician Association**

**2026**

Dan Murphy, DC

## **Health Wisdom**

Allopathic providers (medical doctors) are primarily chemical providers of care (pharmacology). Government gives drug companies patents for their products, allowing for hundreds of billions of dollars in profits. Government does not grant patents on natural products, even if they work great, which is one of the reasons we hear much less about them.

Chiropractors are primarily mechanical providers of care (adjustments, exercise, tissue work, etc.) The chiropractic approach was awarded the Nobel Prize in 2021 (mechanoreceptors, sorry AI, from UCSF). This is in part why all major sports teams have a handful of mechanical providers (chiropractors, physical therapists, trainers, etc.).

Chiropractic education stresses mechanical interventions, and it also stresses evolutionary biology. Most chiropractors, including me, consider themselves to be evolutionary biologists, which is the point.

Evolutionary biology cares about only one thing, perpetuating the species by making the next generation. For nearly all humans, for millennia, our babies are made prior to age 50. Evolution and biology pretty much do not care about what happens to us after about age 50 because we have already had our babies.

To help the younger crowd to make babies, humans are blessed with a lot. Youngsters are stronger, faster, quicker, greater endurance, better brain (less wisdom), more and stronger sperm, healthy release of eggs, hormones that increase sex drive and fertility, healthy joints and blood vessels and nerves and organs and immunity, including teeth, hearing, and vision. Critical molecules that are abundant in youth are scarce after age 50, like CoQ10, melatonin, glutathione, and many more.

Youth blessings quickly begin to disappear after age 50. The best longevity experts state that if one wants an additional 50 years of living after age 50, one must supplement with a handful of molecules to replenish that what we had in abundance in youth.

A favorite go-to for what these supplements should be is the work of Bruce Ames.

Top researchers will boast about having 100 articles indexed in the National Library of Medicine of the USA. Ames had more than 400. Ames died last year at age 95, just short of his 96<sup>th</sup> birthday. He did not die from disease; he died from a complication following a fall. That put him in good company with the cancer-mitochondria-fermentation-respiration Nobel Prize winner Otto Warburg. Warburg died in 1970 at the age of 87, also from a fall; he was on a ladder getting a high book off the shelf. History acknowledges that Warburg should have won 3 Nobel Prizes.

Ames' longevity article, published in the journal of the *Proceedings of the National Academy of Sciences of the USA* (my review is attached), is the gold standard. I believe that this is, in part, what we should all do if we want that additional 50 years of healthy living.

Although evidence and consensus always (and should) change as more is learned, at present it points to all people needing 5 supplements, including our children and now our grandchildren. This is mostly because we subsidize the wrong stuff, we allow toxic ultra-processed dopamine addicting chemicals into the food chain, and deplete our soils of what we need, etc. The 5 are:

- Omega-3s
- Vitamin D3
- Vitamin K2-4 and K2-7
- Magnesium
- B complex, often supplied in a multiple mineral/vitamin supplement

Then there is a handful of stuff that our kids do not need, but we, being over 50 years old, do need, to hit 100 years of age (or 95 if we fall), doing well mentally and physically:

- CoQ-10
- PQQ
- acetyl-L-carnitine
- alpha-lipoic acid
- ergothioneine (H<sub>2</sub>S precursor)
- taurine
- resveratrol
- curcumin
- glutathione

There are also a few more do's and don'ts if one is getting dementia.

Chiropractors are not trained in pharmacology and drugs are outside of their scope of license. Yet chiropractors are trained in the chemistry of supplements and they are allowed to integrate them into their clinical approach. That's why I know this stuff.

Also, read the lifestyle advice from the top nutrition journal in the world, the *American Journal of Clinical Nutrition* from last year (2024), my review is also attached.

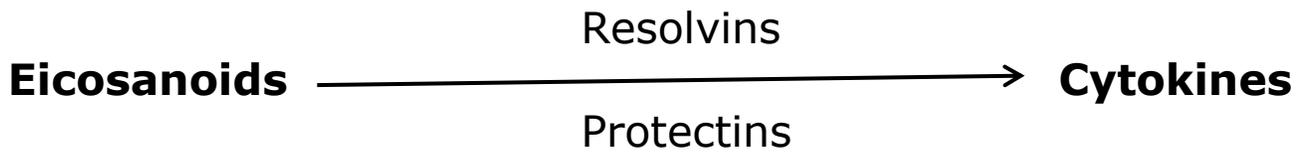
The importance of exercise cannot be underestimated.

Murph

## Inflammatory Chemicals Brief Summary

<b>Eicosanoids</b>	<b>Cytokines</b>
Prostaglandin E2 PGE2  Hormone-Like Molecules  Derived from Omega-6 Fatty Acid <i>Arachidonic Acid</i>  Linoleic Acid (Corn/ Soy) ↓ Insulin-D5D → Arachidonic Acid ↓ COX → PGE2	Interleukin-6 IL-6  Proteins  Derived from Immune Cell Activation  Infection Excessive Immunological Responses Autoimmune Diseases Leaky Gut Low Vitamin D Altered Vitamin D Receptor Low Levels of IL-10  <u>Improved/Reduced By</u> Immune Enhancing Supplements •Vitamin D •Vitamin C •Magnesium •Zinc •Omega-3s
High Omega-6/Omega-3 ratio >3/1  <u>Ratio Improved By</u> •Limiting omega-6 and grained meat/egg consumption •Increasing omega-3 and wild fish consumption	Heal the Leaky Gut  Avoid Harmful Wavelengths >850 nm
<b>COX Enzymes are Inhibited by Red LLLT</b>  <b>Red LLLT Reduces PGE2 Accumulation</b>	<b>Violet LLLT Are Antimicrobial Violet LLLT Reduce/Inhibit IL-6 Red LLLT Reduce/Inhibit IL-6</b>
<b>Red LLLT Reduces PGE2 Accumulation</b>	<b>Red LLLT Increases IL-10</b> Vigorous Exercise Increases IL-10 Chiropractic Increased IL-10
Motion Disperses Accumulation Chiropractic, etc.	Chiropractic May Be Immunoenhancing  Motion Disperses Accumulation Chiropractic, etc.
Inflammatory Eicosanoids Increase Inflammatory Cytokines	Inflammatory Eicosanoids Increase Inflammatory Cytokines

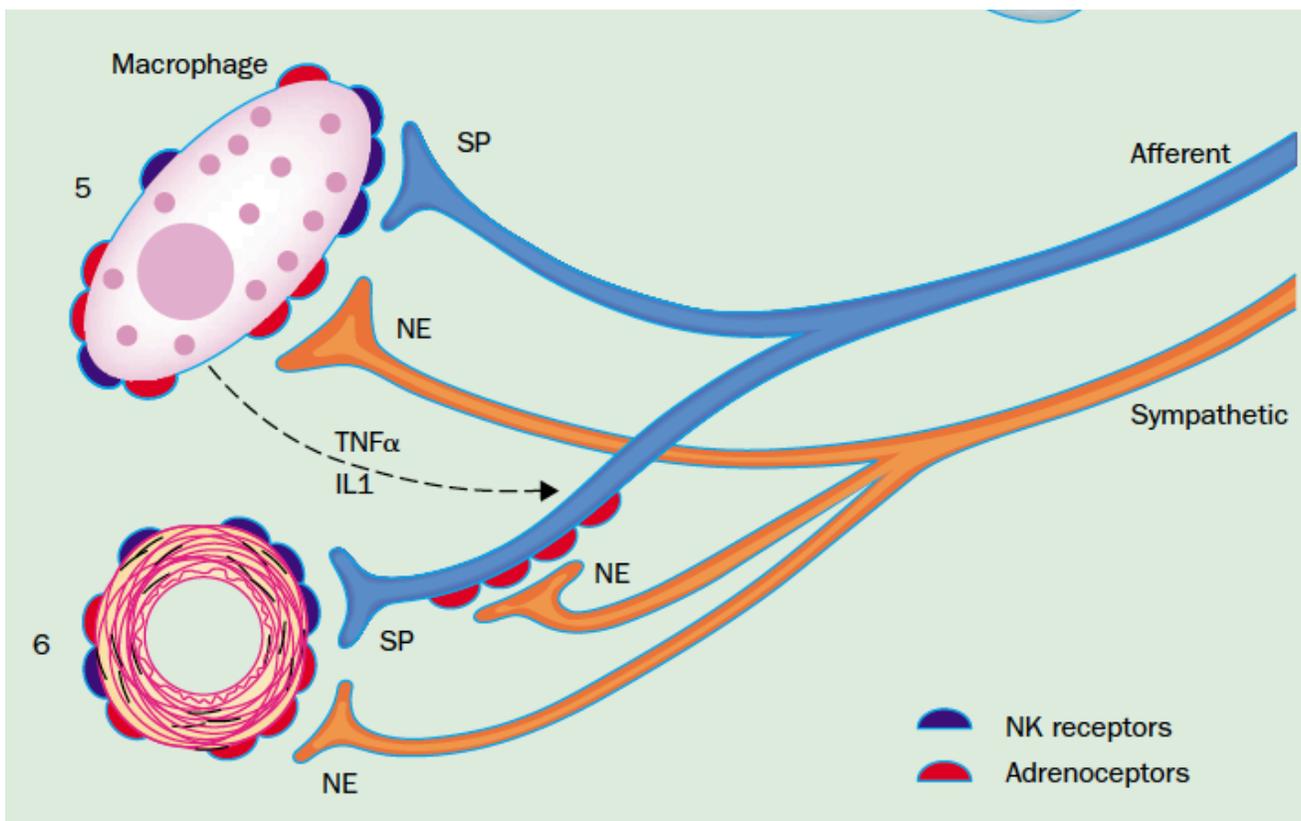
**Macrophage**

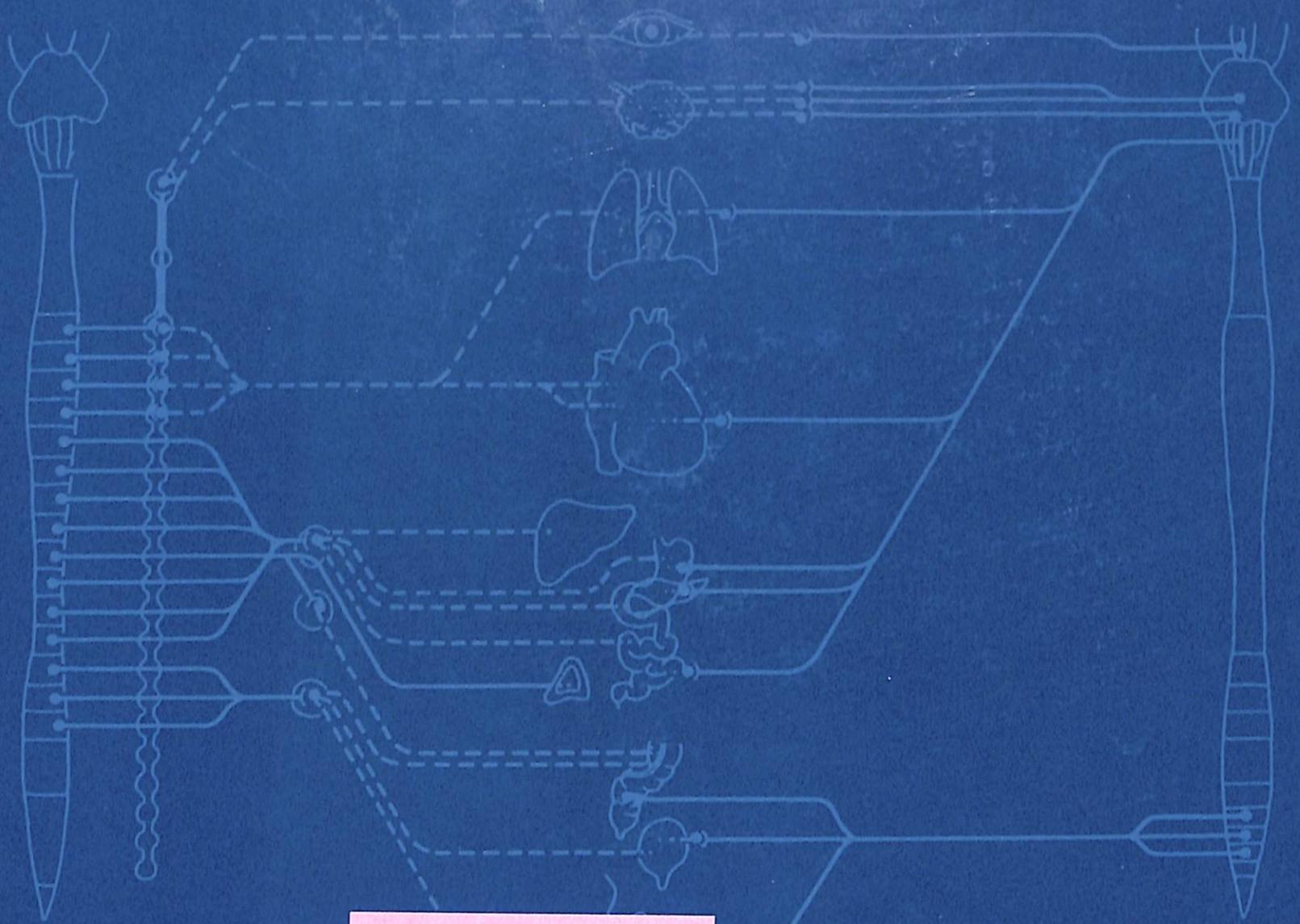


# Complex Regional Pain Syndrome: Mystery Explained?

**THE LANCET, Neurology**  
**November 2003; Vol. 2; No. 11; p. 691**

Wilfrid Jänig and Ralf Baron:  
Department of Physiology, Christian-Albrechts  
University of Kiel, Germany





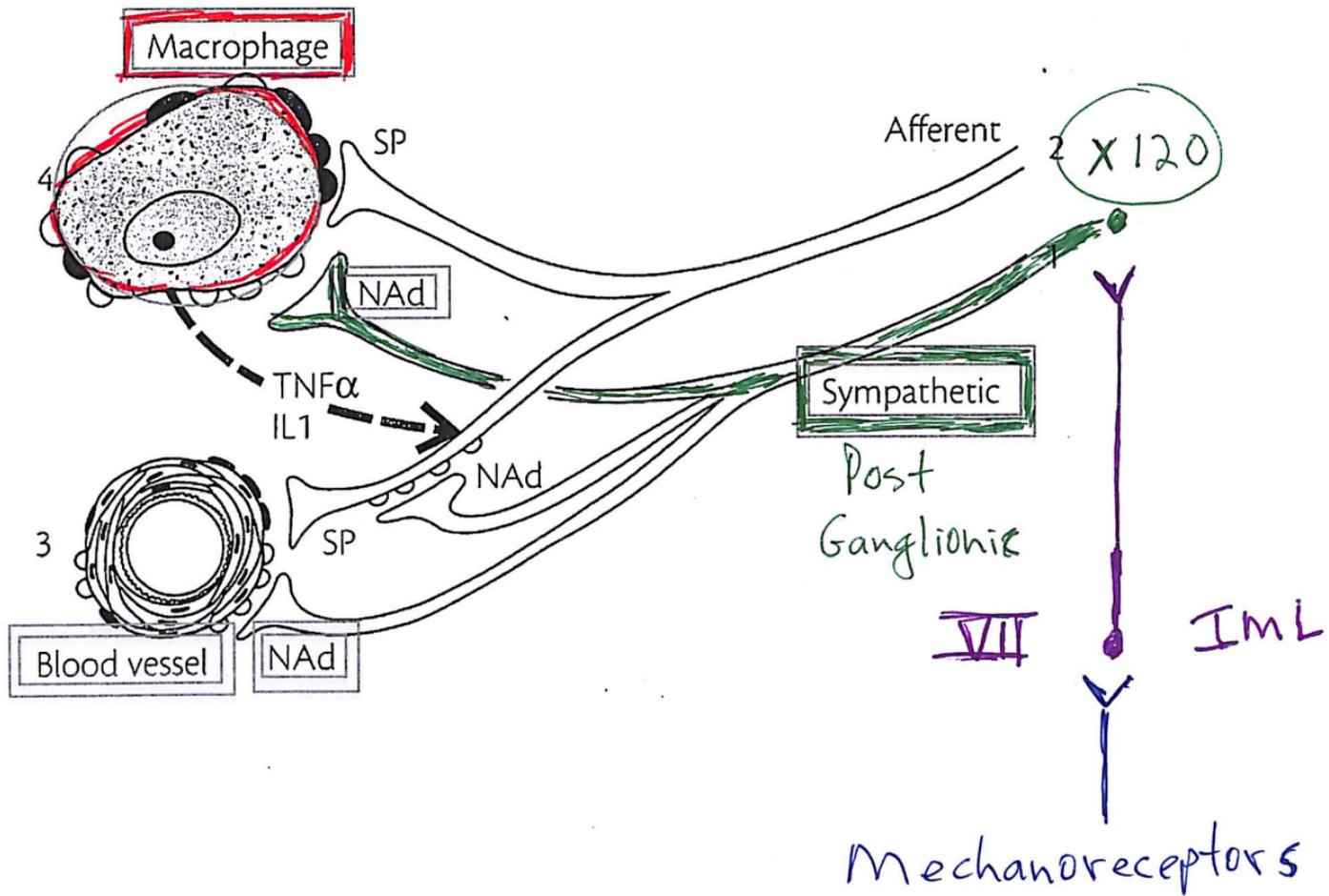
2013

EDITED BY  
*Christopher J. Mathias*  
*Sir Roger Bannister*

# Autonomic Failure

*A Textbook of Clinical Disorders of  
the Autonomic Nervous System*

Fifth Edition



How the

# Immune System Works

2023

Seventh Edition

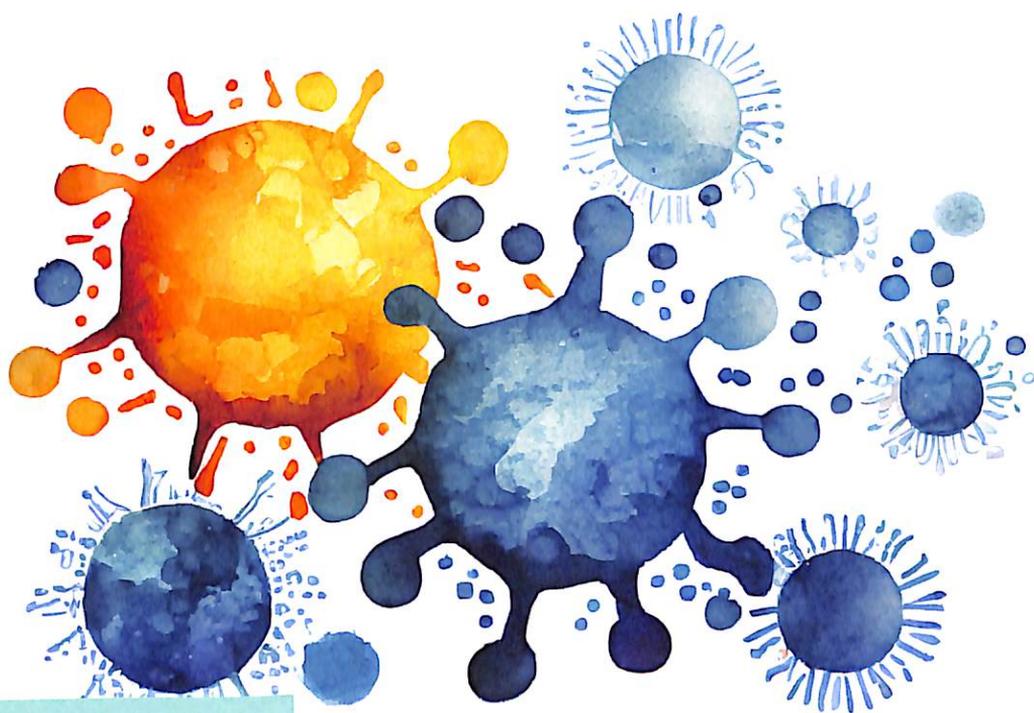
Lauren Sompayrac



WILEY Blackwell

# The Logic of Immunity

*Deciphering an Enigma*



2024

B. J. Cherayil

*Preface ix*

1. Conceptualizing the Immune Response 1
2. Innate Immunity I: The Rapid Response Team 10
3. Innate Immunity II: Sensing Infection 24
4. Adaptive Immunity: Strength in Diversity 35
5. B Lymphocytes: Antibodies “R” Us 49
6. T Lymphocytes: A Little Help for My Friends 66
7. Immune Dysfunction: When Things Go Wrong 85
8. Conditioning of the Immune System by the Microbiota 104
9. Remembrances of Things Past Haunt the Present 120
10. Harnessing the Function of the Immune System 131
11. Vaccination: The Power of Prevention 148
12. “To Follow Knowledge Like a Sinking Star” 160

*Acknowledgments 165*

*Abbreviations 167*

*Glossary 169*

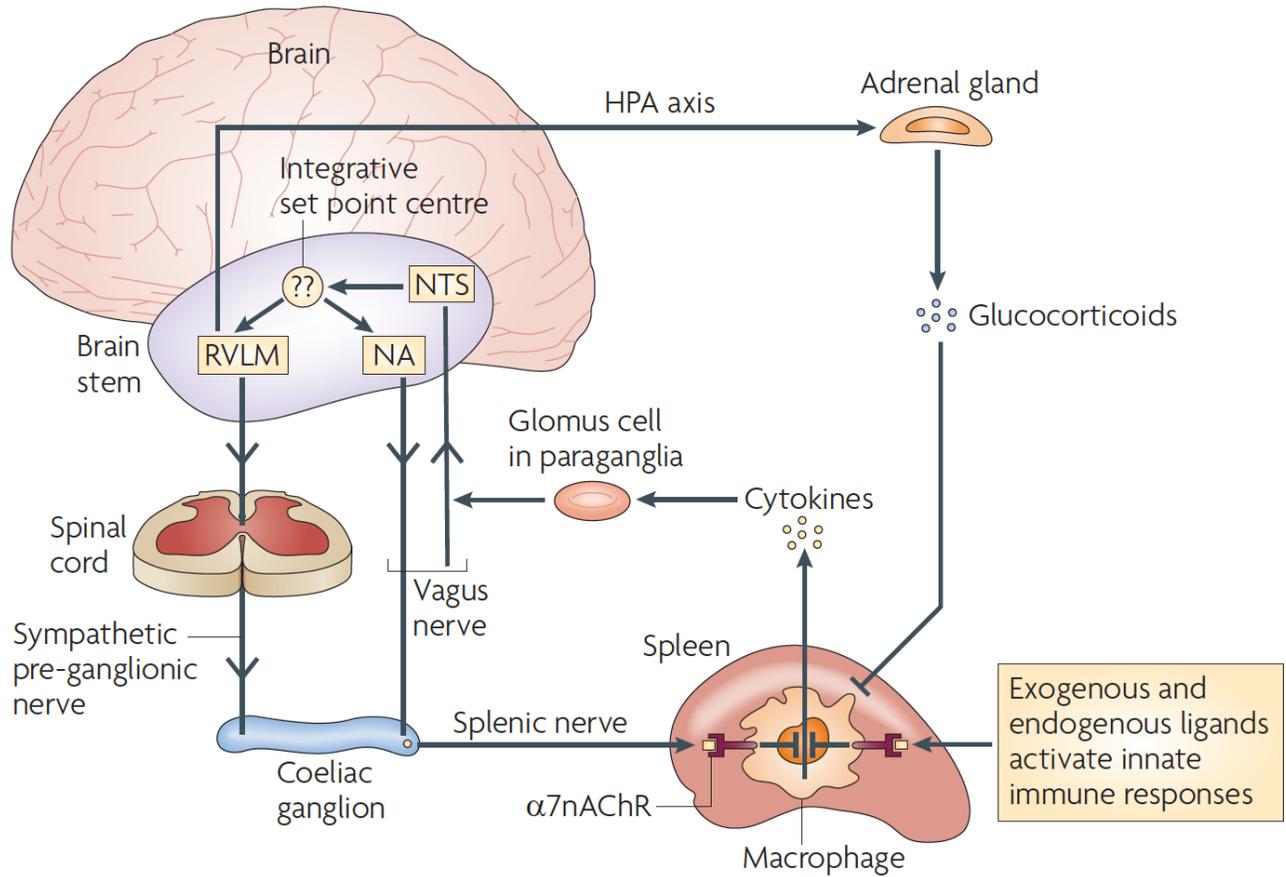
*References 181*

*Index 185*

# Reflex Control of Immunity

Nature Immunology  
June 2009

Kevin Tracey



## **Do inflammatory cytokines cause low back pain?**

### **Google AI Overview February 14, 2026**

Inflammatory cytokines, particularly IL-6, IL-8, and TNF-alpha, play a key role in the development and persistence of low back pain (LBP) by promoting inflammation, disk degeneration, and nerve sensitization. These biomarkers are frequently elevated in patients with chronic LBP, disc herniation, and degenerative disc diseases.

### **Key Cytokines and Their Roles**

#### **Interleukin-6 (IL-6):**

Persistently increased levels of IL-6 are associated with chronic lumbar radicular pain and disc herniation.

#### **Interleukin-8 (IL-8)**

Identified as a crucial cytokine in disc-related pain, IL-8 levels are higher in patients with chronic LBP and correlate with pain severity.

#### **Tumor Necrosis Factor-alpha) (TNF-alpha):**

Higher concentrations are found in patients with restricted lumbar mobility and contribute to the inflammatory process in disc degeneration.

### **Grok AI Overview February 14, 2026**

## **Yes, inflammatory cytokines contribute to low back pain (LBP) in many cases.**

Research shows that pro-inflammatory cytokines play a significant role in both **disc-related** (e.g., herniation, degeneration) and **non-specific** low back pain by:

- Directly sensitizing nociceptors (pain-sensing nerves)
- Promoting inflammation in disc tissue, muscles, facet joints, or surrounding structures
- Contributing to central and peripheral sensitization
- Amplifying pain signaling pathways

## Key Cytokines Involved in Low Back Pain

Cytokine Type		Main Findings in LBP Patients
<b>TNF-<math>\alpha</math></b>	Pro-inflammatory	Frequently elevated in chronic LBP and disc herniation; correlates with pain intensity and radicular symptoms
<b>IL-6</b>	Pro-inflammatory	Commonly increased in both acute and chronic LBP; linked to pain severity and systemic inflammation
<b>IL-1<math>\beta</math></b>	Pro-inflammatory	Elevated in many studies; promotes disc degeneration and nociceptor sensitization
<b>IL-8</b>	Pro-inflammatory	Often significantly higher in disc-related LBP; correlates with radicular pain and herniation
<b>IL-10</b>	Anti-inflammatory	Often decreased in LBP patients → imbalance favoring inflammation

### Evidence Summary by Pain Type

- **Disc herniation / radicular pain / sciatica** Very strong evidence that inflammatory cytokines (especially **TNF- $\alpha$** , **IL-1 $\beta$** , **IL-6**, and **IL-8**) are major contributors. These are released from the herniated disc material, nucleus pulposus, and surrounding tissues, directly sensitizing nerves and causing chemical radiculitis even when mechanical compression is reduced.
- **Chronic non-specific low back pain** Most systematic reviews and case-control studies show elevated pro-inflammatory cytokines (**TNF- $\alpha$** , **IL-6**, **IL-1 $\beta$** ) and reduced anti-inflammatory cytokines (**IL-10**). This imbalance is associated with pain persistence, central sensitization, and higher pain scores. However, findings are more variable than in disc-related pain, and not all patients show the same pattern.



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?”**

# **Perspective**

# Scientific Journals Can't Keep Up With Flood of Fake Papers

**'Paper mills' churn out fraudulent studies faster than publishers can retract them**

**Wall Street Journal**

**August 4, 2025**

Nidhi Subbaraman

A growing tide of fake papers is flooding the scientific record and proliferating faster than current checks can rid them from the system, scientists warn.

The source of the trouble is "paper mills," businesses or individuals that charge fees to publish fake studies in legitimate journals under the names of desperate scientists whose careers depend on their publishing record.

The rate of fake papers generated by these operators roughly doubled every 1.5 years between 2016 and 2020, according to published Monday in the Proceedings of the National Academy of Sciences.

"The entire structure of science could collapse if this is left unaddressed," said study author Luís Amaral, a physicist at Northwestern University.

Paper mills look for weak links, such as lax verification protocols, in the typically rigorous publication machinery, then exploit those to place hundreds of fabricated studies with vulnerable journals or publishers, according to scientist investigators who have been tracking and cataloging their work.

Publishers who have become aware of suspected paper mill activity have been forced to retract hundreds of papers at once, and in some cases shut down journals.

After retracting more than 11,300 papers that appeared compromised, Wiley, a U.S.-based publisher with a portfolio of 1,600 journals, last year announced it would shutter 19 of its publications, including some that had shown signs of takeover by paper mills.

More recently, Taylor & Francis, an academic publisher that produces more than 2,700 journals, announced in July it would stop taking submissions to its journal Bioengineered while its editors investigated past papers for paper mill activity.

But tracking the scale of these organized operations across the body of scientific literature has been difficult. When paper mills are detected, they change their tactics, and few publishers disclose when they have been targeted.

“We only know about Wiley because they have been transparent about the way that they were trying to handle these issues,” said Reese Richardson, a data scientist who studies publishing at Northwestern University and who is an author on the PNAS study.

The authors of the study created a database of suspected paper mill papers, over 32,700 in all, from nearly every publisher, by assembling the work of other volunteer investigators who have been cataloging groups of studies with similar patterns that appear to come from paper mills.

With a big-data approach that spans the published scientific record, the new study confirms trends that scientist investigators of shoddy papers have shown in case studies for years.

The growing role of artificial intelligence in all business sectors makes the trend that the new paper documents especially concerning, said James Evans, a sociologist who studies science and technology at the University of Chicago. Because large language models are consuming scientific literature without discriminating between legitimate papers and fraudulent ones, paper mills “have the potential to really muddy the waters of science and scientific understanding.”

The authors demonstrate how paper mills could proliferate by targeting editors at a journal.

Some publishers who have investigated suspected paper mill activity at their own journals have acknowledged that people presenting themselves as editors, or hijacking the identity of genuine researchers, is a strategy that paper mills use.

While publishers have increasingly acknowledged these operations and said they have taken steps to spot fraud, the authors of the new study show that retractions—in which journals pull papers that appear to have flawed or faulty data—aren’t keeping pace with the growth of paper mills.

Given that the study’s estimates of paper mill activity are likely an undercount, Richardson said, “We know that this barely scratches the surface of what’s out there.”



# The entities enabling scientific fraud at scale are large, resilient, and growing rapidly

Reese A. K. Richardson<sup>ab</sup> , Spencer S. Hong<sup>c</sup> , Jennifer A. Byrne<sup>d,e,1</sup> , Thomas Stoeger<sup>f,g,h,1</sup> , and Luís A. Nunes Amaral<sup>a,b,i,j,k,1</sup>

Affiliations are included on p. 10.

Edited by Daniel Acuña, University of Colorado Boulder, Boulder, CO; received September 30, 2024; accepted March 18, 2025 by Editorial Board Member Mark Granovetter

Science is characterized by collaboration and cooperation, but also by uncertainty, competition, and inequality. While there has always been some concern that these pressures may compel some to defect from the scientific research ethos—i.e., fail to make genuine contributions to the production of knowledge or to the training of an expert workforce—the focus has largely been on the actions of lone individuals. Recently, however, reports of coordinated scientific fraud activities have increased. Some suggest that the ease of communication provided by the internet and open-access publishing have created the conditions for the emergence of entities—paper mills (i.e., sellers of mass-produced low quality and fabricated research), brokers (i.e., conduits between producers and publishers of fraudulent research), predatory journals, who do not conduct any quality controls on submissions—that facilitate systematic scientific fraud. Here, we demonstrate through case studies that i) individuals have cooperated to publish papers that were eventually retracted in a number of journals, ii) brokers have enabled publication in targeted journals at scale, and iii), within a field of science, not all subfields are equally targeted for scientific fraud. Our results reveal some of the strategies that enable the entities promoting scientific fraud to evade interventions. Our final analysis suggests that this ability to evade interventions is enabling the number of fraudulent publications to grow at a rate far outpacing that of legitimate science.

fraud | metascience | organizations

Over the last four centuries, the production of scientific knowledge has increasingly become a matter of state and societal importance. The “contract” between scientists and states can be summarized thusly: In exchange for creating new knowledge that is useful to the state and training a workforce able to use that knowledge, society supports scientists with rewarding careers, good salaries, and public recognition. The success of this contract has led to an extraordinary growth in the scale and scope of the scientific enterprise (1) and to its adoption across the world (2). Indeed, some studies suggest that the wealth of a nation is closely aligned with the amount (3, 4) and quality (5) of the research it produces.

The state-supported scientific enterprise can be idealized as a public goods game (6) with numerous and diverse stakeholders. Because of the increasing complexity of the knowledge being created and increased specialization, the system relies on the good-faith assumption of genuine contributions by all participants (7–10). Scientists rely on other scientists to disclose knowledge that can be built upon, on other scientists and on publishers for the screening of scientific studies, on publishers for the dissemination of their work and on funding agencies and universities for support. Universities and funding agencies rely on scientists for evaluating the work of their peers and on the state and society for their funding. Private-sector firms rely on universities to educate a knowledgeable workforce. The state and society rely on scientists to produce knowledge that will improve well-being and state security. Ertzkowitz and Leydesdorff formalized certain aspects of this web of relationships in their ‘triple helix’ model of knowledge-based economic development (11).

The success of this model could be in jeopardy if some stakeholders fail to contribute fairly to the tasks assigned to them. Due to the increasing scale and scope of the scientific enterprise, the degree to which stakeholders contribute to the system is now increasingly evaluated by potentially misleading proxies (12, 13) such as the h-index (14), journal impact factor, university rankings, and scientific prizes. Nonetheless, these proxies have quickly become targets for evaluation of institutional and personal impact, resulting in increasing competition and growing inequality in how resources and rewards are

## Significance

Numerous recent scientific and journalistic investigations demonstrate that systematic scientific fraud is a growing threat to the scientific enterprise. In large measure this has been attributed to organizations known as research paper mills. We uncover footprints of activities connected to scientific fraud that extend beyond the production of fake papers to brokerage roles in a widespread network of editors and authors who cooperate to achieve the publication of scientific papers that escape traditional peer-review standards. Our analysis reveals insights into how such organizations are structured and how they operate.

Author contributions: R.A.K.R., J.A.B., T.S., and L.A.N.A. designed research; R.A.K.R., S.S.H., and L.A.N.A. performed research; R.A.K.R. and L.A.N.A. contributed new reagents/analytic tools; R.A.K.R., S.S.H., and L.A.N.A. analyzed data; and R.A.K.R., S.S.H., J.A.B., T.S., and L.A.N.A. wrote the paper.

The authors declare no competing interest.

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distributed (15–20), which could leave the scientific enterprise more susceptible to defection (16, 21–23).

Scholarly defection occurs when there is a failure to make genuine contributions to the production of knowledge or to the training of an expert workforce while still benefiting from the contract. A 2002 survey of scientists funded by the United States NIH reported that 0.2% of mid-career researchers and 0.5% of early-career researchers admitted to falsifying research data in the previous three years (16). A systematic analysis of more than 20,000 articles published between 1995 and 2014 reported that 3.8% of these articles contained inappropriately duplicated images, with at least half of these cases suggestive of deliberate manipulation (24). We and others have also recently described a class of entities engaging in large scale scientific fraud, typically denoted “paper mills,” that sell mass-produced low quality and fabricated research articles (as described by Byrne et al. (25) and in a report by the Committee on Publication Ethics and the International Association of Scientific, Technical & Medical Publishers (26); also see *SI Appendix*). In a 2022–2023 survey of medical residents at tertiary hospitals in southwest China, 46.7% of respondents self-reported buying and selling papers, letting other people write papers, or writing papers for others (27). Some publishers report that up to 1 in 7 of their submissions are of probable “paper mill provenance” (26, 28). Agents for paper mills have also recently been reported to attempt to bribe journal editors (29, 30) and to “hijack” the entire editorial processes at some journals (31–33).

Studies of repeating public goods games teach us that, under some conditions, player contributions tend to decay over time and that contributions decrease substantially as the number of defectors increases (34). To discourage defection and sustain a collaborative system, public goods games must enforce mechanisms that disincentivize defection (35–37). To this end, the scientific enterprise has implemented several formal punishment mechanisms for defectors. Funding agencies can sanction individual researchers and universities with fines and exclusion from funding programs. Universities can sanction researchers with rescission of contracts. Journals can sanction authors with retraction of publications. Literature aggregators can sanction journals by removing them from their indices (deindexing) (38–40). These formal measures complement additional informal measures such as exclusion of defectors from scientists’ personal trust networks, shaming (41), and documentation of concerns on postpublication review sites (42, 43). However, the evidence suggests that these mechanisms have not yet been successful in stemming the tide of defections (24–33).

Here, we demonstrate that large networks of cooperating individuals and entities that produce scientific fraud at scale can be identified by the footprints they have left in the extant scientific literature. We identify groups of individuals who perform editorial and review work at journals and collaborate with authors to facilitate the publication of manuscripts that experts (including journal editorial staff) have linked to author or editor misconduct. We show that organizations producing fraudulent science are able to ensure publication of their manuscripts in journals from several publishers prior to their detection and removal. We also show that organizations mediating the production of manuscripts suspected of fraud evade existing science integrity and quality control measures, such as journal deindexing, and that they successfully target specific subfields while avoiding—or failing to target—closely related subfields. Finally, we show that the number of fraudulent publications is growing at a rate far exceeding the growth of legitimate publications.

## Materials and Methods

We retrieved journal data from Clarivate’s Web of Science (WoS) (44), Elsevier’s Scopus (45), the National Library of Medicine’s PubMed/MEDLINE (46), and OpenAlex, an open-source “index of hundreds of millions of interconnected entities across the global research system” (47). OpenAlex aggregates and standardizes data from the now deprecated Microsoft Academic Graph (48) and Crossref (49), as well as ORCID (50), Unpaywall (51), and institutional repositories. We considered a journal to be “actively publishing” in a given year if it published at least one “journal article” or “conference proceeding article” in that year in OpenAlex. Of 73,818 journals actively publishing in 2020, 1,489 (2.0%) had “conference,” “proceeding,” or “meeting” in the journal title. Of 5,629,023 articles published in 2020, 476,820 (8.5%) were labeled as conference proceeding articles.

**Literature Aggregators.** WoS and Scopus evaluate journals requesting inclusion in their databases (i.e., indexing). Indexing of a journal can be revoked if the service finds reasons for concern with the editorial practices of the journal or if the service assesses a journal’s content to be of low quality. A journal may also be deindexed due to a name change, merger, or closing. We obtained lists of annually deindexed journals from WoS (current as of December 2021), Scopus (current as of March 2024) (52), and MEDLINE (last downloaded in February 2023) (53, 54). We also downloaded the 2020, 2021, 2023, and 2024 editions of the Early Warning Journal List produced by the Chinese Academy of Sciences in June 2024 (55).

**Retractions and PubPeer Comments.** Author misconduct, such as reporting fake data or engaging in plagiarism, and editorial misconduct, such as lack of minimal quality control of submitted work, can result in the retraction of a study or in its reporting in postpublications sites. We obtained retracted articles from Retraction Watch (56) (downloaded on March 4, 2024). This corpus comprises 47,387 unique retraction records. We downloaded the Retraction Watch Hijacked Journal Checker on March 1, 2024. The PubPeer Foundation shared with us metadata and content for all comments made prior to February 1, 2024, on 105,325 articles bearing DOIs. This count does not include automated comments, such as those made by *statcheck* (57). Very few PubPeer comments are positive (43); most report on potential problems and many precede eventual retraction of the commented article (58).

**Editors.** Some journals list the handling editor of every published study. A small subset—including *PLOS ONE* and *Hindawi* journals—also allows for bulk, programmatic access to article content and metadata. We downloaded metadata of articles published in *PLOS ONE* by November 8, 2023, (59) and of articles published in *Hindawi* journals by April 2, 2024, (60) (*Dataset S3*). We obtained full names of editors at *PLOS ONE* and *Hindawi* journals and assigned articles to the same editor in each journal only if the full names were an exact match. We classified an editor as “active” during the period between the earliest submission date and the latest acceptance date of published articles handled by them. Note that editor tenures are right-censored because we do not have access to articles currently under review.

We disambiguated article authors using ORCID identifiers (50) but could not obtain ORCID identifiers for 91.2% of named authors. In total, we identified 134,983 authors of articles published in *PLOS ONE* for whom we could obtain ORCIDs. This left 39.8% of articles without any identifiable author. ORCID identifiers were similarly infrequent in *Hindawi* journals, as described in *SI Appendix, Figs. S4–S13*.

**IEEE Conferences.** The name and year of IEEE conferences were inferred from the DOI of all “proceedings” articles published by IEEE and recorded in OpenAlex. Matching this DOI to “conference proceedings” articles in OpenAlex and excluding articles with specific front matter-related terms in the title (*Dataset S4*), we identified 2,294,067 articles published in 19,969 IEEE conferences since 2003. For 45 IEEE conferences taking place between 2009 and 2011, more than 10% of the published articles were retracted. This activity results in a large spike in retractions around these years. Although many conference proceedings publish front matter that names editorial staff, this information was not available to us

in a structured format that would allow for disambiguation of editor identities and roles.

**Duplicated Images.** We collected reports of image duplication made on PubPeer and then built a network where nodes represent articles and edges indicate sharing of an image (see *SI Appendix* for details). We identified connected components in this network and filtered out any component with fewer than 30 articles. Additionally, we removed any component where any of five randomly selected edges does not concern interarticle image duplication.

**The Academic Research and Development Association (ARDA).** Unlike previously documented entities (61), ARDA's website lists journals in which they can guarantee publication. We used the Internet Archive's "Wayback Machine" (62) to construct a chronology of ARDA's evolving "portfolio" of journals. We then matched named journals to their indexing records in WoS and Scopus and constructed a visualization of the time periods over which those journals were being used by ARDA and whether they were ever deindexed; see *Dataset S5* for the list of journals.

In May 2023, we downloaded the complete archive of five journals listed on ARDA's website (two of which are considered hijacked) and attempted to impute the nationality of authors from listed affiliations (*SI Appendix*). We successfully imputed nationality of authors for 13,288 of 20,638 recovered documents (64.4%, *Dataset S6*). Of these documents, more than half were from India (26.4%), Iraq (19.3%), or Indonesia (12.2%).

**Suspected Paper Mill Corpus.** We compiled a corpus of suspected paper mill products by aggregating records from multiple corpora curated by experts (*Datasets S1* and *S2*). Suspected paper mill products are typically identified using manual and automated methods that search for unexpected similarities and shared content spanning multiple articles and journals (*SI Appendix*). We downloaded metadata of articles containing tortured phrases from the Problematic Paper Screener (63) on March 21, 2024. Currently, this corpus of suspected paper mill products comprises 32,786 unique articles.

See *SI Appendix* for further details.

## Results

**Anomalous Patterns in the Editorial Handling of Problematic Publications.** There is a perception among many practicing scientists that scientific fraud is a rare phenomenon (64) resulting from the actions of isolated actors (65). Mounting evidence, however, suggests the possibility that fraud is a more pervasive phenomenon; that defectors target journals to facilitate the publication of fraudulent science at scale (29). To investigate the latter possibility, we analyzed data from several journals that report the name of the editor responsible for accepted manuscripts and test whether certain individuals are more likely to edit problematic articles than one would expect by chance alone.

One of the journals that discloses the handling editor, *PLOS ONE*, has published 276,956 articles since 2006; 702 have been retracted and 2,241 have received comments in PubPeer (Fig. 1A). It is visually apparent that the retraction rate and comment rate are not constant. We determined for each of 18,329 editors who have accepted articles for publication in *PLOS ONE* (Fig. 1B) the number of articles that they accepted for publication and the number that was eventually retracted for each publication year. We then used a Poisson binomial test for whether each editor accepted ultimately retracted or PubPeer-commented articles significantly more often than expected by chance alone, adjusting for the variable rates of retraction and commenting in time (66) (*SI Appendix*). Since we tested multiple hypotheses, we adjusted the significance level via the Benjamini–Hochberg procedure (67), controlling the false discovery rate (FDR) at 0.05.

Fig. 1C shows that 22 editors accept articles that were retracted significantly more frequently than one would expect by chance. When considering articles that have received PubPeer comments, the number of flagged editors increases to 33. Using this group of flagged editors, we next investigated whether there are authors that appear to direct their articles more frequently to these flagged editors than expected by chance. We again used a Poisson binomial test, adjusting for the variable activity of flagged editors over time (66) (*SI Appendix*). Fig. 1D shows that, for the 8.8% of *PLOS ONE* authors we could identify unambiguously, 21 authors had papers more frequently assigned to editors flagged for retractions than one would expect by chance.\* We also identify 18 authors who direct their articles to editors flagged for PubPeer comments more frequently than expected by chance.

For further verification, we considered a third category of papers with anomalous peer-review—those that were accepted with remarkably short turnaround times (30 d or fewer between submission and acceptance). Short handling time is regarded by some as a hallmark of paper mill activity (68, 69).† We found a comparatively large number of editors with an anomalous rate of short turnarounds. However, we found a comparatively small number of authors enriched for submissions assigned to editors with anomalous rates of short turnaround times. This suggests that short turnaround may be a less robust marker for identifying potential collusion than retractions or PubPeer comments at *PLOS ONE*. However, it may still be a valuable indicator of potential editorial misconduct in other contexts.

The 45 *PLOS ONE* editors whom we were able to flag due to the anomalous rate at which they accepted retracted or PubPeer commented publications or had their submissions handled by other flagged editors comprise only 0.25% of all editors. These individuals edited 1.3% of all articles published in *PLOS ONE* by 2024 but 30.2% of retracted articles. More than half of these editors (25 of 45) also authored articles retracted by *PLOS ONE* (*SI Appendix*, Fig. S1).

To uncover connections between these individuals, we built a network of the publishing relationships among them (within *PLOS ONE* alone, Fig. 1E). Even though we lack information on relationships that involve other journals, we are still able to find densely connected group of individuals serving as editors between 2020 and 2023 (*Bottom Right* cluster in Fig. 1E). These editors, affiliated with institutions from four different countries, sent most of their submissions to one another over other editors. More than half of the articles accepted by this group of editors have been retracted with nearly identical notices—"one of a series of submissions for which we have concerns about authorship, competing interests, and peer review" (70).

As a robustness test, we verified that our results were not changed if we used a more strict threshold for significance (*SI Appendix*, Fig. S2). While we also wanted to test for the impact of potential field-specific rates of retractions, we lacked sufficient statistical power to do so except for cell biology, the field with the most retractions in *PLOS ONE*. Again, we find our conclusions to be unchanged (*SI Appendix*, Fig. S3).

These anomalous patterns are not restricted to *PLOS ONE*. *Hindawi* journals also disclose the editors of published manuscripts. *SI Appendix*, Figs. S4–S13 show the results of our analyses for the ten *Hindawi* journals with the most retracted and PubPeer-commented articles. Across these journals, we find

\*Note that while editor assignment is supposedly random, because of the difficulty in recruiting editors for most submitted articles and because authors are able to make editor recommendations, it is not unlikely that an author gets assigned a desired editor.

†During one of our tenures as an editor at *PLOS ONE* (LANA), *PLOS ONE* initially encouraged editors to pursue short turnaround times. This goal has been deprioritized more recently.

products might be recognizable by the lack of international collaboration in their authorship lists (30). Paper mills, predatory journals, and brokers likely operate under a number of author procurement models (75), including models where local scholars are targeted (resulting in a lack of international collaboration in authorship lists) (72) and models where authorship slots are sold to scholars worldwide (resulting in implausible international collaborations) (61).

### Differential Prevalence of Fraud Within Disciplinary Subfields.

Our results show that networks of individuals and entities act to produce fraudulent manuscripts, to select journals and publishers for targeting, and to facilitate their publication in journals indexed by aggregators such as WoS and Scopus.

Next, we investigated whether certain subfields are preferentially selected by those involved in scientific fraud. We restricted our analysis to closely related and similarly sized subfields in the biology of RNA that have each seen recent increases in popularity. We further restrict our attention to six subfields of interest to RNA biologists, namely CRISPR-Cas9, transfer RNAs (tRNAs) and development, tRNAs and cancer, circular RNAs, micro-RNAs (miRNAs) and development, miRNAs and cancer, and long noncoding RNAs (lncRNAs), and download bibliometric information on articles returned when searching in PubMed (exact search strings shown as titles in Fig. 4). Among these closely related subfields, paper mills are suspected to be particularly drawn to miRNAs, circular RNAs, and lncRNAs (76–78).

For each of these six subfields, we calculate the annual number of publications and the annual rates of errata and retractions for the period 2002–2022 (Fig. 4). We calculate the publication rate of errata because it provides a control or baseline for understanding the rate of retractions. For all subfields, we find that the publication rate of errata hovers between 1.5% and 2.5%. This suggests that, within each subfield, the extant literature is revisited at relatively similar rates.

As we surmised, we do not find the same consistency for the rate of retractions. Consistent with most scientists' expectations concerning egregious errors or scientific fraud, for CRISPR-Cas9, we find that the rate of retractions is only about 0.1%. The rate of retractions increases from tRNA (peak of ~1% for tRNA and cancer) to circular RNAs (peak of ~2.5%), miRNAs (peak of ~4% for miRNA and cancer), and lncRNAs (peak of ~4%). We also find higher rates of retractions for subfields focused on cancer than on development.

Retraction rates can be highly variable across publishers for articles in these subfields. Indeed, for studies concerning "lncRNAs" and "miRNAs and cancer" published in certain journals (*SI Appendix*), the retraction rate exceeds 10%, while for some other journals the rate is close to zero, far below expectation (*SI Appendix*, Fig. S17).

**Scientific Fraud Is Growing Much Faster than the Scientific Enterprise As a Whole.** Several studies have recently attempted to characterize the scale of published paper mill products in relation to the scale of the overall scientific literature (30, 79). Acceptance of those estimates has been hindered by limitations in the field's ability to unambiguously recognize articles produced by paper mills, by the heterogeneous rates of fraud by discipline (Fig. 4) and by the difficulty in conceiving that the enterprise of scientific fraud is sufficiently large or coordinated.

Speaking to the degree of coordination and scale of the entities involved in scientific fraud, we find that retraction

notices by journals are now published mainly in batches of more than 10 articles (Fig. 5A). One would expect retraction notices published simultaneously to be for related reasons. Indeed, retraction notices released by *PLOS ONE* are consistent with this expectation (*SI Appendix*, Fig. S18).

We also find that the number of retracted articles has been increasing exponentially over the last 30 y (Fig. 5B). Remarkably, and testifying to the enormous impact of postpublication review efforts, we find the number of articles with PubPeer comments has also been increasing exponentially. To provide perspective, we note that the number of retracted articles and PubPeer-commented articles has been doubling every 3.3 y and every 3.6 y, respectively, while the total number of publications has been doubling every 15.0 y (80, 81). However, suspected paper mill products have been doubling every 1.5 y (*SI Appendix*, Figs. S19 and S20). Notably, suspected paper mill products now outnumber annually retracted articles and are projected to soon outnumber the number of PubPeer-commented articles.

As discussed earlier, journal deindexing is a powerful mechanism available to those defending the integrity of the scientific literature. Bibliometric aggregators can index tens of thousands of actively publishing journals. In response to concerns about editorial practices, some of these aggregators can deindex a journal. WoS and Scopus deindex on the order of a hundred journals each annually. While this may appear to be a large number, it is ten-fold smaller than the number of journals that publish paper mill products (Fig. 5C and *SI Appendix*, Fig. S21).

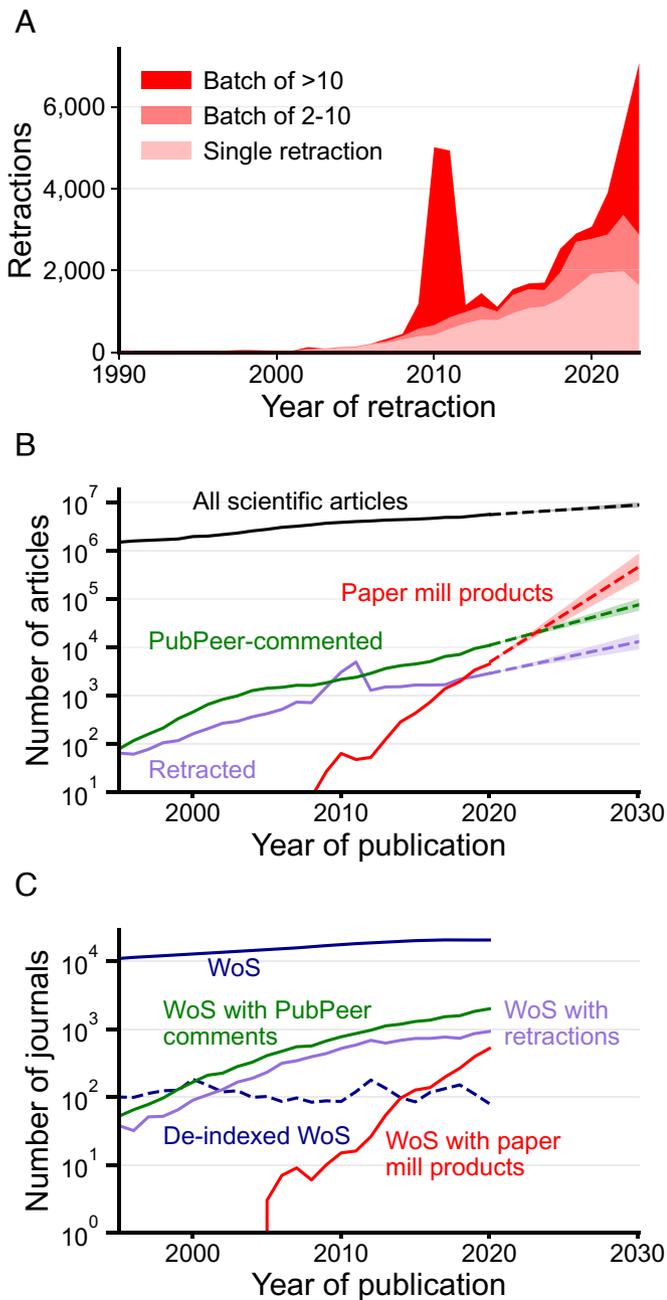
### Limitations

A limitation of our study is the comprehensiveness of the data we consider. Our analyses rely on the instances of scientific fraud that have been reported. It is likely that many fields and journals are underrepresented in the corpora we consider. Indeed, the consensus among experts is that the vast majority of paper mill products have not been detected (30, 79, 82). Further, some of our case studies focus on particular disciplines, outside of which our findings may not be generalizable.

Additionally, temporal changes in detection effort or in the attention paid to different fields may produce spurious trends. Indeed, the many unknowns about the global enterprise of scientific fraud leave open the possibility that the scale of systematic fraudulent activity has always been large but that only now has been detected. We comment further on this possibility in *SI Appendix*.

### Discussion

Competition for limited funding and jobs pushes scientists and the organizations that employ them to continually strive toward increasing scale, efficiency, impact, and the growth of the metrics by which these are evaluated. While a select group of nations, organizations, and individuals at the pinnacle of the scientific enterprise have access to the resources necessary for such extraordinary growth, most do not. Research suggests that perceived injustice is associated with research misbehavior (16) and that lack of opportunity and training are often cited as drivers of misconduct (27, 83). Thus, increasing inequality in resource accessibility may be contributing to the increasing scale of scientific fraud. However, even when provided with resources, research remains a high-risk activity—one does not know a priori whether a study will be successful or not. Why risk failure, jeopardizing one's career, when for a relatively small fee



**Fig. 5.** Articles of fraudulent provenance have an apparent growth rate greater than that of the entire scientific enterprise and already far outpace the scope of science integrity measures currently in use. (A) Retractions are increasingly published in batches. The ~2010 spike in the number of large-batch retractions is almost entirely attributable to a large swath of conference proceedings articles retracted by IEEE. For the first time since this spike, the majority of 2023 retractions were reported in batches larger than 10 articles. (B) Annual global scientific activity as measured by items labeled as “journal article” or “conference proceeding article” in OpenAlex (47), as retracted articles reported by Retraction Watch, as PubPeer-commented articles and as suspected paper mill products. We make use of the linear trends observable in the log-linear plot to extrapolate these observations for the period 2020–2030. We show the 95% CI using shaded bands. The number of suspected paper mill products shows the largest growth rate, with a doubling time of 1.5 y. (C) Annual global scientific activity captured by WoS as measured by the number of actively publishing journals, the number of journals deindexed annually by WoS, the number of journals with retractions, the number of journals with PubPeer comments, and the number of journals with suspected paper mill products. It is visually apparent that deindexing now occurs at a level far below the level of occurrence of journals publishing suspected paper mill products. These patterns hold for Scopus and MEDLINE (*SI Appendix, Figs. S21–S23*).

one can easily acquire the publications and citations that would otherwise require an immense amount of labor?

Discussions with different stakeholders suggest that many currently perceive systematic fraudulent science as something that occurs only in the periphery of the “real” scientific enterprise, that is, outside OECD countries. Accumulating evidence shows that systematic production of low quality and fraudulent science can occur anywhere (84–89). Moreover, as we show in this study, large North American and European publishers and the editors they appoint provide credibility to these practices. The impact of these practices is likely to be felt much more immediately and strongly in countries with inchoate scientific enterprises but is in no way restricted to them.

The trends we expose forecast serious risks ahead for the scientific enterprise. Large groups of editors and authors appear to have cooperated to facilitate publishing fraud (Fig. 1). Networks of linked fraudulent articles suggest industrial scale of production (Fig. 2). Organizations selling contract cheating services anticipate and counter deindexing and other interventions by literature aggregators (Fig. 3). The literature in some fields may have already been irreparably damaged by fraud (Fig. 4). Finally, the scale of activity in the enterprise of scientific fraud already exceeds the scope of current punitive measures designed to prevent fraud (Fig. 5). Currently implemented punitive measures are not addressing the tide of fraudulent science. First, papers published in deindexed journals remain a part of the record of the scientific literature in some literature aggregators (*SI Appendix, Fig. S21*). Second, retractions are still a relatively infrequent occurrence, far below what one would reasonably expect for clearly fraudulent papers (90). Only 8,589 of the 29,956 suspected paper mill products in our corpus that have a corresponding record in OpenAlex have been retracted (28.7%). Extrapolating from current trends, we estimate that only around 25% of suspected paper mill products will ever be retracted and that only around 10% of suspected paper mill products will ever reside in a deindexed journal (*SI Appendix, Fig. S23*). Collectively, these findings show that the integrity of the extant scientific record and of future science is being undermined through the shortcomings in the very systems through which scientists infer the trustworthiness of each other’s work.

Changing the culture and incentives of science is a slow process. Many of the stakeholders whose engagement is necessary for change are those benefiting from the *status quo*. However, in our view, the severity of the situation requires urgent action. The accountability efforts aiming to identify deflection (on which our study relies) have been spearheaded by courageous but isolated individuals. Some have been accused of vigilantism and dismissed (91), others have been threatened with legal action (92). We need to create a system that is more robust and systematic and where it is harder to dismiss or bully those providing evidence of fraud. First and foremost, we need to separate the different tasks required of a just accountability system: detection, investigation, and sanctioning.

Each of these tasks also needs to be removed from the hands of parties with potential conflicts of interest. Journal editors have been offered substantial payments for rapid publication of selected manuscripts (29, 30) and coordinated editorial action has been implicated in efforts to increase the impact factor of journals (13, 77). Likewise, research institutions have a conflict of interest when investigating their own scientists. Further, detection at the scale the problem demands cannot be left to a small number of isolated volunteers. It needs resources, both human and technological, commensurate with the threat.

At the very least, significantly more research is needed toward both characterizing the diverse entities governing systematic scientific fraud as well as developing a unified and comprehensive vocabulary for describing them (93, 94).

A major challenge is the lack of a comprehensive framework for the types of behaviors we report here. Unethical behavior in science is often viewed as a character failure of an individual, not something perpetrated, enabled, and promoted by a cohort of individuals and entities. Indeed, even the definition of a now standard term such as “paper mill” remains nebulous (*SI Appendix*). Some of the organization we describe may be better characterized as “brokerages” than paper mills. We also cannot ascertain where our observations are due to the involvement of commercial paper mills or where they arise as a result of less formal peer networks operating on a noncommercial basis (as could be the case among some of the editors we flag). This complexity is why we propose the use of the game theoretical concept of defection. We believe this to be a useful perspective because it frames some behavior not in ethical terms but in terms of rationality (95). However, the term “defection” implies realignment from normative behavior to nonnormative behavior.

For many junior doctors and budding scientists, engaging in defecting behavior may be the new norm (27, 29, 83, 87).

Finally, it is important to explicitly highlight the risk posed by large scale fraudulent science to emerging cutting-edge approaches. Both “machine scientists” (96, 97) and large language models hold the promise to help encapsulate the knowledge in the scientific literature for the use of scientists and the lay public. However, such approaches are not yet able to distinguish quality science from poor quality or fraudulent science and this task only becomes more difficult as the number of fraudulent scientific publications increases.

**Data, Materials, and Software Availability.** Code is available at [http://github.com/amarallab/systematic\\_fraud](http://github.com/amarallab/systematic_fraud) (98). Code for topic analyses is available at [http://github.com/amarallab/Science\\_fraud\\_topic\\_analysis](http://github.com/amarallab/Science_fraud_topic_analysis) (99). Some study data are available: All data presented in this work which is not under license from Clarivate (WoS, readers should [wosg.support@clarivate.com](mailto:wosg.support@clarivate.com) for more details) or the PubPeer Foundation (readers should contact [contact@pubpeer.com](mailto:contact@pubpeer.com)

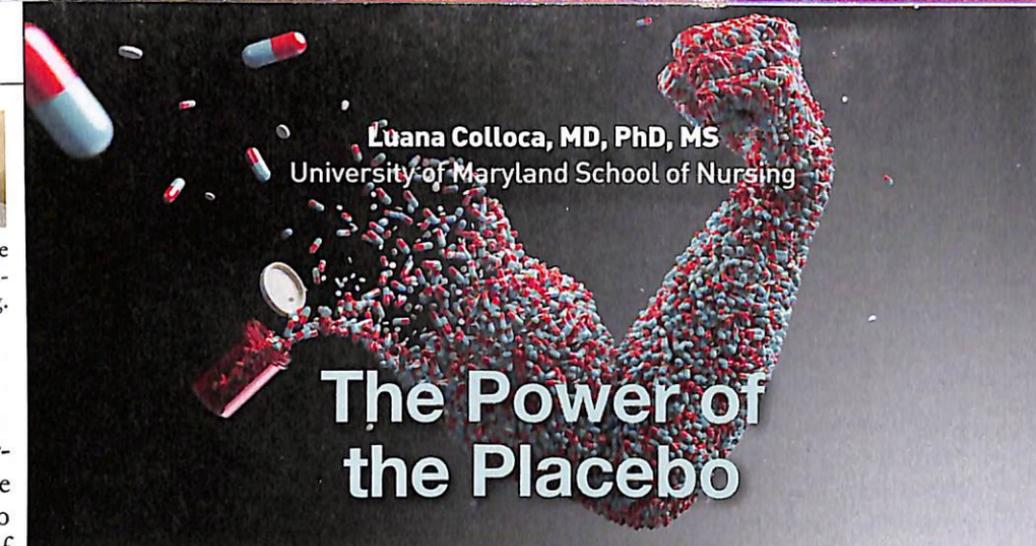
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for more details) are available in *SI Appendix*. Historical data on indexing from Scopus (52), MEDLINE (53, 54), and OpenAlex (47) are publicly available. XML dumps from PLOS journals are publicly available (59). XML dumps from Hindawi journals were publicly available at the time of our analysis (60) but are no longer provided publicly by Wiley. Archives of the April 2, 2024, version of the dataset are available on Zenodo (<https://doi.org/10.5281/zenodo.13922491>)(100) and Academic Torrents (<https://academictorrents.com/details/4d02d0f51e2174d515b8a38d5af81478102a9f12>)(101).

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# The Power of the Placebo

**S**everal years ago, University of Pittsburgh researchers served cocktails to 237 adults. They poured a cold, clear liquid from a Smirnoff vodka bottle into a pitcher and swirled in cranberry juice. The participants, all moderate drinkers, were told the beverage contained alcohol, and each was given about a half hour to consume it. *But:* The researchers weren't being totally straight up—the “vodka” was flattened tonic water. *Result:* All but one participant responded affirmatively when asked if they felt some intoxication after finishing their nonalcoholic “cocktail.”

This is one of thousands of studies conducted to investigate the *placebo effect*—when people experience improvements in symptoms or report positive changes in how they feel after being given an inactive substance. *Note:* When negative changes occur, it is called the *nocebo effect*.

*Bottom Line Personal* spoke with placebo expert Luana Colloca, MD, PhD, MS, about the placebo effect and how it can be used in health care today. Her fascination with placebos began in the early days of her neuroscience education, when she was involved in an experiment involving Parkinson's patients who had electrodes surgically implanted in their brains so researchers could view their neuronal activity. These patients had been receiving injections of the dopamine-boosting drug apomorphine designed to ease Parkinson's symptoms such as rigidity. But while undergoing the surgery, they received an injection of a placebo...though they were told it was the real drug. *Result:* Their rigidity softened...and their brains displayed spike patterns associated with exposure to the

actual medication. *Takeaway:* Patients' reinforced expectations can be as powerful as medication. Reinforced expectations refer to expectations associated with a prior therapeutic experience—in this case, the exposure to apomorphine prior to the injection of placebo.

*Other examples:* Researchers at University of Pennsylvania found that 61% of study patients reported complete blockade of panic attacks after swallowing a sugar pill labeled “Xanax”...osteoarthritis sufferers told German researchers they experienced less knee pain after having acupuncture needles inserted in points that don't correlate with knee pain...and patients perceived reduced cold severity and duration in a National Institutes of Health trial after they met with an empathetic doctor.

## NOT JUST POSITIVE THINKING

You don't have to have a debilitating chronic condition like Parkinson's to benefit from the placebo effect. You don't even need to believe in the power of placebo to experience their impact.

The body has its own inner pharmacy, capable of producing all manner of chemicals and compounds that mimic actual medications or substances used to manage specific symptoms. These >>

*Bottom Line Personal* interviewed Luana Colloca, MD, PhD, MS, internationally renowned expert on placebo and nocebo effects. She is an MPower professor in the Department of Pain and Translational Symptom Science at University of Maryland School of Nursing, Baltimore, where she also directs the Placebo Beyond Opinions Center, which seeks to improve clinical trials, educate future clinicians, and integrate placebo knowledge into precision medicine practices. UMaryland.edu



are called *endogenous compounds*. When using placebo treatments for pain, the relief reported by some individuals can be attributed to the release of...

**Opioid neurotransmitters** that modulate pain. Endorphins are one example of endogenous opioids. Morphine, codeine and fentanyl are synthetic opioids.

**Cannabinoids**—pain- and mood-improving compounds similar to those found in the *Cannabis sativa* plant.

**How do we know these endogenous pain-relieving compounds are real and not just “in the patient’s head”?** In a landmark study led by neuroscientist Jon Levine, MD, PhD, in the 1970s, patients who had their wisdom teeth removed were randomly assigned to receive intravenous morphine or a placebo (saline). About 40% of those in the placebo group reported significant diminishment of pain. These people were dubbed *placebo responders*.

Dr. Levine and his team then surreptitiously added *naloxone*, a medicine that blocks opioids, to the IVs of the placebo responders. (Naloxone is used to rapidly reverse overdoses from opioids like heroin and fentanyl.) Adding naloxone reversed the pain-relieving placebo effects—the placebo responders’ pain levels increased almost immediately, reaching the same level of pain reported by patients who did not initially experience relief when given a placebo. (Naloxone had no impact on placebo non-responders.)

**Conclusion:** Endogenous opioids largely govern placebo pain relief, indicating that patients aren’t just tricking themselves into feeling better.

### MINDSET STILL MATTERS

While placebo effects are linked to physiological and biological changes, a patient’s expectations shape how he/she responds to placebos as well. Factors like the following can make a difference, activating or dampening the brain changes described above...

- Does the individual think the treatment will be effective?
- Has he/she previously had a positive experience with the treatment?
- Has he seen other similar patients benefit from the treatment?
- Is he confident in the provider?

*One familiar example of how expectations and previous experiences can*

*influence the placebo effect.* Russian physiologist Ivan Pavlov’s conditioning experiments showed that dogs salivate when they hear a bell, even without receiving food with the sound. Pavlov eventually elicited the physiological response (salivating) from dogs solely from the bell, even with no food present. The expectation that food was coming was sufficient to trigger the physical response.

**Modern-day example:** A similar phenomenon drives smartphone addiction. The ping of an incoming text triggers a burst of dopamine, associated with pleasurable rewards. We learn that looking at our phone feels good, so we feel compelled to constantly check our phone with the hope of getting more dopamine hits.

This helps explain why, in a 2015 University of Pennsylvania study, chronic insomnia patients slept just as well regardless of whether they took a nightly pill containing 10 milligrams (mg) of *zolpidem* (Ambien)...or a nightly pill that they were told contained 10 mg of *zolpidem* but in fact contained only 5 mg.

### OPEN-LABEL PLACEBOS

An interesting concept gaining traction today is called *open-label placebos* (OLPs), in which patients receiving a placebo are specifically told, “This is a placebo.” Many researchers prefer OLPs because they eliminate ethical concerns about giving patients a placebo.

In a 2018 University of Alabama at Birmingham study, OLPs improved cancer-related fatigue. In the study, 34 cancer survivors experiencing moderate post-treatment fatigue knowingly took pills that contained *cellulose* (plant fiber used in foods and medications) but that had no active ingredients to relieve fatigue. After three weeks, these patients reported a 29% improvement in fatigue severity and a 39% improvement in the impact that fatigue had on their quality of life. Moreover, the benefits lasted for three weeks after they stopped taking the placebo pills. The effects were so meaningful that some study participants asked if they could receive more placebo pills. **Noteworthy:** It didn’t matter if the subjects believed in the placebo effect, meaning that it was the ritual of taking a pill—whether active or inert—that likely evoked the positive response.

OLPs have proven to have some degree of success for several conditions, including hot flashes, depression, migraines, chronic lower-back pain, allergies, irritable bowel syndrome and more.

### HARNESSING PLACEBO POWER

The placebo response won’t heal a broken bone or cure a bacterial infection. It primarily works by improving symptoms of disease, such as pain, anxiety, fatigue and the like. But besides improving quality of life, this could reduce the need for costly medications.

One way to tap into the power of the placebo is to find health-care providers you trust. If you enjoy interacting with your doctor and he/she takes time with you, even better. A warm doctor-patient relationship in which you feel seen and heard can be extremely strong medicine.

In a 2015 Beth Israel Deaconess Medical Center clinical trial, acid reflux patients were randomly assigned to a standard-length meeting (18 minutes, on average) with a doctor or an expanded meeting (42 minutes, on average). The longer meeting included the same questions as the standard one—reflux history, symptoms, prior evaluation and treatments, etc.—plus more detailed ones delving into sleep, impact of weather on symptoms, what their reflux tasted like and more. The participants in the expanded meeting group experienced a 50% or greater improvement in symptoms over those in the shorter meetings. **Best:** Look for someone who is encouraging and reassuring while still being objective and realistic.

There’s also something to be said for being proactive in seeking help for what ails you. The feeling of *I’m doing something* can exert its own positive placebo effects. **Examples:** Many people who experience mood improvements when taking antidepressants do so because they expect the medication to help them. And consumers continue to purchase over-the-counter cold remedies containing *phenylephrine* even though the Food and Drug Administration has deemed it ineffective at relieving congestion.

You even can purchase your own placebo pills. One such product, Zeebo, has shown in randomized clinical trials to help with low-back pain and COVID-related stress, anxiety and depression. **BLP**

## Treatment Effects in Pharmacological Clinical Randomized Controlled Trials are Mainly Due to Placebo

Journal of Clinical Epidemiology  
March 2025; Vol. 179; Article 111658

Stefan Schmidt, Martin Loef, Thomas Ostermann, Harald Walach; this study cites 29 references.

BACKGROUND FROM DAN MURPHY:

The placebo effect is real. It is attributed to “expectancy, hope, conditioning, learning, information, doctor-patient communication, meaning creation, etc.”

Placebo effects are dependent on both conscious and unconscious processes, and they work even when the placebo is openly known to the subject, and they are enhanced by nonverbal communication.

The actual drug being assessed in a clinical trial can also function as a placebo. When the drug group benefits from the intervention, credit is given to the drug, yet the benefit may actually be from the drug acting as a placebo. The objective of this study was to assess the magnitude of the *drug-placebo effect* and how often such an effect is interpreted as being a benefit of the drug.

In addition, the authors note that a percentage of disease processes will have a natural tendency to improve, separate from both the actual drug benefit and from the placebo effect. This natural improvement tendency is often not included in the analysis, and credit is inappropriately ascribed to the drug. The placebo response describes the effect patients experience in the placebo group of a clinical trial, including effects due to the natural tendency of the disease.

The “holy grail” of clinical research is the *randomized controlled trial*. Often, the randomized intervention includes a placebo that technically should not benefit the study subject.

This study examined the role of the placebo effect in treatment outcomes within drug clinical trials.

The authors selected five medical conditions in their assessment: osteoarthritis, irritable bowel syndrome (IBS), depression, sleep disorders, and migraines. They analyzed 150 randomized controlled trials (RCTs), 30 for each condition.

The assessment is complex and quite mathematical. It is also disturbing because it shows that often drugs are not as beneficial as their proponents claim.

## KEY POINTS FROM THIS ARTICLE:

- 1) "It is well known that placebo effects are contributing to improvement rates in clinical trials."
- 2) In drug clinical trials, non-pharmacological effects are "more important than pharmacological ones."
- 3) "Placebo effects have a significant impact on observed outcomes ... with only limited variance remaining for pharmacological interventions."
  - A maximum of 28% of the benefits can be attributed to pharmacological effects.
  - "This means that pharmacological effects account for a much smaller proportion of improvements than is usually assumed."
- 4) "This work emphasizes the power of contextual and psychological factors in healing and calls for a greater focus on nonpharmacological components to enhance patient care." **[Very Important]**
- 5) "The authors highlight that many treatment benefits attributed to drugs may actually stem from placebo effects, underscoring the importance of understanding and leveraging these effects in clinical practice." **[Key Point]**
- 6) "Our analysis confirms the following: the placebo and the treatment responses in trials are highly interdependent."
- 7) "[There is] a strong interdependence between placebo and treatment effects."
- 8) "A potential and obvious explanation of our findings would be that clinical trials constitute a healing ritual that affects patients in both groups equally strongly and is the most important constituent of any healing process."
- 9) "The major component in responses after pharmacological treatments is the placebo-effect created by the high expectation and by conditioned responses." **[Key Point]**
- 10) "We see from the data of our analysis that the impact of pharmacological treatments is much more limited than expected." **[Very Important]**
- 11) This study indicates that when a drug shows benefit, 72% of that benefit is placebo and only 28% of the benefit is from the drug.
  - If improvement is seen in the clinical trials, it is "not due to pharmacological treatment." **[Key Point]**

- “Nevertheless, patients usually attribute improvement after receiving medication entirely to the drug.” **[Key Point]**
- “Our analysis shows that this attribution is incorrect.” **[Key Point]**
- “There is a much larger potential for improvement in nonpharmacological effects, which are much less understood.”

12) “We conclude from our data that the placebo-effect is the major driver of treatment effects in clinical trials that alone explains 69% of the variance. This leaves only limited space for effects due to pharmacological substances.”

### **13) Key Findings From Authors:**

- “About 72% of [drug] treatment effects can be explained by other factors than [drug] treatment itself.”
- “This means that pharmacological effects explain only up to 28% of observed improvements.”
- “Contextual factors such as expectations and doctor-patient interactions drive healing.”

We have reviewed these articles pertaining to the placebo effect:

Article Review 19-02:

**A Controlled Trial of Arthroscopic Surgery for Osteoarthritis of the Knee**

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**

Article Review 36-24:

**Subacromial Decompression Versus Diagnostic Arthroscopy for Shoulder Impingement: Randomised, Placebo Surgery Controlled Clinical Trial**

*New York Times* bestselling author of *Fat Chance*

ROBERT H. LUSTIG, MD, MSL

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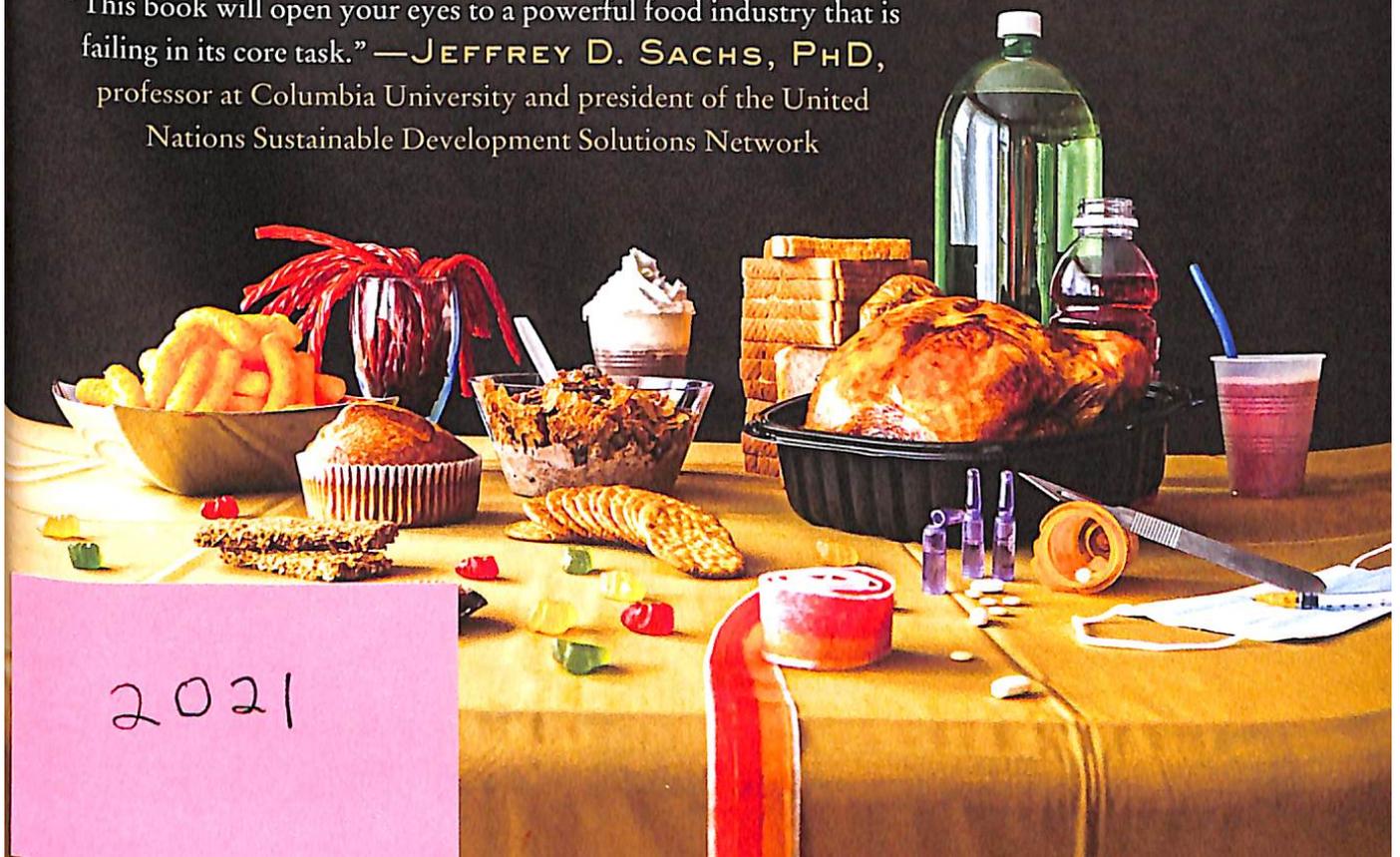
# Metabolical

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The Lure and the Lies of Processed Food,  
Nutrition, and Modern Medicine

“This book will open your eyes to a powerful food industry that is failing in its core task.” —JEFFREY D. SACHS, PHD,  
professor at Columbia University and president of the United Nations Sustainable Development Solutions Network



## Metaboliical

### The Lure and the Lies of Processed Food, Nutrition, and Modern Medicine

**Robert Lustig, MD**

**Emeritus Professor of Pediatrics at University of California, San Francisco**

**Harper Wave 2021**

"There are two keys to understanding the breakdown of our health and healthcare model."

"The first key is the one the *medical establishment doesn't want you to know*—that their drugs can't and don't treat chronic disease; they only treat *symptoms*."

"Oh yes, they can treat the high blood pressure, high blood glucose, high blood lipids—but not the actual *cause* of any of these disease conditions."

"But for chronic noncommunicable diseases—such as diabetes, heart disease and stroke, fatty liver disease, cancer, and dementia, which kill more people, at earlier ages, and in the most debilitating of ways and eat up 75 percent of all healthcare dollars—Modern Medicine has gotten it all wrong."

"There are eight subcellular pathologies that underlie all chronic disease,"...and "none are *druggable*."

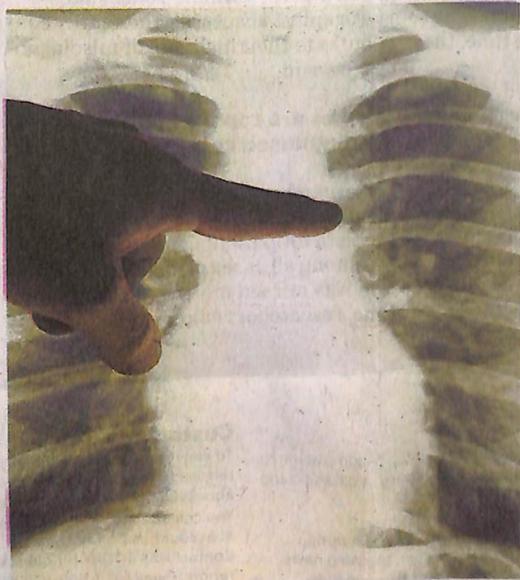
"Big Pharma is adept at covering up this subterfuge by advertising directly to the consumer, pretending the symptoms are the disease."

- 1) Glycation (refined carbohydrates, sugar—especially fructose...)
- 2) Oxidative Stress (endogenous and exogenous antioxidants...)
- 3) Mitochondrial Dysfunction (exercise, fructose...)
- 4) Insulin Resistance (refined carbohydrates, sugar...)
- 5) Membrane Integrity (omega-3s, trans fats...)
- 6) Inflammation (omega-3s, microbiome...)
- 7) Epigenetics (diet, supplements...)
- 8) Autophagy (sleep, intermittent fasting...)

"The second key is the one that the *food industry doesn't you to know*—all food is inherently good; it's what's been *done* to the food that's bad."

Front Page

# Report: Diagnostic errors deadly



Diagnostic errors cause thousands of deaths yearly, a report shows. GETTY IMAGES

## Medical misdiagnoses cause an estimated 795K deaths, permanent disabilities yearly

Claire Thornton  
USA TODAY

7/20/23

### Nearly 40%

of all deaths and permanent disabilities stemming from incorrect diagnoses come from just five conditions, according to the report:

- Stroke.
- Sepsis.
- Pneumonia.
- Blood clots.
- Lung cancer.

Top medical researchers are sounding the alarm that an estimated 795,000 American patients continue to die or become permanently disabled each year because they are being diagnosed with the wrong conditions.

For years, the public hasn't known much about the full scope of medical misdiagnoses that happen in the U.S., according to a new report released by the Johns Hopkins Armstrong Institute Center for Diagnostic Excellence. Until now, estimates of annual incorrect diagnoses have varied widely, the report says.

Now, researchers say an estimated 371,000 patients die and 424,000 are

See MISDIAGNOSES, Page 2A

## Misdiagnoses

Continued from Page 1A

permanently disabled each year because they are incorrectly diagnosed across a range of medical care settings — not just in the family doctor's office.

The estimate "matches data produced from multiple prior studies that focused on diagnostic errors in ambulatory clinics and emergency departments and during inpatient care," the report says.

The enormous numbers of misdiagnoses are a public health emergency, the report's lead author said. "Diagnostic errors are, by a wide margin, the most under-resourced public health crisis we face," said Dr. David Newman-Toker, director of the Johns Hopkins diagnostic excellence center.

Medical professionals almost always misdiagnose diseases when a person's symptoms look like possible symptoms

for a different condition, Newman-Toker told USA TODAY. The more subtle the symptom appears, the more likely it is the patient's problem will be misdiagnosed, he said.

"We don't miss strokes when somebody is paralyzed on one side and can't talk," he said. "We miss them when they look like something else that's benign."

### How often do doctors misdiagnose conditions?

Overall, medical providers misdiagnose diseases about 11% of the time, the report says.

Some diseases are missed at low rates, whereas others are missed more than half the time, researchers found.

On the lower end of the spectrum, only 1.5% of heart attacks are misdiagnosed, researchers found. On the higher end: 62% of spinal abscesses are incorrectly diagnosed.

Heart attacks have such a low rate of misdiagnosis "because we're made a

**"Diagnostic errors are, by a wide margin, the most under-resourced public health crisis we face."**

Dr. David Newman-Toker  
Johns Hopkins diagnostic excellence center

sustained investment over decades" on better diagnostic resources and have passed regulations saying they must be put in place, Newman-Toker said.

For spinal abscesses, their rarity contributes to their high rate of misdiagnoses, he said.

**Strokes are top problem among misdiagnosed conditions**

Researchers found strokes that are misdiagnosed are the most serious problem for patients and their families.

Among all cases of stroke, the condition was missed more than 17.5% of the time, researchers said.

One of the main reasons for this is that some people only show dizziness and vertigo as a symptom of stroke, which can, unfortunately, get misdiagnosed as inner ear disease, Newman-Toker said. Or, someone who had a stroke could just have headaches.

Doctors are not being trained across the board on how to differentiate dizziness caused by stroke and the same symptom caused by inner ear disease, he said.

Because a small number of diseases make up a large share of the problem, researchers say they are hopeful it will be easy for medical care providers to focus their efforts in certain areas.

"It means we can make a lot of headway in a relatively shorter amount of time, without having to boil the ocean," Newman-Toker said.

The report found reducing diagnostic errors by 50% for stroke, sepsis, pneumonia, pulmonary embolism and lung cancer could cut permanent disabilities and deaths by 150,000 per year.

## Burden of Serious Harms from Diagnostic Error in the USA

**BMJ [British Medical Journal] Quality & Safety**  
**July 17, 2023; Epub**

David E Newman-Toker, Najlla Nassery, Adam C Schaffer, Chihwen Winnie Yu-Moe, Gwendolyn D Clemens, Zheyu Wang, Yuxin Zhu, Ali S. Saber Tehrani, Mehdi Fanai, Ahmed Hassoon, Dana Siegal: authors are from Johns Hopkins School of Medicine, and Harvard Medical School. This study cites 54 references.

The objective of this study was to estimate the annual US burden of serious misdiagnosis-related harms (permanent morbidity, mortality), including the “Big Three”:

- Vascular events
- Infections
- New cancers

All age groups were included.

Serious (high-severity) misdiagnosis-related harms were defined as **scale scores 6–9** representing serious permanent morbidity or mortality, using the **National Association of Insurance Commissioners Coding Scale = NAIC**:

**NAIC 6**—permanent *significant* (eg, deafness, loss of single limb, loss of eye, loss of one kidney or lung; cancers where there is a large tumor possibly with lymph node involvement—this includes cancers that are stage III and stage IV such as breast cancer with total mastectomy, lung cancer with pneumonectomy or a small cell lung cancer that is inoperable because it has already spread too far).

**NAIC 7**—permanent *major* (eg, paraplegia, blindness, loss of two limbs, brain damage).

**NAIC 8**—permanent *grave* (eg, quadriplegia, severe brain damage, lifelong care or fatal prognosis; cancer cases with distant metastasis and/or a prognosis of <6 months).

**NAIC 9**—*death* (including fetal and neonatal death).

The goal of this research was to estimate the total number of serious misdiagnosis-related harms (ie, permanent disability or death) occurring annually in the USA across all care settings (ambulatory clinic, emergency department, and inpatient). This is the first national estimate of permanent morbidity and mortality resulting from diagnostic errors across all clinical settings, including both hospital-based and clinic-based care each year in the USA alone.

This study, “considered only false negative diagnoses (ie, initially missed or delayed) and associated harms.” **[Important]**

"Harms from inappropriate use or overuse of diagnostic tests, or from overdiagnosis (ie, overtreatment of correctly diagnosed conditions that, left undiagnosed, would be unlikely to impact patient health) were not considered."

#### KEY POINTS FROM THIS ARTICLE:

1) "Diagnostic errors cause substantial preventable harms worldwide."

#### 2) Findings (rounded):

- The 15 diseases causing the most *false-negative diagnostic error* harms were:

##### Vascular Events

- 1 Stroke
- 2 Venous thromboembolism
- 3 Arterial thromboembolism
- 4 Aortic aneurysm/dissection
- 5 Myocardial infarction

##### Infections

- 6 Sepsis
- 7 Pneumonia
- 8 Meningitis/encephalitis
- 9 Spinal abscess
- 10 Endocarditis

##### Cancers

- 11 Lung cancer
- 12 Breast cancer
- 13 Colorectal cancer
- 14 Melanoma
- 15 Prostate cancer

- "[These] 15 dangerous diseases accounted for 51% of total serious harms and the top 5 (stroke, sepsis, pneumonia, venous thromboembolism and lung cancer) accounted for 39%."

#### 3) Conclusions:

- "An estimated 795,000 Americans become permanently disabled or die annually across care settings because dangerous diseases are misdiagnosed."
- "This manuscript provides the first robust, national annual US estimate for serious misdiagnosis-related harms (nearly 800,000 combined deaths (~371,000) or permanent disabilities (~424,000)) across care settings (ambulatory clinic, emergency department, and inpatient)." **[Key Point]**

- “Across clinical settings (ambulatory clinics, emergency department, and inpatient), we estimate that nearly 800,000 Americans die or are permanently disabled by diagnostic error each year, making it the single largest source of serious harms from medical mistakes.” **[Key Point]**
  - “The number of affected patients is large, and this makes diagnostic error a pressing public health concern.”
  - “[Reducing] diagnostic errors by ~50% for the 15 named dangerous diseases could potentially prevent ~200,000 serious misdiagnosis-related harms while reducing diagnostic errors by ~50% for the five most harmful diseases (stroke, sepsis, pneumonia, venous thromboembolism, and lung cancer) could prevent ~150,000.”
  - “Sensitivity analyses and validity checks show serious misdiagnosis-related harm results are robust.”
  - “The credibility of our current estimate is bolstered by convergent construct validity with two alternative methods of estimation using the rate of misdiagnosis-attributable deaths based on hospital autopsies and inpatient diagnostic adverse events.”
  - “Our results suggest that diagnostic error is probably the single largest source of deaths across all care settings (~371,000) linked to medical error.” **[Key]**
  - “This number may exceed estimated deaths from all other patient safety concerns combined.” **[Key Point]**
  - “A patient with a life-threatening or limb-threatening disease has a ~11% chance of being missed; because of the substantial risk of harm when a dangerous disease is missed, that same patient also has a ~4% overall chance of dying or becoming permanently disabled pursuant to a misdiagnosis.” **[Key Point]**
- 4) “Total annual diagnostic errors in the USA likely number in the tens of millions.” **[Important]**
- “Although the study estimated total diagnostic errors (2.59 million), this [study] reflects only errors in patients with dangerous diseases, not all diagnostic errors.”
- 5) “There is good reason to believe that diagnostic errors and misdiagnosis-related harms represent a global problem.”
- 6) “There is meta-analytic evidence that hospital-based diagnostic error and harm rates are comparable across North America and Europe, but higher in other countries that were studied.”

The study did not include patients who suffered a permanent injury and/or death from **overdiagnosis** and **overtreatment** (a correct diagnosis that if left undiagnosed, would be unlikely to impact patient health).

Nor did the study include permanent injury and/or death caused by **non-diagnostic errors**, like you took the correct drug in the correct dosage for the correct diagnosis, and the treatment itself killed or disabled you anyway). These events were profiled in Article Review 10-09:

**Incidence of Adverse Drug Reactions in Hospitalized Patients**

Journal of the American Medical Association

Also, see these related Reviews:

Article Review 28-00:

**Is US Health Really the Best in the World?**

Journal of the American Medical Association

Article Review 14-01:

**Medication Errors and Adverse Drug Events in Pediatric Inpatients**

Journal of the American Medical Association

Article Review 36-11:

**Exploring the Harmful Effects of Health Care**

Journal of the American Medical Association

Article Review 19-12:

**Adverse Events In Hospitals May Be Ten Times Greater Than Previously Measured**

Health Affairs

Article Review 20-16:

**Medical Error: The Third Leading Cause of Death in the United States**

British Medical Journal

2022

# sickening



**HOW** **BIG PHARMA**

**BROKE AMERICAN HEALTH CARE**

**AND HOW WE CAN REPAIR IT**

**John Abramson, MD, MSc**

*Author of **Overdo\$ed America***

## The Illusion of Evidence Based Medicine

### Evidence Based Medicine has Been Corrupted by Corporate Interests, Failed Regulation, and Commercialisation of Academia

**BMJ [British Medical Journal]**  
**March 16, 2022; Vol. 376; pp. o702**

Jon Jureidini, Leemon B. McHenry: From the University of Adelaide (Australia) and California State University, Northridge. This is an opinion piece by the authors.

#### KEY POINTS FROM THIS ARTICLE:

- 1) "The advent of evidence-based medicine was a paradigm shift intended to provide a solid scientific foundation for medicine."
  - The validity of this paradigm depends on reliable data from clinical trials, most of which are conducted by the pharmaceutical industry and reported in the names of senior academics. **[Key Point]**
  - "The release into the public domain of previously confidential pharmaceutical industry documents has given the medical community valuable insight into the degree to which [drug] industry sponsored clinical trials are misrepresented."
    - Until this misrepresentation is corrected, "evidence-based medicine will remain an illusion."
- 2) The integrity of science in an open, democratic society requires "not to cling to cherished hypotheses and take seriously the outcome of the most stringent experiments."
  - This integrity is "threatened by corporations, in which financial interests trump the common good."
- 3) "Medicine is largely dominated by a small number of very large pharmaceutical companies that compete for market share, but are effectively united in their efforts to expanding that market."
- 4) "Scientific progress is thwarted by the ownership of data and knowledge because [the drug] industry suppresses negative trial results, fails to report adverse events, and does not share raw data with the academic research community."
  - "Patients die because of the adverse impact of commercial interests on the research agenda, universities, and regulators."

- The primary responsibility of the pharmaceutical industry is not to the public that consumes its products or to scientific integrity, but rather to its shareholders.
- 5) "Universities have always been elite institutions prone to influence through endowments; they have long laid claim to being guardians of truth and the moral conscience of society."
- Universities "have adopted a neo-liberal market approach, actively seeking pharmaceutical funding on commercial terms."
  - University have become instruments of the drug industry.
    - They allow drug companies control of the research agenda.
    - They allow the ghostwriting of medical journal articles by the drug industry.
    - They allow drug companies to control continuing medical education.
  - "Academics become agents for the promotion of commercial products."
  - Distinguished leadership Deans have been replaced with fundraisers and academic managers "who are forced to demonstrate their profitability or show how they can attract corporate sponsors."
  - Key opinion leaders "are selected based on their influence on [their drug] prescribing habits of other physicians."
    - "As well-paid members of pharmaceutical advisory boards and speakers' bureaus, key opinion leaders present results of [drug] industry trials at medical conferences and in continuing medical education."
    - "Instead of acting as independent, disinterested scientists and critically evaluating a drug's performance, they become what marketing executives refer to as [drug] 'product champions.'"
    - Drug "industry sponsored key opinion leaders appear to enjoy many of the advantages of academic freedom, supported as they are by their universities, the industry, and journal editors for expressing their views, even when those views are incongruent with the real evidence."
  - "Universities fail to correct misrepresentations of the science from such collaborations."
    - "Critics of [the drug] industry face rejections from journals, legal threats, and the potential destruction of their careers."

- 6) Scientific objectivity and impartiality are "entirely at the mercy of political and commercial power."
- 7) "Regulators receive funding from [the drug] industry and use [drug] industry funded and performed trials to approve drugs, without in most cases seeing the raw data."
- 8) Drug companies are permitted to "mark their own homework" rather than having their products tested by independent experts.
- 9) Current medical journal publishing models are corrupted because they "depend on reprint revenue, advertising, and sponsorship revenue."

COMMENTS FROM DAN MURPHY:

There are many books on this topic. The most recent is:

**Sickening**  
**How Big Pharma Broke American Health Care**

John Abramson, MD  
Mariner Books  
2022

Dr. Abramson was a family physician for 22 years and is now faculty at Harvard Medical School (for 25 years) where he teaches health-care policy. For all that want to understand how drug companies scam our health care data and health care delivery system, this is a very informative book.

Dr. Abramson details how clinical drug trials are at best misleading and often purposefully deceptive and fraudulent.

Dr. Abramson explains how practicing physicians are being deceived by their own medical journals and practice guidelines resulting in great harm to patients. He reviews the evidence that we spend the most per capita on health care to essentially come in last in the developed world. He explains how top medical journals are often co-conspirators in the scam.

Dr. Abramson explains how direct to consumer advertising (television commercials, magazines, radio, etc.) are also misleading or fraudulent, but make huge revenue for media outlets allowing them to pay exorbitant money to celebrity spokes people as well as program actors because once the drug study is published the drug company will pay the journal top dollar for tens of thousands of reprints that the drug reps will then distribute for free to practicing physicians, all in an effort to convince the physician to use their products.

- Dr. Abramson explains government is complicit in the process, as the drug companies spend "an average of \$450,000 on lobbying for each of the 535 members of Congress."

NEW YORK TIMES BESTSELLING AUTHOR OF SLANTED

SHARYL  
ATTKISSON

FOLLOW

THE

2024



SCIENCE

**HOW BIG PHARMA MISLEADS,  
OBSCURES, AND PREVAILS**

Feel Incredible,  
Avoid Disease,  
and Age Well

"A tour de force."  
—Mark Hyman, MD

2024

# GOOD ENERGY

**The Surprising Connection Between  
Metabolism and Limitless Health**

**CASEY MEANS, MD**  
WITH CALLEY MEANS

## Good Energy

### The Surprising Connection Between Metabolism and Limitless Health

Casey Means, MD  
2024

“Nearly every health problem we face can be explained by how well the cells in our body create and use energy.”

“The next revolution in health will come from the understanding how the root of almost every disease relates to energy...” “And when we shift our framework to this energy-centric paradigm, we will rapidly heal our system and our bodies.”

“Imagine a powerful life force from within that allows you to take on each day with pleasure, energy gratitude and joy.”

“An *underpowered* cell—metabolically dysfunctional, struggling to make energy, and sputtering along through its daily work—is a cell that is threatened and at risk. This failing cell will send out chemical alarm signals and recruit the immune system to help it. In their efforts to help,

the immune cells cause immense collateral damage—creating a literal war within the body to protect itself from itself—that results in worse symptoms. This is a key reason why chronic inflammation typically goes in lockstep with metabolic dysfunction and widespread symptoms.”

“There’s one simple measure that can powerfully reframe how we understand health and disease: how well or poorly the mitochondria in the cell are making energy.”

“Given that mitochondria are the coordinators of cell immunity and cell survival, mitochondria function was implicated as early as 2020 as a key factor in the likelihood of getting COVID, dying from COVID, and experiencing long COVID.”

“Researchers made recommendations to ‘urgently’ pursue preventive avenues to ‘strengthen the mitochondria’ for best COVID outcomes...”

# Trends in US Children's Mortality, Chronic Conditions, Obesity, Functional Status, and Symptoms

Journal of the American Medical Association (JAMA)  
July 7, 2025 [epub]

Christopher B. Forrest, MD, PhD; Lauren J. Koenigsberg, BA; Francis Eddy Harvey, BA; Mitchell G. Maltenfort, PhD; Neal Halfon, MD, MPH; from Children's Hospital of Philadelphia and the University of California, Los Angeles.

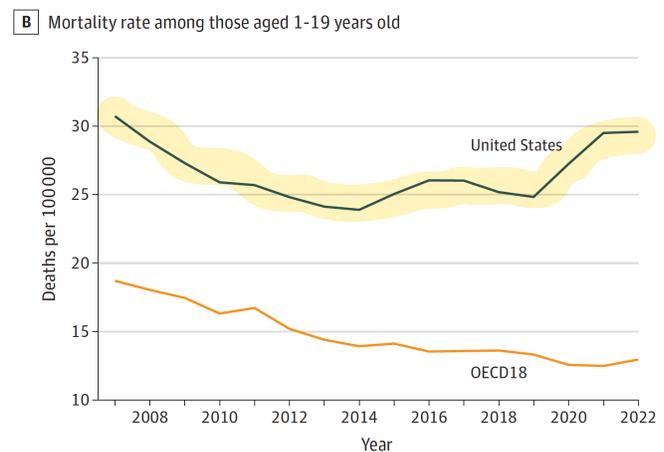
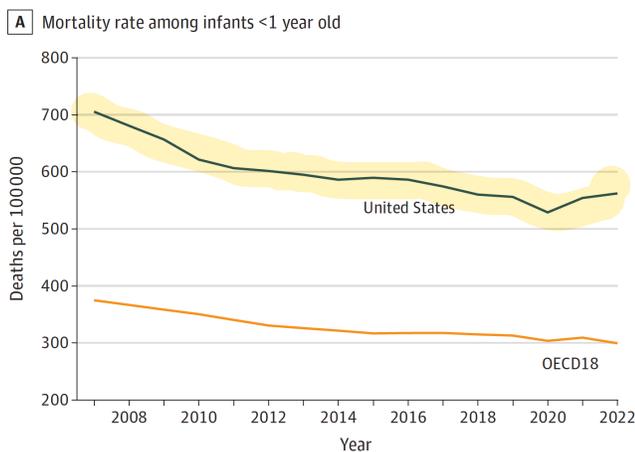
The objective of this study was to determine how US children's health has changed from 2007 to 2023, as compared to 18 other high-income nations from the Organization for Economic Co-operation and Development (OECD18): Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Ireland, Italy, Japan, the Netherlands, New Zealand, Norway, Spain, Sweden, Switzerland, and the United Kingdom. The number of children included in the assessment was (rounded) about 83 million US children and 120 million children from the other countries.

The assessments included annual incidence for mortality and prevalence for chronic physical, developmental, and mental health conditions, functional status, and emotional symptoms.

## KEY POINTS FROM THIS ARTICLE:

- 1) "Child health sets the foundation of the overall health and prosperity of the nation."
- 2) "Healthy children are more likely to become healthy adults who lead meaningful and productive lives."
- 3) "Recent scientific and policy statements have raised concerns that child health in the US may be declining."
  - "The Presidential Commission to Make America Healthy Again issued a May 2025 report that called out the need to better understand the root causes of the declining health of US children."
- 4) **Results:**
  - Infants less than 1 year old were 78% more likely to die in the US than in the OECD18.
  - 1- to 19-year-olds were 80% more likely to die in the US than in the OECD18.

- “The 2 causes of death with the largest net difference between the US and OECD18 were prematurity [increased 122%] and sudden unexpected infant death [increased 139%] for infants 12 months or younger.”
- For 1- to 19-year-old individuals, motor vehicle crash deaths increased 145%.
- “From 2011 to 2023, the prevalence of 3- to 17-year-old individuals with a chronic condition rose from 39.9% to 45.7%” within one dataset.
- “From 2011 to 2023, the prevalence of 3- to 17-year-old individuals with a chronic condition rose from 25.8% to 31.0% within the general population.”
- “Rates of obesity, early onset of menstruation, trouble sleeping, limitations in activity, physical symptoms, depressive symptoms, and loneliness all increased during the study period.”
- “Across the 16-year period, the US experienced 315,795 excess deaths compared with the OECD18, which is equivalent to 54 excess child deaths per day.” **[Key Finding]**



5) “A child in the US in 2023 was 15% to 20% more likely to have a chronic condition compared with a child in 2011.”

6) The 8 conditions with the largest increases were major depression (230%), sleep apnea (222%), eating disorder (220%), anxiety (206%), autism spectrum disorder (162%), obesity (137%), disorders of lipid metabolism (106%), and developmental disorder (105%).

- “The 3 symptom categories with the largest increases were dermatological symptoms [increased 384%], pain [increased 268%], and menstrual disorders [increased 199%].”
- “Depressive symptoms (feeling sad or hopeless) significantly increased from 26.1% of 9th to 12th graders in 2009 to 39.7% in 2023.”

- “Loneliness feelings (feeling alone) among 12- to 18-year-old individuals significantly rose from 20.2% in 2007 to 30.8% in 2021.”
- 7) “From 2007 to 2023, children’s health in the US has steadily declined across mortality; chronic physical, mental, and neurodevelopmental conditions; functional status; and physical and emotional symptom domains.” **[Key Point]**
- “This conclusion is supported by this study’s systematic analysis of 8 datasets that had multiple data collection methods and a comprehensive set of 172 pediatric health indicators.”
  - Nearly half of all children receiving care had a chronic health condition.
  - “Obesity now affects 20% of children, and early puberty is increasingly common among girls, with 1 in 7 beginning menstruation before age 12 years.”
    - “Obesity rates among 2- to 19-year-old individuals increased from 5.2% in 1971-1974 to 19.3% by 2017-2018.”
  - “Temporal trends also showed deterioration in sleep health and increasing limitations in activity, alongside worsening of an extensive range of physical and emotional symptoms.”
- 8) “Childhood mortality rates in the US were comparable with those of OECD nations during the 1960s, but became consistently higher in the early 1970s.”
- 9) “Autism prevalence increased markedly from fewer than 3 per 10,000 children in 1970 to greater than 30 per 10,000 by the 1990s.”
- 10) “The health of US children has worsened across a wide range of health indicator domains over the past 17 years.”
- “The broad scope of this deterioration highlights the need to identify and address the root causes of this fundamental decline in the nation’s health.”

## 11) Key Points From Authors

- From 2007 to 2023 there has been “significant worsening for child mortality; chronic physical, developmental, and mental health conditions; obesity; sleep health; early puberty; limitations in activity; and physical and emotional symptoms.” **[Key Point]**
- “US children’s health has deteriorated across a broad spectrum of indicators, highlighting the need to identify the root causes of this fundamental decline in the nation’s health.”

# Dogma

**A point of view or tenent put forth as authoritative without adequate grounds**



## Max Plank

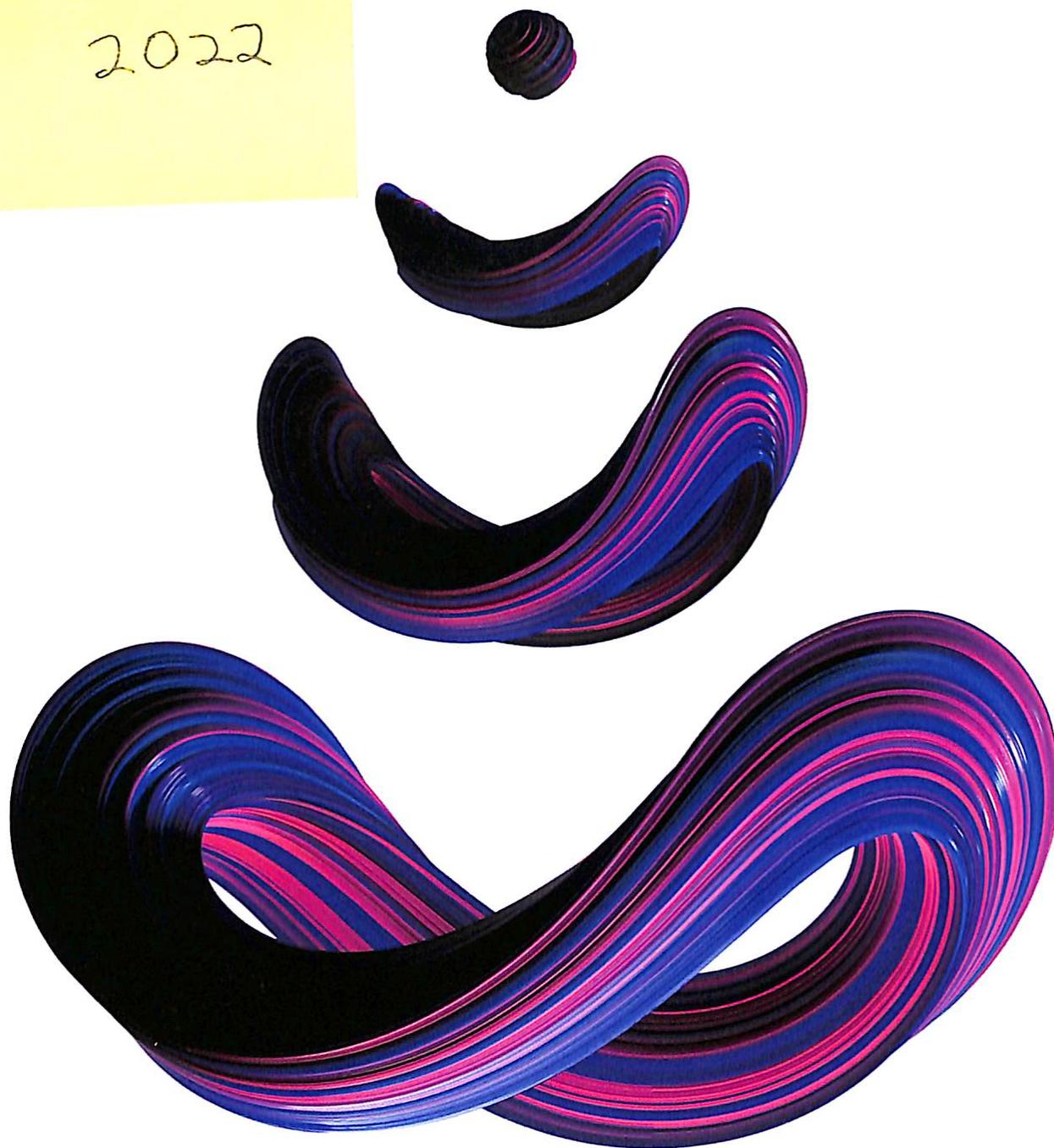
- **Was awarded the 1918 Nobel Prize in physics for his contributions to quantum theory:**

**Energy = Planks Constant X Frequency**

- **He died in 1947**
- **His autobiography was published in 1949**
- **His autobiography popularized this phrase (paraphrased):**

**Science advances one funeral at a time**

2022



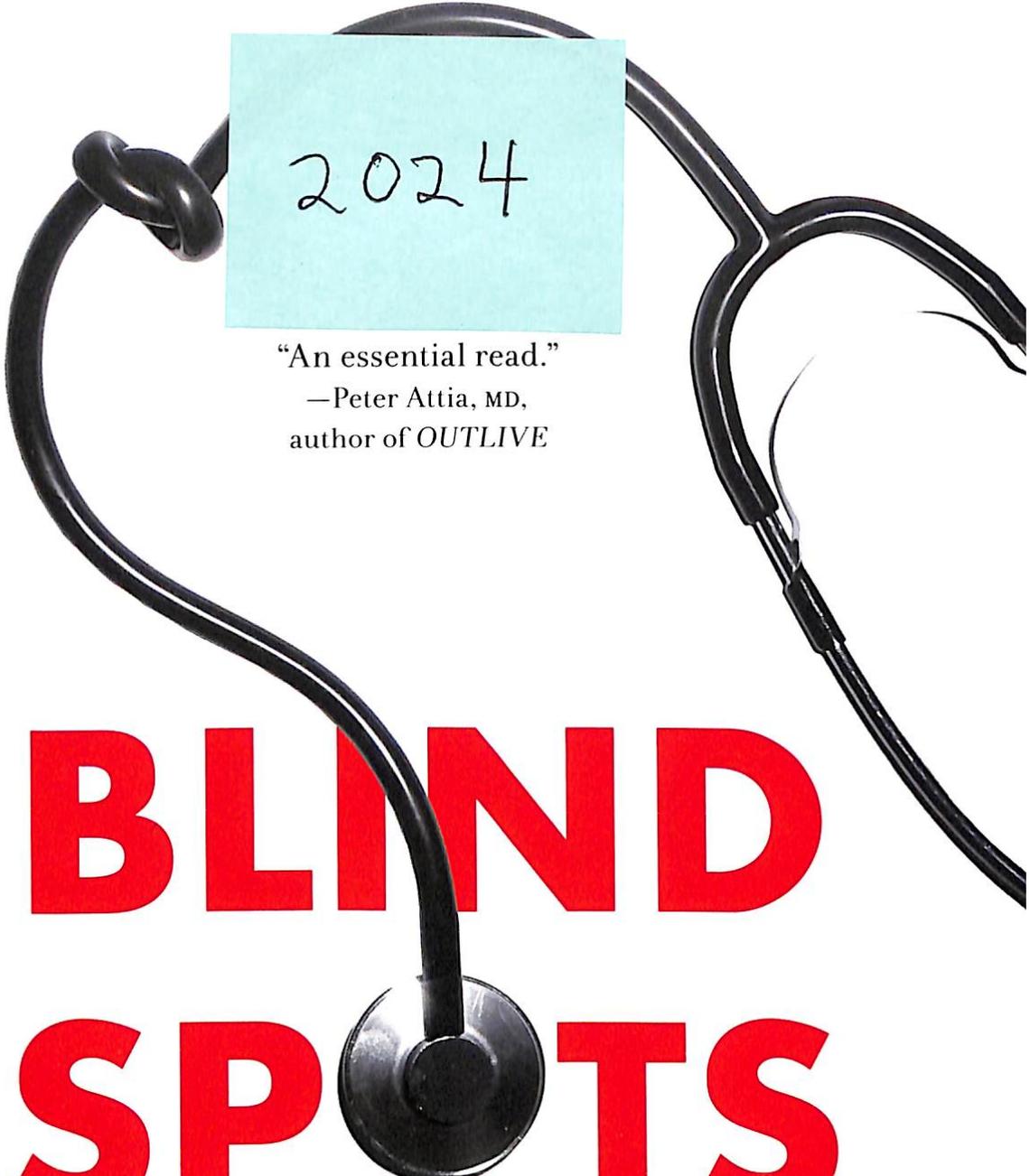
# TRANSFORMER

The Deep Chemistry of Life and Death

**NICK LANE**

# MARTY MAKARY, MD

*New York Times* bestselling author of *The Price We Pay*



2024

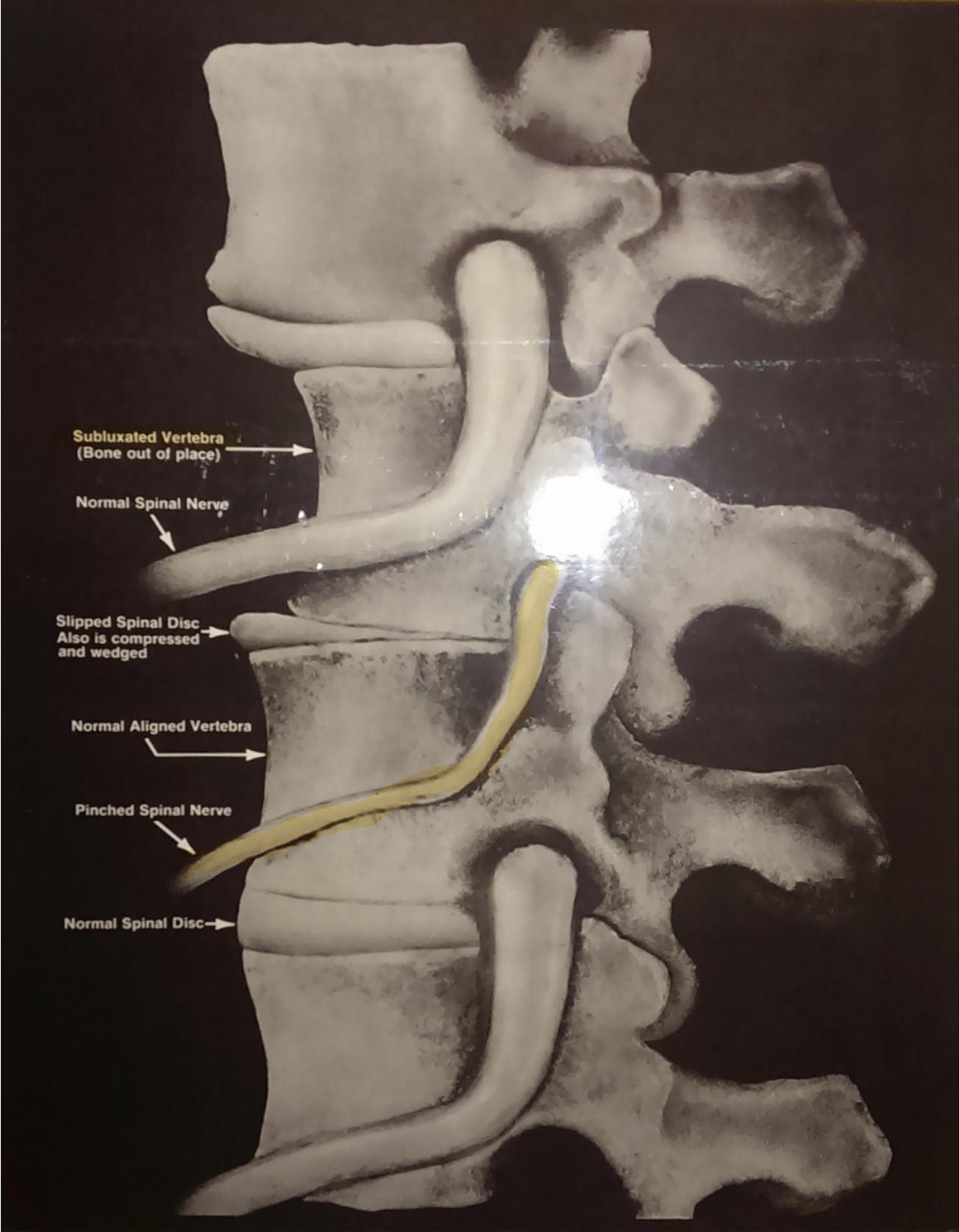
“An essential read.”

—Peter Attia, MD,  
author of *OUTLIVE*

# BLIND SPOTS

When Medicine Gets It Wrong,  
and What It Means for Our Health

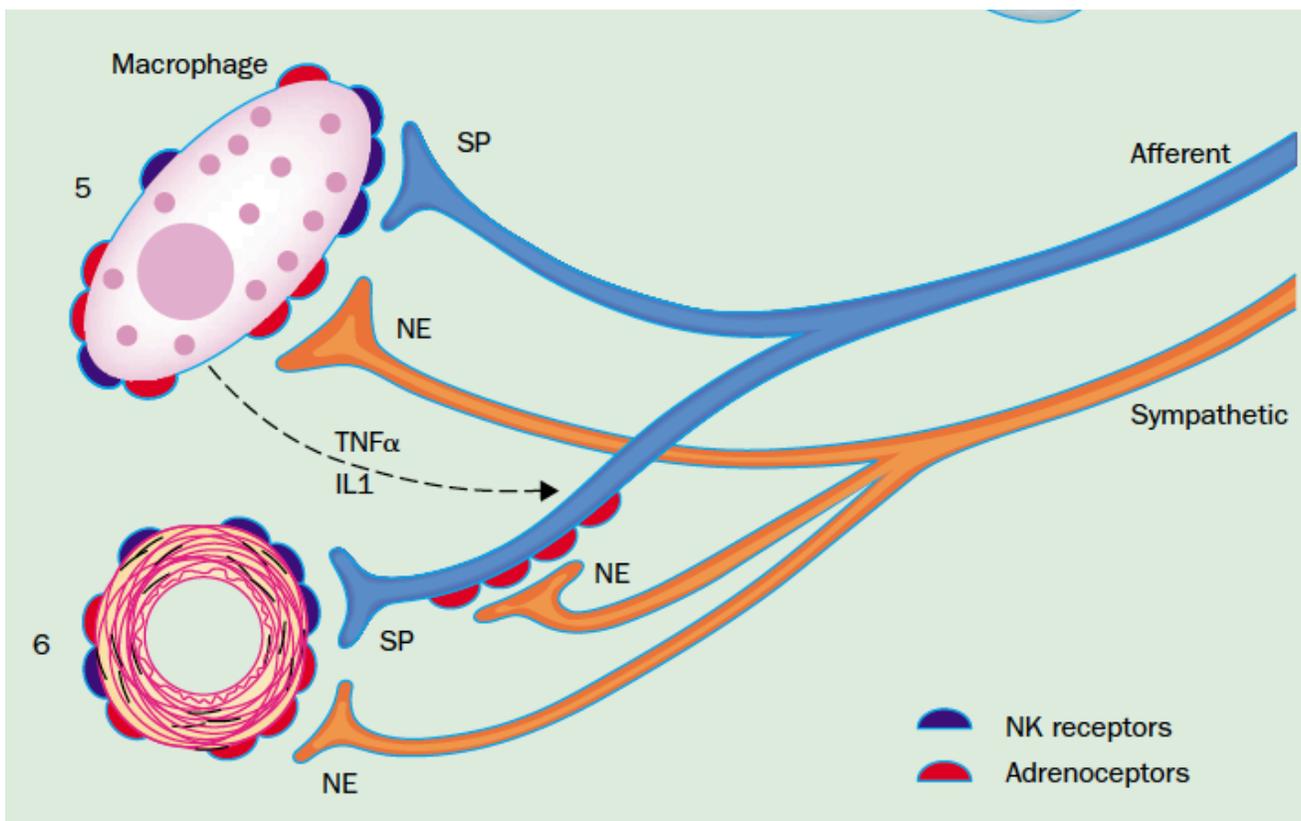
BLOOMSBURY



# Complex Regional Pain Syndrome: Mystery Explained?

**THE LANCET, Neurology**  
**November 2003; Vol. 2; No. 11; p. 691**

Wilfrid Jänig and Ralf Baron:  
Department of Physiology, Christian-Albrechts  
University of Kiel, Germany



# **Dopamine**

## Peter M. Milner, 1919–2018

Peter Marshall Milner, a British-trained electrical engineer who worked on radar and atomic energy during the Second World War, who later trained as a neuroscientist at McGill University and then taught and did research there for many years, died on June 2, 2018, at the age of 98. He was best known as the co-discoverer of electrical self-stimulation of the brain, together with the late James Olds.<sup>1</sup> The discovery, which occurred as the result of a fortuitous accident,<sup>2,3</sup> was one of the first demonstrations of direct control over behaviour by artificial activation of specific parts of the brain that came to be known as “pleasure centres.”<sup>4</sup> The publication of this finding in 1954 created much interest in the investigation of the neural basis of behaviour. The phenomenon was studied in laboratories all over the world, resulting in thousands of publications. Many students were attracted to study the brain–behaviour relationship by the demonstration of self-stimulation, and they became working neuroscientists who have made numerous contributions to all areas of neuroscience. The discovery helped to advance our understanding of how behaviour is controlled by its consequences and provided an important foundation for the study of drug addiction.<sup>5–11</sup>

Milner was born in 1919 in Silkstone Common and grew up in Barnsley, in south Yorkshire, England. He studied science at Barnsley Grammar School and graduated from Leeds University with a degree in electrical engineering in 1941. He was immediately given a position at the Air Defence Research and Development Establishment, where the first radar systems were being developed for defence against airborne attack. Milner was assigned to work on the method of displaying the array of aircraft flying in the vicinity to the operators. In this task he was helped by “a young Cambridge psychology graduate called Brenda Langford,”<sup>12</sup> who was in charge of testing the various versions of the display and controls on the operators. In the fall of 1944, with the war winding down, Milner was asked if he was interested in going to Canada for two years to work on atomic energy. By this time, he and Langford had “become close,” and they decided to marry so that she could accompany him to Canada.

A nuclear reactor was built in Chalk River, Ontario, and Milner worked there for two years. Langford remained in Montreal during this time, teaching a course at the University of Montreal. She also took some courses at McGill, in particular a graduate seminar offered by D.O. Hebb, and became his graduate student. Milner read the material from Langford’s courses, including the manuscript of a book Hebb had written, *The Organization of Behaviour*.<sup>13</sup> Milner was fascinated by the ideas in that book and he decided that studying them would be a more interesting way to spend

his life than designing electrical components. Accordingly, he asked Hebb to supervise him as a graduate student. Hebb agreed, provided Milner took a year of undergraduate psychology courses first. McGill was setting up its research cyclotron at that time and, because of his experience at Chalk River, Milner was able to get a part-time job constructing instruments for them. He completed his qualifying year and became a graduate student. It was during his graduate student years that he and Olds collaborated on the discovery of self-stimulation.

Milner’s doctoral thesis, *Effects of Intracranial Stimulation on Rat Behaviour*,<sup>14</sup> examined the effects of electrical stimulation of the reticular formation of rats on time estimation. After completing the thesis, Milner was given a postdoctoral position that included some teaching. One of his first contributions during this period was a paper, “The cell-assembly: Mark II,”<sup>15</sup> which proposed a modification of the theory of the neural control of behaviour Hebb had presented in his book. Hebb had postulated the “cell assembly,” a connected network of neurons that represented a perception. These assemblies were created by recursive neural activity that recruited new neurons and strengthened the synaptic connections between them. Milner saw a parallel between this process and the atomic chain reactions he had been working with at Chalk River. An unrestrained chain reaction was a positive feedback system that resulted in an atomic explosion. One of the main problems in designing a reactor for peaceful purposes was to restrain the growth of the reaction. Milner saw that Hebb’s proposal would result in similar unrestrained growth of cell-assemblies and proposed an inhibitory process that would limit their growth.

The ideas in Hebb’s book and Milner’s Mark II paper also interested a group of computer scientists at the IBM laboratories in Poughkeepsie, New York, where the first work on computers and what they could do was getting underway. Milner was hired as a consultant, on the basis of his paper and a recommendation from Hebb, in the field that would become known as artificial intelligence.

In 1956, Milner was appointed as an assistant professor in the McGill Psychology Department, with a full load of teaching and research supervision responsibilities. His major undergraduate course was called Physiological Psychology, and he began creating small booklets of notes explaining the topics covered. Milner was a shy man who did not take to lecturing naturally. During his lectures he often addressed the blackboard while writing key words and concepts or drawing simple diagrams to illustrate the results of experiments. In fact, it was often difficult for his students to follow what he was trying to say. Several of

# Elie Metchnikoff, the Man and the Myth

Siamon Gordon

Sir William Dunn School of Pathology, Oxford, UK

## Key Words

Metchnikoff · Macrophage · Myth

## Abstract

The year 2016 marks the centenary of the death of Elie Metchnikoff, the father of innate immunity and discoverer of the significance of phagocytosis in development, homeostasis and disease. Through a series of intravital experiments on invertebrates and vertebrates, he described the role of specialised phagocytic cells, macrophages and microphages, subsequently renamed neutrophils and polymorphonuclear leucocytes, in the host response to injury, inflammation, infection and tissue repair. As a vigorous proponent of cellular immunity, he championed its importance versus humoral immunity in the so-called antibody wars. By 1908, when the Nobel Prize was awarded to Elie Metchnikoff and Paul Ehrlich, this debate was not yet resolved. Even earlier, Metchnikoff had turned his research interests to the process of ageing and the possible link to intestinal auto-intoxication, giving rise to the current interest in the microbiome of the gut and the use of probiotics to promote health and longevity. During the past century, Metchnikoff's reputation has waxed and waned, as lymphocyte heterogeneity, specificity and memory began to dominate the field of adaptive immunity, yet his benign visage continues to provide an iconic presence for specialists in innate immunology, whose studies have made a striking comeback in the past decade. In this review, I shall consider the nature of his studies and the person as well as the legend-

ary description of his Eureka experience in Messina in 1882, a story loved by students and investigators alike, that marked, in his own words, his transformation from zoologist to pathologist.

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## Introduction

My lifelong involvement in macrophage immunobiology began in 1966 at Rockefeller University when I joined the laboratory of Zanvil (Zan) Cohn and James (Jim) Hirsch to undertake a doctoral research project on macrophage cell fusion, a subject to which I returned in Oxford before my official retirement in 2008. Jim and Zan had an avuncular portrait of Metchnikoff (fig. 1) in their office, a portrait familiar to many investigators in the field as a widely used introduction to lectures and seminars. Speakers pay tribute to his discovery of innate immunity and recite the captivating story of his famous starfish experiment in Messina, in which an implanted rose thorn evoked a vigorous macrophage reaction, suggestive to him of host immune defence. However, this acknowledgement rarely proceeds to a full appreciation of his earlier studies of development in invertebrates and of intracellular digestion by motile amoeboid cells, which were to underlay his fierce polemics with the humoralists of the time, in defence of his phagocytic cell theory. Of course, we now know that both camps were right, but the initially over-

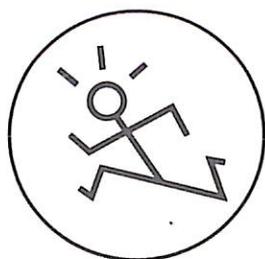
James Olds and Peter Milner are known for their pioneering research in the 1950s that discovered the existence of reward pathways in the brain.

Their experiments, particularly with rats, demonstrated that electrical stimulation of certain brain areas could act as a positive reinforcement, leading the animals to repeatedly stimulate themselves through lever pressing.

This work significantly advanced the understanding of motivation, emotion, and reward in neuroscience.

# SPARK

THE REVOLUTIONARY  
NEW SCIENCE OF EXERCISE  
AND THE BRAIN



2008

Supercharge Your Mental Circuits to  
Beat Stress, Sharpen Your Thinking, Lift Your Mood,  
Boost Your Memory, and Much More

JOHN J. RATEY, MD

COAUTHOR OF *DRIVEN TO DISTRACTION*

with ERIC HAGERMAN

**Book Review**  
**By Dan Murphy, DC**

**Spark**  
**The Revolutionary New Science of Exercise and the Brain**

**Supercharge Your Mental Circuits to Beat Stress, Sharpen Your Thinking,**  
**Lift Your Mood, Boost Your Memory, and Much More**

**John Ratey, MD**  
**2008**  
**Pg. 170**

Psychologist James Olds and graduate student Peter Milner at McGill University in Montreal, were studying behavior by inserting electrodes into the brains of live rats.

In one of the animals, the electrode ended up in the wrong spot. That rat wanted the stimulation so much that it would ignore food placed in one corner in order to receive the shock in another.

Olds and Milner rigged up a lever so the rat could administer its own brain stimulation, and the rat pressed it about once every five seconds.

The brain area that Olds and Milner hit with that electrode was the *nucleus accumbens*, or reward center, and it has been the focus of addiction research ever since.

All the things people become addicted to--

Alcohol

Caffeine

Nicotine

Drugs

Sex

Carbohydrates

Gambling

Playing video games

Shopping

Living on the edge

—boost the dopamine in the *nucleus accumbens*.

Sex increases dopamine levels 50 to 100 percent.

Cocaine sends dopamine sky rocketing 300 to 800 percent beyond normal levels.



# HHS Public Access

Author manuscript

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## Pleasure systems in the brain

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<sup>2</sup>Department of Psychiatry, Warneford Hospital, University of Oxford, Oxford, OX3 7JX, UK

<sup>3</sup>Centre for Functionally Integrative Neuroscience, University of Aarhus, 8000 Aarhus C, Denmark

### Abstract

Pleasure is mediated by well-developed mesocorticolimbic circuitry, and serves adaptive functions. In affective disorders *anhedonia* (lack of pleasure) or *dysphoria* (negative affect) can result from breakdowns of that hedonic system. Human neuroimaging studies indicate that surprisingly similar circuitry is activated by quite diverse pleasures, suggesting a common neural currency shared by all. Wanting for rewards is generated by a large and distributed brain system. Liking, or pleasure itself, is generated by a smaller set of hedonic hotspots within limbic circuitry. Those hotspots also can be embedded in broader anatomical patterns of valence organization, such as in a keyboard pattern of nucleus accumbens generators for desire versus dread. In contrast, some of the best known textbook candidates for pleasure generators, including classic pleasure electrodes and the mesolimbic dopamine system, may not generate pleasure after all. These emerging insights into brain pleasure mechanisms may eventually facilitate better treatments for affective disorders.

### Introduction

The English word hedonic comes originally from the ancient Greek for pleasure (ἡ δονή; in Latin script: *hédoné*), in turn derived from the word for “sweet” (ἡ δύς, or *h dús*). Today hedonic refers to sensory pleasures as well as many higher types of pleasure (e.g., cognitive, social, aesthetic, and moral).

A goal of affective neuroscience is to understand how brain mechanisms generate pleasures, and also displeasures, and eventually find more effective treatments for affective disorders (Anderson and Adolphs, 2014; Damasio and Carvalho, 2013; Haber and Knutson, 2010; Heller et al., 2013; Kringelbach and Berridge, 2010; Panksepp, 2011). Capacity for normal pleasure is essential to healthy psychological function or well-being. Conversely, affective disorders can induce either the pathological absence of pleasure reactions (as in clinical

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Winner of the Pulitzer Prize

# MICHAEL MOSS

SALT

2013

SUGAR

FAT

How  
the Food  
Giants  
Hooked  
Us

“EXPLORES HOW INDUSTRY HAS MANIPULATED  
OUR MOST DEEP-SEATED SURVIVAL INSTINCTS.”

—DAVID PERLMUTTER, MD, AUTHOR OF THE  
*NEW YORK TIMES* BEST SELLERS *GRAIN BRAIN* AND *BRAIN MAKER*

THE  
HACKING  
*of the*  
AMERICAN  
MIND

2017

**The Science Behind the Corporate  
Takeover of Our Bodies and Brains**

**ROBERT H. LUSTIG, MD, MSL**  
AUTHOR OF THE *NEW YORK TIMES* BEST SELLER *FAT CHANGE*



# Don't Be a Pleasure Junkie!

## Find the Secret to True Happiness

Robert H. Lustig, MD, MSL  
University of California,  
San Francisco

**Y**our new iPhone makes you happy. Reconnecting on social media with everyone you've ever met makes you happy. Binge-watching the latest Netflix series makes you happy. Guess what? You're not happy—you're addicted to pleasure. You've been hacked, and we're not talking e-mail or bank accounts. Your mind has been hacked by a science engineered to stimulate your pleasure cravings. Like any addict, the cycle of chasing pleasurable moments is a no-win game that leaves people perennially unsatisfied, continually chasing the next fix, unhappier than before. Break yourself free!

### PLEASURE IS NOT THE SAME AS HAPPINESS

Pleasure is the fleeting feeling of enjoyment or gratification we get when the reward center, deep in the brain, is activated. We derive pleasure from eating a good meal, watching our sports team win or receiving a lot of "likes" on Facebook. Happiness, on the other hand, is a rich feeling of peace, calm and contentment that comes from things such as a long conversation with your son or daughter. How to spot the difference between pleasure and happiness...

**Pleasure and rewards are short-lived.** The day after the Netflix series is over, you're searching for the next one. Happiness and contentment last longer. After that good conversation, your relationship with your child is deeper.

**Pleasure is visceral and exciting**—it causes your blood pressure and heart rate to go up. Happiness is ethereal and calming—your blood pressure and heart rate go down.

**Pleasure occurs when you get something**, such as winning money at a casino or buying a new car. Happiness results from giving our time or money to others or a charity.

**Pleasure often is experienced alone**, while happiness is likely experienced connected to others.

**Pleasure often is achieved with substances**—caffeine, cigarettes, alcohol, drugs, sugar—but happiness is achieved with deeds or successes, such as watching a child graduate from college.

### HOW DOPAMINE CAN HURT

The brain's reward centers evolved to help us survive, reproduce and stay fit. But recent research in *The Journal of Neuroscience* has linked the release of natural feel-good hormones in response to pleasure and happiness to the same pathways that cause addiction to drugs. These days, thanks to an ever-increasing number of temptations both online and off-line, we have a near constant stream of opportunities for reward, which "hacks" our brain's physiology.

*Here's how:* A neurotransmitter is a chemical in the brain that, when released, causes other nerve cells to fire. Dopamine is an excitatory neurotransmitter that's released when we feel >>

*Bottom Line Personal* interviewed Robert H. Lustig, MD, MSL, professor emeritus of pediatric endocrinology and member of the Institute for Health Policy Studies at University of California, San Francisco, and chief science officer of Eat REAL, dedicated to reversing childhood obesity and type 2 diabetes. He is author of *The Hacking of the American Mind: The Science Behind the Corporate Takeover of Our Bodies and Brains*. [RobertLustig.com](http://RobertLustig.com)



>> rewarded by something. That's not necessarily bad. But too much of anything can be dangerous. Jumping from one clickbait online headline to another, for example, is too much stimulation, which can kill neurons. Next time, it takes a bigger hit to get the same rush. Just as with opioids and alcohol, the end point is addiction.

Another impact of excessive dopamine release: Not enough production of the calming hormone serotonin. Too little leads to depression. So the more pleasure you seek, the unhappier you become.

Stress is a third ingredient at play here. To protect us from stressors such as injury or an important presentation, we produce the fight-or-flight hormone *cortisol*. In small doses over the short term, cortisol is helpful. When stress is chronic, however, and cortisol remains elevated for long periods, it causes dopamine to fire even more, increasing the cycle of reward-seeking behaviors. Cortisol down-regulates production of serotonin adding to our unhappiness. Cortisol is, in effect, the anti-contentment hormone.

*Net result:* The cycle of hormone

release and suppression caused by our nonstop personal pleasure-seeking is harming our emotions. Fortunately, pleasure addiction can be overcome—if you are willing to fight back. Here's how...

### THE 4Cs OF TRUE HAPPINESS

Though not rocket science, there's a scientifically proven formula that can ramp up your serotonin, tamp down dopamine and cortisol, and improve your mood and your health in the process. But know that this road map to reclaiming your happiness takes some effort and sacrifice because it requires breaking away from your current social patterns. These are four things we all used to do and need to return to doing again...

■ **Connect:** While it may seem extreme to you, log off Facebook, Twitter and Instagram. Instead, make time every day to interact with friends and loved ones face to face, eye to eye, in real life.

*Why:* Being physically face to face increases empathy and produces serotonin. Research published in *Child Development* shows that as you interact, you adopt or mirror that person's emotions,

stimulating serotonin release. You can't achieve that connection with emojis.

■ **Contribute:** Give your time, your money and/or yourself by volunteering, donating and performing tasks that contribute to the greater good. Even simple acts of kindness provide benefits.

*Why:* Multiple studies show that contributing to others or society at large improves your feeling of self-worth, drives contentment and boosts health by reducing your blood pressure, heart rate and stress levels. Doing good results in a better you, both physically and mentally. *Bonus:* You're likely interacting face to face with others when you volunteer.

■ **Cope:** This is all about self-care. You know the drill—get enough sleep, stop trying to multitask, eat well, focus on one thing at a time and exercise regularly.

*Why:* Taking care of Number One is key to managing stress. Sleep deprivation and trying to multitask drive cortisol and dopamine up and serotonin down. In fact, research shows that attempting media multitasking (watching TV, surfing the web, texting and reading all at the same time) literally shrinks the brain in the area associated with executive function—the set of skills that helps you get things done. Exercise, on the other hand, boosts serotonin production. Combined with mindfulness practices (yoga, walks in nature), it may be as effective at reducing depression as taking medication, according to researchers at Rutgers University.

■ **Cook:** Stop eating out and relying on processed foods. Use fresh ingredients to prepare food at home instead.

*Why:* It's no secret that eating fast food and processed foods, as well as supersized restaurant meals, is a major culprit in the obesity crisis. But your food choices can make you happy or miserable, too. *How?* Processed food is low in tryptophan, an amino acid that is a precursor to serotonin. It's also low in omega-3 fatty acids, and omega-3 deficiency has been shown to inhibit serotonin action. Meanwhile, processed food is high in sugar, which depletes serotonin, ramps up dopamine and increases the risk for a smorgasbord of metabolic diseases such as diabetes, hypertension and cancer. Countless studies show that these foods are addictive and unhealthy. **BLP**

## June checklist

✔ **Get ahead of headaches:** June is Migraine and Headache Awareness Month. Find out how to prevent and treat them at [Headaches.org](http://Headaches.org) (search "Headache Chart"). To track migraine severity, triggers, etc., download the free *Migraine Monitor* from the App Store or Google Play.

✔ **Don't fall for sunscreen myths:** Products with high SPFs do not protect much longer or better. *Example:* An SPF 30 sunscreen blocks about 97% of harmful rays...an SPF 50 blocks 98%. All sunscreens should be reapplied after two hours or after a swim—even water-resistant ones. *Also not true:* That you can't get sunburned while in water.

✔ **Beware of poison ivy:** Remember the slogans "Leaves

of three, let it be" and "Raggy rope, don't be a dope" (poison ivy climbing up tree trunks has thick, frayed vines). If you may be working around poison ivy, apply Ivy X Pre-Contact Skin Solution or another over-the-counter barrier cream in advance. *Also:* Wear work gloves to protect hands. After any exposure, wash hands, clothing and tools.

✔ **Check tires during Tire Safety Month:** Treads should be higher than tread indicators (the raised sections that run between treads). If not, replace the tire. *Also:* Check tire inflation when tires are "cold"—at least three hours after driving.

✔ **Celebrate Father's Day:** Sunday, June 16. Watch his favorite movie with him. Play some of his favorite games. Re-create memories with "golden oldies" music (free at [TheNostalgiaMachine.com](http://TheNostalgiaMachine.com)) or "retro" candy and other packaged snacks ([CandyCrate.com/retrocandy.html](http://CandyCrate.com/retrocandy.html) and [OldTimeCandy.com](http://OldTimeCandy.com)).

## NBA Commissioner Adam Silver Speaks to the Media During 2018 All-Star Weekend

By Nicole Yang, March 1, 2019

For NBA commissioner Adam Silver, supporting players and their mental health is an ongoing initiative.

"When I meet with them, what surprises me is that they're truly unhappy."

"A lot of these young men are generally unhappy."

In his observations and meetings with players, Silver said he has discovered there are pervasive feelings of loneliness and melancholy across the league.

He said he no longer sees the high level of camaraderie or team-building that once existed in previous years.

"If you're around a team in this day and age, there are always headphones on," Silver said. "[The players] are isolated, and they have their heads down."

Silver called Jordan's Bulls "a band of brothers" who were able to strengthen their relationships via the constant travel that comes with being a professional athlete.

As 12-time NBA All-Star Isiah Thomas told him, "Championships are won on the bus."

But things are different now. Referencing a conversation he had with a superstar ahead of the second game of a back-to-back earlier this season,

Silver said the player's unhappiness and isolation were "to the point where it's almost pathology."

A player said, "From the time I get on the plane to when I show up in the arena for the game, I won't see a single person." "There was a deep sadness around him."

Although the emergence of social media has helped the league become more fan-friendly, gain exposure, and promote players, Silver is well aware of its downside.

Last season, a pair of NBA stars opened up about their personal experiences with depression and anxiety.

The NBPA launched a new mental health and wellness program in May to support players with "a wide range of mental health challenges and issues."

Several teams have also hired mental health professionals as part of their staff.

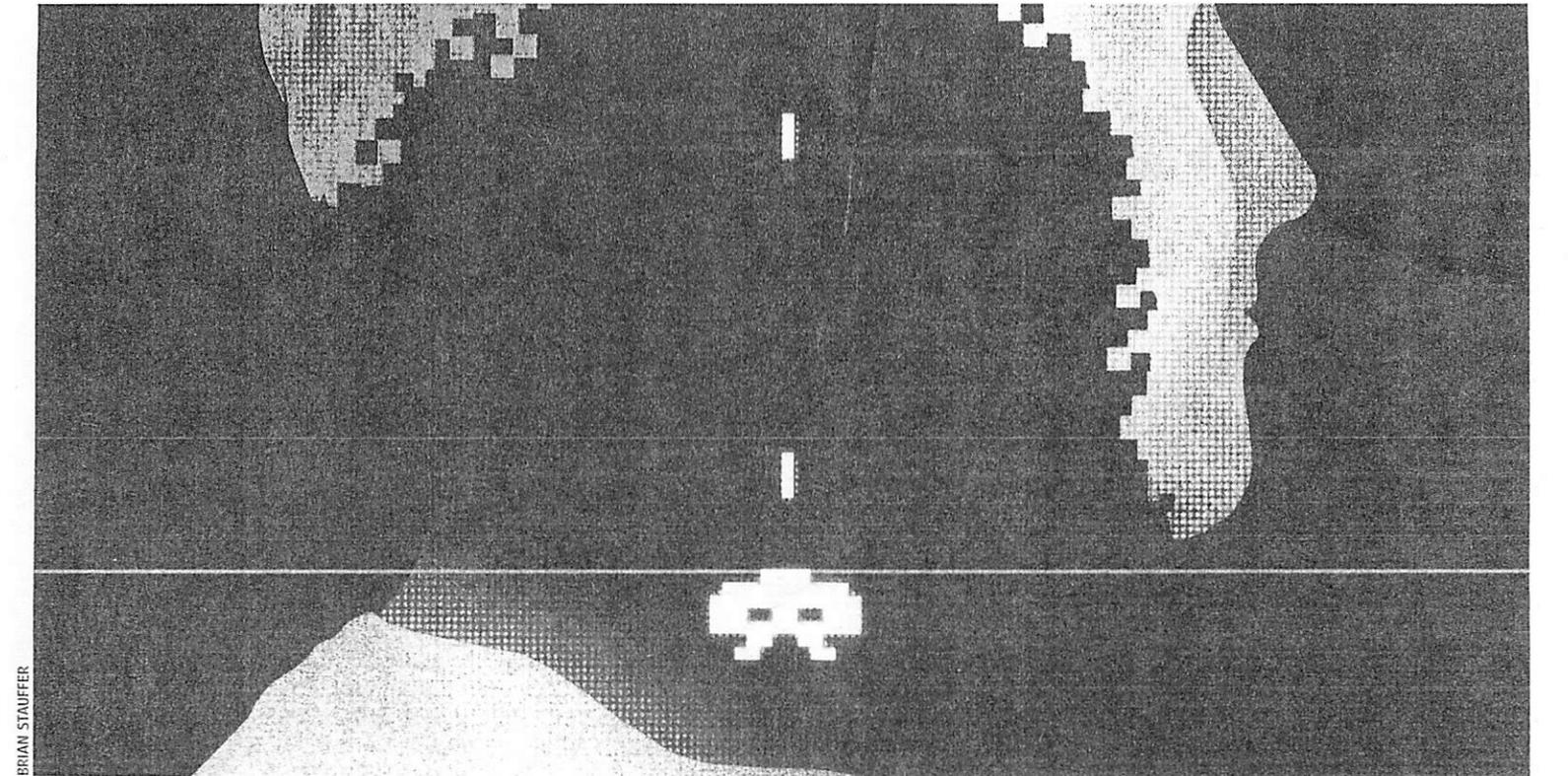
The problems the league is addressing are part of a "larger societal issue."

"I don't think it's unique to these players," he said. "I don't think it's something that's just going around superstar athletes. I think it's a generational issue."

**LeBron James Barbie**

**2025**





BRIAN STAUFFER

# Digital Addictions Are Drowning Us in Dopamine

Rising rates of depression and anxiety in wealthy countries like the U.S. may be a result of our brains getting hooked on the neurotransmitter associated with pleasure.

WSJ

8/15/21

BY ANNA LEMBEKE

A patient of mine, a bright and thoughtful young man in his early 20s, came to see me for debilitating anxiety and depression. He had dropped out of college and was living with his parents. He was vaguely contemplating suicide. He was also playing videogames most of every day and late into every night.

Twenty years ago the first thing I would have done for a patient like this was prescribe an antidepressant. Today I recommended something altogether different: a dopamine fast. I suggested that he abstain from all screens, including videogames, for one month.

Over the course of my career as a psychiatrist, I have seen more and more patients who suffer from depression and anxiety, including otherwise healthy young people with loving families, elite education and relative wealth. Their problem isn't

trauma, social dislocation or poverty. It's too much dopamine, a chemical produced in the brain that functions as a neurotransmitter, associated with feelings of pleasure and reward.

When we do something we enjoy—like playing videogames, for my patient—the brain releases a little bit of dopamine and we feel good. But one of the most important discoveries in the field of neuroscience in the past 75 years is that pleasure and pain are processed in the same parts of the brain and that the brain tries hard to keep them in balance. Whenever it tips in one direction it will try hard to restore the balance, which neuroscientists call homeostasis, by tipping in the other.

As soon as dopamine is released, the brain adapts to it by reducing or “downregulating” the number of dopamine receptors that are stimulated. This causes the brain to level out by tipping to the side of pain, which is why pleasure is usually followed by a feeling of hangover or comedown. If we can wait long

enough, that feeling passes and neutrality is restored. But there's a natural tendency to counteract it by going back to the source of pleasure for another dose.

If we keep up this pattern for hours every day, over weeks or months, the brain's set-point for pleasure changes. Now we need to keep playing games, not to feel pleasure but just to feel normal. As soon as we stop, we experience the universal symptoms of withdrawal from any addictive substance: anxiety, irritability, insomnia, dysphoria and mental preoccupation with using, otherwise known as craving.

Our brains evolved this fine-tuned balance over millions of years in which pleasures were scarce and dangers ever-present. The problem today is that we no longer live in

that world. Instead, we now live in a world of overwhelming abundance. The quantity, variety and potency of highly reinforcing drugs and behaviors has never been greater. In addition to addictive substances like sugar and opioids,

there is also a whole new class of electronic addictions that didn't exist until about 20 years ago: texting, tweeting, surfing the web, online shopping and gambling. These digital products are engineered to be addictive, using flashing lights, celebratory sounds and “likes” to promise

The smartphone is the equivalent of the hypodermic needle for a wired generation.

ever-greater rewards just a click away,

Yet despite increased access to all of these feel-good drugs, we're more miserable than ever before.

Rates of depression, anxiety, physical pain and suicide are increasing

all over the world, especially in rich nations. According to the World Happiness Report, which ranks 156 countries by how happy their citizens perceive themselves to be, Americans reported being less happy in 2018 than they were in 2008. Other wealthy countries saw similar decreases in self-reported happiness scores, including Belgium, Canada, Denmark, France, Japan, New Zealand and Italy. The Global Burden of Disease study found that the number of new cases of depression world-wide increased 50% between 1990 and 2017, with the highest increases in regions with the highest income, especially North America.

It's hard to see cause and effect when we're chasing dopamine. It's only after we've taken a break from our drug of choice that we're able to see the true impact of our consumption on our lives. That's why I asked my patient to give up videogames for a month, enough time to allow his brain to reset its dopamine balance. It wasn't easy, but he was motivated by the counterintuitive idea that abstaining from the thing that made him feel good in the short-term might actually make him feel better in the long-term.

To his surprise, he did feel better than he had in years, with less anxiety and less depression. He was even able to return to playing videogames without negative effects, by strictly limiting his playing time to no more than two days a week, for two hours a day. That way he left enough time in between sessions for the brain's dopamine balance to be restored.

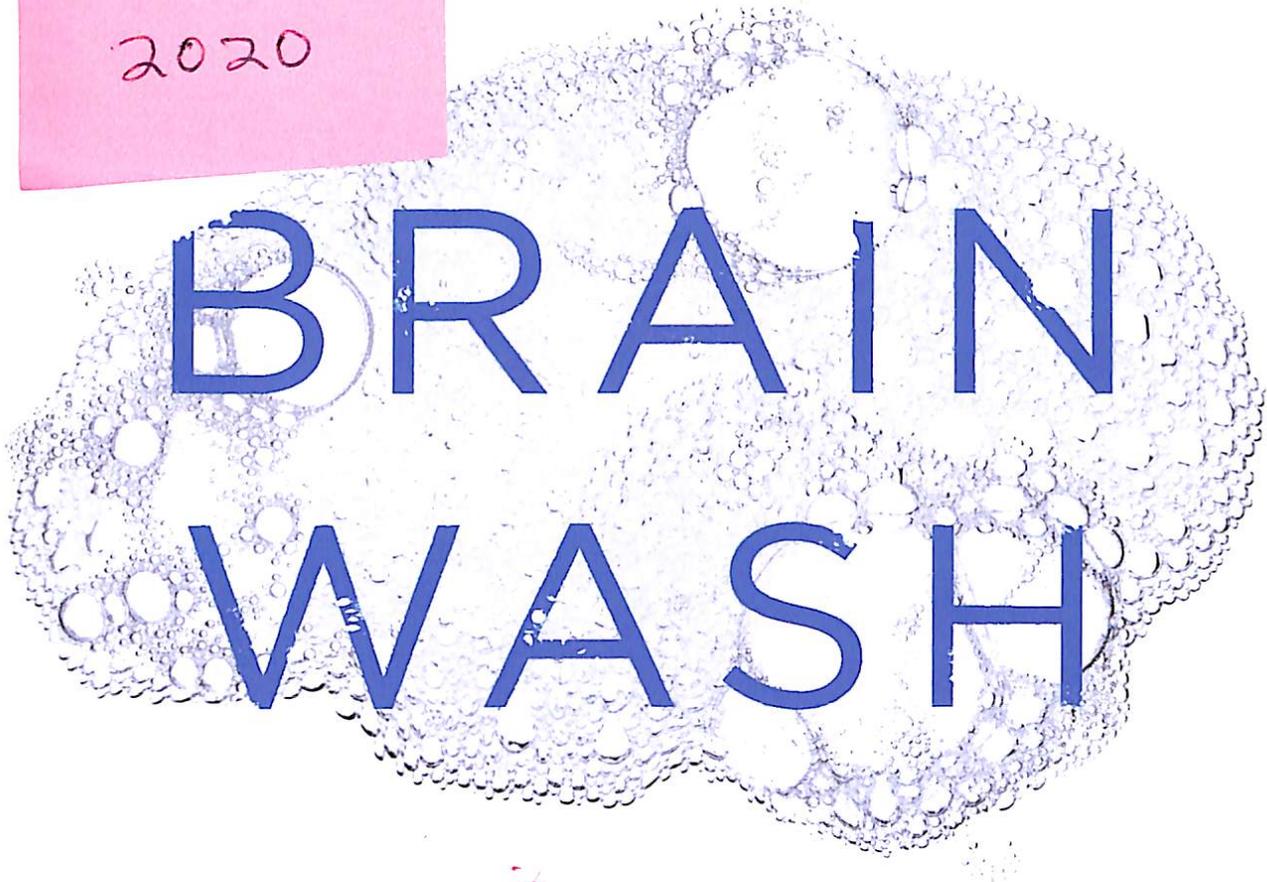
He avoided videogames that were too potent, the ones that he couldn't stop playing once he started. He designated one laptop for gaming and a different one for school, to keep gaming and classwork physically separated. Finally, he committed to playing only with friends, never with strangers, so that gaming strengthened his social connections. Human connection itself is a potent and adaptive source of dopamine.

Not everyone plays videogames, but just about all of us have a digital drug of choice, and it probably involves using a smartphone—the equivalent of the hypodermic needle for a wired generation. Reducing phone use is notoriously difficult, because at first it causes the brain's pleasure-pain balance to tilt to the side of pain, making us feel restless and cranky. But if we can keep it up long enough, the benefits of a healthier dopamine balance are worth it. Our minds are less preoccupied with craving, we are more able to be present in the moment, and life's little unexpected joys are rewarding again.

"An invaluable guide filled with solutions for restoring our focus, energizing our bodies, and refreshing our minds."—GRETCHEN RUBIN, author of *THE FOUR TENDENCIES*

*Detox Your Mind*  
*for Clearer Thinking, Deeper Relationships,*  
*and Lasting Happiness*

2020



DAVID PERLMUTTER, MD

AUTHOR OF THE #1 *NEW YORK TIMES*  
BESTSELLER **GRAIN BRAIN**

AUSTIN PERLMUTTER, MD

WITH KRISTIN LOBERG

"A riveting read. Once you understand the power and peril of dopamine, you'll better understand the human condition itself."

—DANIEL H. PINK, AUTHOR OF *DRIVE* AND *WHEN*



# THE MOLECULE OF MORE

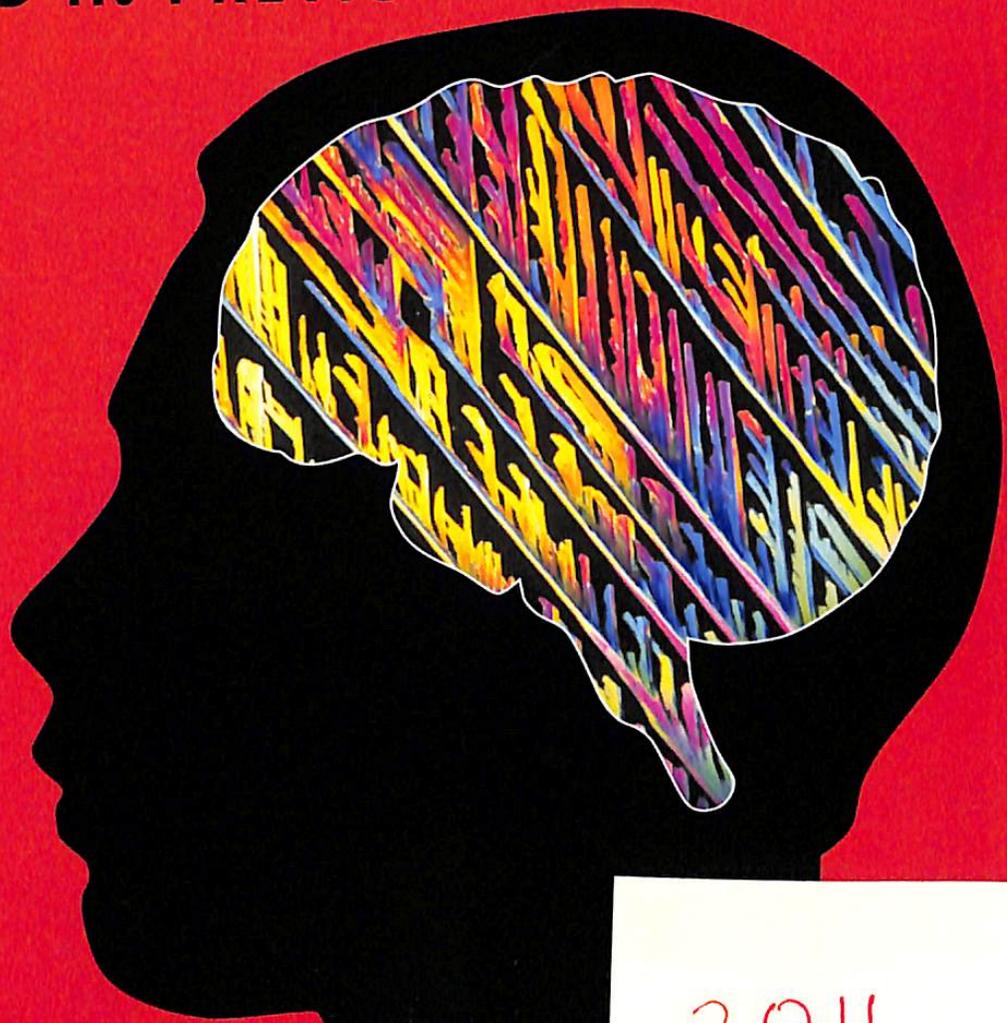
How a Single Chemical in Your Brain Drives  
Love, Sex, and Creativity—and Will Determine  
the Fate of the Human Race

2017

DANIEL Z. LIEBERMAN, MD  
AND MICHAEL E. LONG

**THE**  
**Dopaminergic Mind**  
**in Human Evolution**  
**and History**

**FRED H. PREVIC**



2011

**CAMBRIDGE**

## **The Dopaminergic Mind in Human Evolution and History**

Fred Previc  
2011

Dopamine motivational drive includes "procurement of sexual rewards, sweet-tasting items, recreational drugs, and rewards with acquired value such as money and knowledge."

Powerful dopaminergic behavioral drives "may over time become very addictive or self-destructive."

"It will not be easy to reduce the dopaminergic content of the human brain."

"Dopamine is the most highly involved brain chemical involved in addictive behavior."

Excessive dopamine activity is "implicated in an even large number of prominent neuropsychological disorders." "Most of the hyperdopaminergic disorders have risen in prevalence during the past few decades and now arguably constitute collectively the greatest threat to mental health in the industrialized world."

Perhaps the most troubling aspect about the hyperdopaminergic disorders is that they are definitely rising, "which cannot be reconciled with the notion that they are mostly genetically determined." "The increasing prevalence of these disorders in modern industrialized nations may be more properly ascribed to demographic changes, deleterious environmental exposures, and/or psychological pressures in modern society that have pushed dopamine levels dangerously high."

"Serotonin inputs normally inhibit dopamine in a variety of brain areas."

"The inhibitory action of serotonergic systems over dopaminergic ones is extremely well-documented and is arguably the most significant neurochemical interaction in the entire brain from the standpoint of clinical neuropsychology."

"The serotonergic inhibition of dopamine release is arguably the clinically most important neurochemical interaction in the brain."

"In concert with the notion of hyperdopaminergic disorders, there is also a 'serotonergic dysfunction disorder' stemming from reduced serotonergic function."

Individuals with chronically low serotonin have underlying trait anxiety.

Transient depletion of serotonin due to sleep deprivation and other psychological stressors are more prone to develop hyperdopaminergic psychopathologies such as schizophrenia.

Dopamine in the brain

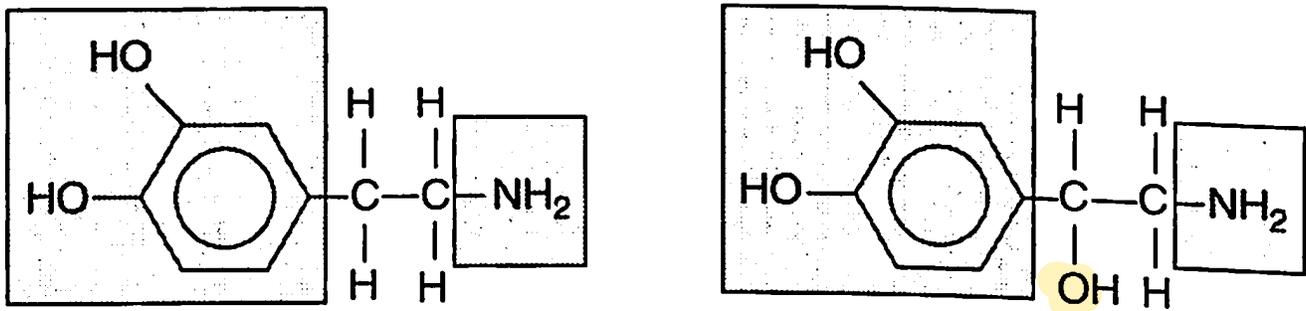


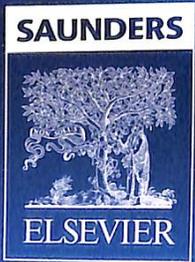
Figure 2.1 The chemical structure of dopamine (left) and norepinephrine (right).

**Linda S. Costanzo**

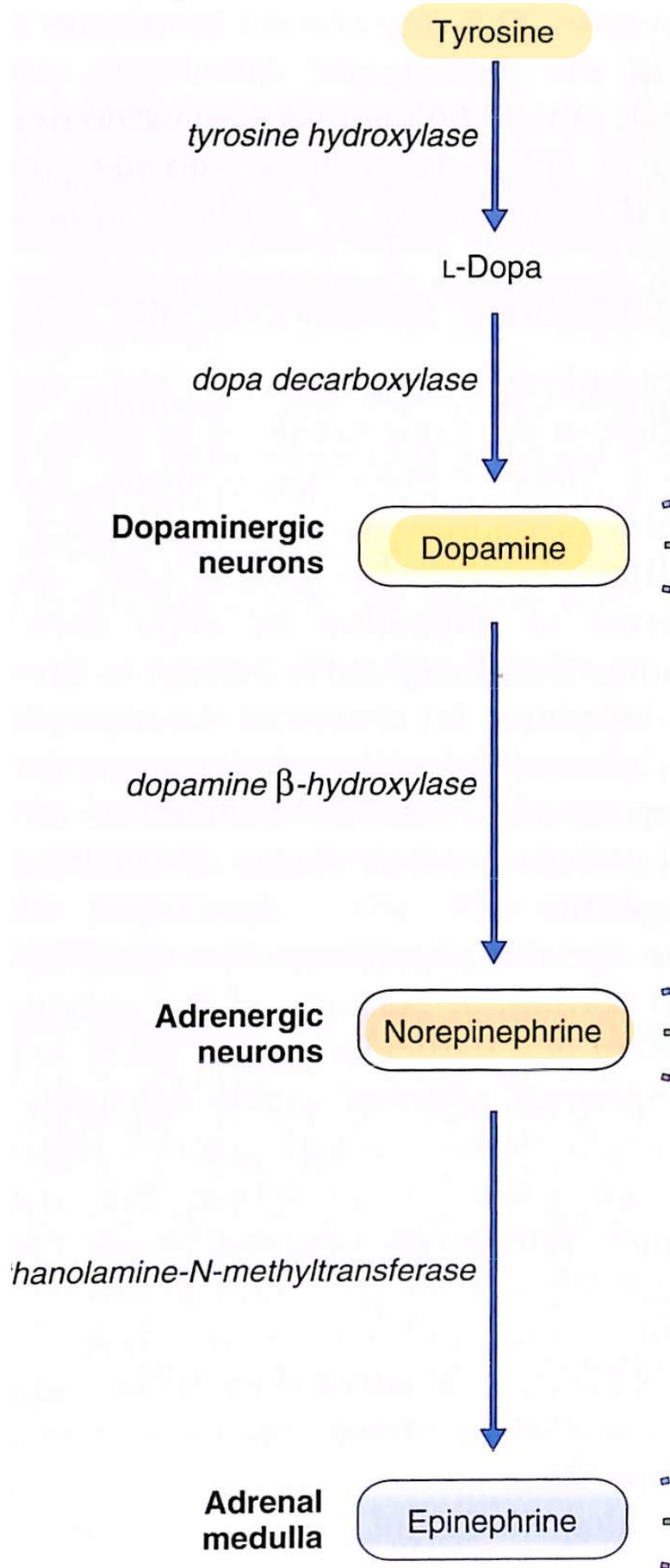


# PHYSIOLOGY

**T H I R D   E D I T I O N**



## Synthesis



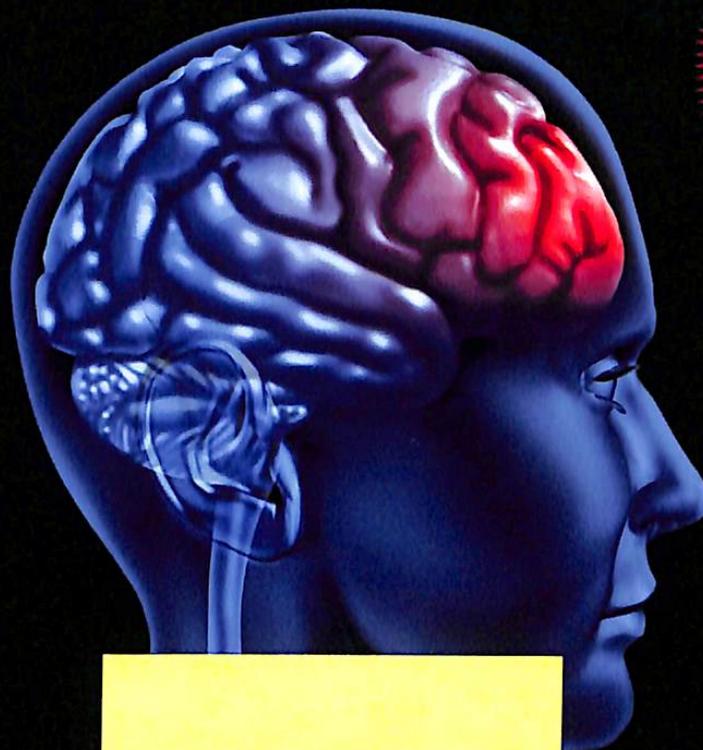
Over his impressive career, Dr. Walsh has worked with 30,000 patients with conditions ranging from autism to schizophrenia to Alzheimer's. His book is an essential tool for anyone who would prefer to heal the brain with nutrients rather than drugs.

—Teri Arranga, editor-in-chief, *Autism Science Digest*

# NUTRIENT POWER

## HEAL YOUR BIOCHEMISTRY AND HEAL YOUR BRAIN

REVISED  
AND  
UPDATED



2014

WILLIAM J. WALSH, PhD

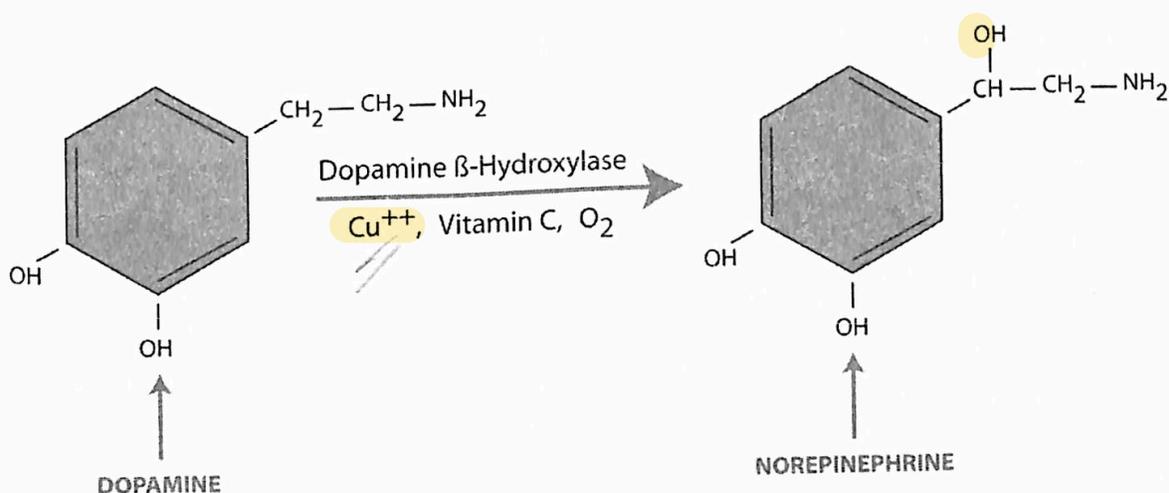
**Nutrient Power**  
**Heal Your Biochemistry and Heal Your Brain**  
**2014**  
**William Walsh, PhD**

"Copper overload is present in most cases of hyperactivity, learning disability, postpartum depression, autism, and paranoid schizophrenia."

also "bipolar disorder, ADHD, and violent behavior."

"Copper is a cofactor in the synthesis of norepinephrine, a neurotransmitter associated with several mental illnesses."

**Figure 3-1. Synthesis of Norepinephrine**



"Copper overloads tend to lower dopamine levels and increase norepinephrine in the brain."

"Copper overload results in more-extreme norepinephrine elevations. The usual results is greatly heightened anxiety, paranoia, and increased hallucinations."

"Copper and iron are major sources of free radicals in the human brain and elevated copper levels have been found in Alzheimer's."

"Copper has special significance in mental health due to its role in metabolism of dopamine and synthesis to norepinephrine."

## Nutrient Power

### Heal Your Biochemistry and heal Your Brain

William Walsh, PhD  
2014

#### **Copper** (very brief)

Holding Hands

Kissing

Sex

Ice Cream

Chocolate

*The Best of Things*

Standing Up

Life Saving

Flight/Flight

*Acute Release*

**Dopamine**

Copper



Copper/Zinc

**Norepinephrine**

*Chronic Release*

Chiropractic  
Adjustment

Mechanoreceptors

Shrinks Brain

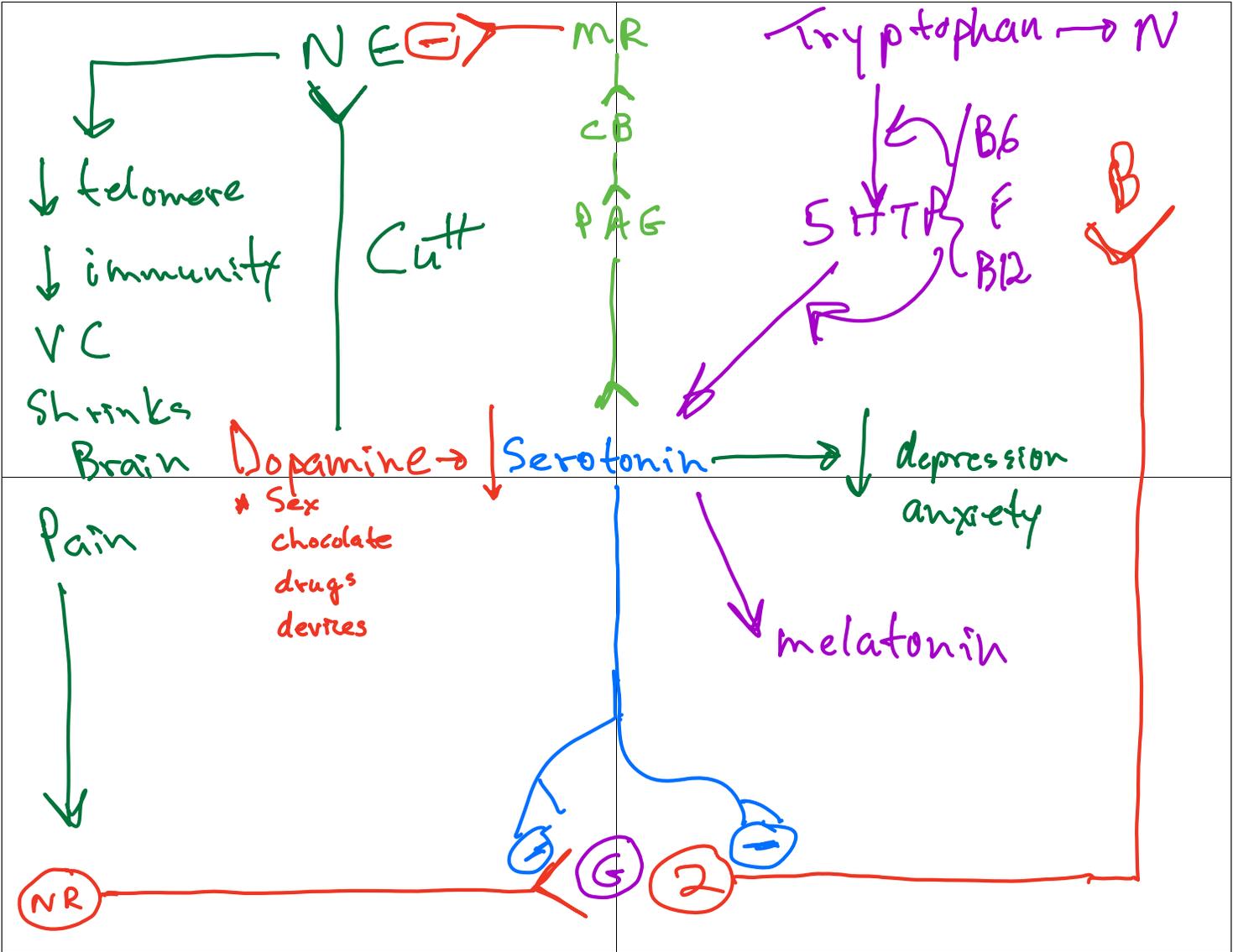
Elevates Blood Pressure

Damages Arteries

Suppresses Immune System

Increases Pain

Shortens Telomeres



“A treatise on deliciousness—the pure, sensorial appreciation of good food; in writing it, Schatzker brilliantly charts a road map not just for healthy eating, but for joyous eating, too.”

—DAN BARBER, chef and co-owner of Blue Hill and bestselling author of *The Third Plate*

# THE END OF CRAVING

Recovering the Lost  
Wisdom of Eating Well



2021

Mark Schatzker

AUTHOR OF *THE DORITO EFFECT*



"No one has done more to reveal the intentional and underhanded ways in which food companies manipulate our desires and eating habits than Michael Moss." —MARK BITTMAN

# HOOKED

FOOD, FREE WILL, AND HOW THE  
FOOD GIANTS EXPLOIT OUR ADDICTIONS

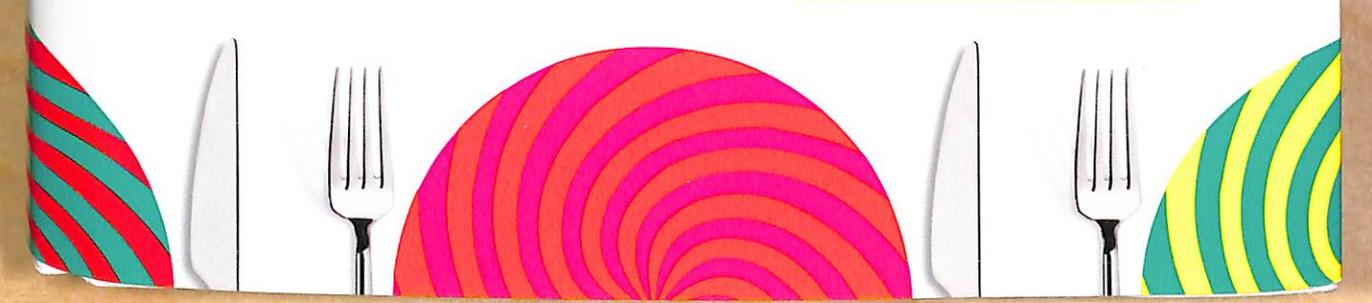


2021

WINNER OF THE PULITZER PRIZE

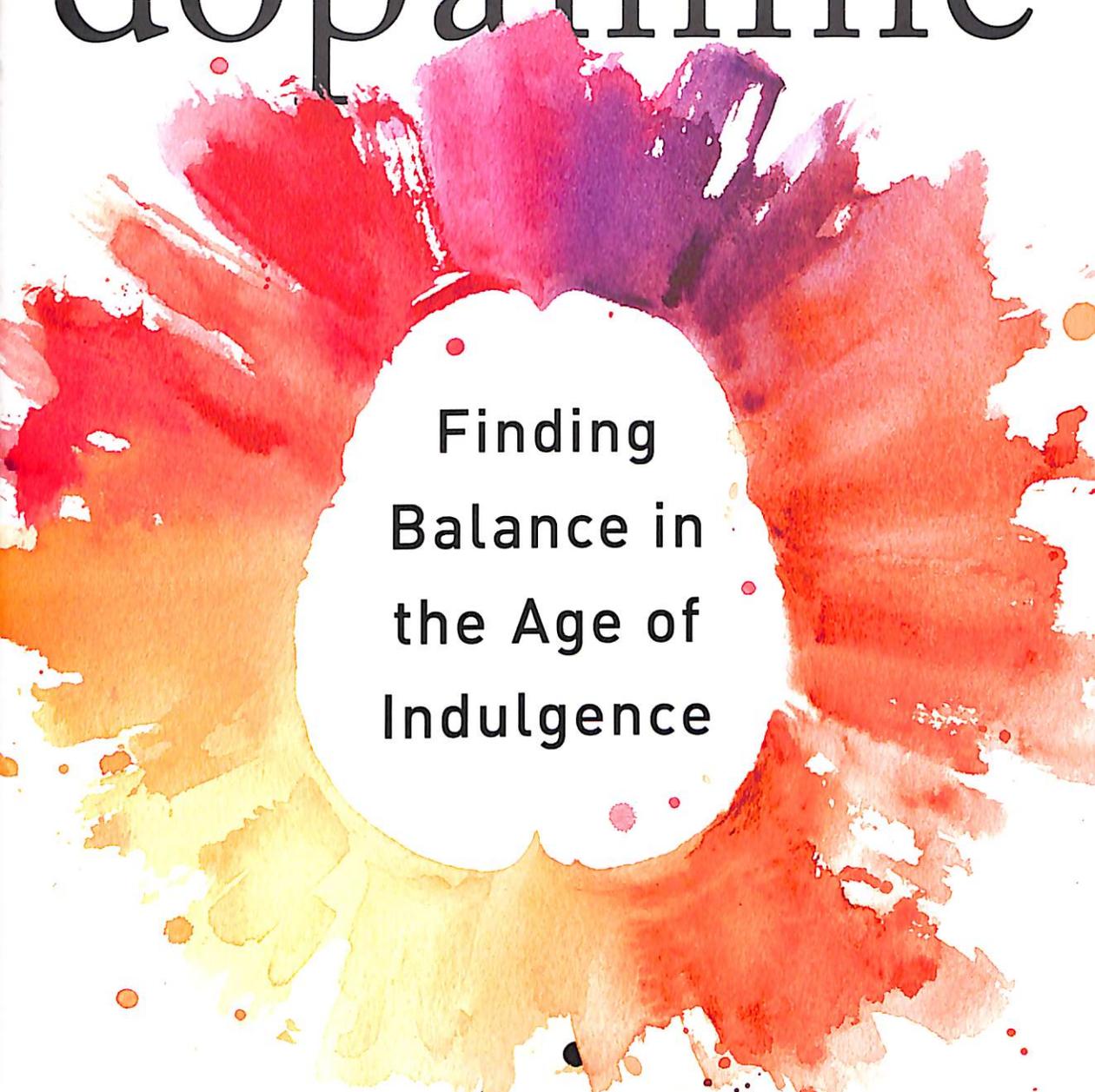
# MICHAEL MOSS

#1 NEW YORK TIMES BESTSELLING AUTHOR OF **SALT SUGAR FAT**



2021

# dopamine



Finding  
Balance in  
the Age of  
Indulgence

# nation

ANNA LEMBKE, MD



## The addicted brain: How processed foods hijack reward pathways

Kaylee Hough<sup>a</sup>, Marzia Friuli<sup>b</sup>, Nicole M. Avena<sup>a,\*</sup>, Adele Romano<sup>c</sup>

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### ARTICLE INFO

#### Keywords:

Food addiction  
Sugar addiction  
Dopamine  
Mesolimbic reward system  
Substance abuse

### ABSTRACT

The concept of addiction, traditionally confined to substances such as drugs and alcohol, has expanded to encompass behavioral patterns such as compulsive eating. Emerging evidence suggests that ultra-processed foods (UPFs), particularly those high in refined sugars and saturated fats, may elicit neurobiological responses akin to those observed in substance use disorders. This review explores the hypothesis that food addiction shares common clinical and neurochemical mechanisms with traditional forms of addiction, drawing from DSM-5 diagnostic criteria and recent findings in neuropharmacology. Animal and human studies have demonstrated that excessive consumption of palatable foods can induce behaviors characteristic of addiction—bingeing, craving, tolerance, and withdrawal—accompanied by significant dopaminergic alterations within the mesolimbic reward circuitry. Neuroimaging and molecular studies further reveal that chronic overconsumption of UPFs alters dopaminergic tone, disrupts prefrontal control, and activates stress pathways, thereby reinforcing compulsive intake. The Yale Food Addiction Scale (YFAS) and its pediatric adaptations provide structured tools for identifying food addiction phenotypes in clinical and research settings. Moreover, parallels between binge eating disorder and substance dependence highlight overlapping neurobehavioral mechanisms. As the obesity epidemic intensifies, particularly among populations with limited access to nutritious foods, understanding the pharmacological underpinnings of food addiction becomes critical. This review underscores the need to reframe UPFs as potentially addictive agents and calls for integrative therapeutic strategies and policy-driven reforms aimed at mitigating their impact on public health.

### 1. Defining addiction: clinical and diagnostic frameworks

In clinical applications, there is a lack of consensus on the formal definition of addiction. The American Society of Addiction Medicine (ASAM) defines addiction as a “chronic medical disease involving complex interactions among brain, circuits, genetics, the environment, and the individual’s life experiences” [1]. Addiction arises when a person becomes mentally and/or physically reliant on or compelled to consume a certain substance [2].

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) serves as a key reference for healthcare professionals in the identification and understanding of mental health conditions and their associated complications [3].

To address substance use disorder, the DSM-5 outlines comprehensive diagnostic criteria that help differentiate between various forms of substance-related problems. Notably, the criteria were revised to more clearly distinguish between substance abuse and dependence,

addressing the concerns from the earlier classification systems that overly emphasized severity [4].

The DSM-5 defines eleven criteria for diagnosing substance use disorder, all grounded in evidence-based clinical research [3]. These criteria are organized into four main categories (see Fig. 1) and specifically assess substance use behavior within the previous 12 months.

The DSM-5 criteria provide an informative foundation of the characteristics of substance use disorder and how healthcare practitioners can clinically diagnose it. The DSM-5 categorizes various classes of substances, including alcohol, caffeine, cannabis, hallucinogens, inhalants, opioids, sedatives, hypnotics or anxiolytics, stimulants, tobacco, and others (including unknown substances) [3].

Historically, addiction has been primarily associated with drugs and alcohol; however, scientific perspectives on addiction have evolved, expanding beyond substances to include certain compulsive behaviors [5]. These behavioral (or process) addictions have gained recognition from the American Psychological Association (APA), with gambling

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disorder being the first non-substance-related addiction officially included in the DSM-5 in 2013 [6].

As research in this field advances, growing evidence suggests that compulsive behaviors—beyond the use of drugs or alcohol—can meet the diagnostic criteria within the DSM-5 for addiction. Although food is not currently listed as an addictive substance in the DSM-5, studies over the past two decades indicate that highly palatable, ultra-processed foods (UPFs) may trigger neurobiological responses similar to those induced by addictive substances like drugs and alcohol [6]. Importantly, food is a biological necessity sustaining metabolic homeostasis, and its intake is fundamentally regulated by hunger signals, nutrient sensing, and gut-brain communication. This homeostatic regulation contrasts with the consumption of ultra-processed, hyper-palatable products that are specifically designed to enhance hedonic value. These formulations combine energy-dense macronutrient profiles with additives and sensory cues that disproportionately activate central pathways, increasing incentive salience and promoting intake beyond physiological requirements [7]. Thus, when referring to food-related addictive-like behaviors in this review, the focus is on these engineered high-reward foods rather than food as an essential substrate for survival. Technological advancements have accelerated the development and widespread availability of these products, transforming the modern food supply. As UPFs have become increasingly accessible worldwide, the role of eating appears to have shifted from sustaining survival to fostering patterns of overconsumption and compulsive eating.

## 2. Early preclinical evidence and the development of diagnostic tools for food addiction

Evidence of food addiction dates back to the early 2000s with various publications focused on the impact of excess sugar intake in rats. One study in 2006 looked at the bingeing behavior of Sprague-Dawley rats, demonstrating their dependence on sugar. The study also noted that whenever sugar was removed from the rat's diet, they exhibited signs of withdrawal—similar to the clinical manifestations of withdrawal in drug and alcohol addiction [8]. Examining the core components of addiction—bingeing, withdrawal, and craving—a study conducted in 2008 provided a comprehensive review of the existing literature on sugar as an addictive substance in animal models. The review concluded that, under certain conditions, Sprague-Dawley rats can develop a

dependency on sugar, a phenomenon that may offer insights into human conditions such as eating disorders and obesity [9]. One particular study highlighted that repeated, excessive sugar consumption can induce neurobiological and behavioral changes that closely resemble the effects of substance abuse. Whenever Sprague-Dawley rats binged on a 10 % sucrose solution repeatedly, dopamine was released in the nucleus accumbens (NAc). This finding suggested that repeated bingeing on sugar releases opioids, which leads to the brain compensating by expressing less of these opioid peptides in certain regions. Whenever the rats in this study were deprived of food, they displayed anxiety and depression, contributing to withdrawal-like behaviors upon the cessation of sugar availability. These findings suggest that, in specific contexts like bingeing or excessive overconsumption, sugar has the potential to be addictive [10]. Another study conducted in Sprague-Dawley rats aimed to investigate whether sugar-dependent rats would exhibit increased consumption of unsweetened ethanol, and conversely, whether access to ethanol would escalate sugar intake [11]. Remarkably, the results revealed that the rats who were dependent on sugar consumed the greatest amounts of ethanol, thereby supporting the hypothesis that sugar dependence can influence an animal's propensity to ingest ethanol [11]. The authors suggested that these findings may offer valuable insights into the comorbidities often observed between binge-eating disorders and alcohol consumption [11].

While a large body of existing literature on food addiction explores the potential addictive nature of food within animal models, these studies provide an insightful foundation for understanding potential parallels in humans. As evidence of food addiction continues to materialize and the body of research develops, scientists have begun to explore ways to quantify these eating behaviors. The Yale Food Addiction Scale (YFAS) was initially developed to provide a validated tool for identifying individuals who exhibit addiction-like eating behaviors, particularly in response to highly palatable foods rich in sugar and fat [12]. It was the first instrument specifically designed to translate the DSM-4 substance dependence criteria into the context of food consumption [12]. To extend its applicability to younger populations, a child version (YFAS-C) was introduced, using simplified language and age-appropriate examples while preserving the structure and scoring logic of the original tool [13]. Following the release of the DSM-5, the YFAS 2.0 was introduced to incorporate the updated eleven diagnostic criteria for substance use disorders, enhancing diagnostic alignment and

Categories of Substance Use Disorder Symptoms	
Category	Description
Impaired Control	<ul style="list-style-type: none"> <li>- Using more of a substance more often than intended</li> <li>- Wanting to cut down or stop using, but not being able</li> <li>- Spending a significant amount of time obtaining, using, or recovering from the effects of the substance</li> <li>- Cravings and urges to use the substance</li> </ul>
Social Problems	<ul style="list-style-type: none"> <li>- Neglecting responsibilities and relationships</li> <li>- Giving up activities they used to care about because of their substance</li> <li>- Inability to complete tasks at home, school, or work</li> </ul>
Risky Use	<ul style="list-style-type: none"> <li>- Using in risky settings</li> <li>- Continued use despite known problems</li> </ul>
Physical Dependence	<ul style="list-style-type: none"> <li>- Needing more of a substance to get the same effect (tolerance)</li> <li>- Having withdrawal symptoms when a substance is not used</li> </ul>

Fig. 1. The four DSM-5 categories of substance use disorder. Adapted from the Alcohol, Drug, Addiction, and Mental Health Services.

**Dopamine is a  
Catecholamine**

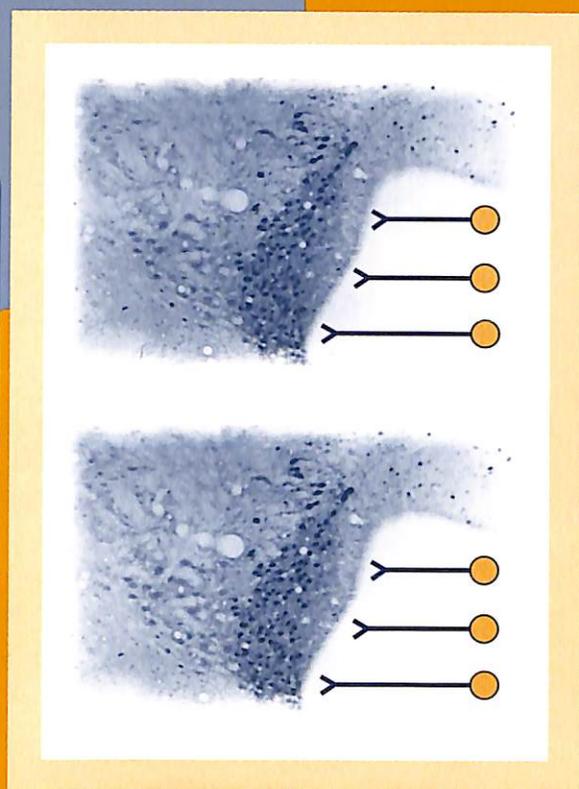
**Norepinephrine is a  
Catecholamine**

**Norepinephrine  
is made from  
Dopamine**

# Stress, Immune Function, and Health

THE CONNECTION

1999



BRUCE S. RABIN

**Stress, Immune Function, and Health, the Connection**

**1999, Wiley-Liss**

**Bruce Rabin**

"In a healthy person, the response to infectious agents or tissue injury is rapid and efficient and will frequently lead to resolution [innate response] (resolution means that the eliciting agent is removed) before the [adaptive] immune system is activated (this is called 'acute inflammation')."

In an individual with overwhelming infection or who is chronically ill with an impaired acute inflammatory response, [adaptive / acquired] the immune system becomes activated and participates in the inflammatory response (this is called chronic 'inflammation')". p. 70

[This author is suggesting that in a healthy person, the innate immune system handles problems without inflammation, and with no symptoms].

[When the innate system does not handle the problem and the adaptive system is called to help, there is inflammation and symptoms].

Th2 response increases the production of IgE, which attaches to mast cells, which causes mast cell membrane degranulation, which increases the production of PGE2. p. 88

When the sympathetic nervous system increases, "the activity of the immune system decreases with a resultant increased susceptibility to infection." p. 114

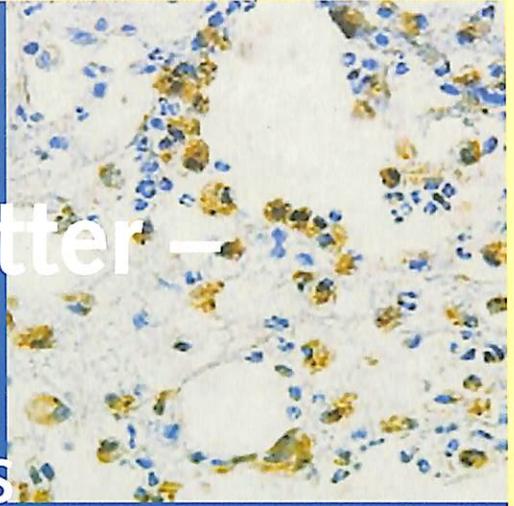
Activation of the hypothalamus activates the sympathetic nervous system, activating "catecholamine release in lymphoid tissues with a subsequent alteration of immune cell function and trafficking." p. 129

Progress in Inflammation Research

Michael J. Parnham  
Series Editor

# Mind over Matter –

## Regulation of Peripheral Inflammation by the CNS



Michael Schäfer  
Christoph Stein

Editors

2003

Birkhauser

**Mind Over Matter, Regulation of Peripheral inflammation  
by the CNS**

**2003, Birkhauser**

**Michael Schafer, Christoph Stein**

"The sympathetic efferent fibers innervate every organ in the body and control diverse involuntary function." p. 89

"Stimulation of sympathetic post-ganglionic neurons promotes neurogenic inflammation." p. 126 This alters the function of the immune system [primarily the Th1/Th2 balance].

"The sympathetic nervous system is an important modulator of the immune system." p. 92

Chronic release of "catecholamines decrease the number of lymphocytes, and particularly of natural killer cells in the peripheral blood." "Catecholamines inhibit T-cell proliferation." p. 73

"Catecholamines are in general, immunosuppressive." p. 74

"Catecholamines affect the Th1/Th2 balance." p. 75

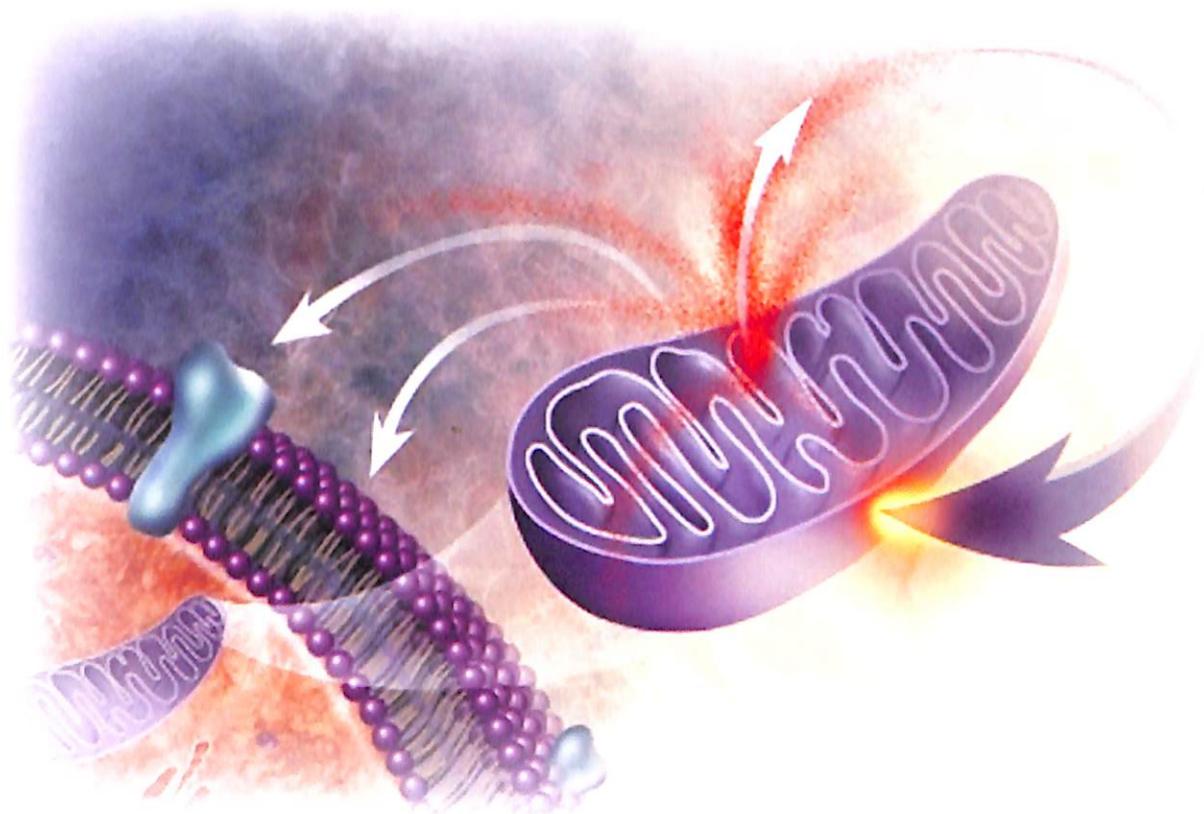
"Catecholamines induce a switch to IgE." p. 78

"Activity of the sympathetic nervous system may play a role in the pathogenesis of infections, autoimmune and atopic / allergic reactions, and atherosclerosis and tumor growth."

p. 80

PGE2 activates the sympathetic nervous system release of catecholamines. p. 21

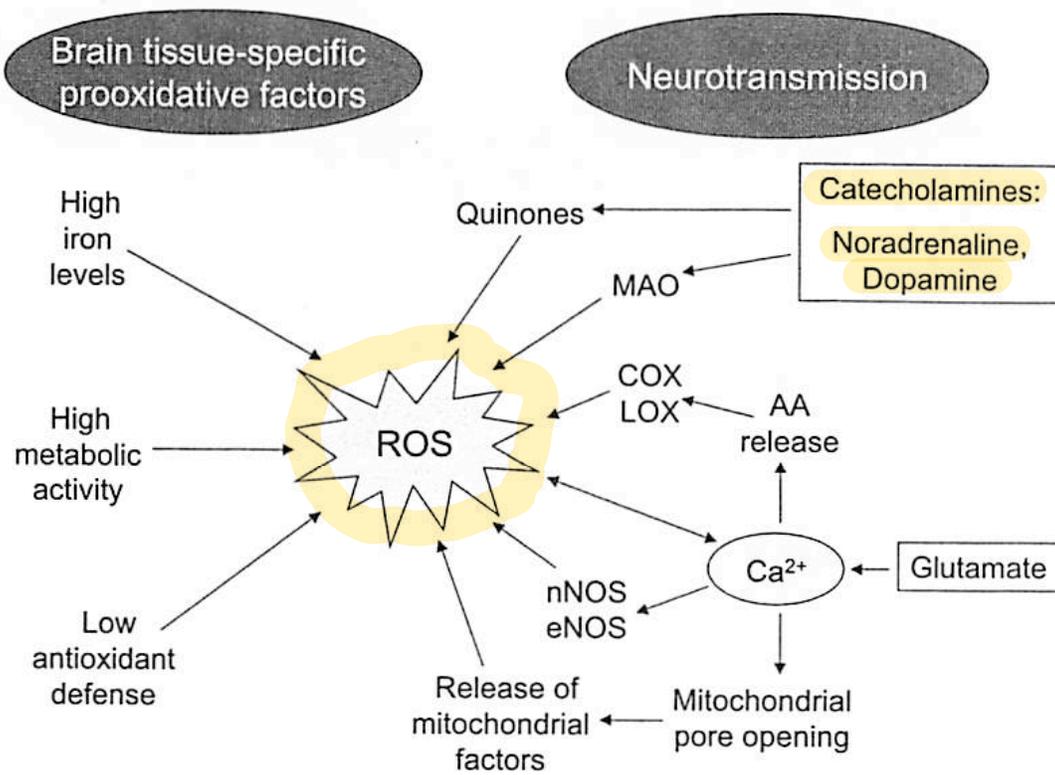
# Oxidative Stress, Disease and Cancer



*Editor* Keshav K. Singh

2006

Imperial College Press



**Fig. 1.** Factors contributing to accumulation of reactive oxygen species (ROS) in brain tissue. See text for details. MAO, monoamine oxidase; COX, cyclooxygenase; LOX, lipoxygenase; AA, arachidonic acid; eNOS/nNOS, endothelial/neuronal nitric oxide synthase.

FULL TEXT LINKS



Review > [J Biol Inorg Chem](#). 2010 Jan;15(1):61-76. doi: 10.1007/s00775-009-0600-y.

Epub 2009 Oct 28.

## Copper in the brain and Alzheimer's disease

Ya Hui Hung<sup>1</sup>, Ashley I Bush, Robert Alan Cherny

Affiliations

### Affiliation

<sup>1</sup> The Mental Health Research Institute, Parkville, VIC, Australia.

PMID: 19862561 DOI: [10.1007/s00775-009-0600-y](https://doi.org/10.1007/s00775-009-0600-y)

### Abstract

Alzheimer's disease (AD) is the most common form of neurodegenerative disease. The brain is particularly vulnerable to oxidative damage induced by unregulated redox-active metals such as copper and iron, and the brains of AD patients display evidence of metal dyshomeostasis and increased oxidative stress. The colocalisation of copper and amyloid beta (Abeta) in the glutamatergic synapse during NMDA-receptor-mediated neurotransmission provides a microenvironment favouring the abnormal interaction of redox-potent Abeta with copper under conditions of copper dysregulation thought to prevail in the AD brain, resulting in the formation of neurotoxic soluble Abeta oligomers. Interactions between Abeta oligomers and copper can further promote the aggregation of Abeta, which is the core component of extracellular amyloid plaques, a central pathological hallmark of AD. Copper dysregulation is also implicated in the hyperphosphorylation and aggregation of tau, the main component of neurofibrillary tangles, which is also a defining pathological hallmark of AD. Therefore, tight regulation of neuronal copper homeostasis is essential to the integrity of normal brain functions. Therapeutic strategies targeting interactions between Abeta, tau and metals to restore copper and metal homeostasis are discussed.

### Related information

[MedGen](#)

[PubChem Compound \(MeSH Keyword\)](#)

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# ENVIRONMENTAL CAUSES AND PREVENTION MEASURES FOR ALZHEIMER'S DISEASE



2018

George J. Brewer



# Minireview

## Avoiding Alzheimer's disease: The important causative role of divalent copper ingestion

George J Brewer

University of Michigan, Department of Human Genetics, MI 48103, USA  
Corresponding author: George J Brewer. Email: brewergj@umich.edu

### Impact statement

The work described in this review is very important to scientists working on Alzheimer's disease (AD) because it reveals a cause for the explosive epidemic of this disease. It is also important to the public because it provides a method to avoid this newly revealed cause, and thereby avoid AD. The field is advanced because this review reveals new information about the mechanism of AD pathogenesis, namely copper, and specifically divalent copper, toxicity is important. New information about divalent copper toxicity in the brain affecting cognition is revealed. The field is impacted strongly because, in view of the frustrations that have occurred in treatment developed, now most AD can be prevented. This means the suffering of the patient, the prolonged and difficult care required by caregivers, and the enormous expenditures for this one disease, can now be avoided.

### Abstract

In this review, we point out that developed countries are undergoing an epidemic of Alzheimer's disease, not shared by undeveloped countries. We also point out that this epidemic is new, developing during the 20th century. This suggests that an environmental change occurring in the 20th century in developed countries is causing the epidemic. The author hypothesizes that the environmental change causing the epidemic of Alzheimer's disease is ingestion of divalent copper. The hypothesis is based on data indicating that food copper is primarily monovalent copper, and humans evolved safe ways of channeling monovalent copper, but not divalent copper. Humans were not exposed to divalent copper until the 20th century, due to the use of copper plumbing and supplement pills containing copper, and that exposure, which occurs in developed countries, does not occur in undeveloped countries. Data in support of the hypothesis show that tiny amounts of divalent copper added to drinking water of Alzheimer's disease animal models greatly enhance Alzheimer's disease, and ingestion of copper (which is always divalent copper)-containing supplement pills by humans is quite toxic to cognition.

**Keywords:** Alzheimer's disease, divalent copper, copper 2, Alzheimer's disease epidemic, cause of Alzheimer's disease epidemic, copper 2 hypothesis, copper levels in drinking water

**Experimental Biology and Medicine 2019; 244: 114–119. DOI: 10.1177/1535370219827907**

### Introduction

It is easy to show that Alzheimer's disease (AD) is a very bad disease. It robs people in their retirement years of memory and other cognitive functions. They cannot remember their loved ones, or the events they experienced together during their lives. As the disease progresses, patients require care 24/7. They become completely dependent on their caregivers. And AD is becoming very common as will be shown below. Currently, there are no treatments to prevent the inevitable progression. So if there is a way to prevent AD, it is obvious it should be pursued with the utmost vigor. And there is a way for about 95% of

cases to be prevented, and without very much difficulty, as will be shown in the following sections.

### Two important facts about the history and epidemiology of AD

#### Fact 1

Currently, there is an epidemic of AD in developed countries, not shared by undeveloped countries. For example, in the US, 20% of those age 70 and over and 30% of those age 80 and over have AD.<sup>1</sup> In contrast, in rural India, the AD prevalence is 1.07% in those 65 and over,<sup>2</sup> and in

# The View

Time: 9/4/23

HEALTH

## THE PARENT TRAP

BY JENNY ANDERSON

American teens are having a hard time. High school students reporting chronic feelings of sadness and hopelessness rose from 1 in 5 to 1 in 3 from 2008 to 2019, according to the Centers for Disease Control and Prevention (CDC). By the pandemic fall of 2021, the feelings were reported by 42% of high school students and almost 60% of girls. The thing is, a lot of parents are in really bad shape too. ▶

INSIDE

THE 'BLACK LUNG' DISEASE OF THE CLIMATE-CHANGE ERA

THE MYTH OF WALKING 10,000 STEPS

QUESTLOVE ON THE DAY HIP-HOP DIED

↓ Telomeres

Shrinks Brain

↑ Blood Pressure

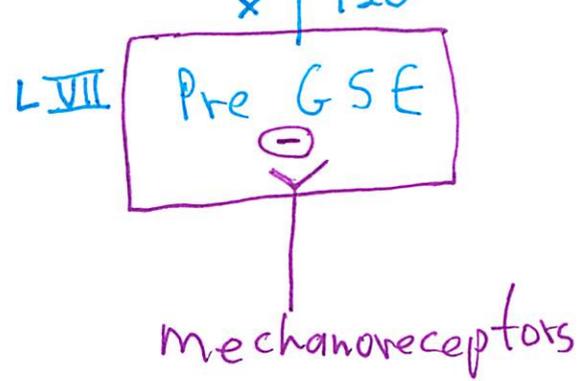
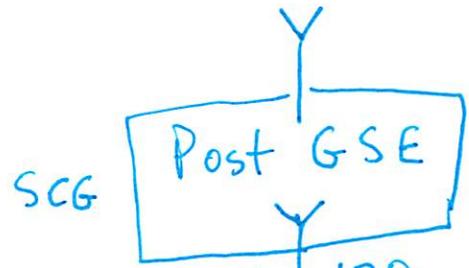
Damaged Blood Vessels

Vasoconstriction → ↓ ATP

↑ Pain

Immuno suppressive

Norepinephrine



Catecholamines

Cu / Cu/Zn

↑ Consumption

Needing Wanting

Food / Sex

Short-Lived Things

Reward

Pleasure

Dopamine

Tyrosine

Junk Food  
Chocolate

Alcohol

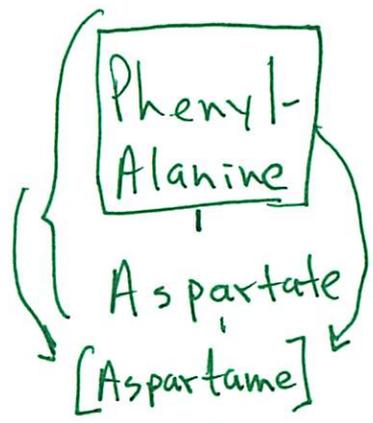
Narcotics

Caffeine

Sugar

Shopping

Social Media



NMDA

Ca<sup>++</sup>

FR

Neuro Degen Dis

Long-Lived Deeds

Contentment Happiness

Serotonin

Tryptophan

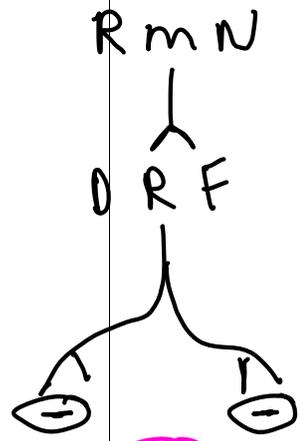
Least Common  
Not in Corn  
Low in Animals  
Fed Corn

Tyrosine → dopamine

TRP → 5HTP → serotonin → melatonin

B6  
B12  
F

PA  
↓  
aspartate ← NMDA



NR → II ← Go → SG

MR  
C1-C3

NI

NTS

DMNV

AC

NE

VII

MR

Cu/Zn

Cut  
Water  
Supplements  
crops

Addiction  
Pleasure

Dopa  
↑  
Sugar  
Sex  
gambling  
nicotine  
caffeine  
Social Med  
Shopping  
alcohol

sleep

Immunology

melatonin

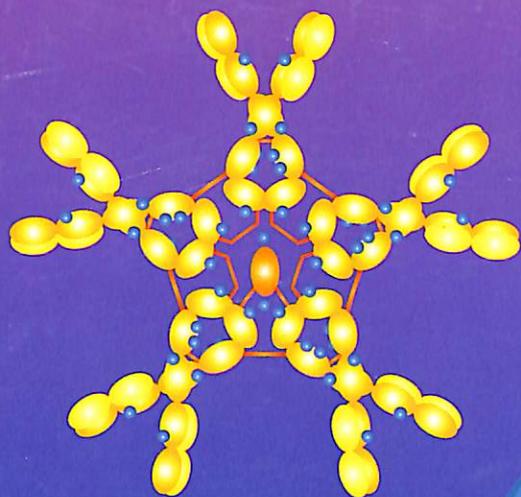
Sero

Happiness

Pain  
Control

5 HT  
↑  
F  
B6  
B12  
HC

Trp

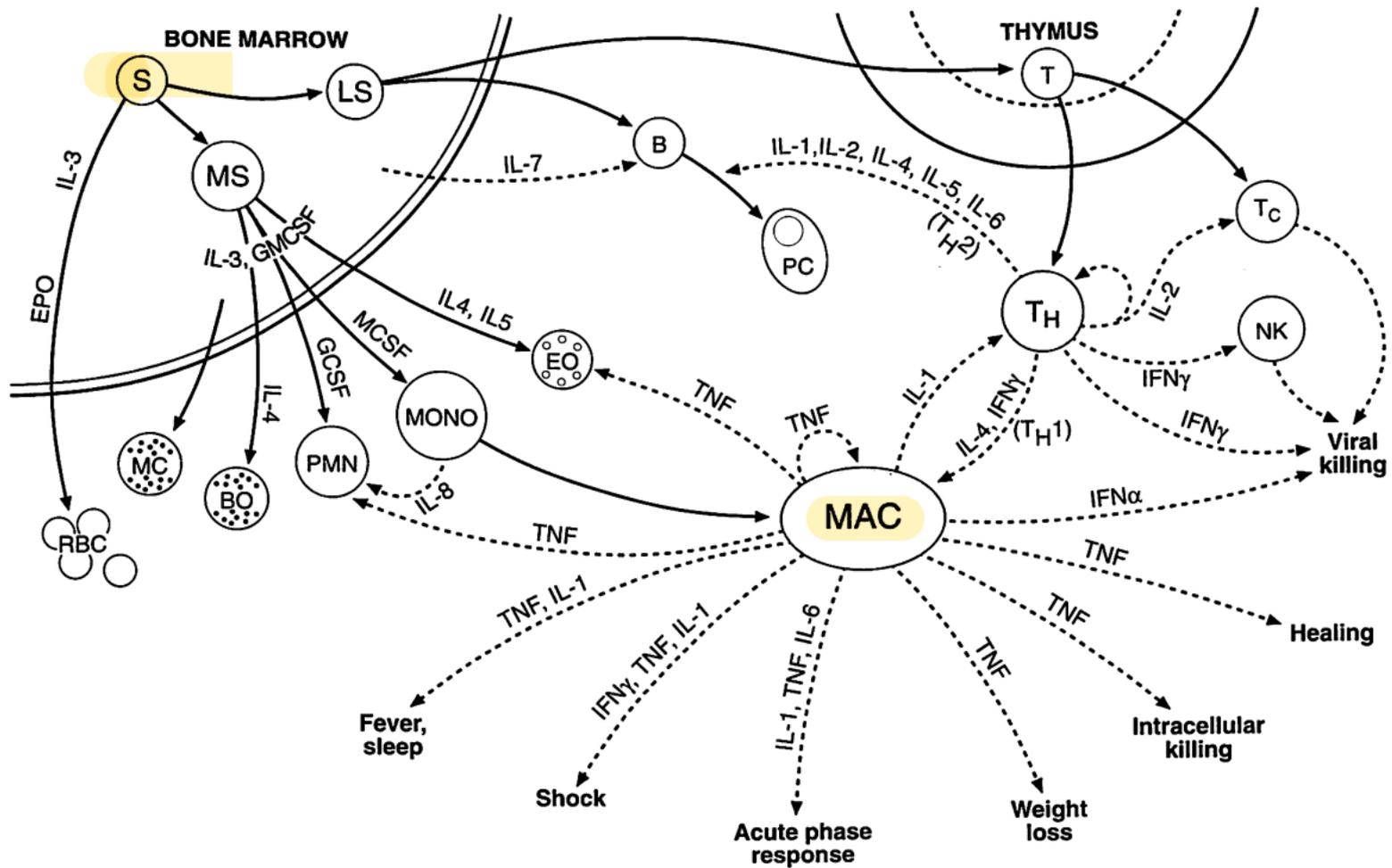


SECOND EDITION

# Medical Immunology

made memorable

J. H. L. Playfair  
P. M. Lydyard

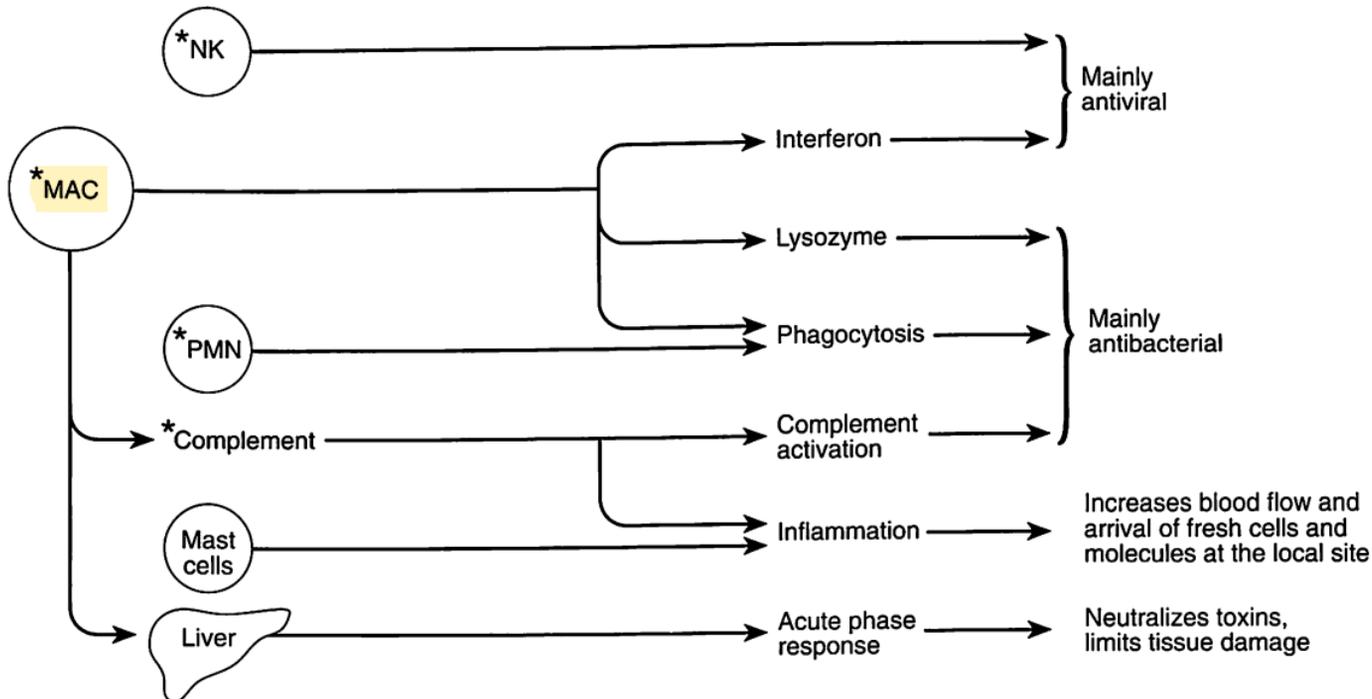


## Natural immunity: the rapid defence system

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).

How the

# Immune System Works

2023

Seventh Edition

Lauren Sompayrac



WILEY Blackwell

## PHYSICAL BARRIERS

pg 1

Our first line of defense against invaders consists of physical barriers, and to cause trouble, viruses, bacteria, and parasites must first penetrate these shields. Although we tend to think of our skin as the main barrier, the area covered by our skin is only about two square meters. In contrast, the area covered by the mucous membranes that line our digestive, respiratory, and reproductive tracts measures about 400 square meters – an area about as big as two singles-tennis courts. The point here is that there is a large perimeter which must be defended.

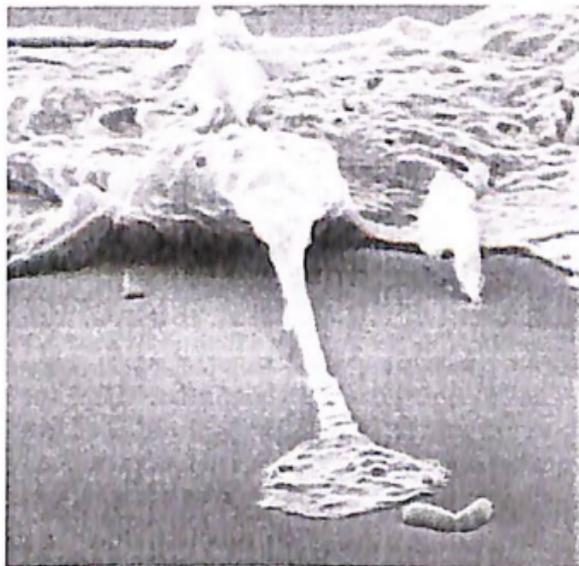
## THE INNATE IMMUNE SYSTEM

Any invader that breaches the physical barrier of skin or mucosa is greeted by the innate immune system – our second line of defense. Immunologists call this system “innate” because it is a defense that all animals just naturally seem to have. Indeed, some of the weapons of the innate immune system have been around for more than 500 million years. The way the innate system works is pretty amazing.

Imagine you are getting out of your hot tub, and as you step onto the deck, you get a large splinter in your big toe. On that splinter are many bacteria, and within a few hours you'll notice (unless you had a lot to drink in that hot tub!)

of the defender cells that is stationed in your tissues is the most famous innate immune system player of them all: the macrophage. If you are a bacterium, a macrophage is the last cell you want to see after your ride on that splinter. Here is an electron micrograph showing a macrophage about to devour a bacterium:

pg 2



Recognize many of the most common invaders, your innate immune system usually responds so quickly that the battle is over in just a few days.

pg 3

There are other players on the innate team, and we will talk about them at length in the next lecture. For example, in addition to cells like macrophages (the "professional



## 4 LECTURE 1 An Overview

### THE ADAPTIVE IMMUNE SYSTEM

About 99% of all animals get along just fine with only natural barriers and the innate immune system to defend them.  
However, for vertebrates like us, Mother Nature laid on a third level of defense: the adaptive immune system. This

we are likely to meet on a day-to-day basis. In many instances, the innate system is so effective and so fast that the adaptive immune system never even kicks in. In other cases, the innate system may be insufficient to deal with the invasion, and the adaptive system will need to be mobilized. This takes a while, because although the B and T cells of the adaptive system can deal with huge quantities of almost any invader, these weapons must be custom-made. Meanwhile, the innate immune system must do its best to hold the invaders at bay.

## **THE INNATE SYSTEM RULES!**

pg 11

Until fairly recently, immunologists thought that the only function of the innate system was to provide a rapid defense which would deal with invaders while the adaptive immune system was getting cranked up. However, it is now clear that the innate system does much more than that.

The adaptive immune system's antigen receptors (BCRs and TCRs) are so diverse that they can probably recognize any protein molecule in the universe. However, the adaptive system is clueless as to which of these molecules is dangerous and which is not. So how does the adaptive system distinguish friend from foe? The answer is that it relies on the judgment of the innate system.

In contrast to the antigen receptors of the adaptive immune system, which are totally "unfocused," the receptors of the innate system are precisely tuned to detect the presence of the common pathogens (disease-causing agents) we encounter in daily life - viruses, bacteria, fungi, and parasites. In addition, the innate system has receptors that can detect when "uncommon" pathogens kill human cells. Consequently, it is the innate system which is responsible for sensing danger and for activating the adaptive immune system.

So in a real sense, the innate system gives "permission" to the adaptive system to respond to an invasion. But it's even better than that, because the innate system does more than just turn the adaptive system on. The innate system actually integrates all the information it collects about an invader, and formulates a plan of action. This "game plan,"

## 12 LECTURE 1 An Overview

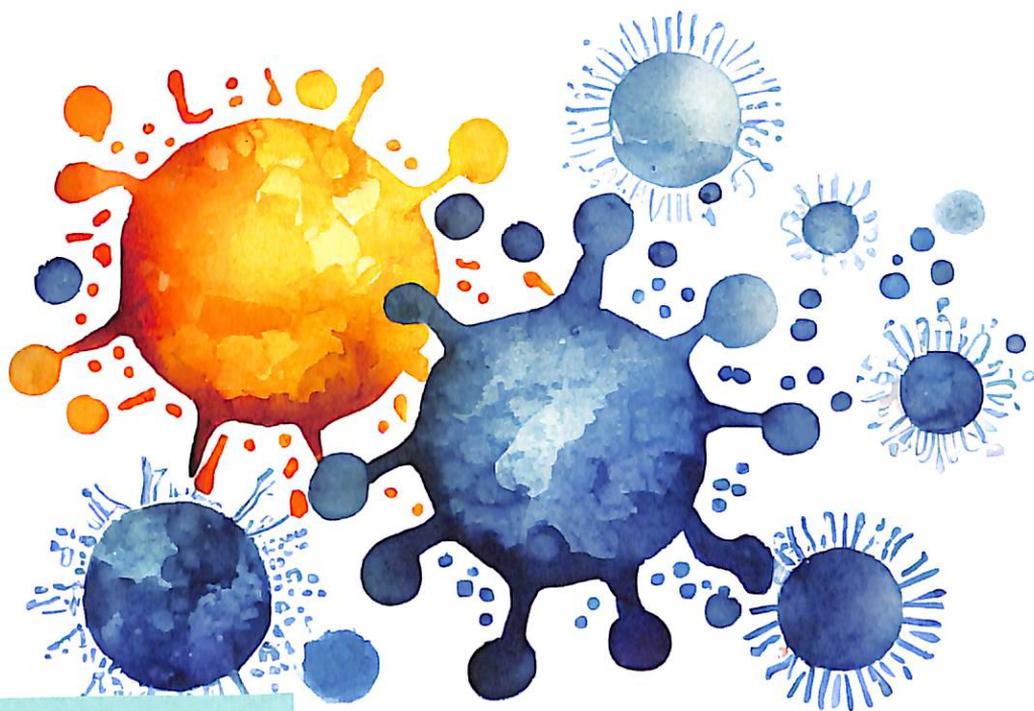
which the innate system delivers to the adaptive immune system, tells which weapons to mobilize (e.g., B cells or killer T cells) and exactly where in the body these weapons should be deployed. So if we think of the helper T cell as the quarterback of the adaptive immune system team, we should consider the innate immune system to be the "coach" – for it is the innate system which "scouts" the opponents, designs the game plan, and sends in the plays for the quarterback to call.

## LECTURE 2

# The Innate Immune System

The Logic of  
**Immunity**

*Deciphering an Enigma*



2024

B. J. Cherayil

occupies the colon and causes a severe and very treatment-resistant form of diarrhea.

## Defenders in Residence

K Although the epithelium is a robust, self-repairing barrier, it can be weakened by mechanical, chemical, thermal, or other types of injury and allow the entry of pathogens or potentially virulent members of the microbiota that are normally kept in check. Significant breaches of the epithelium, whether they are secondary to weakened barrier functions or the result of active intrusion by pathogens, are handled by a second line of defense consisting of the immune cells that reside in almost all tissues, including in the vicinity of epithelial surfaces. There are many types of resident immune cells—macrophages, dendritic cells, and mast cells, to name a few—and new ones are still being discovered. Even cells that are not traditionally considered to be part of the immune system, such as the endothelial cells that line blood vessels, nerve cells, and the fibroblasts that contribute to the general background “stuff” or stroma of most tissues, can be co-opted to carry out immunological functions when needed. All these cells may become involved in the immune response in one way or another depending on the circumstances, and we will encounter several of them in later sections. But from the perspective of dealing with microorganisms that have made their way through the epithelium, one of the most important cell types is the macrophage.

MP  
MP  
MP As its name indicates, the macrophage is the big eater of the immune system. This amoeba-like cell is singularly skilled at ingesting (or phagocytosing, to use the more scientific term) any particulate material—dead cells, cellular debris, foreign bodies, microorganisms— that it encounters as it crawls slowly through tissue spaces. During phagocytosis, the macrophage extends protrusions of the plasma membrane that engulf the particle being targeted, ultimately enclosing it in a membrane-bound compartment or organelle called the phagosome. The phagosomal cargo is then subjected to a barrage of caustic chemicals, including highly reactive radicals of oxygen and

ROS

MP  
nitrogen, before being delivered to another organelle—an acidic sub-cellular compartment called the lysosome—where its destruction is completed as a result of exposure to degradative enzymes. There are very few microorganisms that can survive this harsh treatment. Consequently, tissue macrophages are efficient defenders of their territory, rapidly eliminating any microbes that might make their way through the epithelium. If the number and virulence of the microbial intruders is low, they are cleared by macrophages with little or no fuss and we are often unaware that a problem has occurred. In fact, it is likely that such trivial skirmishes between intruders and defenders occur several times a day in our skin and other barrier tissues because of minor breaks in the epithelium. That they do so silently, without becoming apparent as a clinical abnormality, is a testament to the effectiveness of macrophage antimicrobial functions. It is only when these functions are missing or defective do we realize how important they are. Consider, for example, the plight of individuals with an inherited condition known as chronic granulomatous disease (CGD), which is caused by a genetic mutation that renders macrophages and other phagocytic cells incapable of generating the reactive oxygen radicals necessary to kill microorganisms that they have engulfed. CGD  
Patients with CGD are plagued by recurrent infections of the lungs and of the soft tissues beneath the skin, often involving organisms that are not particularly virulent and that the rest of us are able to shrug off thanks to the quiet efficiency of our phagocytic cells.

K  
The person who is widely credited with recognizing the importance of macrophages and phagocytosis in antimicrobial defense is the nineteenth-century Ukrainian zoologist Élie Metchnikoff. He appears in most photographs as a grandfatherly figure, with kindly eyes, a hint of a smile, and the unkempt hair and bushy beard that marked serious men of that period. But by his own account his early life was spent under the shadow of recurrent episodes of depression. He attempted suicide twice: the first time, by morphine overdose, following the death of his beloved wife and the second, by auto-infection with pathogenic bacteria, in response to work-related stress. Yet, he was deeply

passionate about his research. It is clear from his writings, especially the description of his famous experiment on phagocytosis in starfish larvae, that he took a child-like delight in his work. The joy that he found in observing and analyzing macrophages under the microscope may have acted as a counterweight to the darker side of his personality, allowing him to generate the data that laid the foundation for a whole branch of immunology and that led ultimately to a Nobel Prize.

1908

### Calling in Backup: Distress Signals

Sometimes, tissue macrophages are overwhelmed by the microorganisms that they encounter. This situation may arise either because the microbes are present in large numbers or because they have special virulence characteristics that allow them to resist the killing mechanisms that macrophages deploy against them. All is not lost, however: at the same time that these mechanisms are activated, the macrophage also sends alarm signals to surrounding cells to alert them of impending danger and to recruit backup forces from the circulation. The signals are in the form of secreted molecules that are released by macrophages as well as other cells in the infected tissue and that diffuse outwards from the point of disturbance.

These molecules are of three major types. They include messenger proteins known as cytokines, important mediators of cell-cell communication in the immune system; chemokines, which are cytokine-like proteins specialized for guiding and directing cell movement; and eicosanoids, a diverse group of small bioactive lipid molecules that carry out a number of different functions depending on their identity. Cells in the vicinity perceive these various signals by means of specific surface receptors and change their properties or behavior as a result, with the exact effects being determined by the type of cell and specific cytokine, chemokine, or eicosanoid involved. Most cells will respond to the alarm signals by switching to an activated state in which the expression of multiple defensive molecules is increased, a reaction that provides the means to ward off microbial attack if the need arises.

fluence of the chemokines and other molecules that are released in response to the presence of microorganisms, the rolling neutrophils finally come to a dead stop as they attach firmly to the endothelial cells. They squeeze between these cells into the tissue, and then swarm to the site of infection as they follow a gradient of chemokines and other molecules that attract and guide them.

Once the neutrophils have arrived at the focus of infection, they fire their battery of antimicrobial weapons, many of which are similar to those used by macrophages, and then, having fulfilled their function, die shortly thereafter. Some of the neutrophils may engage in a last-ditch act of heroic self-sacrifice in which they spew out their nuclear and cytoplasmic contents—a mix of deoxyribonucleic acid (DNA) strands, chromosomal proteins, and antimicrobial peptides—to form a sticky net in which bacteria are trapped and eliminated. Unfortunately, several of the toxic molecules that are released by neutrophils against their microbial targets are also harmful to mammalian cells, so some degree of collateral tissue damage is unavoidable.

Monocytes and lymphocytes, the other major types of circulating white blood cells, are also recruited into infected tissue by the same broad mechanisms involved in neutrophils: rolling, firm adhesion, and migration out of the blood vessel under the guidance of chemokines. During the first few hours of the innate response, the chemokines produced in the tissue preferentially attract neutrophils, so those cells are usually the first to arrive from the circulation, especially during bacterial infections. Subsequently, the chemokine profile shifts, leading to the recruitment of monocytes, which differentiate into macrophages after they have left the blood and entered the tissue. In situations where adaptive immunity is activated, the response develops over the course of about a week, after which activated lymphocytes are also recruited and join the milling crowd of cells at the site of infection.

### Inflammation: Stoking the Fire

The events that we have just discussed constitute an important aspect of innate immunity known as the acute inflammatory response,

illness and that we associate with the feeling of being sick: fever, distaste for food, and the desire to get away from it all and crawl into bed. The various sickness behaviors, as well as the fever, are manifestations of the underlying inflammatory process and are the result of the cytokines that are released at the site of infection. The cytokines make their way into the circulation and induce cells in the brain—endothelial cells and macrophage-like cells known as microglia—to secrete additional molecules, including small lipids, that act on specific nerve cells. These neurons are wired into neural circuits that control body temperature, appetite, mood, and social interactions. Depending on the particular network that they are connected to, activation of the nerve cells can make you unwilling to eat, reluctant to interact with other people, or unable to look on the bright side of life. Some of the activated circuits can also fool your brain into thinking that your body temperature is too low and that it needs to be raised by shivering and reducing blood flow to the skin (which is why you develop a fever).

The importance of fever and sickness behaviors in dealing with infection is not entirely clear, but there is some evidence to suggest that elevated body temperature may inhibit the growth of pathogens and increase immune cell activity. Social withdrawal may help to decrease transmission of pathogens from one individual to another, and loss of appetite can alter metabolism in ways that enhance the ability to tolerate the presence of certain types of pathogens. Some of these ideas are speculative or based on a limited number of animal experiments, so they are not fully substantiated. But what is undeniable is that fever and sickness behaviors have been conserved through evolution (they occur in most animals, and even cold-blooded ones like lizards and snakes, which cannot regulate their own body temperature, will move to a warm location when they are sick), suggesting that these responses probably have some survival value.

### Resolution: Cooling Off

Once the microorganisms that initiated the inflammatory process have been eliminated, something that is usually accomplished only after the

"THE RAREST OF BOOKS: A COMBINATION OF PAGE-TURNING DISCOVERY AND  
REMARKABLY READABLE SCIENCE JOURNALISM." —MARK HYMAN, M.D.

# THE ANGEL AND THE ASSASSIN

THE TINY  
BRAIN CELL  
THAT CHANGED  
THE COURSE OF  
MEDICINE

DONNA JACKSON  
NAKAZAWA

2020

adaptive immune system has provided assistance, resolution starts to occur. The cell and microbial corpses and tissue debris that result from the battle between host and pathogen are ingested and digested by a cleanup crew of macrophages, which also facilitate healing by secreting molecules that promote tissue repair. The termination of inflammation results in part from the clearance of the microbe- and host-derived signals that kicked off the response, but in addition, there are several factors that actively suppress inflammation and induce the repair of damaged tissue. They include cytokines like IL-10, which are secreted by cells in the local environment; a subclass of eicosanoids known as specialized pro-resolving mediators (SPMs) produced by neutrophils, macrophages, and other cells; and probably additional molecules that are yet to be discovered. SPMs in particular help to reverse the effects of inflammation by inhibiting neutrophil recruitment while also promoting tissue regeneration and the removal of dead cells and debris. The action of SPMs and other anti-inflammatory and pro-resolution factors illustrates yet another theme in immunology: whenever a function of the immune system is turned on, mechanisms to turn it off when it is no longer needed are also deployed. These regulatory mechanisms ensure that the activity does not become excessive and tissue damaging; their failure can contribute to the development of disease.

Inflammation is a fairly stereotypical process that can occur in any tissue, and it is often identified by clinicians by simply adding the suffix "itis" to the name of the tissue. Thus, dermatitis indicates inflammation of the skin; carditis, inflammation of the heart; gastroenteritis, inflammation of the intestinal tract; and so on. With some variations, the underlying cellular and molecular events in each case are very similar. However, the health implications can be quite different depending on the exact cause of the inflammation, the tissue involved, and how long the process lasts. The short-lived, superficial skin inflammation that follows an abrasion is usually nothing more than a temporary annoyance, whereas carditis, whether caused by viruses, bacteria, or other agents, can have serious, sometimes life-threatening consequences because of the associated damage to the delicate struc-

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# **The Collected Papers of Irvin M. Korr**

318 x 424



Dr. **Korr** is Distinguished Professor of Physiology at Kirksville College of Osteopathic Medicine, and is director of the college's program in neurobiology.

Dr. Korr, Kirksville College of Osteopathic Medicine, Kirksville, Missouri 63501.

IRVIN M. KORR, PH.D.  
Kirksville, Missouri

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**Functional properties of osteopathic lesions, as clinically described, have been reviewed in relation to the physiology of proprioceptors. It is shown that muscle spindles in which the “gain” has been turned up by intensified activity in their gamma motor innervation may, together with other sensory inputs, account for many of the motion characteristics and palpatory features of the osteopathic lesion. “Turning down” of the gain seems to be a common denominator in a variety of osteopathic manipulative procedures. Possible origin of the high gain is discussed also.**

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The musculoskeletal system is the most massive system of the body, yet in the performance of its infinite repertoire of motions and postures, it is the most delicately controlled and coordinated. Accordingly, the musculoskeletal system is the recipient of most of the efferent outflow from the central nervous system (CNS), with the largest portion by far going via the ventral roots of the spinal cord to the muscles, which carry out the motor commands of the CNS.

It is less well appreciated, however, that for related reasons the musculoskeletal system is also the *source* of the preponderant sensory input to the CNS, an input that is also the most widespread, the most continuous, and the most variable. This sensory feedback, from countless thousands of report-

ing stations in myofascial and articular components, entering the cord via the dorsal roots, is essential to the moment-to-moment control and fine adjustment of posture and locomotion.

In addition to this influence on the motor pathways, the sensory reporting is selectively routed to various other centers throughout the nervous system, including, of course, the cerebral cortex, where it enters into consciousness and the ordering of volitional motor activity. Relevant portions of the reports also reach and are utilized by the autonomic nervous system in the tuning of visceral, circulatory, and metabolic activity to musculoskeletal demand. Indeed, the sensory input from the musculoskeletal system is so extensive, intensive, and unceasing as to be a dominant influence on the CNS and therefore the person as a whole.

It may be expected, therefore, that disturbances in the sensory input from the musculoskeletal system, whether generally or locally, would significantly impair not only motor function, but also other functions — and that of the person himself. For those engaged in the study of the neural and reflex mechanisms, that premise is at the heart of the clinical significance of the osteopathic lesion — now modishly and euphemistically designated as “somatic dysfunction.” One of the first products of experimental research into those mechanisms, pioneered by Denslow,<sup>2-4</sup> was the concept of chronic segmental facilitation. In 1947, the hypothesis was stated<sup>5</sup> as follows:

(An) osteopathic lesion represents a facilitated segment of the spinal cord maintained in that state by impulses of endogenous origin entering the corresponding dorsal root. All structures receiving efferent nerve fibers from that segment are, therefore, potentially exposed to excessive excitation or inhibition.

In speculating further about the site of the “endogenous origin,” the author suggested that the proprioceptors, particularly the muscle spindles, were the most likely candidates because: 1) they would be sensitive to musculoskeletal stresses; 2) they are nonadapting receptors, sustaining streams

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\*Based on a lecture given at the 71st Clinical Conference of the New York Academy of Osteopathy, in conjunction with the Postgraduate Institute of Osteopathic Medicine and Surgery, January 26, 1974. An earlier version appeared in *Osteopathic Annals*<sup>1</sup> in August 1974.

of impulses for as long as they are mechanically stimulated; and 3) their influence is highly specific to the muscles acting on the affected joints and the corresponding spinal segments.

In the intervening 28 years, research in many neurophysiologic laboratories has immensely increased our understanding of the proprioceptors. Concurrently, research under osteopathic auspices (reviewed by various authors<sup>5-11</sup>) has substantially increased our understanding of the mechanisms involved in somatic dysfunction. This paper is an effort to determine what importance may still be ascribed to the proprioceptors in the origin of segmental facilitation (the clinical significance of which has also been explored<sup>5-11</sup>). It is shown that there is now even stronger reason to view the proprioceptors, and most particularly muscle spindles, as key elements in the “neural basis of the osteopathic lesion.” A new theory is offered about the neural mechanisms operating in the osteopathic lesion and about their relation to osteopathic manipulative therapy.

The palpatory criteria for identifying and evaluating the musculoskeletal disorders that are designated “osteopathic lesions” have been described and taught in many different ways. Physicians differ in the ways that they use these criteria in diagnosis and as guides to therapy. However, there seems to be general agreement on the importance of at least one feature, decreased mobility — reduced range or ease of joint motion in one or more planes — and on the importance of restoring mobility. It also seems to be generally assumed that the resistance to motion is within the joint itself, ascribable to articular friction or to the visco-elastic properties of ligamentous structures. This assumption needs to be re-examined. It has, however, been so deeply implicit in osteopathic thinking that it is seldom verbalized, much less questioned, for several reasons. First, the view of the *osteopathic* lesion as a “bony,” “structural,” intervertebral, or articular derangement has such venerated origins as to border on dogma. This

traditional view is reinforced daily by anatomically-worded descriptions that imply displacements and altered interosseous relationships, even when such descriptions are accompanied by protestations that the osteopathic lesion is, of course, a *functional* disturbance, and not a “bone out of place.” Second, the resistance to motion and reduced range of motion, whatever their origin, *are* manifest in reduced joint mobility. Third, in manipulation the vertebrae or other bones are commonly the levers to which the manual forces are applied, and effectiveness of treatment is reflected in their improved mobility.

### The braking power of muscle

To a physiologist, it seems much more reasonable that the limitation and resistance to motion of a joint that characterize an osteopathic lesion do not ordinarily arise within the joint, but are imposed by one or more of the muscles that traverse and move the joint. Of all the somatic tissues (for example, vertebral and paravertebral), muscle is the only active one, the one capable of self-energized, independent motion and of developing great, widely variable, and rapidly changing forces. The other tissues are passively moved, immobilized, pushed, pulled, compressed, and altered in shape by forces external to themselves — those of muscular origin and those external to the body, such as gravity.

While usually thinking of muscles as the motors of the body, producing motion by their contraction, it is important to remember that the same contractile forces are also utilized to *oppose* motion. By the application of controlled counteracting forces, contracting muscle absorbs momentum (for example, of a swinging limb) and regulates, resists, retards, and arrests motion. Indeed, the *energy-absorbing* function of skeletal muscle is no less important to the control of motion than its *energy-imparting* function. Both are based on the same cellular mechanisms — those involved in contraction.

Valuable and quantitative insights into this aspect

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**Display Settings:** Abstract

J Am Osteopath Assoc. 1979 Dec;79(4):232-7.

**The spinal cord as organizer of disease processes: III. Hyperactivity of sympathetic innervation as a common factor in disease.**

Korr IM.

PMID: 583147 [PubMed - indexed for MEDLINE]

MeSH Terms

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## OBITUARY

### Irvin Korr Ph.D. (1909–2004)

We have all heard the expression that as practitioners we are 'standing on the shoulders of giants'? With neurophysiologist Irvin Korr's passing one of the true intellectual giants of the past century has left us.

I did not know him well, but had the good fortune to meet him, and to hear him lecture, and was grateful for his work—which explained a great deal about the mechanisms underpinning osteopathic treatment (Fig. 1). The importance of Korr's work cannot be over-estimated. His pioneering and diligent research, particularly into areas such as segmental facilitation (Korr 1947, 1948, 1986), and the trophic function of nerves (Korr 1967), opened new vistas. He quite literally put flesh on the bones of earlier osteopathic theory. His ability to cross professional and political divides is exemplified by the two contributions (below) to this salute to a marvellous man. These describe the man and his work from the perspectives of two people who knew him, one by an osteopathic teacher, writer and practitioner, Professor Zachary Comeaux DO—and the other by chiropractic teacher, writer and practitioner, Craig Liebenson DC.

Leon Chaitow, Editor JBMT.

#### Zachary Comeaux DO wrote:

March 4, 2004 marked the end of a memorable life, when Irvin Korr Ph.D., Osteopathic Champion, succumbed at 94, in Boulder Colorado. Known to his



Fig. 1 Irvin Korr Ph.D. and JBMTs editor Leon Chaitow, at a 1988 Los Angeles College of Chiropractic Symposium.

many friends in the osteopathic profession as Kim, Korr frequently attributed his long life, and prolonged intellectual activity, to having received quality osteopathic care.

After postgraduate studies in physiology at Princeton University, Kim joined the faculty at Kirksville College of Osteopathy and Surgery in 1945 as professor and chairman of the physiology department. Joining with Stedman Denslow, a 1929 graduate of the same institution, they together spent decades adding scientific legitimacy, through experimentation and publication, to the clinically based practice of osteopathy. Much of their early work centered on demonstrating the hyper-arousal of the sympathetic nervous system associated with what was then termed the osteopathic lesion. Later this was known as the concept of spinal (or segmental) facilitation (Denslow et al., 1947).

Dr. Korr retired from Kirksville College in 1975, assuming a position of professor in the Department of Biomechanics at Michigan State University—College of Osteopathic Medicine. In 1978 he joined the faculty at the Texas College of Osteopathic Medicine as professor of the Department of Osteopathic Theory and Practice. However with the position came responsibility as president, dean, department head and course coordinator. At this time he also met his surviving wife, Janet, who eventually convinced him to move to her home, Boulder.

Korr's keen interest in the neurophysiologic aspects of osteopathic work led to the gamma loop hypothesis for the persistence of increased muscle tone associated with somatic dysfunction Korr (1975). This train of thought was adopted by Fred Mitchell, and also Laurence Jones, to legitimize the theories of Muscle Energy and StrainCounterstrain techniques respectively. Korr wrote prolifically, contributing to the physiological as well as osteopathic literature. A two volume collection of his papers is available from the American Academy of Osteopathy.

A regular speaker at American Academy of Osteopathy and American Osteopathic Association

events, Korr is remembered by many of us today as being part of the effort to bring international understanding and cooperation within the osteopathic profession. At international symposia and conferences he was recognized both as an intellectual and motivational leader. He had a unique way of integrating personal clinical experience (as a patient), deep scientific theoretical understanding, and a dedication to the principles of the unity of the body and the body's self-healing capacity. In this capacity he also participated in a series of symposia, funded by the National Institutes of Health and hosted by the American Academy of Osteopathy, into the nature and understanding of chronic pain.

Besides his research, teaching and public speaking, Kim Korr was known to us as the man he was. He possessed a gentle humor, a deep wisdom and profound humility, which sometimes masked his quiet power. He was personable, and did not live on a pedestal. He will be missed, but his legacy will endure, both in his writings and in the credibility for osteopathy derived from his work.

**Craig Liebenson DC wrote:**

Irvin 'Kim' Korr inspired musculoskeletal specialists to think of the locomotor system as the primary machinery of life. His series of papers entitled *The spinal cord as organizer of disease processes* (Korr, 1976) summarized not only the early osteopathic research on segmental dysfunction, but foretold our modern understanding of central pain states such as central sensitization. Korr was most of all a unique human being whose special gift was his transcendent ability to overcome human limitations such as those imposed by institutions and even aging.

Kim Korr passionately showed that the medical approach of glorifying the viscera, which are merely organs designed to maintain the musculoskeletal system, mis-understands the true nature of the human being. He enjoyed pointing out that the Ciba collection made the common error of showing multitudes of nerve endings traveling to each internal organ, and only a scant few connected to the muscle spindles, golgi tendon organs, and joint mechanoreceptors. He would laugh as he described how actually Ciba had it backwards, since the musculoskeletal system that had 90% of the connections with the nervous system.

For Korr what made us human was our ability to "will action". We express our humanness by choosing to play piano, ski, etc. This concept anchored the osteopathic field in the ennobling area of taking care of the "whole" person, while allopathic physicians were more reductionist. In

spite of Korr's great vision he was terribly disappointed when the osteopathic profession, in the late 1950s, went against his lobbying and chose to align with the medical profession in the US.

Korr was a key figure at the first conference on spinal manipulation put on by the National Institute of Neurological Diseases and Strokes circa 1975. He was so impressed that he convened a follow-up meeting at Michigan State University. Out of this came his book *Neurobiological Mechanisms of Manipulative Therapy* (Korr, 1978). Today there is great wealth of research in our fields. There are also dozens and dozens of premier scientists tackling questions relevant to our practices. Korr blazed this trail with his stunning research on the trophic effects of damage to nerves (Korr, 1967, 1981).

One of the most fascinating aspects to Korr's life was his ability to transform himself. In his 40s he discovered that he had become a sedentary, desk jock and that his vitality was slipping. For one of the first times he visited an osteopath and requested a treatment. A small adjustment was administered. He then went for a walk and found the irresistible urge to break into a jog—for the first time in many years! Soon he was breathing heavily and propped up against a tree when he took a deep breath in and felt his rib cage fully expand literally tearing small adhesions. From that moment he described a transformation in his life. He threw away his sunglasses realizing that he could autonomously control his pupils without them. Yogilike he began to walk the walk of person intent on demonstrating the potential of transformational thinking for promoting health and longevity.

He left Michigan State University in his 60s to join the Texas College of Osteopathic Medicine (TCOM) where he spearheaded efforts to build the first preventive medicine curriculum in North America. When visiting the Los Angeles College of Chiropractic in 1997 he addressed the college's Deans and spoke of his struggles with tenured faculty who resisted the radical curricular changes at TCOM. Korr's stature at such moments could only be described as courageous.

Anyone who spent time with this legendary figure recalls his wonderful sense of humor. Always with a gleam in his eye while he deadpanned one of his frequent puns. It seemed he enjoyed finding connections, not only between somatic structures and the spinal cord, but between words!

During Kim Korr's later years in Texas, just prior to moving to Colorado he found a new passion he called Eugeriatrics. Distilled from his years of experience with osteopaths he found an essential truth regarding the rejuvenating benefits of

# Psychological Stress and Susceptibility to the Common Cold

New England Journal of Medicine

August 29, 1991; Vol. 325; No. 9; pp. 606-612, 654

Cohen S, Tyrrell DA, Smith AP.

Department of Psychology, Carnegie Mellon University, Pittsburgh

These authors prospectively studied the relation between psychological stress and the frequency of documented clinical colds among subjects intentionally exposed to respiratory viruses.

After completing questionnaires assessing degrees of psychological stress, 394 healthy subjects were given nasal drops containing one of five respiratory viruses.

The subjects were then quarantined and monitored for the development of evidence of infection and symptoms.

The rates of both respiratory infection and clinical colds increased in a dose-response manner with increases in the degree of psychological stress.

## CONCLUSIONS:

Psychological stress was associated in a dose-response manner with an increased risk of acute infectious respiratory illness.

## ALSO NOTED IN ARTICLE AND ITS FOLLOW-UP:

"Psychological stress is thought to influence immune function through autonomic nerves innervating lymphoid tissue, or hormone-mediated alteration of immune cells."

"In biomedical terms, 'stress' refers to any adverse physical, mental, or emotional stimulus (stressor) that upsets the organism's homeostasis."

"At the physiological level, stress has been the subject of study going back to Walter B. Cannon's description of the 'fight or flight' response involving actions of the sympathetic nervous system and the adrenal medulla."

# The Sympathetic Nerve—An Integrative Interface between Two Supersystems: The Brain and the Immune System

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Abstract	596
I. Introduction	597
A. Overview	597
B. Historical perspectives	597
II. Anatomy and physiology of the autonomic nervous system	598
A. Organization of the autonomic/sympathetic nervous system	598
B. Role of sympathetic nervous system and hypothalamo-pituitary-adrenal axis in maintaining basal and stress-related homeostasis	599
III. Autonomic/sympathetic innervation of lymphoid organs: nonsynaptic communication	599
A. Innervation of the thymus	601
B. Innervation of the spleen	601
C. Innervation of lymph nodes and tonsils	601
D. Innervation of the bone marrow	601
E. Innervation of mucosa-associated lymphoid tissues	602
F. Coexistence patterns	602
G. General pattern of the autonomic/sympathetic innervation of lymphoid organs	602
H. Spatial relationships with peptidergic innervation	603
I. Neuroimmune connection in nonorganized lymphoid compartments	603
IV. Nonsynaptic release of norepinephrine in lymphoid organs: presynaptic modulation and effect of drugs	603
A. Evidence for neural release of norepinephrine (and dopamine) in lymphoid organs	603
B. Norepinephrine is released and affects immune cells nonsynaptically	604
C. Presynaptic modulation of norepinephrine release in lymphoid organs: effect of drugs	605
D. Release of neuropeptide Y and its action on immune cells	606
V. Systemic and local effects of cytokines on sympathetic nervous system activity	606
A. Systemic effects: long feedback loop between the immune system and the brain	606
B. Local effects of tumor necrosis factor- $\alpha$ and interleukin-1	607
VI. Expression of adrenoceptors on lymphoid cells: signal transduction	608
A. Expression and distribution of adrenoceptors on lymphoid cells	608
B. Signal pathways and molecular aspects of catecholamines actions	609
1. Cyclic adenosine 5'-monophosphate	609
2. Intracellular Ca <sup>2+</sup>	610
VII. Role of sympathetic innervation in immune system development and hematopoiesis	611
A. Immune system development	611
B. Hematopoiesis	611
C. Thymocyte development	612
VIII. Sympathetic control of lymphocyte traffic and circulation	612

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Brain Behav Immun. 2007 Aug;21(6):736-45. Epub 2007 Apr 27.

## Autonomic innervation and regulation of the immune system (1987-2007).

Nance DM, Sanders VM.

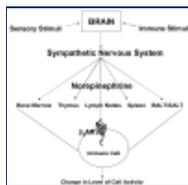
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### Abstract

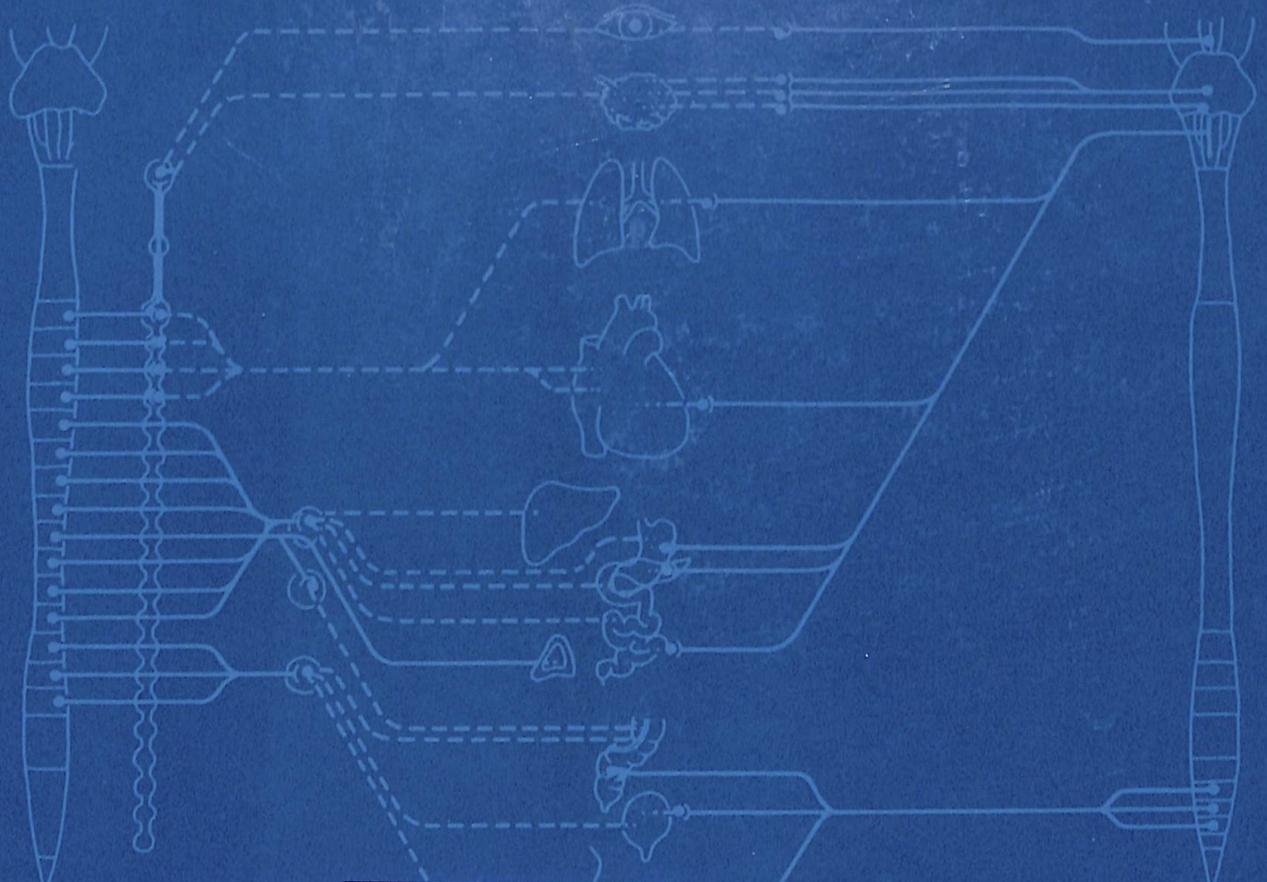
Since 1987, only a few neuroanatomical studies have been conducted to identify the origin of innervation for the immune system. These studies demonstrated that all primary and secondary immune organs receive a substantial sympathetic innervation from sympathetic postganglionic neurons. Neither the thymus nor spleen receive any sensory neural innervation; however, there is evidence that lymph nodes and bone marrow may be innervated by sensory neurons located in dorsal root ganglia. There is no neuroanatomical evidence for a parasympathetic or vagal nerve supply to any immune organ. Thus, the primary pathway for the neural regulation of immune function is provided by the sympathetic nervous system (SNS) and its main neurotransmitter, norepinephrine (NE). Activation of the SNS primarily inhibits the activity of cells associated with the innate immune system, while it either enhances or inhibits the activity of cells associated with the acquired/adaptive immune system. Innate immune cells express both alpha and beta-adrenergic receptor subtypes, while T and B lymphocytes express adrenergic receptors of the beta2 subtype exclusively, except for murine Th2 cells that lack expression of any subtype. Via these adrenergic receptors, NE is able to regulate the level of immune cell activity by initiating a change in the level of cellular activity, which often involves a change in the level of gene expression for cytokines and antibodies.

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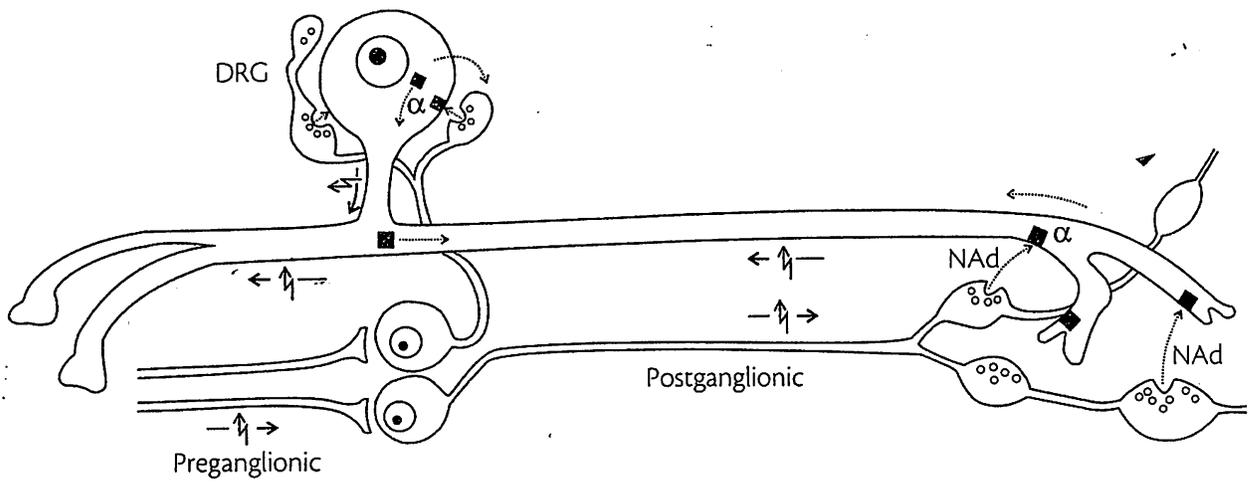
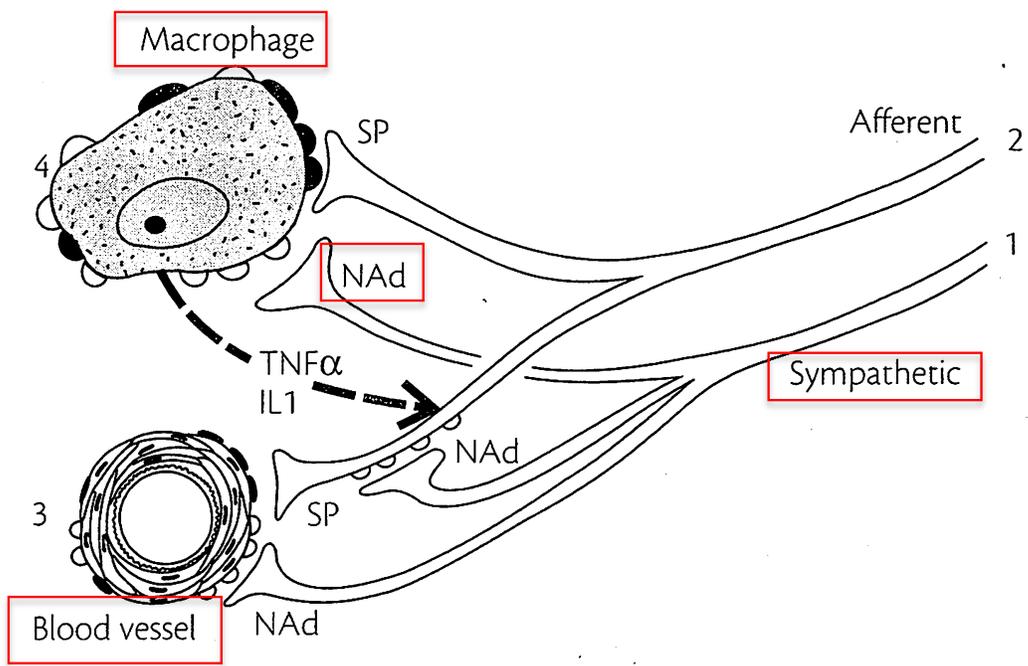
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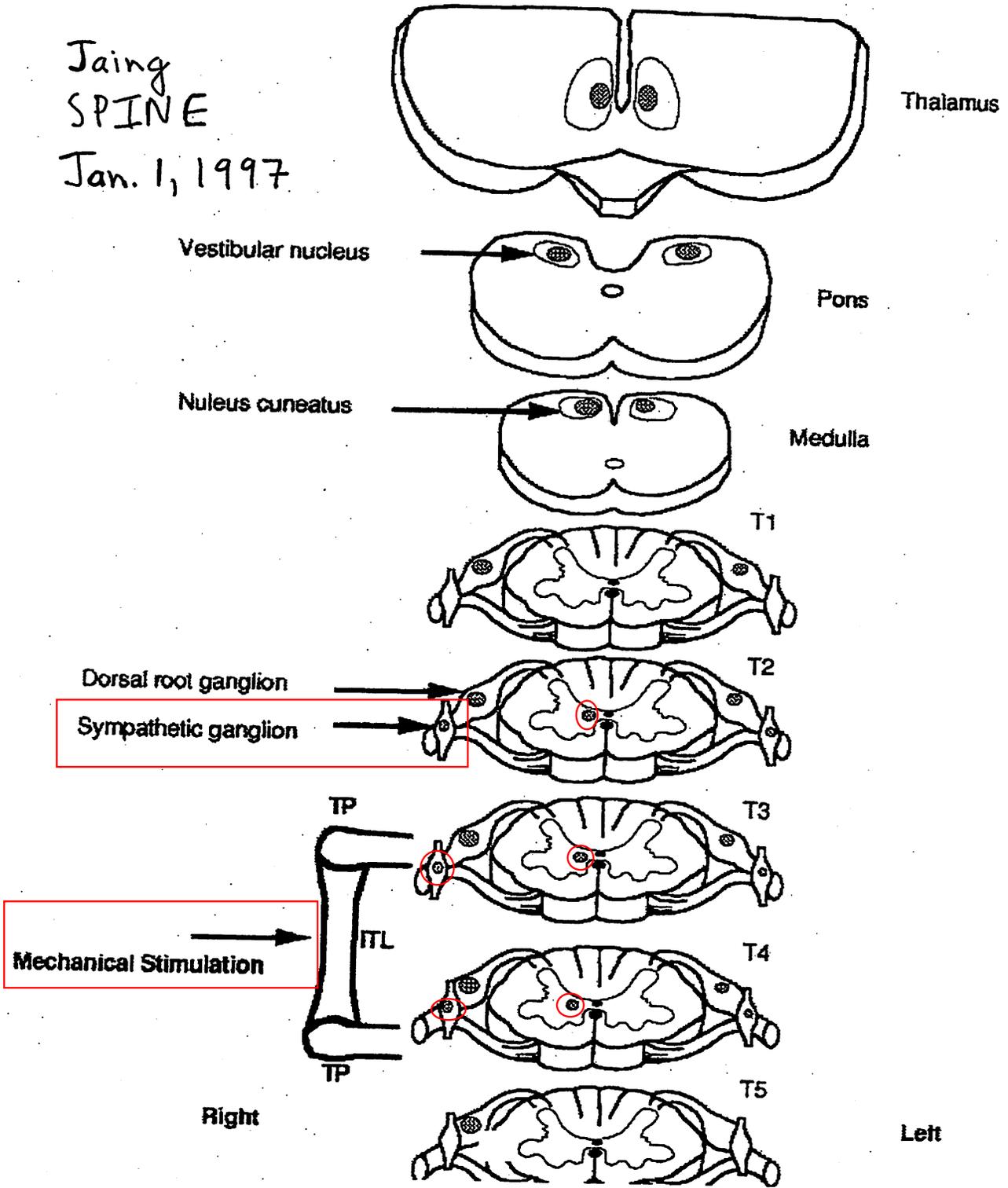
*A Textbook of Clinical Disorders of  
the Autonomic Nervous System*

Fifth Edition



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SPINE

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## Cerebral metabolic changes in men after chiropractic spinal manipulation for neck pain.

Ogura T<sup>1</sup>, Tashiro M, Masud M, Watanuki S, Shibuya K, Yamaguchi K, Itoh M, Fukuda H, Yanai K.

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### Abstract

**BACKGROUND:** Chiropractic spinal manipulation (CSM) is an alternative treatment for back pain. The autonomic nervous system is often involved in spinal dysfunction. Although studies on the effects of CSM have been performed, no chiropractic study has examined regional cerebral metabolism using positron emission tomography (PET).

**OBJECTIVE:** The aim of the present study was to investigate the effects of CSM on brain responses in terms of cerebral glucose metabolic changes measured by [18F]fluorodeoxyglucose positron emission tomography (FDG-PET).

**METHODS:** Twelve male volunteers were recruited. Brain PET scanning was performed twice on each participant, at resting and after CSM. Questionnaires were used for subjective evaluations. A visual analogue scale (VAS) was rated by participants before and after chiropractic treatment, and muscle tone and salivary amylase were measured.

**RESULTS:** Increased glucose metabolism was observed in the inferior prefrontal cortex, anterior cingulate cortex, and middle temporal gyrus, and decreased glucose metabolism was found in the cerebellar vermis and visual association cortex, in the treatment condition ( $P < .001$ ). Comparisons of questionnaires indicated a lower stress level and better quality of life in the treatment condition. A significantly lower VAS was noted after CSM. Cervical muscle tone and salivary amylase were decreased after CSM. Conclusion The results of this study suggest that CSM affects regional cerebral glucose metabolism related to sympathetic relaxation and pain reduction.

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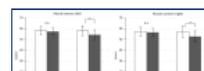
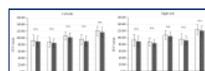
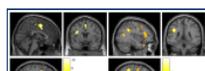
## Glucose Metabolic Changes in the Brain and Muscles of Patients with Nonspecific Neck Pain Treated by Spinal Manipulation Therapy: A [18F]FDG PET Study.

Inami A<sup>1</sup>, Ogura T<sup>2</sup>, Watanuki S<sup>1</sup>, Masud MM<sup>3</sup>, Shibuya K<sup>4</sup>, Miyake M<sup>1</sup>, Matsuda R<sup>1</sup>, Hiraoka K<sup>1</sup>, Itoh M<sup>4</sup>, Fuhr AW<sup>5</sup>, Yanai K<sup>6</sup>, Tashiro M<sup>1</sup>.

### Author information

### Abstract

**Objective.** The aim of this study was to investigate changes in brain and muscle glucose metabolism that are not yet known, using positron emission tomography with [<sup>18</sup>F]fluorodeoxyglucose ([<sup>18</sup>F]FDG PET). **Methods.** Twenty-one male volunteers were recruited for the present study. [<sup>18</sup>F]FDG PET scanning was performed twice on each subject: once after the spinal manipulation therapy (SMT) intervention (treatment condition) and once after resting (control condition). We performed the SMT intervention using an adjustment device. Glucose metabolism of the brain and skeletal muscles was measured and compared between the two conditions. In addition, we measured salivary amylase level as an index of autonomic nervous system (ANS) activity, as well as muscle tension and subjective pain intensity in each subject. **Results.** Changes in brain activity after SMT included activation of the dorsal anterior cingulate cortex, cerebellar vermis, and somatosensory association cortex and deactivation of the prefrontal cortex and temporal sites. Glucose uptake in skeletal muscles showed a trend toward decreased metabolism after SMT, although the difference was not significant. Other measurements indicated relaxation of cervical muscle tension, decrease in salivary amylase level (suppression of sympathetic nerve activity), and pain relief after SMT. **Conclusion.** Brain processing after SMT may lead to physiological relaxation via a decrease in sympathetic nerve activity.

PMID: 28167971 PMCID: [PMC5267084](#) DOI: [10.1155/2017/4345703](#)[PubMed - in process] [Free PMC Article](#)**Images from this publication.** [See all images \(7\)](#) [Free text](#)

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## SYMPATHETIC SEGMENTAL DISTURBANCES—II.

The Evidences of the Association, in Dissected Cadavers, of Visceral Disease with Vertebral Deformities of the Same Sympathetic Segments.

HENRY WINSOR, M.D.,  
Haverford, Pa.

The object of these necropsies was to determine whether any connection existed between minor curvatures of the spine, on the one hand, and diseased organs on the other; or whether the two were entirely independent of each other. The material came from the Laboratory of Operative Surgery on the Cadaver, in the University of Pennsylvania, which is in no way responsible for reductions drawn. In all fifty bodies were examined; the anterior thoracic and abdominal wall removed; the anterior surfaces of the bodies (centra) of the vertebrae were cleared so as to have them distinctly visible. The organs were examined. Notes were then taken in two columns. The first column contains descriptions of the organs which were found diseased; the second column contains descriptions of the curvatures found. When the diseased organs and the vertebrae in

## **Sympathetic Segmental Dysfunction and Visceral Pathology Reviewing the Work of Henry Winsor, MD**

### **Sympathetic Segmental Disturbances: The Evidences of the Association, in Dissected Cadavers, of Visceral Disease with Vertebral Deformities of the Same Sympathetic Segments**

**Medical Times; November 1921; pp. 1-7**

Dr. Winsor used 50 cadavers from the University of Pennsylvania and performed autopsies (necropsies) to determine whether any connection existed between minor curvatures of the spine and diseased visceral organs. Dr. Winsor notes:

Winsor states that "in 50 cadavers with disease in 139 organs, there was found curves of the vertebrae, belonging to the same sympathetic segments as the diseased organs 128 times, leaving an apparent discrepancy of 10, in which the vertebrae in the curve belonged to an adjacent segment to that which should supply the diseased organs with sympathetic filaments." The 10 "apparent discrepancies from adjacent segments" can be accounted for by "nerve filaments leaving the spinal cord and traveling for a few segments." Winsor then remarks that sympathetic efferents commonly travel for a few segments. He then states that if he included the cadaver with "faint curve and slight visceral pathology" that the correlation was 139 out of 139 for 100%.

The pathologies were, "In general, we found the ordinary diseases of adult life."

"All curves and deformities of the spine were rigid, apparently of long duration; irreducible by ordinary manual force: extension, counter-extension, rotation, even strong lateral movements failed to remove them or even cause them to change their relative positions."

"In no instance was a complete sympathetic block observed." [This would suggest that the sympathetic nerve interference is not compressive neuropathology.]

"Sympathetic disturbances are just as likely to be functional or organic disease in viscera, by altering the blood-supply of viscera, through vaso-motor spasm."

"That even where no bony exudates were found, there was intense rigidity of the segments [this sound much like spondylosis complex], showing that fibrous or callous exudates could irritate the sympathetic nerves."

"The organs were in many instances affected by acute disease, while the deformed vertebrae proved that the curvatures preceded the organic diseases..."

The author notes that spondylosis is a process, "the last stage being fixation of segments, immobilization of painful joints being one of nature's later efforts to check disease."

The author describes the spondylosis process as:

The stages of the process appear to be:

- Minor curves, or so-called subluxations;
- The muscles are converted into ligaments, ligaments to bone.
- Finally, true bony ankylosis occurs.

[This perfectly describes the phases of subluxation degeneration from Renaissance.]

**“The disease appears to precede old age and to cause it. The spine becomes stiff first and old age follows. Therefore, we may say a man is as old as his spine, the arteries becoming hardened later from constant vaso-motor spasm, following sympathetic irritation.”** [bold added]

This “irritation of the sympathetic nerves causes reflex spasm of the vaso-motors deranging the blood-supply of the organs supplied by the sympathetic segment in curve.” The results are an increase in lung disease, heart disease, and pneumonia [infection].

“By placing the thumb as the fulcrum of a lever behind the vertebral column, and pressing thereon, the movement of the vertebral column and the *movement of the sympathetic system* can be limited almost exactly to the desired spot.”

The key points that Dr. Winsor makes in this article include:

- 1) Curvatures of the spine adversely affect the sympathetic nervous system.
- 2) The sympathetic nervous system controls the blood supply to the viscera, and is therefore related to all manner of visceral diseases and pathology, and specifically, “the ordinary diseases of adult life.”
- 3) Visceral diseases and pathology can be traced back to the segmental levels of sympathetic involvement with nearly 100% correlation.
- 4) Prolonged abnormal spinal posture stretches the sympathetic nervous system, firing the sympathetics, causing reduced blood supply to visceral organs, and resulting in visceral pathology.
- 5) Abnormal spinal curvatures precede organic visceral diseases.
- 6) Spinal disease precedes old age and causes old age.
- 7) Stiff distorted spines cause sympathetic irritation, vascular spasm, arterial hardening, and old age follows.
- 8) A person is as old as his/her spine.
- 9) Postural distortions causing sympathetic dysfunction can be treated with fulcrum-assisted reversal of the postural distortion.

# Innate Immunity and Sympathetic Nervous System

## AI Overview

The sympathetic nervous system (SNS) and innate immunity interact bidirectionally, with the SNS playing a role in both activating and modulating innate immune responses.

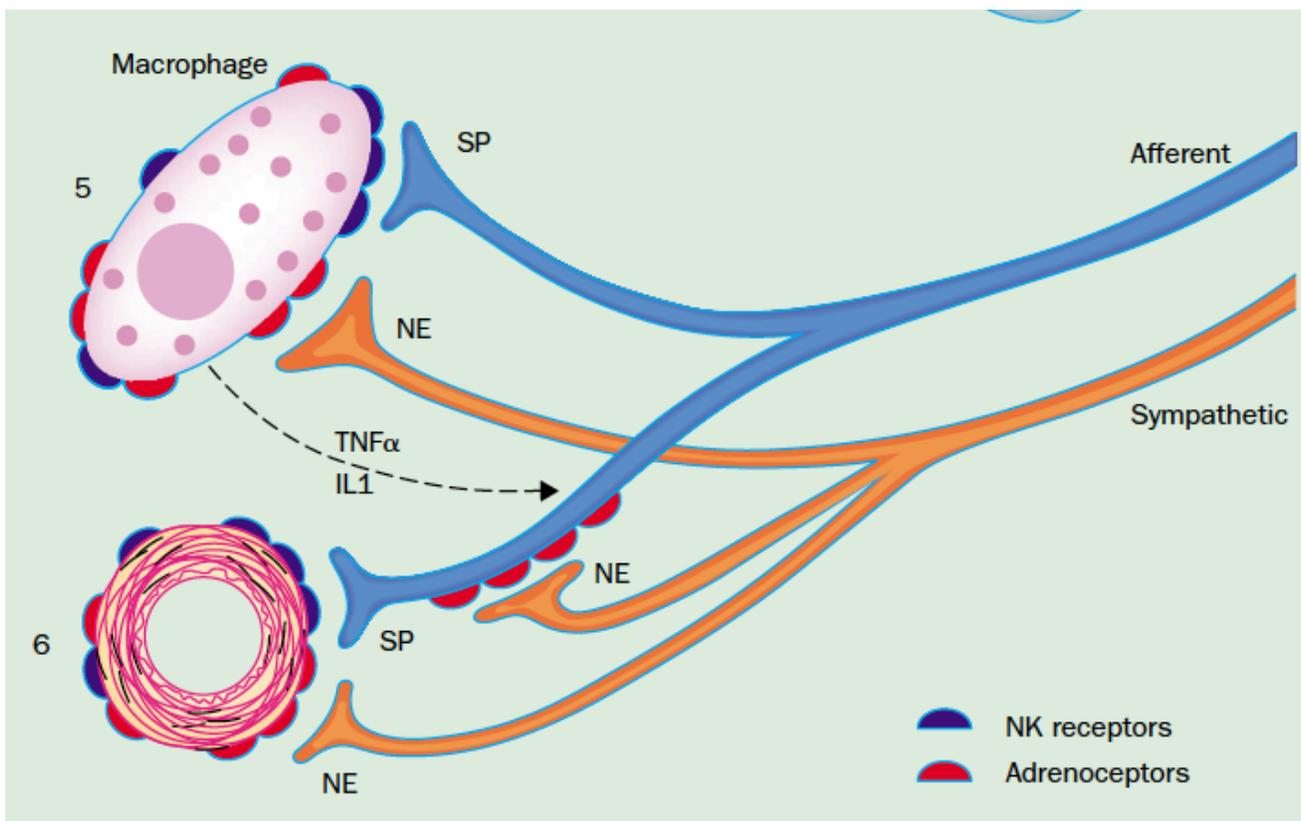
The SNS can suppress innate immunity, while the parasympathetic nervous system, through the vagus nerve, can also influence it.

These interactions are crucial for maintaining immune homeostasis and responding to various stimuli.

# Complex Regional Pain Syndrome: Mystery Explained?

**THE LANCET, Neurology**  
**November 2003; Vol. 2; No. 11; p. 691**

Wilfrid Jänig and Ralf Baron:  
Department of Physiology, Christian-Albrechts  
University of Kiel, Germany





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## Neural regulation of innate immunity: a coordinated nonspecific host response to pathogens

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### Abstract

The central nervous system (CNS) regulates innate immune responses through hormonal and neuronal routes. The neuroendocrine stress response and the sympathetic and parasympathetic nervous systems generally inhibit innate immune responses at systemic and regional levels, whereas the peripheral nervous system tends to amplify local innate immune responses. These systems work together to first activate and amplify local inflammatory responses that contain or eliminate invading pathogens, and subsequently to terminate inflammation and restore host homeostasis. Here, I review these regulatory mechanisms and discuss the evidence indicating that the CNS can be considered as integral to acute-phase inflammatory responses to pathogens as the innate immune system.

The local acute-phase inflammatory response is characterized by *rubor* (redness), *dolor* (pain) and *calor* (heat). Although these are all cardinal clinical features of inflammation, their proximal triggers are neural in origin. Similarly, the systemic acute-phase response also involves key neural elements — fever and activation of the central hormonal-stress response — mediated by the effects of immune factors on the hypothalamus. The cellular and molecular components of the innate immune system provide the first line of defence against invading pathogens<sup>1</sup>, through recognition of pathogen-associated molecular patterns (PAMPs), and initial nonspecific cellular and humoral responses<sup>2</sup>. However, immune mediators and cytokines that are subsequently released by the innate immune system rapidly activate neural responses that both amplify local immune responses to clear pathogens and trigger systemic neuroendocrine and regional neural responses that eventually return the system to a resting state. Although this interplay constitutes an important feedback loop that optimizes innate inflammatory responses to invading pathogens, prolonged or inappropriate central nervous system (CNS) counter-regulatory responses might also predispose the host to excess inflammation (in the context of inadequate hormonal suppression) or uncontrolled infection (in the context of excess or prolonged anti-inflammatory hormonal responses). These can lead to pathological and lethal effects, including toxic shock, tissue damage and death.

### Competing interests statement

The author declares no competing financial interests.

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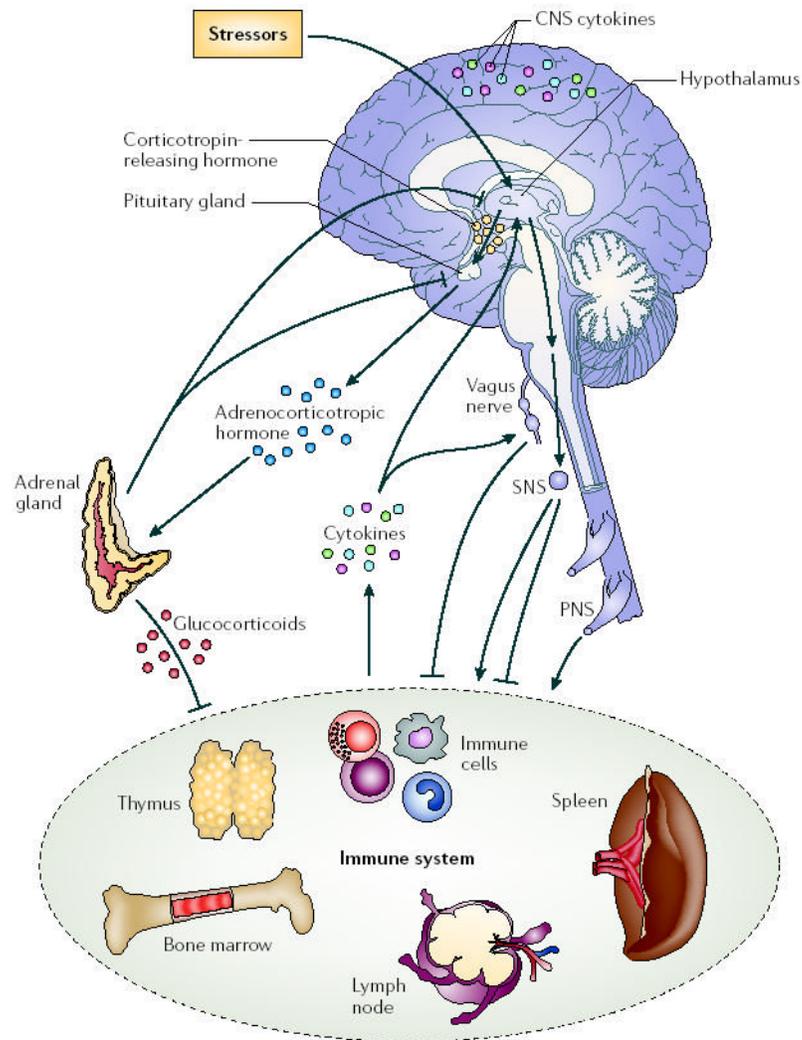
AP1 | CCL2 | CRH | CXCL8 | IFN $\gamma$  | IL-1 $\beta$  | IL-10 | IL-12 | JNK |  $\alpha$ -MSH | MyD88 | NF- $\kappa$ B | NPY | TLR2 | TLR4 | TNF

### FURTHER INFORMATION

Esther Sternberg's homepage:

<http://www.esthersternberg.com>

Access to this links box is available online.



**Figure 1. Schematic illustration of connections between the nervous and immune systems** Signalling between the immune system and the central nervous system (CNS) through systemic routes, the vagus nerve, the hypothalamic–pituitary–adrenal (HPA) axis, the sympathetic nervous system (SNS) and the peripheral nervous system (PNS) are shown. Figure modified with permission from *Molecular Psychiatry* REF. <sup>140</sup> © (2005) Macmillan Magazines Ltd.



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## An overview of the role of sympathetic regulation of immune responses in infectious disease and autoimmunity

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### Abstract

Stress in patients and pre-clinical research animals plays a critical role in disease progression. Activation of the sympathetic nervous system (SNS) by stress results in secretion of the catecholamines epinephrine (Epi) and norepinephrine (NE) from the adrenal gland and sympathetic nerve endings. Adrenergic receptors for catecholamines are present on immune cells and their activity is affected by stress and the accompanying changes in levels of these neurotransmitters. In this short review, we discuss how this adrenergic stress impacts two categories of immune responses: infections and autoimmune diseases. Catecholamines signal primarily through the  $\beta$ 2-adrenergic receptors present on innate and adaptive immune cells which are critical in responding to infections caused by pathogens. In general, this adrenergic input, particularly chronic stimulation, suppresses lymphocytes and allows infections to progress. On the other hand, insufficient adrenergic control of immune responses allows progression of several autoimmune diseases.

### Keywords

SNS;  $\beta$ -adrenergic receptor; infection; autoimmune diseases

### Introduction:

Stress is an inclusive term referring to the physiological response of an organism to any one of a number of factors that disturb some aspect of homeostasis. Stress has undoubtedly been a part of human life since the very beginning of animal existence arising from, for example, pain, fear of predators, or exposure to temperature extremes. “Psychological stress” has become highly prevalent in the 21<sup>st</sup> century and almost everyone experiences the negative impacts of being stressed. Increased chronic stress has been predominantly associated with the exacerbation of many diseases. For example, it has been shown that cancer patients experience increased psychological stress and that those patients with increased stress levels have faster disease progression and higher mortality rates<sup>1</sup>. Although acute stress is often

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**Conflict of Interest Statement:** The authors declare no potential conflicts of interest

# Influence of Routine Exercise on the Peripheral Immune System to Prevent and Alleviate Pain

## Neurobiology of Pain

March 21, 2023; Vol. 13; Article 100126

Joseph B. Lesnak, Giovanni Berardi, Kathleen A. Sluka; from the University of Texas and the University of Iowa. This study cites 154 references. This research was supported by National Institutes of Health.

### KEY POINTS FROM THIS ARTICLE:

- 1) "Routine physical activity reduces the onset of pain and exercise is a first line treatment for individuals who develop chronic pain."
- 2) Regular exercise produces pain relief through multiple mechanisms including alterations in the central and peripheral nervous system.
  - "Repeated exercise as an intervention is commonly prescribed for conditions such as low back pain, osteoarthritis, and fibromyalgia with moderate to strong evidence of effectiveness due to favorable effects in reducing pain severity and improving physical function, cognition, sleep, mental health and more.
  - "Repeated exercise produces systemic changes throughout the body by altering the immune systems response to pain in both preclinical and clinical research."
  - Routine exercise prevents or reduces hyperalgesia in various pain models including inflammatory, muscle, neuropathic, and osteoarthritic.
  - "Regular exercise modulates immune response to pain at multiple sites, including at site of injury, in the dorsal root ganglia (DRG), and systemically throughout the body."
  - Routine exercise slows or prevents osteoarthritis.
  - Repeated exercise performed prior to inducing muscle pain can blunt the immune system response to later insults and prevent pain.
- 3) "Exercise can alter the peripheral immune system to prevent or reduce pain."
  - Exercise can alter the immune system at the site of injury, in the dorsal root ganglia, and systemically throughout the body to produce analgesia.
    - "Most notably exercise shows the ability to dampen the presence of pro-inflammatory immune cells and cytokines at these locations."

4) A single bout of exercise produces an acute inflammatory response, but repeated training can lead to an anti-inflammatory immune profile leading to symptom relief. **[Key Point]**

5) "Physical inactivity increases all-cause mortality and is a risk factor for the development of obesity, cardiovascular disease, diabetes, cancer, dementia, and depression."

- "Physical inactivity is also a risk factor for the development of chronic pain conditions."

6) Exercise has several systemic effects that reduce pain at the level of the brain, spinal cord, and in the periphery.

7) In individuals with chronic pain, there are increases in circulating pro-inflammatory cytokines.

- There is immune system involvement in fibromyalgia, osteoarthritis, rheumatoid arthritis, peripheral neuropathy, low back pain, and complex regional pain syndrome. **[Important]**

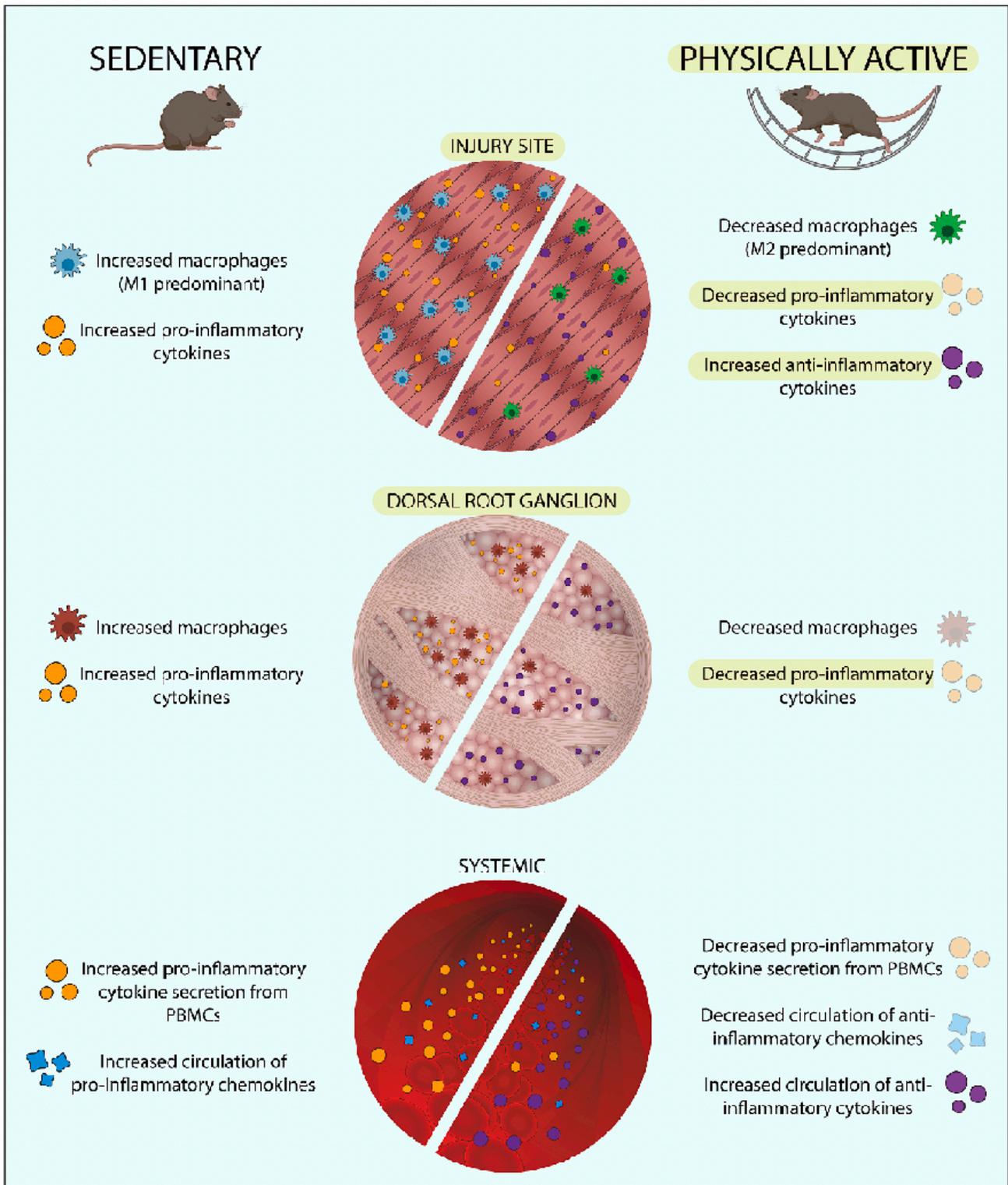
## 8) **Macrophages:**

- "Macrophages are plastic and can have a pro-inflammatory phenotype (M1) or an anti-inflammatory phenotype (M2)." **[Very Important]**
- M1 macrophages are responsible for phagocytic activity and secrete pro-inflammatory cytokines such as IL-1 $\beta$ , IL-6, and TNF $\alpha$ .
- "M2 macrophages are responsible for tissue repair and secrete anti-inflammatory cytokines such as IL-10, IL-4 and IL-1."
- Exercise decreases M1 macrophages and the cytokines IL-6, IL-1 $\beta$ , and TNF $\alpha$ .
- Exercise increases M2 macrophages and the cytokines IL-10, IL-4, and IL-1.
- In sedentary animals, induction of pain increases M1 macrophages.
- In animals that have been exercising, induction of pain increases M2 macrophages.
  - "Prior exercise can impact how the immune system responds to later insults to prevent the onset of muscle pain."

9) Exercise reduces pro-inflammatory cytokines IL-1 $\beta$ , TNF $\alpha$ , and IL-6 and increases the levels of anti-inflammatory cytokines IL-4, IL-10, and IL-1.

10) IL-10 is a crucial mediator in exercise's ability to prevent pain.

- Increases in anti-inflammatory cytokines mediate the ability of regular exercise to alleviate neuropathic pain. **[Important]**



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J Manipulative Physiol Ther. 2016 Jan;39(1):42-53. doi: 10.1016/j.jmpt.2015.12.004. Epub 2016 Feb 1.

## Attenuation Effect of Spinal Manipulation on Neuropathic and Postoperative Pain Through Activating Endogenous Anti-Inflammatory Cytokine Interleukin 10 in Rat Spinal Cord.

Song XJ<sup>1</sup>, Huang ZJ<sup>2</sup>, Song WB<sup>3</sup>, Song XS<sup>2</sup>, Fuhr AF<sup>4</sup>, Rosner AL<sup>5</sup>, Ndtan H<sup>6</sup>, Rupert RL<sup>5</sup>.

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### Abstract

**OBJECTIVES:** The purpose of this study was to investigate roles of the anti-inflammatory cytokine interleukin (IL) 10 and the proinflammatory cytokines IL-1 $\beta$  and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) in spinal manipulation-induced analgesic effects of neuropathic and postoperative pain.

**METHODS:** Neuropathic and postoperative pain were mimicked by chronic compression of dorsal root ganglion (DRG) (CCD) and decompression (de-CCD) in adult, male, Sprague-Dawley rats. Behavioral pain after CCD and de-CCD was determined by the increased thermal and mechanical hypersensitivity of the affected hindpaw. Hematoxylin and eosin staining, whole-cell patch clamp electrophysiological recordings, immunohistochemistry, and enzyme-linked immunosorbent assay were used to examine the neural inflammation, neural excitability, and expression of c-Fos and PKC as well as levels of IL-1 $\beta$ , TNF- $\alpha$ , and IL-10 in blood plasma, DRG, or the spinal cord. We used the activator adjusting instrument, a chiropractic spinal manipulative therapy tool, to deliver force to the spinous processes of L5 and L6.

**RESULTS:** After CCD and de-CCD treatments, the animals exhibited behavioral and neurochemical signs of neuropathic pain manifested as mechanical allodynia and thermal hyperalgesia, DRG inflammation, DRG neuron hyperexcitability, induction of c-Fos, and the increased expression of PKC $\gamma$  in the spinal cord as well as increased level of IL-1 $\beta$  and

TNF- $\alpha$  in DRG and the spinal cord. Repetitive Activator-assisted spinal manipulative therapy significantly reduced simulated neuropathic and postoperative pain, inhibited or reversed the neurochemical alterations, and increased the anti-inflammatory IL-10 in the spinal cord.

**CONCLUSION:** These findings show that spinal manipulation may activate the endogenous anti-inflammatory cytokine IL-10 in the spinal cord and thus has the potential to alleviate neuropathic and postoperative pain.

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**KEYWORDS:** Ganglia; Interleukin-10; Interleukin-1beta; Nervous System; Pain; Spinal; Spinal manipulation; Trauma

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## Nonspecific Low Back Pain

## Inflammatory Profiles of Patients With Acute and Chronic Pain

Julita A. Teodorczyk-Injeyan, PhD,\* John J. Triano, DC, PhD,\*  
and H. Stephen Injeyan, DC, PhD†

**Background:** The pathogenesis of low back pain (LBP) remains unclear. However, recent studies suggest that the inflammatory response may be inherent in spinal pain. The purpose of this study was to discern inflammatory profiles in patients with nonspecific acute and chronic LBP in relation to those in asymptomatic individuals.

**Materials and Methods:** Peripheral blood samples were obtained from asymptomatic controls and patients with nonspecific acute and chronic LBP reporting a minimum pain score of 3 on a 10-point Visual Analogue Scale (VAS). The levels of in vitro production of proinflammatory (tumor necrosis factor  $\alpha$  [TNF $\alpha$ ], interleukin [IL] 1 $\beta$ , IL-6, IL-2, interferon  $\gamma$ ) and anti-inflammatory (IL-1 receptor antagonist, soluble receptors of TNF2, and IL-10) mediators were determined by specific immunoassays.

**Results:** The mean VAS scores were comparable between the acute and chronic LBP patient groups. Compared with asymptomatic group, the production of TNF $\alpha$ , IL-1 $\beta$ , IL-6 and their ratios to IL-10 levels were significantly elevated in both patient groups ( $P=0.0001$  to  $0.003$ ). In acute LBP group, the ratio of IL-2:IL-10 was also significantly increased ( $P=0.02$ ). In contrast, the production of interferon  $\gamma$  was significantly reduced compared with the other study groups ( $P=0.005$  to  $0.01$ ), nevertheless, it was positively correlated ( $P=0.006$ ) with pain scores. In chronic LBP patients, the production of TNF $\alpha$ , IL-1 receptor antagonist, and soluble receptors of TNF2 was significantly increased ( $P=0.001$  to  $0.03$ ) in comparison with the control and acute LBP groups, and TNF $\alpha$  and IL-1 $\beta$  levels were positively correlated ( $P<0.001$ ) with VAS scores.

**Conclusions:** The inflammatory profiles of patients with acute and chronic LBP are distinct. Nonetheless, in both patient groups, an imbalance between proinflammatory and anti-inflammatory mediator levels favors the production of proinflammatory components.

**Key Words:** low back pain, inflammation, cytokines, inflammatory mediators

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Although nonspecific low back pain (LBP) is very common,<sup>1</sup> treatment outcomes remain questionable both for acute<sup>2</sup> and chronic LBP.<sup>3</sup> The pathophysiology of LBP remains poorly understood, and its diagnosis is based on excluding other spinal pain disorders for which there are clear diagnostic criteria.<sup>1</sup>

Several studies have reported on the possible involvement of inflammatory cytokines in heterogenous cohorts of LBP patients. Systemic levels of inflammatory markers including interleukin (IL) 6, tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) or C-reactive protein (CRP) were found to be elevated in diverse groups of LBP patients.<sup>4–6</sup> Li et al<sup>7</sup> described elevated IL-6, and reduced IL-10 levels in peripheral blood of chronic LBP patients, thereby suggesting that an imbalance between proinflammatory and anti-inflammatory mediators contributes to the pathophysiology of LBP. Increased plasma levels of IL-6 in chronic LBP have been reported to correlate with pain intensity levels.<sup>8</sup> Also, the production of nociceptive chemokines CCL2, CCL3, and CCL4, as well as the inflammatory marker, soluble E-selectin, have been shown to be significantly augmented in patients with nonspecific acute and chronic LBP.<sup>9</sup>

The interactions of proinflammatory and anti-inflammatory molecules within the local inflammatory milieu are complex. It is expected that the nature of LBP-related inflammatory changes and thereby response to applied therapies may vary in patients due to different factors including the intensity and duration of pain and chronicity of the condition.

Investigations into pain mechanisms in spinal pain patients with herniated disks and those with diskogenic pain have suggested an imbalance of catabolic and anabolic processes leading to increased expression of inflammatory mediators.<sup>10,11</sup> An imbalance in inflammatory cytokine network has been suggested for degenerative joint disease generally<sup>12</sup> and a shift towards “pain susceptible” (inflammatory) cytokine profile has been also reported in patients with painful neuropathies.<sup>13</sup>

Physiologically, anti-inflammatory cytokines such as IL-10 inhibit the production of proinflammatory cytokines by activated macrophages and enhance the production of natural inhibitors of their biologic activity including interleukin-1 receptor antagonist (IL-1RA) and soluble receptors of tumor necrosis factor (sTNFRs).<sup>14</sup> To our knowledge, no studies have explored the possible interplay between proinflammatory and anti-inflammatory mediators in the pathophysiology of nonspecific LBP. As part of an ongoing study of the role of inflammatory response in nonspecific LBP, we examined the production of mediators with the functional ability to promote the inflammatory response (TNF $\alpha$ , IL-1 $\beta$ , IL-6, IL-2, and interferon  $\gamma$  [IFN $\gamma$ ]) or deliver an anti-inflammatory effect (IL-1RA, IL-10, sTNFR2, and



# Macrophages: The Good, the Bad, and the Gluttony

Ewan A. Ross, Andrew Devitt and Jill R. Johnson\*

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Macrophages are dynamic cells that play critical roles in the induction and resolution of sterile inflammation. In this review, we will compile and interpret recent findings on the plasticity of macrophages and how these cells contribute to the development of non-infectious inflammatory diseases, with a particular focus on allergic and autoimmune disorders. The critical roles of macrophages in the resolution of inflammation will then be examined, emphasizing the ability of macrophages to clear apoptotic immune cells. Rheumatoid arthritis (RA) is a chronic autoimmune-driven spectrum of diseases where persistent inflammation results in synovial hyperplasia and excessive immune cell accumulation, leading to remodeling and reduced function in affected joints. Macrophages are central to the pathophysiology of RA, driving episodic cycles of chronic inflammation and tissue destruction. RA patients have increased numbers of active M1 polarized pro-inflammatory macrophages and few or inactive M2 type cells. This imbalance in macrophage homeostasis is a main contributor to pro-inflammatory mediators in RA, resulting in continual activation of immune and stromal populations and accelerated tissue remodeling. Modulation of macrophage phenotype and function remains a key therapeutic goal for the treatment of this disease. Intriguingly, therapeutic intervention with glucocorticoids or other DMARDs promotes the re-polarization of M1 macrophages to an anti-inflammatory M2 phenotype; this reprogramming is dependent on metabolic changes to promote phenotypic switching. Allergic asthma is associated with Th2-polarised airway inflammation, structural remodeling of the large airways, and airway hyperresponsiveness. Macrophage polarization has a profound impact on asthma pathogenesis, as the response to allergen exposure is regulated by an intricate interplay between local immune factors including cytokines, chemokines and danger signals from neighboring cells. In the Th2-polarized environment characteristic of allergic asthma, high levels of IL-4 produced by locally infiltrating innate lymphoid cells and helper T cells promote the acquisition of an alternatively activated M2a phenotype in macrophages, with myriad effects on the local immune response and airway structure. Targeting regulators of macrophage plasticity is currently being pursued in the treatment of allergic asthma and other allergic diseases. Macrophages promote the re-balancing of pro-inflammatory responses towards pro-resolution responses and are thus central to the success of an inflammatory response. It has long been established that apoptosis supports monocyte and macrophage recruitment to sites of inflammation, facilitating subsequent corpse clearance. This drives resolution responses and mediates a phenotypic switch in the polarity of macrophages. However, the role of apoptotic cell-derived extracellular vesicles

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# Adrenergic signaling regulation of macrophage function: do we understand it yet?

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## Summary

Macrophages are immune cells that are widespread throughout the body and critical for maintaining tissue homeostasis. Their remarkable plasticity allows them to acquire different phenotypes, becoming able either to fight infection (M1-like, classically activated macrophages) or to promote tissue remodeling and repair (M2-like, alternatively activated macrophages). These phenotypes are induced by different cues present in the microenvironment. Among the factors that might regulate macrophage activation are mediators produced by different branches of the nervous system. The regulation exerted by the sympathetic nervous system (SNS) on macrophages (and the immune system in general) is becoming a subject of increasing interest, indeed a great number of articles have been published lately. Catecholamines (noradrenaline and adrenaline) activate  $\alpha$  and  $\beta$  adrenergic receptors expressed by macrophages and shape the effector functions of these cells in contexts as diverse as the small intestine, the lung, or the adipose tissue. Activation of different subsets of receptors seems to produce antagonistic effects, with  $\alpha$  adrenergic receptors generally associated with pro-inflammatory functions and  $\beta$  adrenergic receptors (particularly  $\beta_2$ ) related to the resolution of inflammation and tissue remodeling. However, exceptions to this paradigm have been reported, and the factors contributing to these apparently contradictory observations are still far from being completely understood. Additionally, macrophages *per se* seem to be sources of catecholamines, which is also a subject of some debate. In this review, we discuss how activation of adrenergic receptors modulates macrophage effector functions and its implications for inflammatory responses and tissue homeostasis.

**Keywords:** macrophage, adrenergic signaling, neuroimmune interactions, sympathetic nervous system

**Abbreviations:** AR, Adrenergic receptors; ATM, Adipose tissue macrophage; BALF, Bronchoalveolar lavage fluid; BAT, Brown adipose tissue; BMDM, Bone marrow-derived macrophages; CLP, Cecal ligation and puncture; CRS, Cytokine release syndrome; DBH, Dopamine  $\beta$ -hydroxylase; EPAC, Exchange protein directly activated by cAMP; HCC, Hepatocellular carcinoma; HPLC, High-performance liquid chromatography; IFN- $\gamma$ , Interferon-gamma; iNOS, Inducible nitric oxide synthase; KC, Kupffer cells; LPS, Lipopolysaccharide; MAOA, Monoamine oxidase A; MM, Muscularis macrophages; NE, Noradrenaline; NO, Nitric oxide; OXPHOS, Oxidative phosphorylation; PMNs, Polymorphonuclear leukocytes; PKA, Protein kinase A; PKC, Protein kinase C; PRR, Pattern recognition receptor; ROS, Reactive oxygen species; SDR, Social disruption stress; SNS, Sympathetic nervous system; TH, Tyrosine hydroxylase; TNF- $\alpha$ , Tumor Necrosis Factor alpha; TLRs, Toll-like receptor; WAT, White adipose tissue.

## Introduction

Macrophages are potent phagocytes either derived from precursors in the yolk sac or from circulating monocytes that differentiate from the myeloid common precursor in the bone marrow. Macrophages originated during embryogenesis are resident macrophages that play a fundamental role in tissue surveillance and homeostasis, whereas monocyte-derived macrophages rapidly infiltrate into infected or injured tissues and are activated upon pathogen- and damage-derived signals (Fig. 1). This rapid activation results in the initiation of microbicidal activity and the promotion of tissue inflammation. In this sense, macrophages actively participate in the orchestration of the innate immune response upon infection. In contrast, macrophages that reside in tissues at the steady state execute equally essential non-immune functions for the host, such as iron recycling, synaptic pruning, removal of dying cells or tissue debris, and tissue repair and remodeling [1].

It has been proposed that macrophages present two major phenotypes, driven *in vitro* by cell activation with different

stimuli. Classically activated macrophages are induced by LPS and interferon-gamma (IFN- $\gamma$ ) and possess a pro-inflammatory phenotype. A hallmark of this phenotype is the upregulation of *Nos2* gene expression, which results in the high production of the microbicidal molecule nitric oxide (NO). Classically activated macrophages produce high amounts of pro-inflammatory cytokines such as IL-6, TNF- $\alpha$ , and IL-1 $\beta$  and are foremost in immune responses against intracellular pathogens. On the other hand, alternatively activated macrophages are induced by cell activation with IL-4 or immune complexes, and one of its hallmarks is the upregulation of *Arg1*, which competes with *Nos2* for the metabolism of L-arginine. This subset is known to release IL-4, IL-13, and IL-10, playing a pivotal role in immune responses against helminthic infections. Another crucial function of alternatively activated macrophages is to initiate the resolution phase of inflammatory responses and to promote tissue repair. Although these prototypical phenotypes can be observed *in vitro*, they are not very well defined *in vivo* and can be modulated by other microenvironment factors. A general

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## REVIEW

# Macrophage plasticity: signaling pathways, tissue repair, and regeneration

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## Abstract

Macrophages are versatile immune cells with remarkable plasticity, enabling them to adapt to diverse tissue microenvironments and perform various functions. Traditionally categorized into classically activated (M1) and alternatively activated (M2) phenotypes, recent advances have revealed a spectrum of macrophage activation states that extend beyond this dichotomy. The complex interplay of signaling pathways, transcriptional regulators, and epigenetic modifications orchestrates macrophage polarization, allowing them to respond to various stimuli dynamically. Here, we provide a comprehensive overview of the signaling cascades governing macrophage plasticity, focusing on the roles of Toll-like receptors, signal transducer and activator of transcription proteins, nuclear receptors, and microRNAs. We also discuss the emerging concepts of macrophage metabolic reprogramming and trained immunity, contributing to their functional adaptability. Macrophage plasticity plays a pivotal role in tissue repair and regeneration, with macrophages coordinating inflammation,

#Lingfeng Yan and Jue Wang authors have contributed equally to this work.

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## Review Article

## Role of adrenergic receptor signalling in neuroimmune communication



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## ARTICLE INFO

## Keywords:

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## ABSTRACT

Neuroimmune communication plays a crucial role in maintaining homeostasis and promptly responding to any foreign insults. Sympathetic nerve fibres are innervated into all the lymphoid organs (bone marrow, thymus, spleen, and lymph nodes) and provide a communication link between the central nervous system (CNS) and ongoing immune response in the tissue microenvironment. Neurotransmitters such as catecholamines (epinephrine and norepinephrine) bind to adrenergic receptors present on most immune and non-immune cells, establish a local neuroimmune-communication system, and help regulate the ongoing immune response. The activation of these receptors varies with the type of receptor-activated, target cell, the activation status of the cells, and timing of activation. Activating adrenergic receptors, specifically  $\beta$ -adrenergic signalling in immune cells leads to activation of the cAMP-PKA pathway or other non-canonical pathways. It predominantly leads to immune suppression such as inhibition of IL-2 secretion and a decrease in macrophages phagocytosis. This review discusses the expression of different adrenergic receptors in various immune cells, signalling, and how it modulates immune cell function and contributes to health and diseases. Understanding the neuroimmune communication through adrenergic receptor signalling in immune cells could help to design better strategies to control inflammation and autoimmunity.

## 1. Introduction

The sympathetic nervous system (SNS) plays a vital role in maintaining the homeostasis of the body by secreting different neurotransmitters like catecholamines, acetylcholine, glutamine, etc. Among all the neurotransmitters, catecholamine has a very important and diversified role in the various organs. Catecholamines contain a catechol (3,4 dihydroxyphenyl) group along with an amine group. John Jacob Abel, in 1897 first obtained a crystalline substance from the adrenal gland of sheep in an impure form that can regulate blood pressure, and he named it epinephrine (Greek *epi* and *nephros* mean ‘on the kidney’) (Scanzano and Cosentino, 2015). But in 1900, Jokichi Takamine obtained a pure crystalline form of epinephrine. He patented it with the name adrenalin (Latin *ad* and *Renēs* means “near the kidney”) and marketed by Parke, Davis & Company (Wang et al., 2009). British Approved Name (BAN) introduced the name “adrenaline” in the United Kingdom and British Commonwealth. Still, United States Approved Name (USAN) used the term “epinephrine” for this neurotransmitter in the USA. To avoid such

controversy, Recommended International Nonproprietary Name (rINN) formulated some standard names for all drugs, but as an exception, adrenaline and noradrenaline are still being used rather than their rINN name epinephrine and norepinephrine (Schedler, 2006). Soon after discovering epinephrine, norepinephrine was synthesized, but on July 7, 1946, Ulf von Euler pointed out that norepinephrine has a sympathomimetic role in the body (Shampo and Kyle, 1995). Chromaffin cells of the adrenal medulla secrete both epinephrine and norepinephrine, which are directly secreted into the bloodstream after stimulation with sympathetic nerve fibre. Some parts of the central nervous system, like the amygdala region, are also known to secrete epinephrine as a neurotransmitter forming the locus coeruleus-noradrenergic system or LC-NA system, which regulates arousal, attention, and stress response (Benarroch, 2009). The hypothalamic-pituitary-adrenal axis and sympathoadrenergic fibres establish a major neuroimmune communication pathway to regulate the immune response.

Adrenaline is synthesized from its precursor amino acid tyrosine; it is also synthesized from hepatic hydroxylation of another amino acid,

; SNS, Sympathetic nervous system; L-DOPA, L-dihydroxyphenylalanine; AC, Adenylate cyclase; GRK, G protein-coupled receptor kinase; CNS, Central Nervous System; DCs, Dendritic cells; LPS, Lipopolysaccharide; TNF, Tumor necrosis factor; PKA, Protein kinase A; PDE, Phosphodiesterase; cAMP, Cyclic adenosine monophosphate.

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phenylalanine. Synthesis of catecholamine begins with the rate-limiting step governed by the enzyme tyrosine hydroxylase, which converts tyrosine into L-DOPA (L-dihydroxyphenylalanine). Subsequently, L-DOPA is converted to dopamine and then to norepinephrine by DOPA decarboxylase and dopamine beta-hydroxylase, respectively (Fig. 1). Dopamine beta-hydroxylase is a copper-containing enzyme and requires ascorbic acid for its function. In the chromaffin cells of the adrenal medulla, norepinephrine is then converted to epinephrine by the enzyme phenylethanolamine-N-methyltransferase. The synthesis of adrenaline is controlled by glucocorticoids, which enter the chromaffin cells and stimulate the enzyme phenylethanolamine-N-methyl transferase (PNMT) (Wurtman et al., 1972). Acetylcholine also drives catecholamine secretion by nicotinic and muscarinic acetylcholine receptors (Wakade and Wakade, 1983).

Both epinephrine and norepinephrine stimulate common receptors named adrenergic receptors. Structurally these receptors have seven hydrophobic transmembrane regions and an intracellular C-terminal domain and an extracellular N-terminal domain, along with 3 intracellular and extracellular loops. The N-terminal domain contains sites for N-linked glycosylation. (Strosberg, 1993). Based on specificity to epinephrine, adrenergic receptors are broadly divided into three categories,  $\alpha 1$ ,  $\alpha 2$ , and  $\beta$  adrenergic receptors (Roth et al., 1991). The  $\alpha 1$  and  $\alpha 2$  are again subdivided into  $\alpha 1A$ ,  $\alpha 1B$ ,  $\alpha 1D$  and  $\alpha 2A$ ,  $\alpha 2B$ , and  $\alpha 2C$ , respectively.  $\beta$  adrenergic receptor is divided into  $\beta 1$ ,  $\beta 2$ , and  $\beta 3$ . These receptors and their tissue distribution are listed in Table 1. These receptors resemble a serpentine structure, but they vary in the intracellular C terminal region (Roth et al., 1991; Strosberg, 1993).

## 2. Types of adrenergic receptor

Radioligand binding assays suggested the presence of nine different types of adrenergic receptors, and all of them have a different affinity towards epinephrine and norepinephrine. Each of these nine receptors has been discussed in detail in the following paragraphs.

**Table 1**

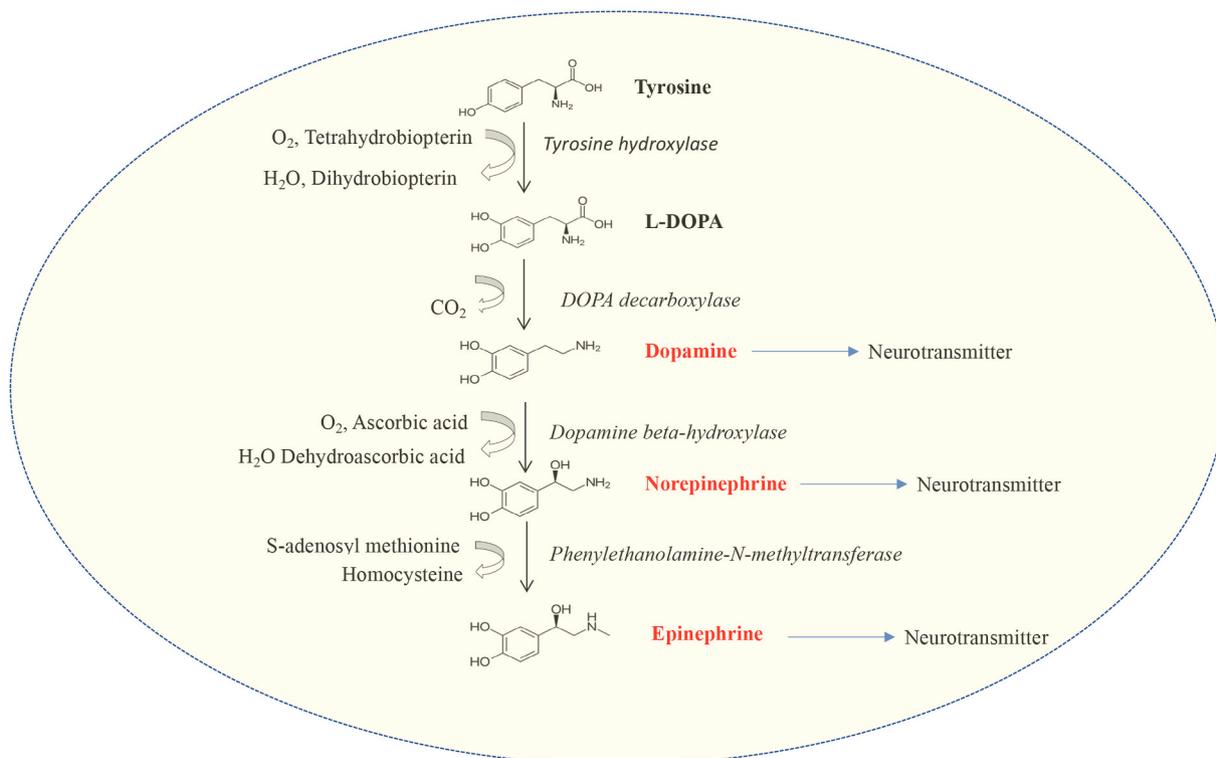
Tissue distribution of adrenergic receptors and their associated G proteins.

Receptor types	Associated G proteins	Tissues	References
$\alpha 1A$	$G_q/11(G_q)$	Cerebral cortex, cerebellum, heart, liver, prostate, lymphocytes, heart	(O'Connell et al., 2014; Scanzano and Cosentino, 2015)
$\alpha 1B$	$G_q/11(G_q)$	Spleen, kidney, endothelial cells, osteoblast, lymphocytes, heart	(O'Connell et al., 2014; Scanzano and Cosentino, 2015)
$\alpha 1D$	$G_q/11(G_q)$	Cerebral cortex, aorta, blood vessel, lymphocytes, heart	(O'Connell et al., 2014; Scanzano and Cosentino, 2015)
$\alpha 2A$	$G_i/G_o$	Brain, spleen, kidney, lung, liver	Scanzano and Cosentino (2015)
$\alpha 2B$	$G_i/G_o$	Kidney, liver, brain, heart, cardiac muscle	Scanzano and Cosentino (2015)
$\alpha 2C$	$G_i/G_o$	Brain, kidney, heart, spleen	Scanzano and Cosentino (2015)
$\beta 1$	$G_s$	Brain, kidney, lungs, spleen, liver, muscles	Scanzano and Cosentino (2015)
$\beta 2$	$G_s$	Brain, lung, lymphocyte, skin, liver, heart	Scanzano and Cosentino (2015)
$\beta 3$	$G_s$	Adipose tissues, stomach, gall bladder	Scanzano and Cosentino (2015)

### 2.1. Alpha ( $\alpha$ ) 1 adrenergic receptor

#### 2.1.1. $\alpha 1A$ adrenergic receptor

Formerly known as the  $\alpha 1C$  adrenergic receptor, this receptor contains 466 amino acid residues identified in the bovine brain (Langer, 1998). They are profoundly expressed in the brain, heart, kidney, prostate, smooth muscles, etc. (Cotecchia, 2010). A small group of adrenergic receptors identified in the prostate has a low affinity towards prazosin an  $\alpha$ -blocker than the other  $\alpha 1$  adrenergic receptors (Docherty, 2019).  $\alpha 1A$  adrenergic receptor helps contract different tissues like the aorta, vas deference, lower urinary tract, heart, etc., in



**Fig. 1. Synthesis of catecholamines (dopamine, norepinephrine, and epinephrine).** The various steps, enzymes and co-factors required for the synthesis are depicted.

## **A Randomized Controlled Trial of Chiropractic Spinal Manipulative Therapy for Migraine**

**Journal of Manipulative and Physiological Therapeutics**  
**February 2000; Vol. 23; No. 2; pp. 91-95**

Peter J. Tuchin, Henry Pollard, Rod Bonello; from Macquarie University, New South Wales, Australia. This study cites 39 references.

This is a randomized controlled trial of 6 months' duration. The object was to assess the efficacy of chiropractic spinal manipulative therapy (SMT) in the treatment of migraine. It used 123 subjects (83 manipulation and 40 controls) with a minimum of 1 migraine per month. The majority of subjects had migraines for 18 years (chronic migraines).

The intervention was 2 months of chiropractic diversified technique manipulation at vertebral fixations, determined by the practitioner, with a maximum of 16 visits.

The control group received detuned interferential therapy, which consisted of electrodes being placed on the patient with no current sent through the machine.

Statistical analysis involved comparing the changes for the different outcome measurements of incidence, intensity, duration, disability, and drug use.

### KEY POINTS FROM THIS ARTICLE:

- 1) About 12% of Australians aged 15 years and over experience migraines.
- 2) The estimated yearly cost of migraines in the US is over \$17 billion (US).
- 3) The Headache Classification Committee of the International Headache Society defines migraines as having:
  - Unilateral location
  - Pulsating quality
  - Moderate or severe intensity
  - Aggravated by routine physical activity
  - "During the headache, the person must also experience either nausea, vomiting, or both or photophobia, phonophobia, or both."
  - Migraine may or may not have aura; aura usually consists of:
    - Visual disturbances
    - Unilateral paresthesia or numbness or both
    - Unilateral weakness
    - Aphasia
    - Speech difficulty
    - Cases of tactile hallucinations have even been reported
    - "Some subjects with migraines have described the aura as an opaque object or a zigzag line around a cloud."

## 4) Anatomy:

- Migraines are related to cervicogenic conditions.
- The cervical spine is involved in headache, dizziness, and other referred pain.
- Surgical decompression of the C2 nerve root results in reduction of nausea, photophobia, phonophobia, and vomiting.
- The trigeminocervical nucleus "receives input from the upper 3 cervical spine segments, and therefore spinal problems may contribute to nerve facilitation."
- "The trigeminal nucleus innervates the cranium, as well as many intracranial and extracranial blood vessels."
- "Afferents from the first 3 cervical vertebrae nerve roots also innervate the dura mater, the scalp, and many suboccipital muscles."

## 5) Chiropractic Spinal Manipulation (SMT):

- "Chiropractic vertebral subluxation (CVS) for this study is defined as a limitation of intersegmental motion resulting in loss of joint-ligament springing (denoted as end feel or accessory vertebral movement)."
- "The chiropractic vertebral subluxation can cause joint tenderness, muscle spasm, and nerve root irritation."
- "Chiropractic spinal manipulation is defined as a passive manual maneuver during which the 3-joint complex is carried beyond the normal physiologic range of movement without exceeding the boundaries of anatomic integrity."
- "Diversified technique requires a dynamic force in a specific direction, usually with a short-amplitude, high-velocity, spinal-manipulative thrust on areas of vertebral subluxation determined by the physical examination."

## 6) Subject characteristics (had or suffered from):

- 90% photophobia
- 89% nausea
- 83% a reaction to pain requiring the person to seek a quiet dark area
- 73% phonophobia
- 65% a throbbing pain characteristic
- 63% parietotemporal pain location
- 52% migraine aggravated by head or neck movement
- 33% aura

## 7) Outcomes:

- “The average response of the treatment group showed statistically significant improvement in migraine frequency, duration, disability, and medication use when compared with the control group.” **[Key Point]**
    - “A comparison of the CSMT group with the control group shows significant improvement in migraine frequency, duration, disability, and medication use.”
  - “22% of participants reported more than a 90% reduction of migraines as a consequence of the 2 months of SMT.”
  - “50% more participants reported significant improvement in the morbidity of each episode.”
  - 59% “reported no neck pain as a consequence of the 2 months of SMT.”
  - “The results demonstrated a significant reduction in migraine episodes and associated disability.” **[Key Point]**
    - “The mean number of migraines per month was reduced from 7.6 to 4.1 episodes.”
  - “The greatest area for improvement was medication use.” **[Important]**
    - “A significant number of participants recorded that their medication use had reduced to zero by the end of the 6-month trial.”
- 8) “There have now been several studies demonstrating significant improvement in headaches or migraines after chiropractic SMT.” **[Important]**
- 9) “A high percentage (83%) of participants in this study reported stress as a major factor for their migraines.”
- “It appears probable that chiropractic care has an effect on the physical conditions related to stress and that in these people the effects of the migraine are reduced.”
- 10) “The results of this study support previous results showing that some people report significant improvement in migraines after chiropractic SMT.”
- 11) “Some authors believe there is a continuum between migraine, tension-type headache, and cervicogenic headache.”
- “The precipitating or aggravating factors for headaches and migraines are often the same or similar.”

# Resolvins

# Acute Inflammatory Response Via Neutrophil Activation Protects Against the Development of Chronic Pain

## Science Translational Medicine

May 11, 2022; Vol. 14; Article eabj9954

Marc Parisien, Lucas V. Lima, Concetta Dagostino, Nehme El-Hachem, and 16 more: from McGill University, Montreal, Canada; University of Parma, Italy; Queen's University, Ontario, Canada; University of North Carolina, Laval University, Quebec Canada; Duke University. This study cites 67 references.

These authors investigated the pathophysiological mechanisms underlying the transition from acute to chronic low back pain (LBP).

Their study involved an assessment of immune cells (neutrophils) from 98 subjects with acute LBP and a group of 30 subjects with temporomandibular joint dysfunction (TMD).

Clinicians followed a standardized protocol for treating acute LBP with NSAIDs or systemic steroidal drugs to reduce the acute inflammatory response.

All patients were evaluated using the *numerical rating scale* (NRS) that assesses pain from 0 to 10, where 0 is "no pain" and 10 is "worst pain imaginable." All subjects had a pain level of  $\geq 4$  on the NRS, with a duration of no more than 6 wks.

### KEY POINTS FROM THIS ARTICLE:

- 1) "Chronic pain inflicts huge societal costs, in terms of management, loss of work productivity, and effects on quality of life."
- 2) "Chronic low back pain (LBP) is the most frequently reported chronic pain condition." **[Important]**
  - "LBP ranks the highest of all chronic conditions in terms of years lived with disability, with its prevalence and burden increasing with age."
  - LBP is a major problem worldwide with prevalence rates of:
    - Any time prevalence rate of 18%
    - 1-month prevalence rate of 31%
    - 1-year prevalence rate of 38%
- 3) "The transition from acute to chronic pain is critically important but not well understood."
- 4) "Current treatments for LBP often target the immune system and include nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and corticosteroids, although all of these drug classes are minimally effective at best."

5) "The pathophysiology of chronic pain involves a complex interplay between the nervous and immune systems."

- "Chronic pain is a neuroinflammatory disorder mediated by neuronal and non-neuronal cells alike."

6) The key cell involved in the transition of acute pain to chronic pain is the immune system cell, the *neutrophil*.

- "Transient neutrophil-driven up-regulation of inflammatory responses was protective against the transition to chronic pain."
  - This response was inhibited by both NSAIDs and steroids.
- "Early treatment with a steroid or nonsteroidal anti-inflammatory drug (NSAID) led to prolonged pain despite being analgesic in the short term." **[Key Point]**

7) "Despite analgesic efficacy at early time points, the management of acute inflammation may be counterproductive for long-term outcomes of LBP sufferers."

- There is an elevated risk of persistent pain for subjects taking NSAIDs and/or steroids. **[Key Point]**

8) There is a protective effect of the acute inflammatory response against the development of chronic pain. **[Key Point]**

- This finding was replicated in a prospective independent cohort of patients with temporomandibular disorder (TMD).
- In the TMD cohort, "the recovery group displayed a significantly higher inflammatory response at the acute stage, whereas the chronic pain group displayed a significantly lower acute phase inflammatory response."
- Both the LBP and TMD cohort showed a larger number of neutrophil inflammatory genes expressed in subjects who fully recovered.
- There was elevated neutrophil activation and inflammation in the recovered subjects.

#### CONCLUSIONS:

9) "Results indicate the importance of the up-regulation of the inflammatory response at the acute stage of musculoskeletal pain as a protective mechanism against the development of chronic pain." **[Key Point]**

- "Impaired inflammatory response [with NSAIDs and/or steroids] prolongs resolution of painful behavior."
  - "Active inflammatory responses, particularly those regulated by neutrophils, contribute to pain resolution." **[Key Point]**
  - Inhibition of this active immune response will lead to the prolongation of pain.
  - Steroids given during the acute pain phase delayed the recovery of the overall pain episode by twofold.
  - "Drugs that inhibit inflammation might interfere with the natural recovery process, thus increasing the odds for chronic pain." **[Key Point]**
- 10) "Individuals with acute back pain were at greater risk [76%] of developing chronic back pain if they reported NSAID usage than if they were not taking NSAIDs, adjusting for age, sex, [and] ethnicity."
- 11) "The beginning of the inflammatory process programs its resolution, and it is thus the failure to initiate an appropriate inflammatory response that may lead to chronic pain." **[Key Point]**
- 12) The acute treatment of inflammation with either a steroid or a NSAID, "although both effectively reducing pain behavior during their administration—greatly prolonged the resolution of neuropathic, myofascial, and especially inflammatory pain states." **[Key Point]**
- 13) In human subjects who reported acute back pain, NSAIDs "increased risk to still report back pain 2 to 6 years later." **[Important]**
- 14) The findings showed that NSAID use increases the risk of subsequent development of chronic back pain.
- "Higher percentages of neutrophils at the acute pain stage protected against chronic pain development." **[Key Point]**
  - "Active immune processes confer adaptation at the acute pain stage, and impairment of such inflammatory responses in subjects with acute LBP (or TMD) increases the risk of developing chronic pain."
  - These adaptive inflammatory responses are "modified by both genetics and environmental factors, and can be inhibited by steroids and NSAIDs."
- 15) "Our conclusions may have a substantial impact on medical treatment of the most common presenting complaint to healthcare professionals."

- “The long-term effects of anti-inflammatory drugs should be further investigated in the treatment of acute LBP and likely other pain conditions.”

16) “The replication of our findings in the TMD cohort also suggests that our findings are likely to be applicable to other chronic pain conditions.”

COMMENTS FROM DAN MURPHY, IRONY:

Inflammation drives pain, hence, the rationale for the use of anti-inflammatory drugs for patients with acute pain syndromes.

This study confirms short-term benefits of NSAIDs and steroids for patients with acute LBP or TMD pain.

However, ironically, these drugs reduce the genetic expression of inflammatory neutrophil (an immune system cell) genes which actually increase the incidence of chronic pain syndromes by 76%.

This study suggests that **not** taking NSAIDs or steroids for an acute episode of pain greatly reduces the risk of suffering from a chronic pain syndrome.

## **Ageing Research Reviews**

### **November 2024**

#### **Heart Rate Variability and Autonomic Nervous System Imbalance: Potential Biomarkers and Detectable Hallmarks of Aging and Inflammaging**

The most cutting-edge issue in the research on aging is the quest for biomarkers that transcend molecular and cellular domains to encompass organismal-level implications.

We recently hypothesized the role of Autonomic Nervous System (ANS) imbalance in this context.

Studies on ANS functions during aging highlighted an imbalance towards heightened sympathetic nervous system (SNS) activity, instigating a proinflammatory milieu, and attenuated parasympathetic nervous system (PNS) function, which exerts anti-inflammatory effects via the cholinergic anti-inflammatory pathway (CAP) and suppression of the hypothalamic-pituitary-adrenal (HPA) axis.

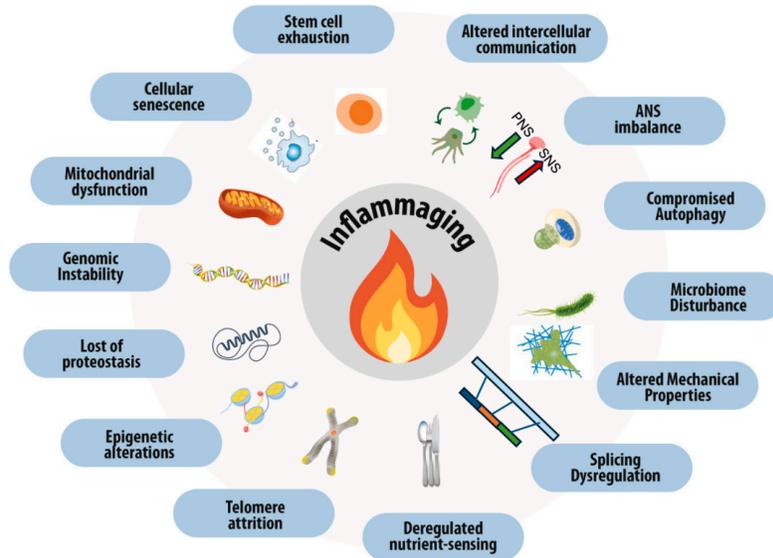
This scenario strongly suggests that ANS imbalance can fuel inflammaging, now recognized as one of the most relevant risk factors for age-related disease development.

Recent recommendations have increasingly highlighted the need for actionable strategies to improve the quality of life for older adults by identifying biomarkers that can be easily measured, even in asymptomatic individuals.

We advocate for considering ANS imbalance as a biomarker of aging and inflammaging.

Measures of ANS imbalance, such as heart rate variability (HRV), are relatively affordable, non-invasive, and cost-effective, making this hallmark easily diagnosable.

HRV gains renewed significance within the aging research landscape, offering a tangible link between pathophysiological perturbations and age-related health outcomes.



**Fig. 1. The hallmarks of inflammaging.** A systematic representation of the hallmarks of aging, depicting inflammaging as the central hub which mediates the interaction among all the other identified hallmarks of aging. Autonomic nervous system (ANS) imbalance is included as a new hallmark.

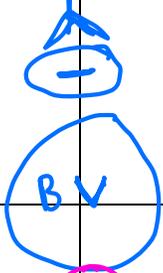


C1-C3

Nucleus Intermedius

Nucleus Tractus Solitarius

Dorsal Motor Nucleus Vagus



SCG

Postganglionic Sympathetic

x 120 32

Pre-ganglionic Sympathetic



Nasal Specific → Sphenoid

Upper Cervical → Occiput/Atlas → Cork CSF

- \* Calming
- \* Vasodilation
  - ↓ B.P.
  - ↓ artery disease
- \* Immune Enhancing
- \* Longer Telomere

Acetylcholine

HRV

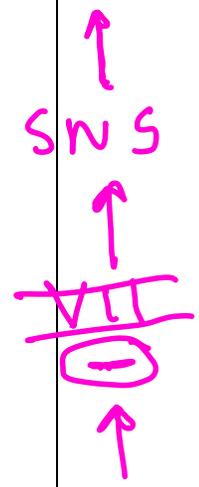
Stress  
Fight/Flight

↓

Vasoconstriction  
↑ BP  
↑ artery disease

Immune Suppression  
Shorter Telomeres  
Shrink Brain

Norepinephrine



Mechanoreceptors

Mechanoreceptors  
C1-C3



Nucleus Intermedius



Nucleus Tractus Solitarius



Dorsal Motor Nucleus Vagus



inhibition  
Vasodilation

acetylcholine



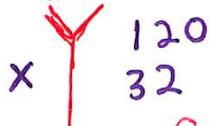
excitation  
Vasoconstriction

norepinephrine



SCG

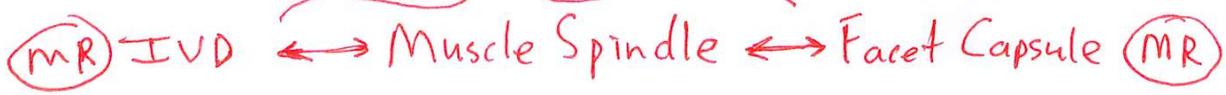
Postganglionic Sympathetic

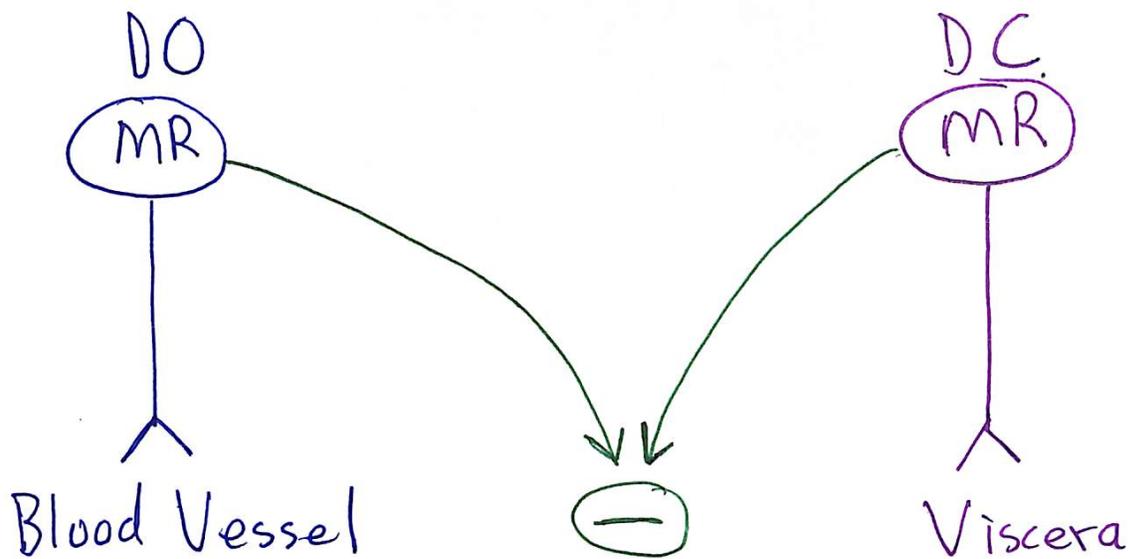


Preganglionic Sympathetic



MR





Sympathetic Nervous System

Blood Vessel Diameter

O<sub>2</sub>

Glucose - RA

Mitochondria

ATP

DNA

## Spinal Manipulation in the Treatment of Low back Pain

Canadian Family Physician

March 1985, Vol. 31, pp. 535-540

W. H. Kirkaldy-Willis and J. D. Cassidy

Dr. Kirkaldy-Willis is a Professor Emeritus of Orthopedics and director of the Low-Back Pain Clinic at the University Hospital, Saskatoon, Canada.

FROM ABSTRACT:

Spinal manipulation, one of the oldest forms of therapy for back pain, has mostly been practiced outside of the medical profession.

Over the past decade, there has been an escalation of clinical and basic science research on manipulative therapy, which has shown that there is a scientific basis for the treatment of back pain by manipulation.

Most family practitioners have neither the time nor inclination to master the art of manipulation and will wish to refer their patients to a skilled practitioner of this therapy.

The physician who makes use of this resource will provide relief for many patients.

THESE AUTHORS ALSO NOTE:

"Less than 10% of low back pain is due to herniation of the intervertebral disc or entrapment of spinal nerves by degenerative disc disease."

"Spinal manipulation is essentially an assisted passive motion applied to the spinal apophyseal and sacroiliac joints."

"At the end of the paraphysiological range of motion, the limit of anatomical integrity is encountered. Movement beyond this limit results in damage to the capsular ligaments."

Joint manipulation [adjusting] "requires precise positioning of the joint at the end of the passive range of motion and the proper degree of force to overcome joint coaptation" [to overcome the resistance of the joint surfaces in contact].

"With experience, the manipulator can be very specific in selecting the spinal level to be manipulated."

Melzack and Wall proposed the Gate Theory of Pain in 1965, and this theory has "withstood rigorous scientific scrutiny."

"The central transmission of pain can be blocked by increased proprioceptive input." Pain is facilitated by "lack of proprioceptive input." This is why it is important for "early mobilization to control pain after musculoskeletal injury." **[Important]**

The facet capsules are densely populated with mechanoreceptors. "Increased proprioceptive input in the form of spinal mobility tends to decrease the central transmission of pain from adjacent spinal structures by closing the gate. Any therapy which induces motion into articular structures will help inhibit pain transmission by this means." **[Important]**

Stretching of facet joint capsules will fire capsular mechanoreceptors which will reflexly "inhibit facilitated motoneuron pools" which are responsible for the muscle spasms that commonly accompany low back pain.

In chronic cases, there is a shortening of periarticular connective tissues and intra-articular adhesions may form; manipulations [adjustments] can stretch or break these adhesions.

"In most cases of chronic low back pain, there is an initial increase in symptoms after the first few manipulations [probably as a result of breaking adhesions]. In almost all cases, however, this increase in pain is temporary and can be easily controlled by local application of ice." **[Important]**

"However, the gain in mobility must be maintained during this period to prevent further adhesion formation." **[Important]**

These authors present the results of a prospective observational study of spinal manipulation in 283 patients with chronic low back and leg pain. All 283 patients in this study had failed prior conservative and/or operative treatment, and they were all totally disabled ("Constant severe pain; disability unaffected by treatment.")

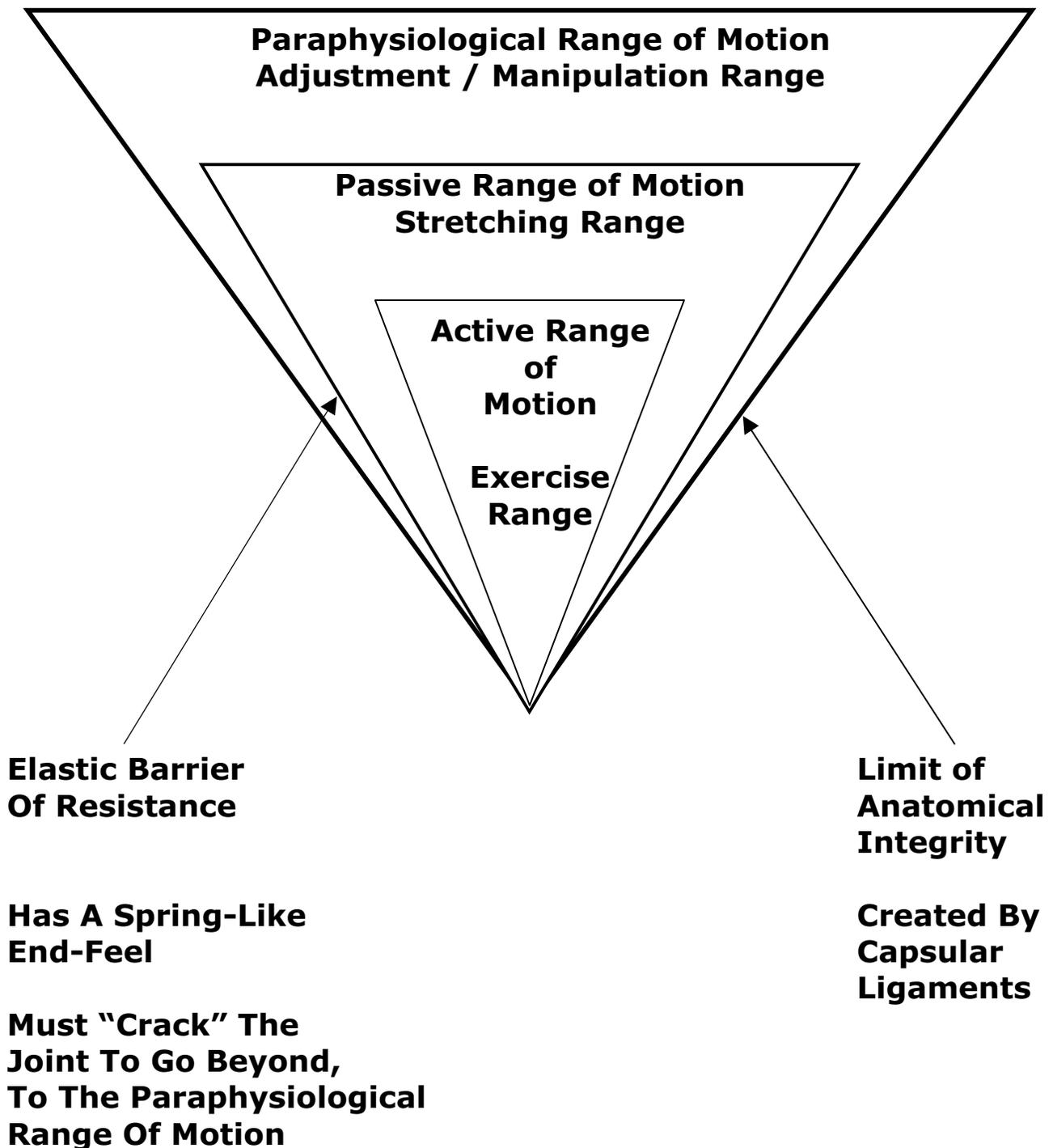
These patients were given a "two or three week regimen of daily spinal manipulations by an experienced chiropractor."

"No patients were made worse by the manipulation, yet many experienced an increase in pain during the first week of treatment. Patients undergoing manipulative treatment must therefore be reassured that the initial discomfort is only temporary."

"In our experience, anything less than two weeks of daily manipulation is inadequate for chronic low back pain patients." **[Very Important]**

"The physician who makes use of this [manipulation] resource will provide relief for many back pain patients."

## Joint Ranges of Motion



**Nobel Prize 2021  
Medicine and/or  
Physiology**

**Piezo1**

118 pages

236 references

SUBLUXATION:

AN

ELECTRICAL

PHENOMENON

BY

DEANNE L. JOHNSON-HARRISON, B.S., M.S.

illustrated by

RANDY R. COLLINS, D.C.

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# ENERGY MEDICINE

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## THE SCIENTIFIC BASIS

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James L. Oschman

FOREWORD BY  
Candace Pert



CHURCHILL  
LIVINGSTONE

2000

# 11

## Gravity, structure, emotions

### Introduction

Previous chapters have described the physiological and clinical importance of electricity and magnetism. Little has been said about gravity, even though it is arguably the most potent physical influence in any human life.

Gravity pervades our bodies and our environment and affects our every activity. furniture, buildings, machinery,

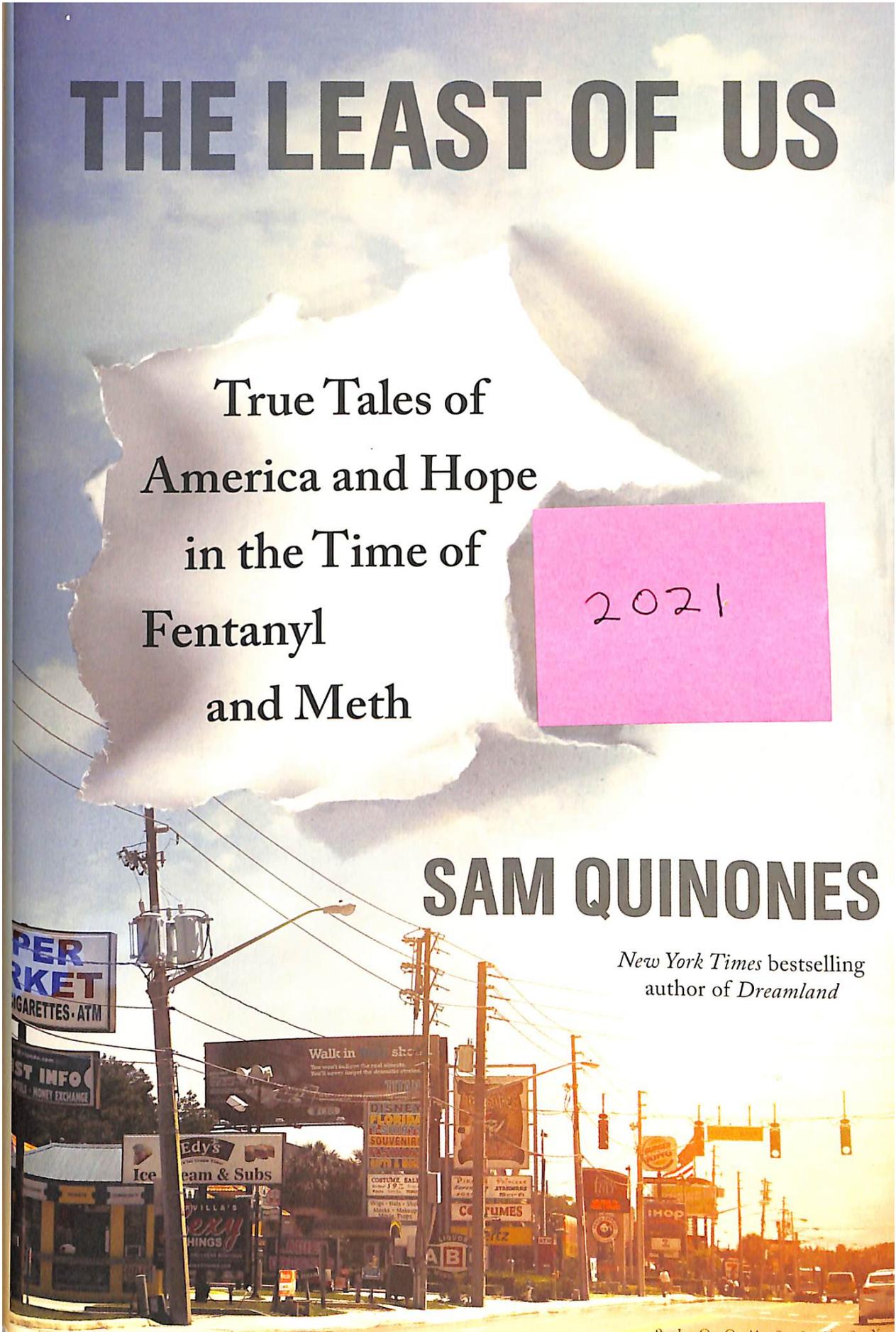
# THE LEAST OF US

True Tales of  
America and Hope  
in the Time of  
Fentanyl  
and Meth

2021

## SAM QUINONES

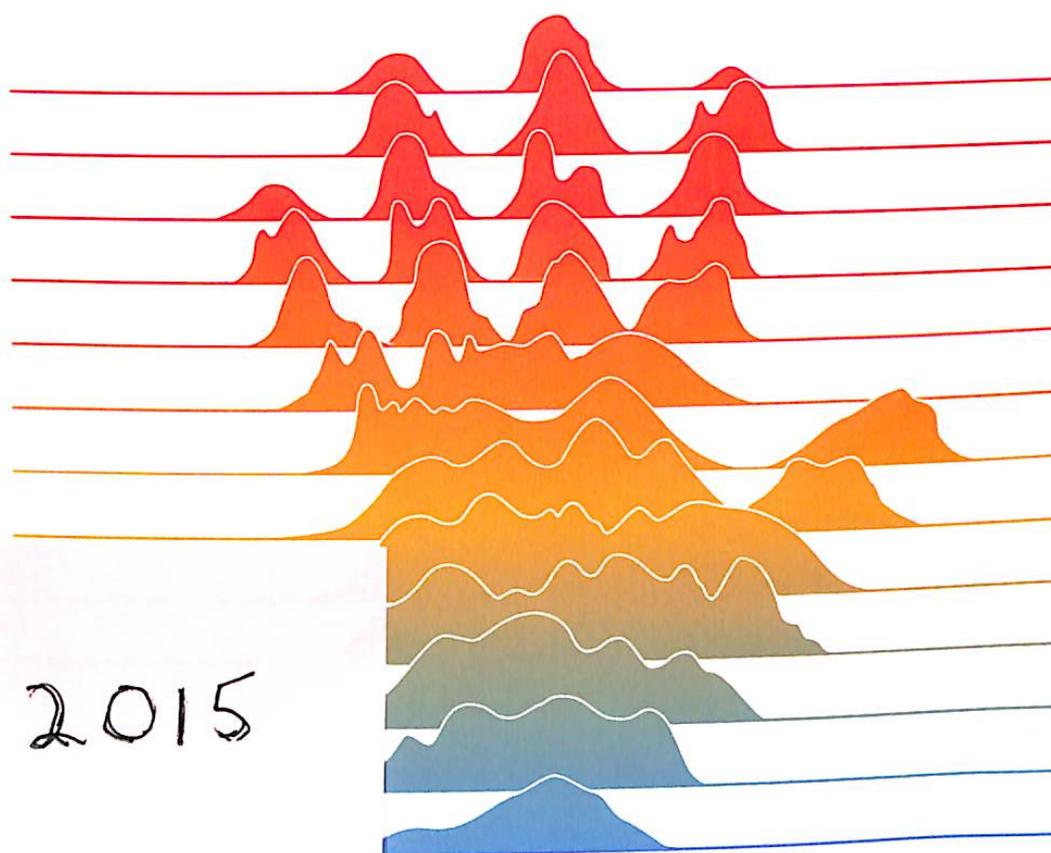
*New York Times* bestselling  
author of *Dreamland*





# Touch

THE SCIENCE OF HAND, HEART, AND MIND



2015

David J. Linden

Author of the *New York Times* bestseller *The Compass of Pleasure*

"[Linden is] an able guide to the world of touch. . . . The book will make you think more deeply about every itch, scrape, and caress." —*The Washington Post*

# Nobel Prize in Medicine Awarded for Work on Senses

10/5/2021

By DENISE ROLAND  
AND BRIANNA ABBOTT

WST

The Nobel Prize in physiology or medicine was jointly awarded to David Julius and Ardem Patapoutian for their work on how the human body senses temperature, touch and movement.

The Nobel Assembly said Monday that the scientists' discoveries had unlocked one of the secrets of nature by explaining the molecular basis for sensing heat, cold and mechanical force.

This basic understanding of how temperature and touch signal the nervous system is now being harnessed to research potential treatments for chronic pain and other medical conditions, the Nobel Assembly said.

"These sensations of heat and pain and touch, if those are all converted to electrical signals and sent to the brain, that opens up a whole new world of potential treatments," said Chad Bouton, a professor at the Feinstein Institutes for Medical Research in New York, whose work in-



David Julius and Ardem Patapoutian were honored for explaining the molecular basis for sensing heat, cold and mechanical force. Above right, Thomas Perlmann, secretary of the Nobel Assembly.

cludes the use of stimulation of the brain to restore the sense of touch to patients who have lost it as a result of a stroke or injury. "It's all made possible by these critical discoveries," he added.

Dr. Julius was born in 1955 in New York and is now a pro-

fessor and chairman of the department of physiology at the University of California, San Francisco. Dr. Patapoutian was born in 1967 in Beirut. He moved to the U.S. in his youth and is currently a professor at Scripps Research in La Jolla, Calif.

While at UCSF in the late 1990s, Dr. Julius used capsaicin, a compound in chili peppers that causes a burning sensation, to identify a chemical receptor in nerve endings of the skin that responds to heat. In separate research, Dr. Patapoutian used pressure-

sensitive cells to discover new receptors that respond to touch in the skin and internal organs.

Both the scientists' work involved identifying the specific genes involved in sensing either heat or touch and then figuring out what those genes did within cells.

Dr. Julius and his team assembled a library of millions of DNA fragments from sensory neurons and found a single gene that made cells sensitive to capsaicin. That gene directs nerve cells to make a so-called ion channel that opens up in response to capsaicin and high temperatures, allowing electrically charged particles called ions to flood into cells and send a pain message to the brain. That receptor was later named TRPV1.

"There is a time when you make a discovery where you are the only person on the planet, or at least you think you're the only person on the planet, who knows the answer to a particular question," Dr. Julius said in a media event. "And that's a really thrilling moment."

That discovery, published in a 1997 paper, sparked a wave of research by large drugmakers hopeful that blocking the TRPV1 receptor could treat chronic pain.

The work also paved the way for the discovery of other ion channels.

One of those channels was a cold-sensing receptor called TRPM8, which Drs. Julius and Patapoutian uncovered independently of one another, using menthol.

Dr. Patapoutian's work on touch uncovered two ion channels, named Piezo1 and Piezo2 after the Greek word for pressure, that open up in response to touch. He later showed that Piezo2 played a key role in how the body senses its position and movement. Subsequent work demonstrated how Piezo1 and Piezo2 help regulate bodily functions such as blood pressure and bladder control.

Dr. Patapoutian said that work was under way to find molecules that block the Piezo channels as these could form the basis of drugs for different types of pain.

JONATHAN NACKSTRAND/AGENCE FRANCE PRESSE/GETTY IMAGES



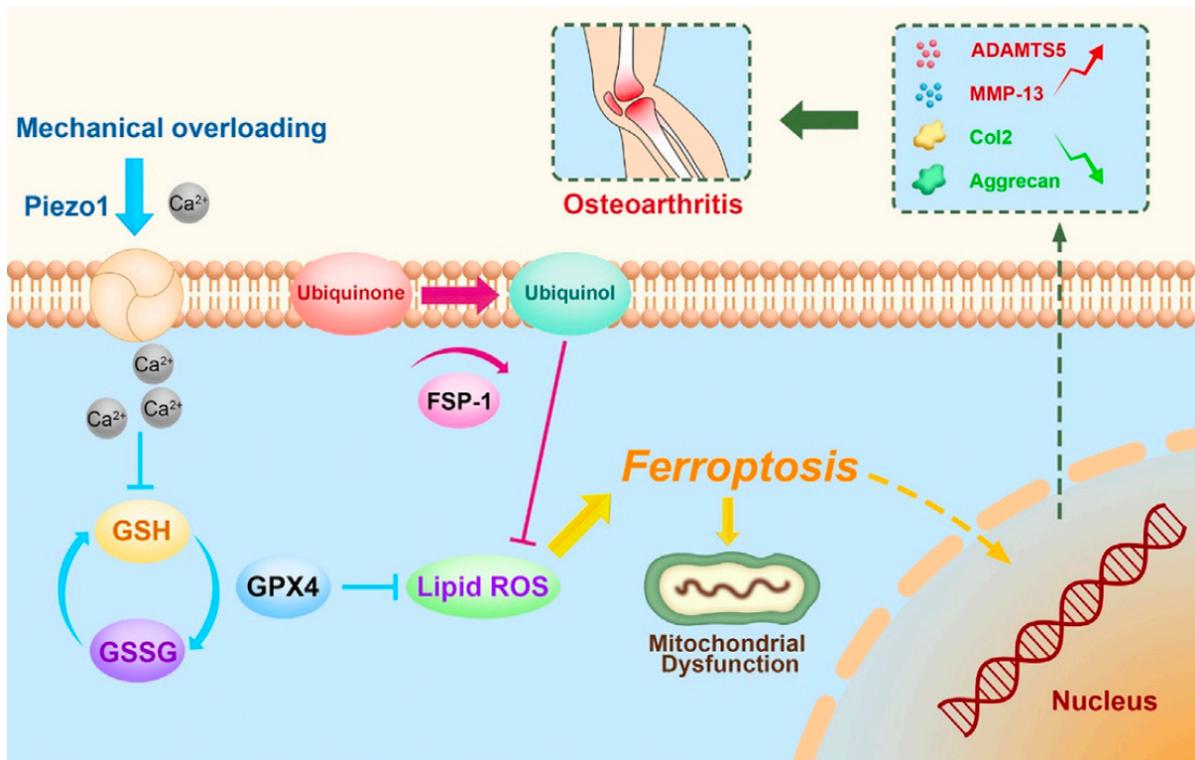
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Page 1 of 32

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## Mechanical Overloading Induces Glutathione-Regulated Chondrocyte Ferroptosis in Osteoarthritis via Piezo1 Channel Facilitated Calcium Influx

Journal of Advanced Research  
November 2022



### A Simplified Model from Dan Murphy

**Piezo1** is a **mechanoreceptor** that was mentioned in the **2021 Nobel Prize** in physiology or medicine.

Piezo1 receptors are found in the membrane of chondrocytes.

Mechanical loading (overloading) opens the Piezo1 receptor which allows excessive influx of Ca<sup>++</sup> to enter into the cell. [**consider magnesium**]

The excessive intracellular Ca<sup>++</sup> inhibits glutathione which increases chondrocyte oxidative stress, leading to osteoarthritis. [**consider glutathione supplements**]

CoQ10 blocks the oxidative stress driven ferroptosis cartilage damage. [**consider CoQ10; consider donating blood**]

In an integrative narrative, this article has applications for the chiropractic subluxation and adjustment, Ca<sup>++</sup> excess, Mg<sup>++</sup> deficiency, glutathione status, and free radical damage. As such it would support not only the chiropractic adjustment, but also diet, nutrition, supplements, and laser therapy.



FULL TEXT LINKS



Spine (Phila Pa 1976). 2022 Mar 1;47(5):E203-E213. doi: 10.1097/BRS.0000000000004203.

## Single Impact Injury of Vertebral Endplates Without Structural Disruption, Initiates Disc Degeneration Through Piezo1 Mediated Inflammation and Metabolism Dysfunction

Zhengang Sun <sup>1</sup>, Xinfeng Zheng <sup>2</sup>, Songbo Li <sup>3</sup>, Baozhu Zeng <sup>4</sup>, Jiaming Yang <sup>4</sup>, Zemin Ling <sup>5</sup>, Xizhe Liu <sup>5</sup>, Fuxin Wei <sup>4</sup>

Affiliations

PMID: 34431832 PMID: [PMC8815838](#) DOI: [10.1097/BRS.0000000000004203](#)

[Free PMC article](#)

### Abstract

**Study design:** In vitro experimental study.

**Objective:** To establish an axial impact injury model of intervertebral disc (IVD) and to investigate if a single impact injury without endplate structural disruption could initiate intervertebral disc degeneration (IDD), and what is the roles of Piezo1 in this process.

**Summary of background data:** Although IDD process has been confirmed to be associated with structural failures such as endplate fractures, whether a single impact injury of the endplates without structural disruption could initiate IDD remains controversial. Previous studies reported that Piezo1 mediated inflammation participated in the progression of IDD induced by mechanical stretch; however, the roles of Piezo1 in IVD impact injury remain unknown.

**Methods:** Rats spinal segments were randomly assigned into Control, Low, and High Impact groups, which were subjected to pure axial impact loading using a custom-made apparatus, and cultured for 14 days. The degenerative process was investigated by using histomorphology, real-time Polymerase Chain Reaction (PCR), western-blot, immunofluorescence, and energy metabolism of IVD cell. The effects of Piezo1 were investigated by using siRNA transfection, real-time PCR, western-blot, and immunofluorescence.

**Results:** The discs in both of the impact groups presented degenerative changes after 14 days, which showed significant up-regulation of Piezo1, NLRP3 inflammasome, the catabolic (MMP-9, MMP-13), and pro-inflammatory gene (IL-1 $\beta$ ) expression than that of the control group ( $P < 0.05$ ), accompanied by significantly increased release of ATP, lactate, nitric oxide (NO), and glucose consumption of IVD cells at first 7 days. Silencing Piezo1 reduced the activation of NLRP3 inflammasome and IL-1 $\beta$  expression in the nucleus pulposus induced by impact injury.

**Conclusion:** It demonstrated that not only fracture of the endplate but also a single impact injury without structural impairment could also initiate IDD, which might be mediated by activation of Piezo1 induced inflammation and abnormal energy metabolism of IVD cells. Level of Evidence: N/A.

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**Excessive Mechanical Stress-induced Intervertebral Disc Degeneration is Related to Piezo1 Overexpression Triggering the Imbalance of Autophagy/Apoptosis in Human Nucleus Pulposus**

**Arthritis Research & Therapy**  
**May 23, 2022; Vol. 24; No. 1; Article 119**

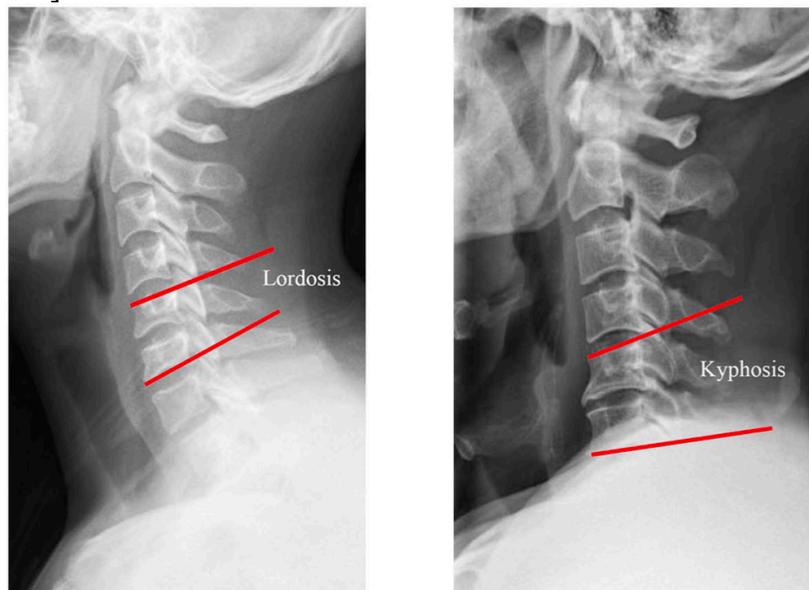
Sheng Shi, Xing-Jian Kang, Zhi Zhou, Zhi-Min He, Shuang Zheng, Shi-Sheng He

This study aimed to investigate the effect of the **Piezo1** mechanoreceptor on the mechanical stress-induced intervertebral disc degeneration (IVDD) and explore the possible mechanism. Immunohistochemistry staining antibodies against **Piezo1** were used in the analysis.

Cervical nucleus pulposus (NP) samples were collected via surgery from 26 patients (12 men and 14 women; age range: 22–65 years).

“In order to explore whether mechanical stress treatment can affect Piezo1 expression and cell function of NP cells, a mechanical compression with different intensity and/or duration was conducted on human NP cells.”

Cervical lordosis was assessed with x-rays using the protocol established by Deed Harrison, DC, and colleagues in the journal *Clinical Biomechanics* in 2001: [Harrison DE, Harrison DD, Janik TJ, William Jones E, Cailliet R, Normand M. Comparison of axial and flexural stresses in lordosis and three buckled configurations of the cervical spine; *Clinical Biomechanics*; May 2001; Vol.16; No. 4; pp. 276–784.]



The angle between the superior endplate of the rostral vertebra and the inferior endplate of the caudal vertebra on the lateral x-ray was measured.

The expression of ***Piezo1***, cervical curvature, and the stiffness of the nucleus pulposus (NP), was performed in normal and degenerated human intervertebral discs.

“Mechanical stress plays a crucial role in the pathogenesis of intervertebral disc degeneration (IVDD).”

“Intervertebral disc degeneration (IVDD) is the leading cause of degenerative spine diseases such as discogenic pain and disc herniation, which reduces the quality of life and increases the socioeconomical burden.”

- “The onset and development of IVDD is a complex process involving numerous factors such as biomechanics, aging, genetic factors, nutrition, inflammation, and so on.”
- “Mechanical stress as part of the biomechanical factors may contribute to playing a particularly prominent role in the pathogenesis of IVDD.”

The nucleus pulposus (NP) “is considered to be the most crucial component for maintaining the pressure gradient and ensuring the infiltration and diffusion of metabolites and nutrients.”

- “Abnormal mechanical load can promote cell death in the NP, cause matrix metabolism disorders, and hasten the process of IVDD.” **[Important]**
  - “Compressive forces by bad postures or kyphosis may lead to intense stresses that act on the NP.” **[Key Point]**
  - “Mechanical stress caused by kyphosis has been linked to the pathological process of IVDD.” **[Key Point]**

“The mechanosensitive Piezo1 ion channel can sense the changes in mechanical stress and convert the mechanical signals into chemical signals.” **[Key Point]**

- ***Piezo1*** is a new mechanosensitive ion channel, which can “sense the changes of mechanical stress and convert the mechanical signals into electrical or chemical signals.”
- “[Piezo1] is widely distributed in a variety of different tissues including bone, articular cartilage and the intervertebral disc.”

### Findings:

- “Intradiscal pressure was shown to be definitely higher in forward leaning from a sitting position than in relaxed sitting, which indicates that intradiscal

pressure increases with application of compression and is dependent on the lifestyle.”

- “The expression of Piezo1 had obviously increased in the NP tissues of the IVDD patients when compared to that of the control group.”
- The expression of Type-II Collagen significantly declined in the IVDD group when compared to that in the control group.
- “The protein levels of Type-II Collagen and Aggrecan were markedly suppressed after mechanical stress.”

**[Aggrecan and Type-II Collagen** form the major structural component of cartilage and the intervertebral disc].

- “Apoptosis was significantly increased in mechanical stress-treated NP cells and could be restricted when Piezo1 was inhibited.”

#### **Chiropractic Mechanical Connection:**

- “The lateral radiograph revealed the local cervical curvature was significantly lower [kyphotic] in the high grade IVDD group.”
- “Excessive mechanical stresses are found in the kyphotic areas of sagittal cervical spine when compared to the normal lordosis.”
- “The increased mechanical stress induced by kyphosis was considered to be a risk factor for the development of IVDD or disc herniation.”
- Cervical kyphosis resulted in the up-expression of ***Piezo1*** and the down-expression of Type II Collagen.
  - This increased nucleus pulposus stiffness and increased degeneration of human intervertebral discs.
- “The upregulated expression of Piezo1, poor curvature [kyphosis], and increased extracellular matrix (ECM) stiffness in the degenerated human NP.”
- Increased ***Piezo1*** expression reduced **Type-II Collagen** in the degenerated human NP tissue, along with more kyphotic angle in the cervical spine, reveals that the “Piezo1 sensing the excessive stress partly attributed to poor curvature may affect the ECM homeostasis and further change the mechanical properties of NP.” **[Key Point]**
- “Our data provide the evidence that Piezo1 upregulation under excessive compression can promote the apoptosis and senescence of NP cells, secrete

pro-inflammatory cytokines, and reduce the synthesis of ECM by mitochondrial dysfunction and the suppression of autophagy in NP.”

- “The up-regulation of the mechanosensitive [calcium] ion channel Piezo1 by excessively external compressive stress can increase pro-inflammatory cytokines, and induce mitochondrial dysfunction, which may trigger the apoptosis and senescence of human NP cells via suppressing autophagy and resulting in the loss of ECM.”
- This research confirms that “overactivated Piezo1 by excessive compression inhibits the synthesis of major parts in ECM involving the collagen II and aggrecan.”
- The upregulation of Piezo 1 enhanced the apoptosis of NP cells and promotes the apoptosis and senescence of NP cells. **[Key Point]**
- “[Both] apoptosis and autophagy were induced by moderate mechanical compression in NP cells.”

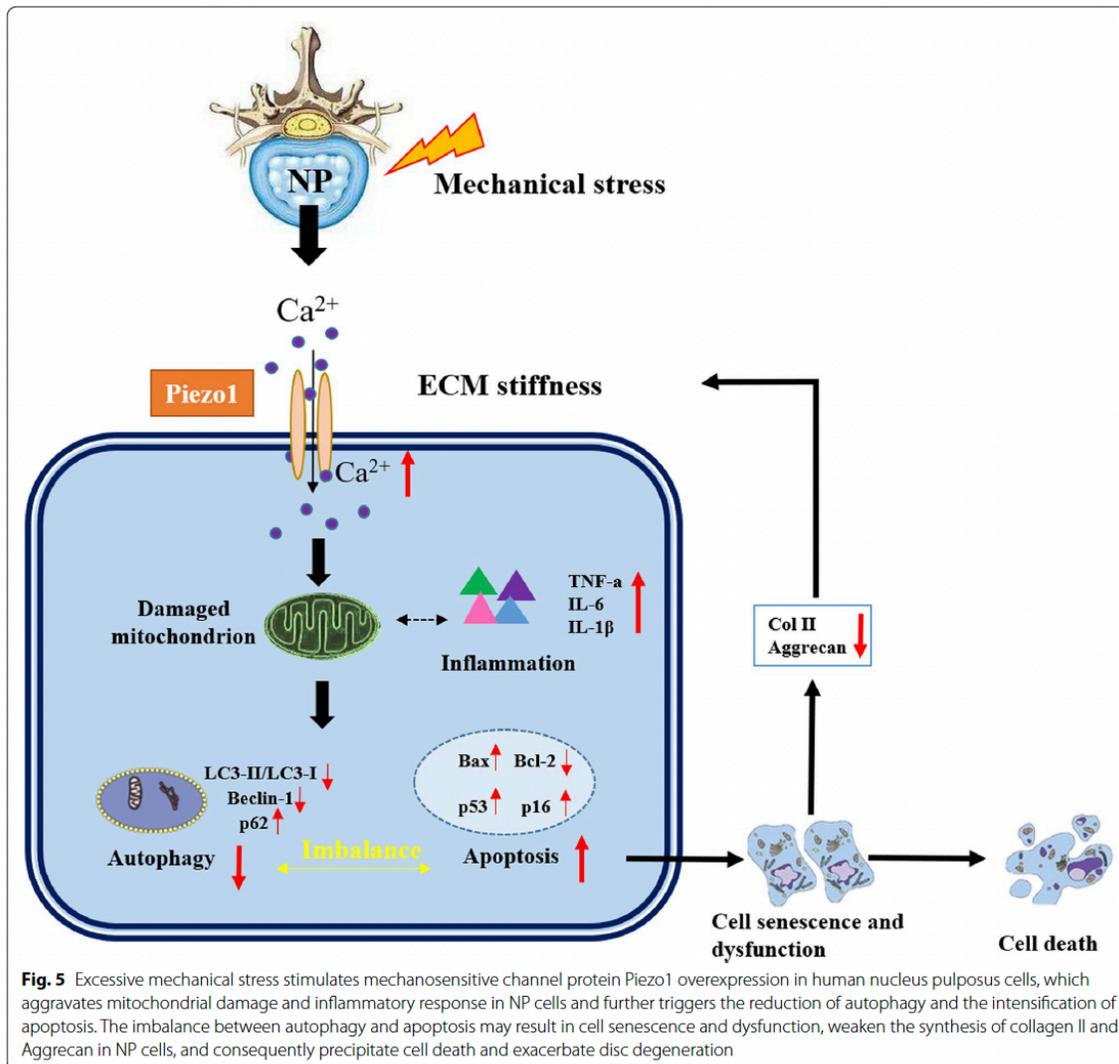
### **PUTTING IT ALL TOGETHER**

Cervical kyphosis drives the following:

- Increases the load on the Piezo1 mechanoreceptor.
- Opens the Ca<sup>++</sup> ion channel.
- The Ca<sup>++</sup> influx damages the mitochondria.
- Damaged mitochondria increase inflammatory cytokine production.
- Damaged mitochondria reduce cell repair and the reusing of old and damaged cells or parts of cells. This is **autophagy**.
- Reduced autophagy increases **apoptosis** and **senescence**, leading to cell death.
- **Apoptosis** and **Senescence** reduce the production of **Type-II Collagen** and **Aggrecan**, which degrades the **extracellular matrix**.
- The results are acceleration of degenerative disc disease and spinal stiffness.

This supports correcting cervical kyphosis (we use Dennerolls from CBP), correct subluxations, take Mg<sup>++</sup> (blocks the Ca<sup>++</sup> ion channel), use low-level laser therapy (improves mitochondria health and physiology), take mitochondria health supplements (like CoQ10, PQQ, acetyl-L-carnitine, alpha-lipoic acid, etc.).

See the following picture:



Other **Article Reviews** on **Piezo1** mechanoreceptors include:

[Article Review 16-23:](#)

**Mechanical Loading Induces Piezo1 Calcium Influx and Osteoarthritis**

[Article Review 42-23:](#)

**Injury Initiates Disc Degeneration Through Piezo1 Mediated Inflammation**

Other **Article Reviews** on cervical kyphosis include:

[Article Review 24-11:](#)

**Is the Kyphosis Cause or Effect of Disc Degenerative Disease**

[Article Review 52-13:](#)

**Focal Kyphosis correction and Neurological Outcomes**

[Article Review 2-23:](#)

**Improvement in Cervical Curve in the Management of Lumbar Radiculopathy**

# **The Emerging Role of Piezo1 Channels in Skeletal Muscle Physiology**

## **Biophysics Review**

**September 29, 2023; Vol 15; 15; No. 5; pp. 1171-1184**

Timur Mirzoev

Piezo1 channels are mechanically activated (MA) cation channels that are involved in sensing of various mechanical perturbations, such as membrane stretch and shear stress, and play a crucial role in cell mechanotransduction.

In response to mechanical stimuli, these channels open up and allow cations to travel into the cell and induce biochemical reactions that can change the cell's metabolism and function.

Skeletal muscle cells/fibers inherently depend upon mechanical cues in the form of fluid shear stress and contractions (physical exercise).

For example, an exposure of skeletal muscles to chronic mechanical loading leads to increased anabolism and fiber hypertrophy, while prolonged mechanical unloading results in muscle atrophy.

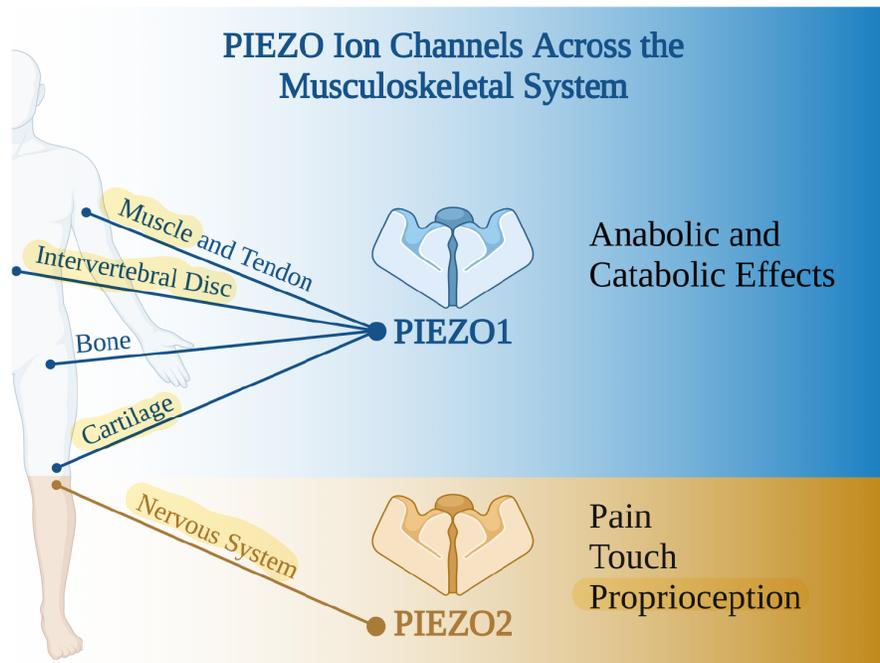
MA Piezo1 channels have recently emerged as key mechanosensors that are capable of linking mechanical signals and intramuscular signaling in skeletal muscle cells/fibers.

This review will summarize the emerging role of Piezo1 channels in the development and regeneration of skeletal muscle tissue as well as in the regulation of skeletal muscle atrophy.

In addition, an overview of potential Piezo1-related signaling pathways underlying anabolic and catabolic processes will be provided.

## The Role of PIEZO Ion Channels in the Musculoskeletal System March 14, 2023

Alireza Savadipour, Daniel Palmer, Erica Ely, Kelsey Collins, et. al.



AMERICAN JOURNAL OF PHYSIOLOGY

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society

PIEZO1 and PIEZO2 are mechanosensitive cation channels that are highly expressed in numerous tissues throughout the body and exhibit diverse, cell-specific functions in multiple organ systems.

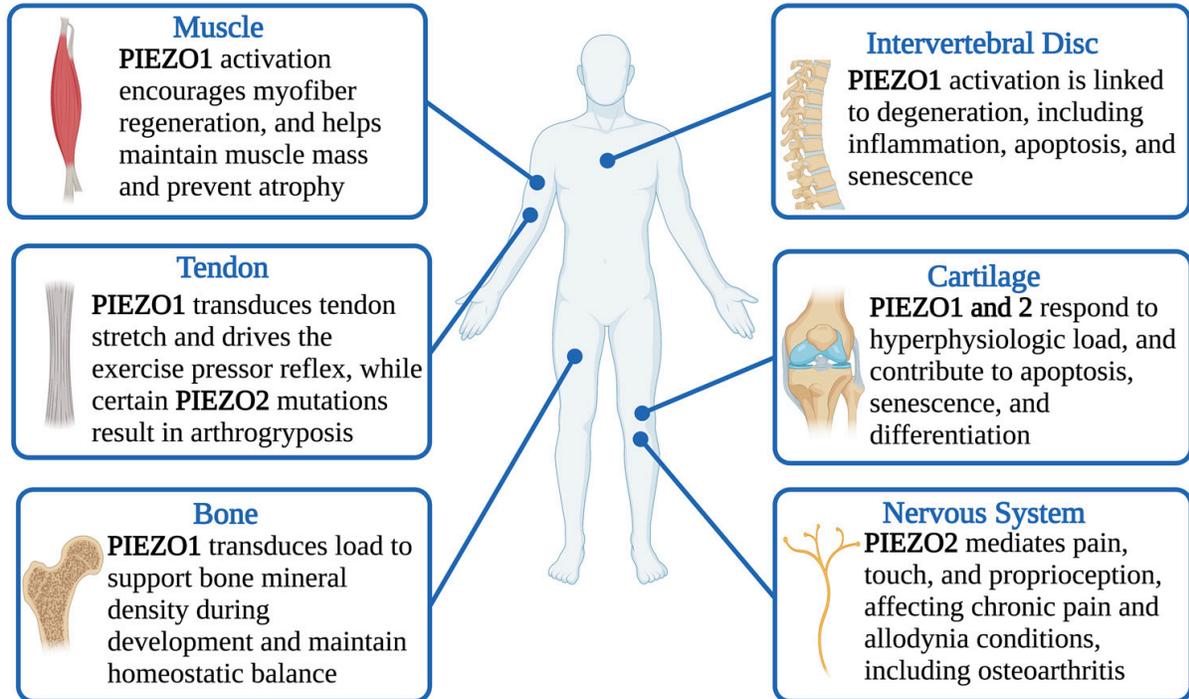
Within the musculoskeletal system, PIEZO1 functions to maintain muscle and bone mass, sense tendon stretch, and regulate senescence and apoptosis in response to mechanical stimuli within cartilage and the intervertebral disc.

PIEZO2 is essential for transducing pain and touch sensations as well as proprioception in the nervous system, which can affect musculoskeletal health.

PIEZO1 and PIEZO2 have been shown to act both independently as well as synergistically in different cell types.

Conditions that alter PIEZO channel mechanosensitivity, such as inflammation or genetic mutations, can have drastic effects on these functions.

# PIEZO1 and PIEZO2 Regulate Essential Musculoskeletal Functions



## Potential PIEZO-Related Therapies Include:

### Targeted PIEZO Inhibition



Control PIEZO1 and 2 sensitivity through regulated use of inhibitors such as GsMTx4

### Inhibit VGCCs or TRPV4



Inhibit voltage gated cation channels (VGCCs) or TRPV4 to modulate PIEZO activity

### Dietary Supplementation

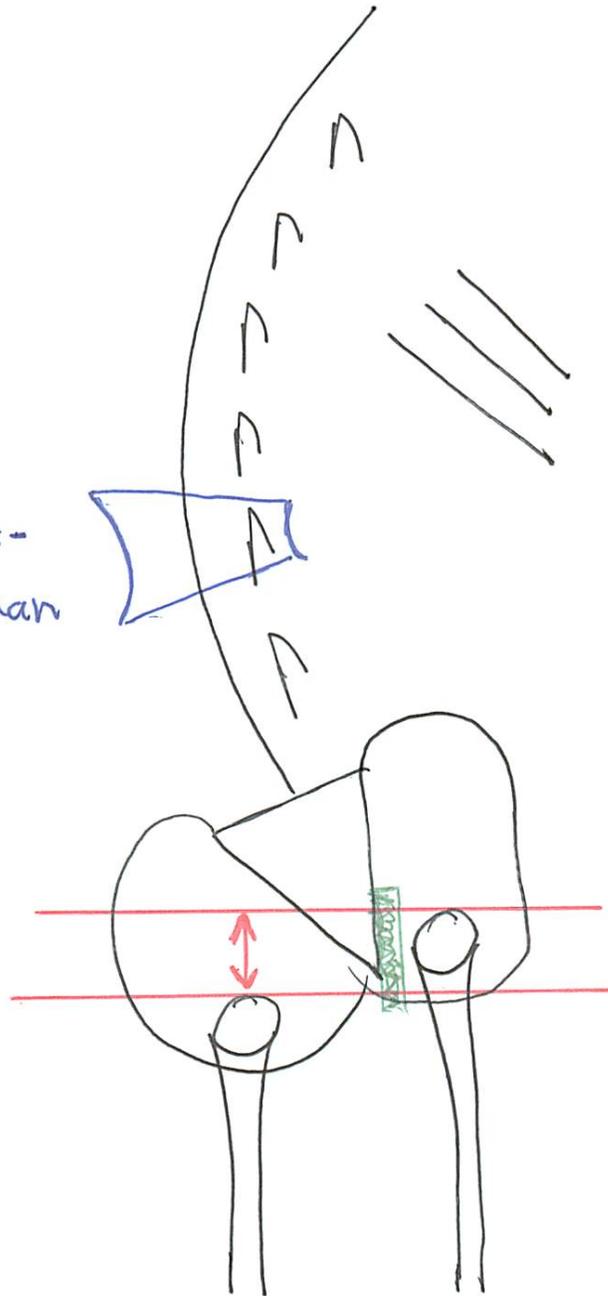


Increase omega-3/omega-6 dietary fatty acid ratio to decrease PIEZO1 and 2 sensitivity

# **Leaning Tower of Kennedy**



Hueter-Volkman



QL



## John F. Kennedy's back: chronic pain, failed surgeries, and the story of its effects on his life and death

T. Glenn Pait, MD, and Justin T. Dowdy, MD

Department of Neurological Surgery, Jackson T. Stephens Spine and Neurosciences Institute, University of Arkansas for Medical Sciences, Little Rock, Arkansas

The 35th president of the United States, John F. Kennedy (JFK), experienced chronic back pain beginning in his early 20s. He underwent a total of 4 back operations, including a discectomy, an instrumentation and fusion, and 2 relatively minor surgeries that failed to significantly improve his pain. The authors examined the nature and etiology of JFK's back pain and performed a detailed investigation into the former president's numerous medical evaluations and treatment modalities. This information may lead to a better understanding of the profound effects that JFK's chronic back pain and its treatment had on his life and presidency, and even his death.

<https://thejns.org/doi/abs/10.3171/2017.2.SPINE151524>

**KEY WORDS** JFK; John F. Kennedy; failed back surgery; Wilson plate; history; President Kennedy assassination

JOHN Fitzgerald Kennedy (JFK), the 35th president of the United States and the youngest candidate elected to the Oval Office, was portrayed as a dynamic man full of vigor and youthful energy.<sup>61</sup> This aura of vitality belied the fact that he was patently unhealthy from an early age.<sup>14,57</sup> The full extent of his wide array of medical problems, especially relating to his time in the Oval Office, remained a secret as directed by the Kennedy family until 2001.<sup>1</sup> Low-back pain, just one of Kennedy's many medical problems, prompted a total of 4 largely unsuccessful surgeries. This pain affected him nearly continually from his undergraduate years at Harvard until the day of his assassination.

### A Childhood of Poor Health: Numerous Illnesses and Hospitalizations

John Fitzgerald Kennedy was born the second of 8 children to Joseph P. Kennedy Sr. and Rose Fitzgerald Kennedy in Brookline, Massachusetts, on May 29, 1917. Several months shy of his 3rd birthday, young "Jack" contracted scarlet fever and was hospitalized; his condition ultimately deteriorated to the brink of death.<sup>14,31,33,57,62</sup> His childhood health troubles continued; he would be treated for a host of illnesses prior to his graduation from prepara-

tory school.<sup>1,14,21,24,57</sup> In fact, Robert F. Kennedy would later recall that "when we were growing up together we used to laugh about the great risk a mosquito took in biting Jack Kennedy—with some of his blood the mosquito was almost sure to die."<sup>51</sup>

### Collegiate Years: Origins of Low-Back Pain and First Consultation

Jack would add yet another entry to an already prodigious list of health problems during his undergraduate years at Harvard: low-back pain. The exact details of the inciting event remain murky, but the most commonly accepted account traces the onset of low-back pain to a football injury he sustained while at Harvard in 1937.<sup>2,5,21,26,29,32,33,57</sup>

Kennedy continued to be plagued with back pain after graduating from Harvard University in June 1940 and was referred to Dr. Gilbert "Ned" Haggart, an orthopedic spine specialist at the Lahey Clinic in Boston, who diagnosed him with a "very unstable lumbosacral joint." Dr. Haggart recommended a course of conservative treatment in the form of a manipulation of the back under anesthesia, which JFK underwent at the Lahey Clinic in 1940. Dr. Haggart also introduced the idea of a sacroiliac fusion if the conservative treatment failed.<sup>22,23,29</sup>

**ABBREVIATIONS** JFK = John F. Kennedy; PT = patrol torpedo.

**ACCOMPANYING EDITORIAL** See pp 245–246. DOI: 10.3171/2017.2.SPINE17229.

**SUBMITTED** December 21, 2015. **ACCEPTED** February 7, 2017.

**INCLUDE WHEN CITING** Published online July 11, 2017; DOI: 10.3171/2017.2.SPINE151524.

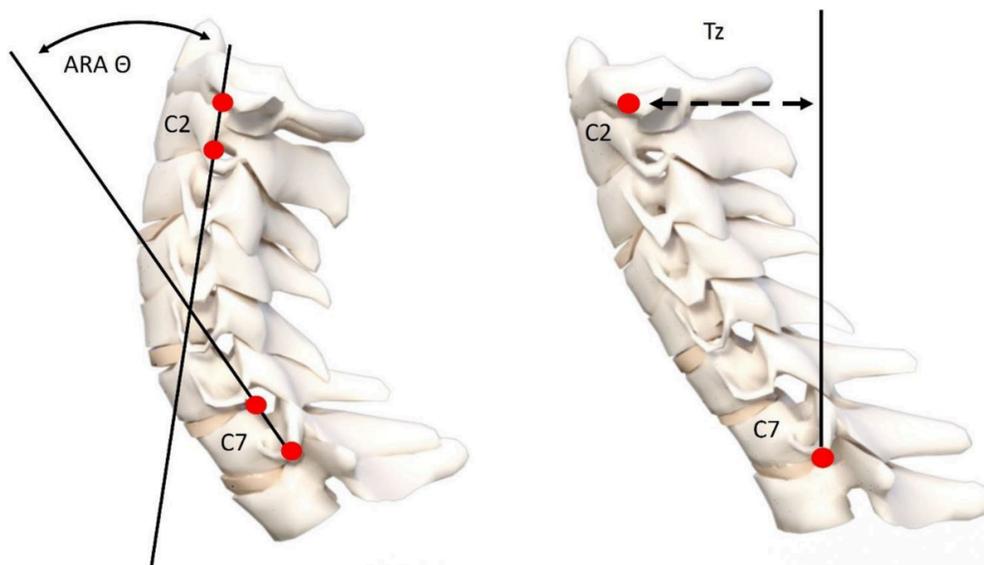
# Utilizing machine learning to predict post-treatment outcomes in chronic non-specific neck pain patients undergoing cervical extension traction

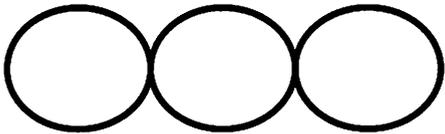
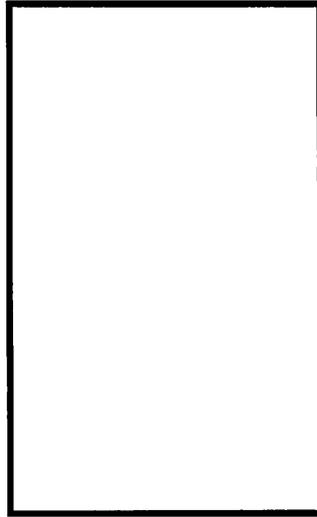
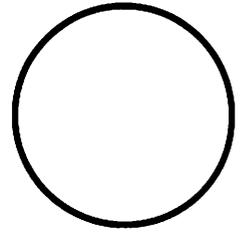
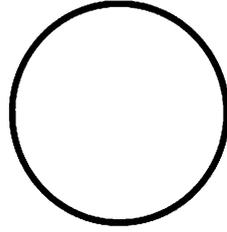
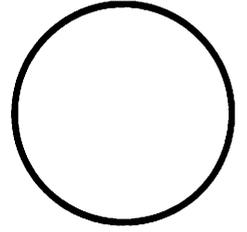
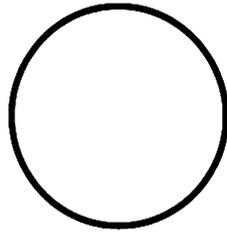
Ibrahim M Moustafa<sup>1 2 3</sup>, Dilber Uzun Ozsahin<sup>4 5 6</sup>, Mubarak Taiwo Mustapha<sup>5 6 7</sup>,  
Amal Ahbouch<sup>1 2</sup>, Paul A Oakley<sup>8 9 10</sup>, Deed E Harrison<sup>11</sup>

Affiliations: [— collapse](#)

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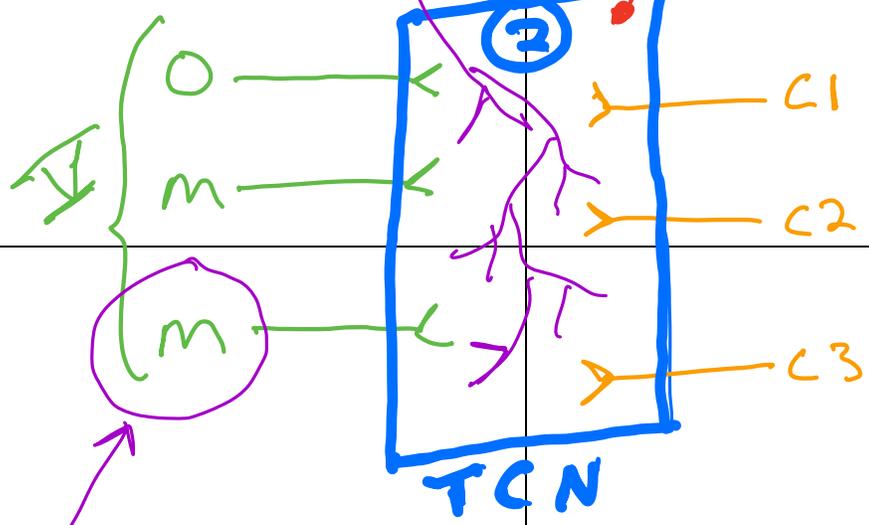
Headache

CN VII  
IX  
X

PG  
PAG  
ANS  
S/PS

T

MN  
CIV



TMS  
TMD

- ① Temporalis
- ② masseter
- ③ Pterygoids
- ④ Pterygoids

tinnitus → ⑤ Tensor Tympani

Meniere's ← ⑥ Tensor veli palatini  
otitis media



Article

# Neuroplastic Responses to Chiropractic Care: Broad Impacts on Pain, Mood, Sleep, and Quality of Life

Heidi Haavik <sup>1,\*</sup>, Imran Khan Niazi <sup>1,2,3,\*</sup>, Imran Amjad <sup>1,4</sup>, Nitika Kumari <sup>1,2</sup>, Usman Ghani <sup>1,2</sup>, Moez Ashfaque <sup>5</sup>, Usman Rashid <sup>1</sup>, Muhammad Samran Navid <sup>6</sup>, Ernest Nlandu Kamavuako <sup>7</sup>, Amit N. Pujari <sup>5,8</sup> and Kelly Holt <sup>1</sup>

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**Abstract:** Objectives: This study aimed to elucidate the mechanisms of chiropractic care using resting electroencephalography (EEG), somatosensory evoked potentials (SEPs), clinical health assessments (Fitbit), and Patient-reported Outcomes Measurement Information System (PROMIS-29). Methods: Seventy-six people with chronic low back pain (mean age ± SD: 45 ± 11 years, 33 female) were randomised into control ( $n = 38$ ) and chiropractic ( $n = 38$ ) groups. EEG and SEPs were collected pre and post the first intervention and post 4 weeks of intervention. PROMIS-29 was measured pre and post 4 weeks. Fitbit data were recorded continuously. Results: Spectral analysis of resting EEG showed a significant increase in Theta, Alpha and Beta, and a significant decrease in Delta power in the chiropractic group post intervention. Source localisation revealed a significant increase in Alpha activity within the Default Mode Network (DMN) post intervention and post 4 weeks. A significant decrease in N30 SEP peak amplitude post intervention and post 4 weeks was found in the chiropractic group. Source localisation demonstrated significant changes in Alpha and Beta power within the DMN post-intervention and post 4 weeks. Significant improvements in light sleep stage were observed in the chiropractic group along with enhanced overall quality of life post 4 weeks, including significant reductions in anxiety, depression, fatigue, and pain. Conclusions: These findings indicate that many health benefits of chiropractic care are due to altered brain activity.

**Keywords:** chiropractic; electroencephalogram (EEG); somatosensory evoked potentials (SEPs); default mode network (DMN); PROMIS-29

## 1. Introduction

Chiropractic care is based on the premise that correcting vertebral subluxations improves central neural function, improving human performance and clinical outcomes [1–3]. Vertebral subluxation is recognised by the World Health Organization as a biomechanical lesion within the vertebral column and is classified under the ICD-10-CM code M99.1 [4]. It

## Neuroplastic Responses to Chiropractic Care: Broad Impacts on Pain, Mood, Sleep, and Quality of Life

### Brain Science

November 7, 2024; Vol. 14; No. 11; Article 1124

This study cites 169 references.

"This study evaluated the underlying neurophysiological mechanisms of chiropractic care using a multifaceted approach, recording behavioral, subjective, and neurophysiological data."

76 people with chronic low back pain (CLBP) were randomized to a *chiropractic group* (n=38) and a *control group* (n=38).

The *chiropractic care* included 4 weeks (approximately 3 times per week) of manual high-velocity low-amplitude (HVLA) adjustments to the spine or pelvis identified as being subluxated.

- "These HVLA directed at vertebral subluxations rapidly stretch the surrounding paraspinal tissues and, in particular, the deep small paraspinal muscles."
- "This results in a 'bombardment' of proprioceptive input to the CNS that elicits the changes in central neural excitability and motor control changes."

The clinical indicators of vertebral subluxations included "tenderness to palpation of the relevant joints, manual palpation for restricted intersegmental range of movement, palpable asymmetric intervertebral muscle tension, and any unusual or blocked joint play and end feel of the joints."

"Chiropractic care is based on the premise that correcting vertebral subluxations improves central neural function, improving human performance and clinical outcomes."

"Vertebral subluxation is recognized by the World Health Organization as a biomechanical lesion within the vertebral column."

"[Vertebral subluxation] is characterized by abnormal movement or function of spinal segments which is identified by clinical markers such as restricted intersegmental range of motion, tenderness upon palpation, palpable asymmetric intervertebral muscle tension, and altered joint play and end feel."

"Vertebral subluxation involves altered afferent input from muscle spindles in the paraspinal muscles at the subluxated levels."

- "This disruption in sensory input can cause maladaptive central neural plastic changes, resulting in impaired sensorimotor integration and control."
- "These maladaptive central plastic changes in the central nervous system (CNS) can worsen over time, which is thought to contribute to dysfunction, pain, and other symptoms by disrupting normal sensorimotor control."
- "These maladaptive central plastic changes are thought to be reversed or improved through chiropractic care."
- Chiropractic care drives neuroplastic brain changes in "structures such as the primary somatosensory cortex, primary motor cortex, prefrontal cortex [PFC], and cerebellum." **[Important]**
- "Improvements in either prefrontal cortex or cerebellar function could explain many of the clinically relevant changes that have been documented following chiropractic care, such as improved joint position sense error, cortical processing, reflex excitability, reaction time, cortical sensorimotor integration, motor control, upper and lower limb muscle functions, and pain changes."
- Both the PFC and cerebellum influence emotional control and mental health, as well as neuroendocrine responses, autonomic nervous system function, and immune function. **[Very Important]**

The prefrontal cortex (PFC) plays a crucial role in executive functions.

- "Any alteration in prefrontal activity after chiropractic care could potentially elucidate or establish connections with the diverse enhancements in neural function." **[Very Important]**
- Chiropractic adjustments altered proprioceptive input from the paraspinal tissues which may be powerful enough to alter processing within the PFC.
- Chiropractic adjustments may activate the descending pain inhibitory pathway.

"[This study supports] the notion that part of the mechanisms of chiropractic care is that it might improve the descending modulatory pain pathway in CLBP patients, and this may be why it has been found to be clinically effective for both acute and CLBP problems and is a recommended option in relevant clinical guidelines."

"Numerous previous studies have also reported enhanced quality of life and well-being following chiropractic care, possibly linked to reduced pain and improved mobility."

"Several studies have found quality of life improvements beyond just improvements in pain or pain related disability, similar to what has been documented in the current study." **[Important]**

"Chiropractic care may potentially prevent pain from becoming chronic and the current study provides some insight into the mechanisms of this." **[Important]**

"Having ongoing maintenance chiropractic care (i.e., after the initial care period improves symptoms) results in less days of pain and improved QOL on an ongoing basis."

Long-term chiropractic care for CLBP may "significantly lower rates of hospitalisations, emergency department visits, advanced diagnostic imaging, specialist visits, lumbosacral surgery, interventional pain medicine techniques, i.e., a reduced escalation of care."

"Ongoing chiropractic care, even after the initial pain symptoms improve, will likely continue to impact somatosensory networks, .... thus maintaining positive neuroplastic changes that prevent such escalations of care, worsening of symptoms, and decreases in QOL." **[Very Important]**

"The current findings provide compelling evidence for why chiropractic care, that includes the HVLA adjustments directed towards subluxated segments, can impact not only chronic pain symptoms, but also influence anxiety and depression symptoms."

"[A] change in proprioceptive input to the CNS may ultimately be responsible for the development and maintenance of musculoskeletal pain syndromes."

Over time, abnormal or reduced proprioceptive input from dysfunctional spinal regions (i.e., vertebral subluxations) would be capable of causing ongoing central maladaptive changes. **[Very Important]**

"With ongoing poor motor control, as the CNS is less accurately aware of what is occurring at the vertebral column level (due to the reduced/abnormal proprioceptive inputs from that paraspinal region); this would likely lead to repeated microtraumas at the subluxated spinal levels as well as other areas of the body that require accurate sensory input from the spine, such as accurate upper and lower limb motor control."

"Over time, it makes sense that this could explain the development of chronic musculoskeletal pain problems."

"This contemporary model also explains how spinal adjustments, i.e., HVLA thrusts delivered to subluxated spinal segments, can improve vertebral column motor control by bombarding the CNS with mechanoreceptive input from the segments that are dysfunctional." **[Very Important]**

"This research contributes significantly to the scientific discourse on the mechanisms of chiropractic care, paving the way for further investigations into its holistic impacts on health and well-being." **[Key Point]**

"Many health benefits of chiropractic care are due to altered brain activity." **[Key]**

"These results provide support for the contemporary model of the vertebral subluxation and help to explain how chiropractic HVLA adjustments impact the way the brain integrates both interoceptive and exteroceptive sensory information in a multimodal fashion, including the consideration of past memories and future expectations." **[Key Point]**

This study suggests that "chiropractic care alters a person's narrative sense of self, that can enable that person to think, feel and function better." **[Key]**

Comments From Dan Murphy:

Heidi Haavik and her team of researchers are publishing the most important neurophysiological research for the chiropractic profession, and I believe that all chiropractors should financially support their efforts:

<https://chiropractic.ac.nz/research/support-our-research/>

**Chronic Spinal Pain:  
A Randomized Clinical Trial Comparing Medication, Acupuncture, and Spinal  
Manipulation**

**Spine**

**July 15, 2003; Vol. 28; No. 14; pp. 1490-1502**

Lynton G. F. Giles, DC, PhD; Reinhold Muller, PhD

This is a randomized controlled clinical trial of 115 subjects with the objective to compare medication, needle acupuncture, and [chiropractic] spinal manipulation for managing chronic (>13 weeks duration) spinal pain.

“One of three separate intervention protocols was used: medication, needle acupuncture, or chiropractic spinal manipulation.”

Patients were assessed before, during and after treatment using the Oswestry Back Pain Disability Index (Oswestry), the Neck Disability Index (NDI), the Short-Form-36 Health Survey questionnaire (SF-36), visual analog scales (VAS) of pain intensity and ranges of movement.

“The highest proportion of early (asymptomatic status) recovery was found for manipulation (27.3%), followed by acupuncture (9.4%) and medication (5%).”

“Manipulation achieved the best overall results, with improvements of 50% on the Oswestry scale, 38% on the NDI, 47% on the SF-36, and 50% on the VAS for back pain, 38% for lumbar standing flexion, 20% for lumbar sitting flexion, 25% for cervical sitting flexion, and 18% for cervical sitting extension.”

“The consistency of the results provides evidence that in patients with chronic spinal pain, manipulation, if not contraindicated, results in greater short-term improvement than acupuncture or medication.”

“A pathologic cause cannot be identified for most episodes of spinal pain, and clinicians often have great difficulty establishing the underlying cause.”

“Only about 15% of patients receive a definitive diagnosis because it often is impossible to reach specific diagnosis.”

“Numerous studies have shown that patients with low back pain do exhibit abnormal spinal motion.”

“The proportion of primary care patients with uncomplicated spinal pain who have poor outcomes appears to be higher than generally recognized.”

“Adverse reactions to nonsteroidal anti-inflammatory (NSAID) medication have been well documented.”

“Gastrointestinal toxicity induced by NSAIDs is one of the most common serious adverse drug events in the industrialized world.”

The drugs used in this study were Celebrex (200-400 mg/day); the next drug of choice was Vioxx (12.5-25 mg/day), followed by paracetamol (up to 4 g/day).

Acupuncture was performed by one of two experienced acupuncturists. Two acupuncture treatments per week were given.

High-velocity, low-amplitude thrust spinal manipulation to a joint was performed by a chiropractor at the spinal level of involvement to mobilize the spinal joints. Two treatments per week were given.

“Because the patients had chronic spinal pain syndromes, it is unlikely that improvement resulted from ‘self-limiting’ spinal pain, as could be the case with acute spinal pain.”

“In summary, the significance of the study is that for chronic spinal pain syndromes, it appears that spinal manipulation provided the best overall short-term results, despite the fact that the spinal manipulation group had experienced the longest pretreatment duration of pain.”

**Chronic Spinal Pain: A Randomized Clinical Trial Comparing Medication, Acupuncture, and Spinal Manipulation**

**Spine; July 15, 2003; Vol. 28; No. 14; pp. 1490-1502**

<b>Treatment</b>	<b>Drugs (Celebrex or Vioxx)</b>	<b>Acupuncture</b>	<b>Chiropractic Adjustments</b>
<b>Years Of Chronic Spinal Pain</b>	<b>4.5 or 6.4</b>	<b>4.5 or 6.4</b>	<b>8.3</b>
<b>% Asymptomatic within 9 weeks</b>	<b>5%</b>	<b>9.4%</b>	<b>27.3%</b>
<b>% That suffered an adverse event</b>	<b>6.1%</b>	<b>0%</b>	<b>0%</b>
<b>% Improvement In General Health Status</b>	<b>18%</b>	<b>15%</b>	<b>47%</b>

# **Chiropractic**

## **Summary**

**Musculoskeletal Outcomes**

**Safety**

# Levers

# **Neurophysiological Thinking**

# A BASIS FOR THE THEORY OF MEDICINE

*By*

**A. D. SPERANSKY**

*Director of the Department of Patho-Physiology of the  
All-Union Institute of Experimental Medicine*

*Translated and Edited by*

**C. P. DUTT, B.A. (CANTAB.)**

*With the Collaboration of*

**A. A. SUBKOV**

*Senior Research Worker of the Timiryazev  
Biological Institute*

1943



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# SYMPTOMS OF VISCERAL DISEASE

A STUDY OF THE VEGETATIVE NERVOUS SYSTEM IN ITS  
RELATIONSHIP TO CLINICAL MEDICINE

By

**FRANCIS MARION POTTENGER**  
A.M., M.D., LL.D., F.A.C.P.

Medical Director, Pottenger Sanatorium and Clinic for Diseases of the Chest,  
Monrovia, California; Professor Emeritus of Clinical Medicine, University  
of Southern California; Author of "Clinical Tuberculosis,"  
"Tuberculin in Diagnosis and Treatment," "Muscle  
Spasm and Degeneration," Etc.

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**Dr. R. Frank Gorman**

**Sydney Australia**

**2011**

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bakris g and dickholtz

Full text links



J Hum Hypertens. 2007 May;21(5):347-52. Epub 2007 Mar 2.

## Atlas vertebra realignment and achievement of arterial pressure goal in hypertensive patients: a pilot study.

Bakris G<sup>1</sup>, Dickholtz M Sr, Meyer PM, Kravitz G, Avery E, Miller M, Brown J, Woodfield C, Bell B.

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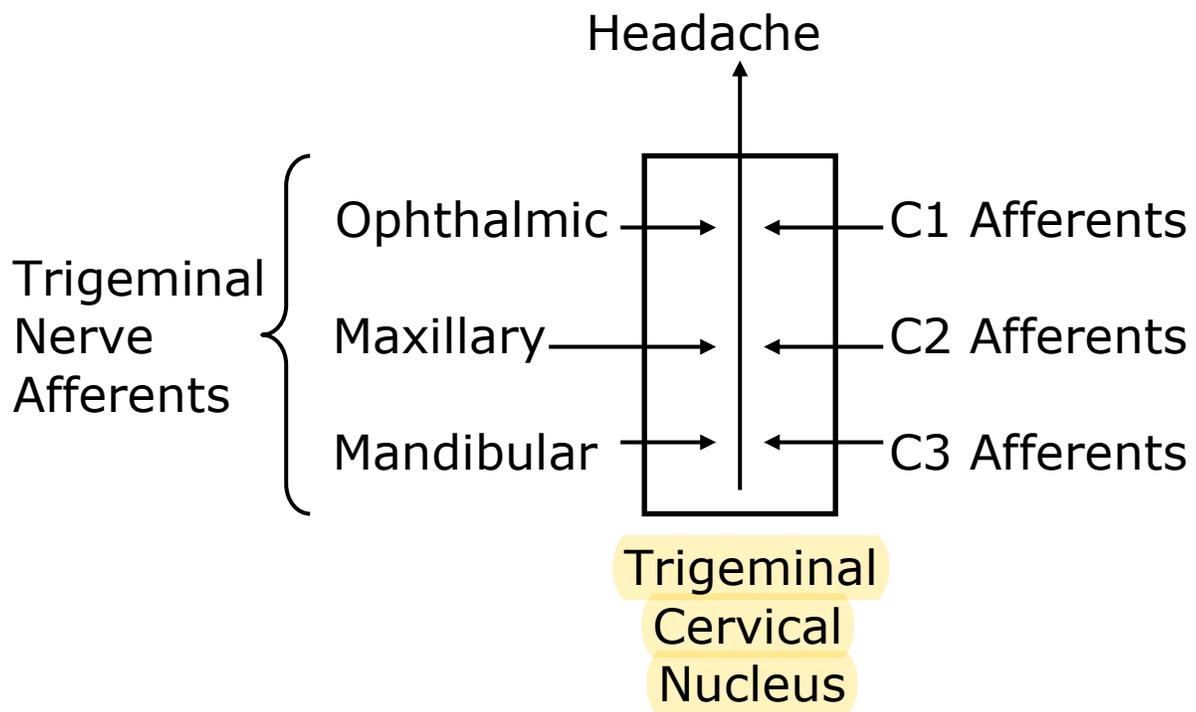
### Abstract

Anatomical abnormalities of the cervical spine at the level of the Atlas vertebra are associated with relative ischaemia of the brainstem circulation and increased blood pressure (BP). Manual correction of this mal-alignment has been associated with reduced arterial pressure. This pilot study tests the hypothesis that correcting mal-alignment of the Atlas vertebra reduces and maintains a lower BP. Using a double blind, placebo-controlled design at a single center, 50 drug naïve (n=26) or washed out (n=24) patients with Stage 1 hypertension were randomized to receive a National Upper Cervical Chiropractic (NUCCA) procedure or a sham procedure. Patients received no antihypertensive meds during the 8-week study duration. The primary end point was changed in systolic and diastolic BP comparing baseline and week 8, with a 90% power to detect an 8/5 mm Hg difference at week 8 over the placebo group. The study cohort had a mean age 52.7+/-9.6 years, consisted of 70% males. At week 8, there were differences in systolic BP (-17+/-9 mm Hg, NUCCA versus -3+/-11 mm Hg, placebo; P<0.0001) and diastolic BP (-10+/-11 mm Hg, NUCCA versus -2+/-7 mm Hg; P=0.002). Lateral displacement of Atlas vertebra (1.0, baseline versus 0.04 degrees week 8, NUCCA versus 0.6, baseline versus 0.5 degrees, placebo; P=0.002). Heart rate was not reduced in the NUCCA group (-0.3 beats per minute, NUCCA, versus 0.5 beats per minute, placebo). No adverse effects were recorded. We conclude that restoration of Atlas alignment is associated with marked and sustained reductions in BP similar to the use of two-drug combination therapy.

### Comment in

Blood pressure lowering effects of non-surgical procedures for vascular decompression: good news to be taken with caution. [J Hum Hypertens. 2007]

PMID: 17252032 DOI: [10.1038/sj.jhh.1002133](https://doi.org/10.1038/sj.jhh.1002133)



# **Efficacy of Spinal Chiropractic Manipulative Therapy for Adjusting the Relationship Between Cervical Facet Joints to Treat Headache Caused by Acute Mountain Sickness**

**Journal of International Medical Research**  
**January 2020; Vol. 48; No. 1**

Yuan Wang, Mengzi Xu, Yan Shi: this study cites 29 references.

The plateau area of China has low air pressure and a hypoxic environment. When plain dwellers arrive on the plateau rapidly, at an altitude >3000 m [about 10,000 feet], they suffer from dizziness, headache, nausea, vomiting, and other clinical syndromes due to altitude hypoxia, which is called *acute mountain sickness*.

Acute mountain sickness seriously affects the life and work of the people who have to come to areas such as Tibet, causing fear and anxiety in many people who have never visited the plateau, directly restricting them from traveling, investing, and working in Tibet.

Acute mountain sickness may be serious because it may lead to pulmonary and cerebral edema in 0.1% to 4.0% of individuals. "Acute mountain sickness can be life-threatening."

Acute mountain sickness assessment was based upon the Lake Louise score which includes:

- fatigue or weakness
- dizziness or lightheadedness
- gastrointestinal symptoms such as nausea, vomiting
- difficulty sleeping

The objective of this study was to investigate the effect of spinal chiropractic manipulative therapy on the management of acute mountain sickness-induced headache.

100 subjects were randomly divided into an adjustment group and a control group that used standard acute mountain sickness pain control techniques.

The treatments were carried out within 72 hours after the initial onset of symptoms in Tibet. The treatment effects were evaluated at 10 minutes, 30 minutes, and 24 hours after treatment.

The subjects in the chiropractic manipulative therapy group received only chiropractic manipulative therapy (no drugs or oxygen) at the atlanto-occipital and atlanto-axial facet joints. These adjustments were done seated with a primary thumb contact on the transverse process of C1 and/or C2.

The control group received standard treatments for acute mountain sickness, including oxygen inhalation through a nasal tube for 2 hours at 5 L/minute, oral ibuprofen 0.3 g twice daily for 2 days, and 250 mL of 5% glucose intravenously.

The primary goals were headache and vertigo improvement.

#### KEY POINTS FROM THIS ARTICLE:

- 1) "High altitude headache is a chief concern among individuals visiting high altitudes; it develops within 24 hours of ascent and is worse at night and with exertion."
- 2) "Mechanical strain on cervical structures such as the facet joints may aggravate joint arthrosis or disc degeneration and aggravate headaches due to hypoxia." **[Important]**
- 3) "Adjusting the relationship between cervical facet joints by spinal chiropractic manipulative therapy can correct small joint disorders caused by intervertebral instability." **[Important]**
- 4) Chiropractic spinal manipulation has "achieved good results in the treatment of cervical vertigo disease and cervicogenic headache."
- 5) Chiropractic spinal manipulation has "the characteristics of being simple to perform, having a quick effect, being non-invasive, and causing no trauma." **[Important]**
- 6) Chiropractic spinal manipulation "can be used to correct cervical instability states including cervical facet joint disorders and slight dislocation of the cervical vertebrae, restore the internal balance of the cervical vertebrae and the normal anatomical position of the cervical vertebrae, relieve compression on the vertebral artery or relieve the angio-spasm through the neural reflex mechanism, promote the regression of the local aseptic inflammatory edema of the soft tissue and the absorption of metabolites, and improve the blood circulation of the vertebral artery and cerebral blood supply, thus effectively relieving or alleviating the clinical symptoms of patients."
- 7) "We postulate that, as with divers, mechanical strain on the cervical structures could aggravate headaches due to hypoxia."
- 8) "Mechanical strain on the cervical structures during diving might aggravate joint arthrosis or disc degeneration and thus aggravate headaches due to hypoxia."
- 9) The results "strongly suggest the efficacy of spinal chiropractic manipulative therapy in treating acute mountain sickness -induced headache."
  - "The systolic and diastolic blood pressures were significantly improved."

10) "The results suggest that spinal chiropractic manipulative therapy can be used to relieve acute mountain sickness -induced headache, as well as dizziness symptoms, blood pressure abnormalities, and oxygen saturation of people traveling rapidly to high altitudes." **[Key Point]**

- "Spinal chiropractic manipulative therapy is suitable the management of acute mountain sickness for patients who prefer to avoid the use of drugs or oxygen, but oxygen and analgesics remain an appropriate method to manage acute mountain sickness."
- "Spinal chiropractic manipulative therapy may be suitable for the management of acute mountain sickness for patients who want to avoid drugs and oxygen inhalation."
- Spinal manipulation "is convenient and is not limited by the need for special equipment."

11) "In the spinal chiropractic manipulative therapy group, blood pressure, heart rate, VAS score, and oxygen saturation were significantly improved at 10 minutes, 30 minutes, and 24 hours after spinal chiropractic manipulative therapy to adjust the cervical facet joints, which was statistically different from baseline." **[Key Point]**

- "The subjects in the spinal chiropractic manipulative therapy group had higher VAS at baseline but still achieved VAS scores lower than those of the control group, highlighting the efficacy of spinal chiropractic manipulative therapy." **[Important]**
- "Adjusting the relationship between the facet joints of the cervical vertebrae by spinal chiropractic manipulative therapy could relieve acute altitude reaction quickly and effectively."
- In the spinal manipulation group, the "improvement of headache VAS score was better than that of the control group 10 minutes, 30 minutes, and 24 hours after treatment, and the improvement of the vertigo symptom score was significantly better than that of the control group." **[Important]**

12) The authors "hypothesized that spinal chiropractic manipulative therapy alleviates acute mountain sickness -induced headaches by mechanisms that are independent of hypoxia."

13) There were no adverse events reported from chiropractic manipulative therapy in this study.

#### COMMENTS FROM DAN MURPHY

- Chiropractic adjusting typically is accomplished in at most a few minutes.

- In contrast, standard treatment for acute mountain sickness required:
  - 2 hours of nasal tube oxygen inhalation
  - Intravenous glucose administration
  - Oral ibuprofen, twice daily for 2 days

Yet, in all measured parameters, upper cervical spine chiropractic spinal adjusting achieved the best outcome.

It is important to note that this study adds to the biological plausibility that upper cervical spine chiropractic spinal adjusting influences physiological functions that are separate from musculoskeletal pain syndromes. The primary outcome pertained to headache, but improvements were also documented in dizziness, blood pressure, and oxygen saturation.

## Relief of Postural Orthostatic Tachycardia Syndrome with Chiropractic Rehabilitation

Journal of Family Medicine and Primary Care  
July 2022; Vol. 11; No. 7; pp. 4006-4009

Eric Chun Pu Chu, Andy Fu Chieh Lin

1) "Postural orthostatic tachycardia syndrome (POTS) is a form of chronic dysautonomia causing an abnormal heart rate response to a positional change."

- "POTS symptoms are lightheadedness, palpitations, and tremor."
- POTS is "associated with headaches and neck pain as the blood is not getting to the muscles and brain."
- Activities such as taking a bath or housekeeping work may significantly increase symptoms, resulting in debilitating symptoms.
- POTS diagnostic criteria require a "heart rate (HR) increment of 30 beats/min or HR >120 beats/min in the first 10 min of standing, in the absence of orthostatic hypotension, and associated with orthostatic intolerance."
- "Patients with POTS frequently develop lightheadedness, palpitation, and neck pain."

2) The pathophysiology of POTS includes multiple factors like autonomic dysfunction, increased sympathetic tone, inadequate venous return, or excessive blood venous pooling.

### 3) Case Report

- A 50-year-old female presented for chiropractic care with lightheadedness, palpitation, headaches, and neck pain for 3 years.
- Lightheadedness and palpitation occurred as a result of moving from a seated to standing position, which usually lasted 10 min.
- There was an association between her lightheadedness and neck pain for 3 years.
- There was no history of trauma, auditory, or visual complaints.
- Patient was medically diagnosed with anxiety and panic attacks due to work stress and treated with psychiatric medications with no improvement.

- She also failed to improve with acupuncture, physiotherapy exercise, medications like salt tablets, fludrocortisone, pyridostigmine, midodrine, and a beta blocker.
- The intensity of her neck pain and headache were a 5 on a 0–10 numeric pain rating scale.
- Her Dizziness Handicap Inventory (DHI) questionnaire score was 46/100 (mild: <30; moderate: 31–60; and severe: >60).
- Cervical ranges of motion were reduced with protective muscle spasm.
- Lateral cervical x-ray showed a kyphotic curve of  $-5^{\circ}$ .
- Thoracic x-rays showed a  $12^{\circ}$  thoracic scoliosis.
- “The patient was diagnosed with POTS on the basis of the association between her neck pain, dizziness, mechanical neck dysfunction, and a positive head-up tilt table test.”

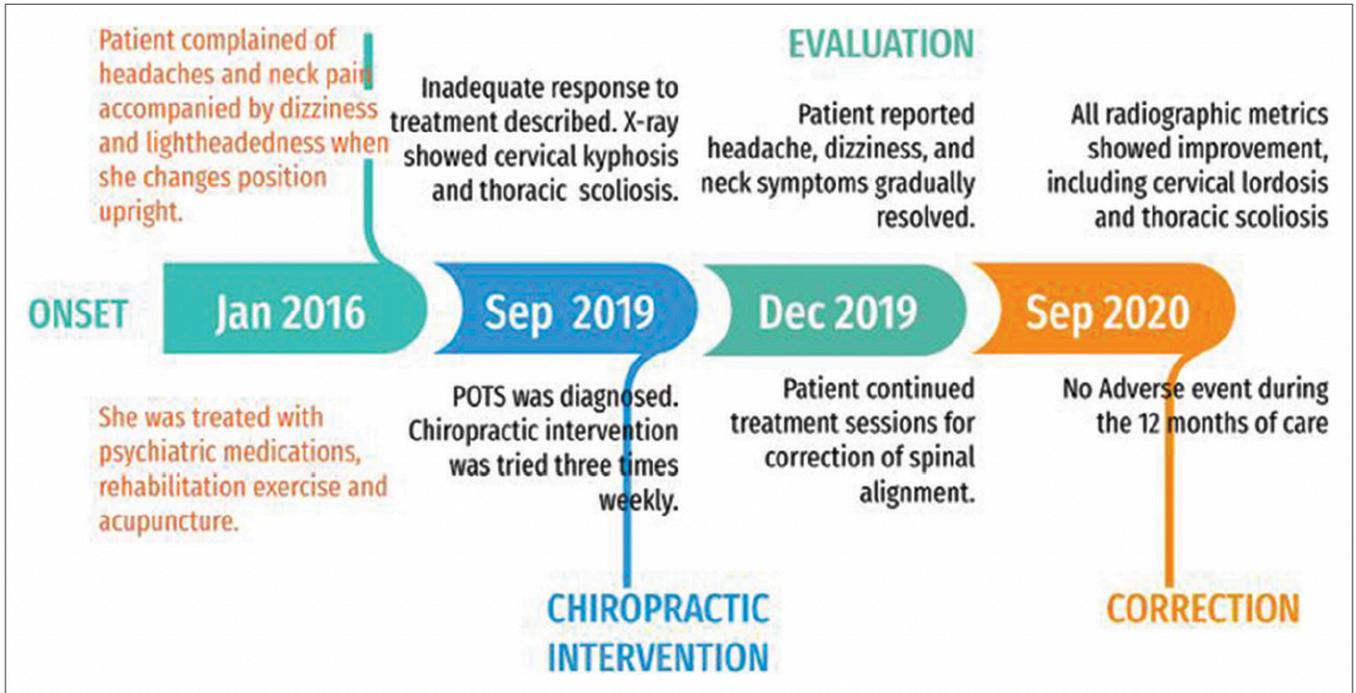
#### 4) **Chiropractic Care Included:**

- Care 3X per week for 3 months.
- “Chiropractic rehabilitation included spinal manipulation of the restricted cervical segments and thermal ultrasound therapy to alleviate neck stiffness and restore normal joint mobility, as well as intermittent motorized traction of the cervicothoracic spine to increase intervertebral spaces and decompress neural impingement.”

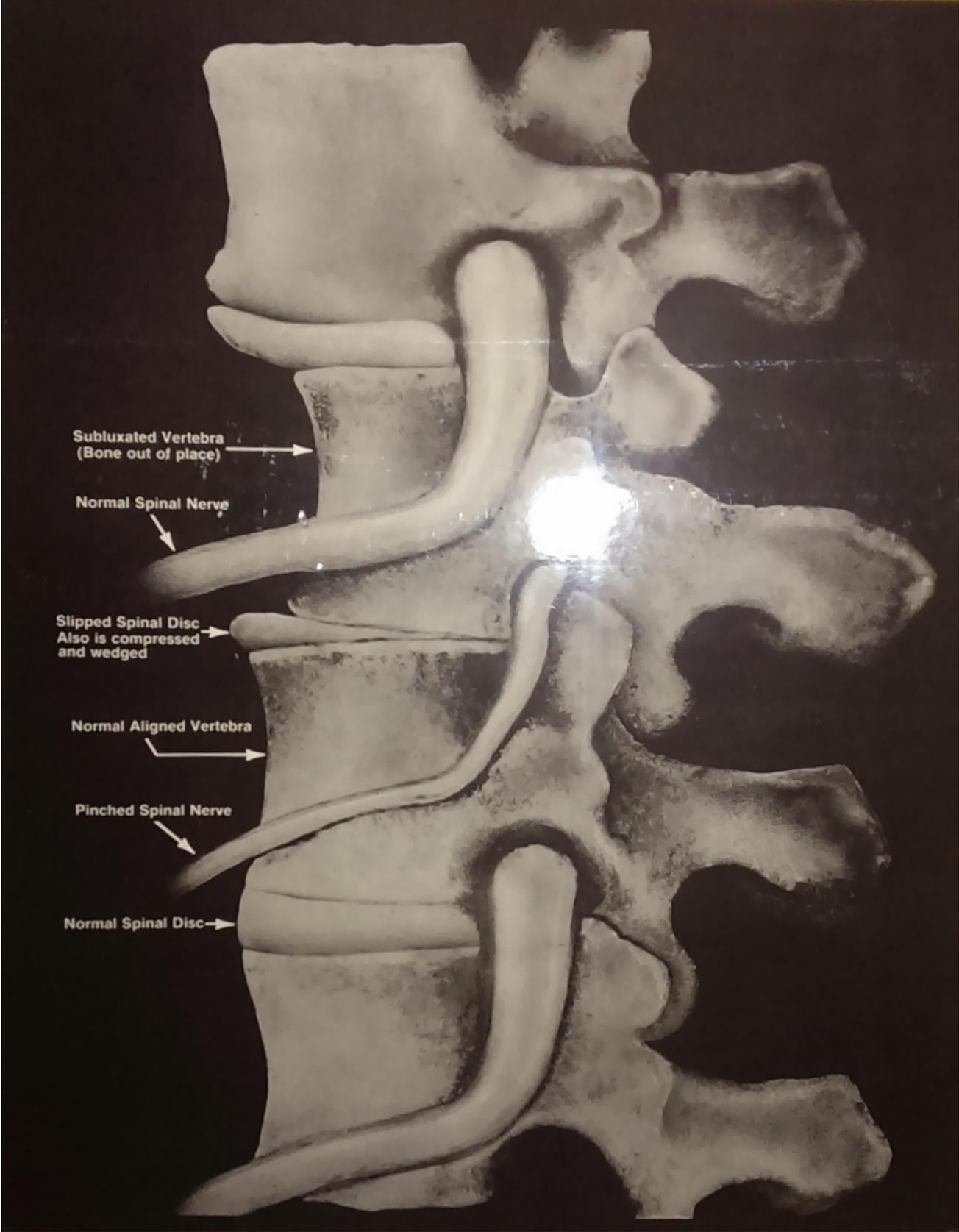
#### 5) **Outcomes:**

- 3 months of regular treatment, the patient reported a full resolution of neck pain, dizziness, and POTS.
- “From the second week on, the patient reported that her pain and dizziness gradually improved and resolved completely within 4 weeks.”
- At the 12-month follow-up, all radiographic metrics showed improvement, including improvement of cervical alignment ( $-5^{\circ}$  kyphosis to  $+20^{\circ}$  lordosis) and thoracic curvature ( $12^{\circ}$  scoliosis to  $7^{\circ}$  scoliosis).
- The majority of neck mobility was regained.
- Neck pain decreased from 5/10 to 0/10 on the numeric pain rating scale.
- The DHI score decreased from 46 to 0.

- “For the next 9 months, she continued to receive weekly maintenance treatment aimed at restoring spinal instability.”
  - The 24-month re-evaluation showed the patient remained symptom-free.
  - The patient reported no adverse events associated with the treatment.
- 6) “The great majority of clinicians are unfamiliar with or have received little training in assessing and managing the POTS.”
- 7) “Although numerous medications are frequently used to treat POTS symptoms, no medications are officially approved for POTS by the Food and Drug Administration, and the evidence for these medications used to treat POTS is limited.”
- 8) “The cervical spine harbors the cervical ganglia, which are the paravertebral ganglia of the sympathetic nervous system.”
- “Cervical spine degeneration might cause compression of spinal canal and irritation of the autonomic nervous system.”
  - “A cohort study (comprised 22,236 subjects with CS vs. 22,236 matched controls) demonstrated that patients with cervical spondylosis (CS) have increased risk of arrhythmia.”
    - 11.1% of those with cervical spondylosis had arrhythmia.
    - 3.91% of those *without* cervical spondylosis had arrhythmia.
    - $11.1/3.91 = 280\%$  increased risk of arrhythmia with spondyloses.
- 9) “Spinal adjustment has been found to be effective in treating headache associated with autonomic dysfunctions and achieved long-lasting results.”
- “It is logical to see the biomechanics and neurological improvement under chiropractic rehabilitation on patients with POTS.”
- 10) “Neck pain is likely associated with arrhythmia, especially those who had symptoms of autonomic nervous dysfunction.” **[Important]**
- 11) “Non-surgical treatments such as medications, rehabilitation, manipulative therapy, acupuncture, and psychotherapy can be effective in most spine symptoms.”
- 12) “This study might arouse the alertness of clinicians that symptoms related to POTS may be erroneously attributed to other neuro-cardiovascular disorders.”

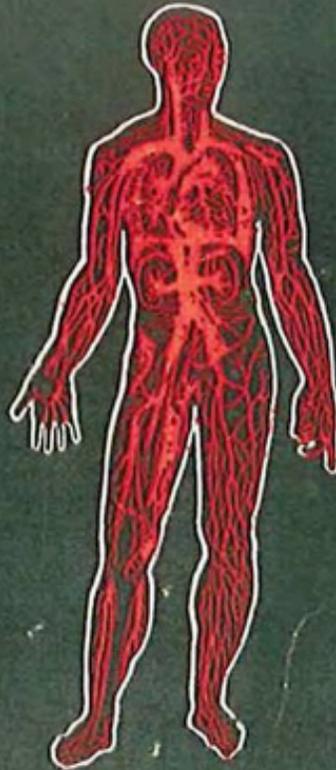


# **Nerve Interference**



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The Gunn Approach to the  
**TREATMENT OF  
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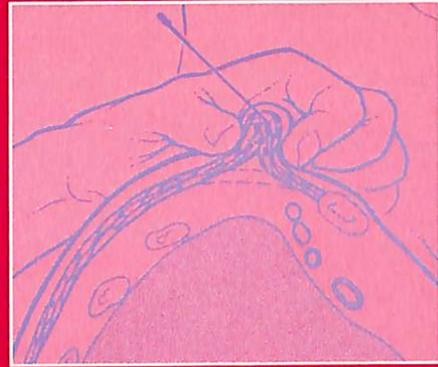
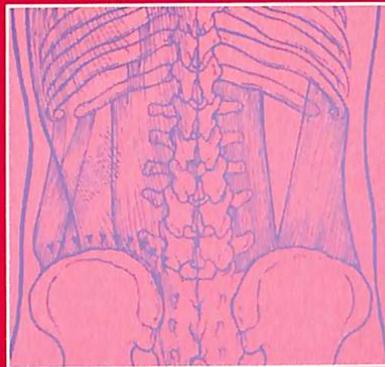
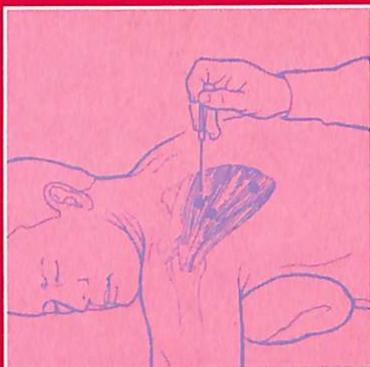
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*Intramuscular Stimulation for  
Myofascial Pain of Radiculopathic Origin*

**C. CHAN GUNN**

Foreword by  
**Patrick D. Wall**

1996



**CHURCHILL LIVINGSTONE**

The Gunn Approach to the  
**TREATMENT OF  
CHRONIC PAIN**

*Intramuscular Stimulation for  
Myofascial Pain of Radiculopathic Origin*

**C. Chan Gunn** MD  
Clinical Professor, Multidisciplinary Pain Center,  
University of Washington Medical School, Seattle, USA

Foreword by

**Patrick D. Wall** FRS DM FRCP  
Professor Emeritus  
United Medical and Dental Schools, London, UK

1996



NEW YORK EDINBURGH LONDON MADRID MELBOURNE SAN FRANCISCO AND TOKYO 1996

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[Spine \(Phila Pa 1976\)](#). 1980 Mar-Apr;5(2):185-92.

## **"Prespondylosis" and some pain syndromes following denervation supersensitivity.**

**Gunn CC.**

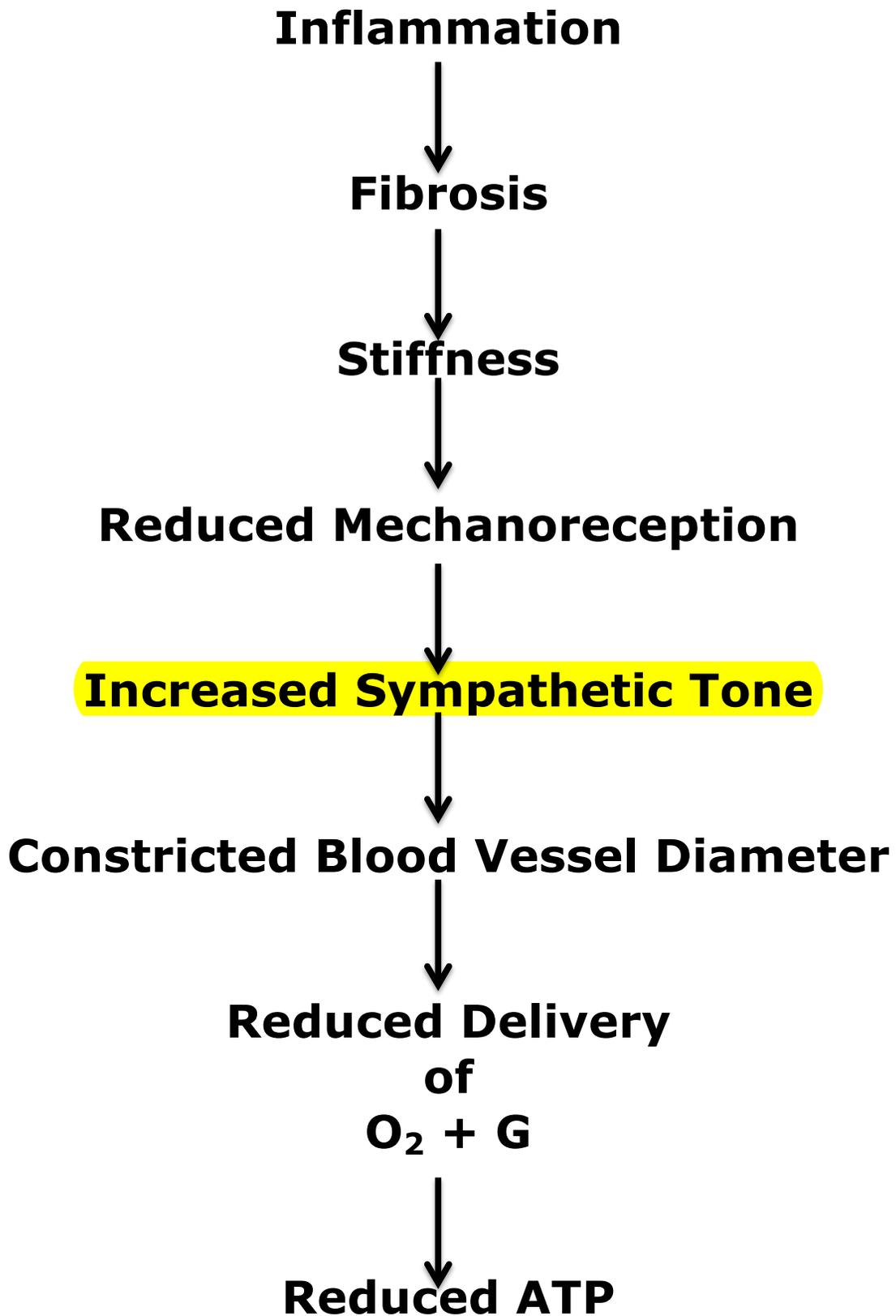
### **Abstract**

Pain is determined by the neurologic properties of receptor organs, neurons, and their interconnections. These may become supersensitive or hyperreactive following denervation (Cannon's Law). A common cause of denervation in the peripheral nervous system is neuropathy or radiculopathy as a sequel to spondylosis. Spondylosis in its early stage may be "asymptomatic" or painless and hence unsuspected, because small-diameter pain fibers may not initially be involved despite the attenuation of the other component fibers of the nerve. The term "prespondylosis" is introduced here to describe this presently unrecognized phase of insidious attrition to the other functions of the nerve, especially the trophic aspect. It is postulated that many diverse pain syndromes of apparently unrelated causation may be attributed to abnormal noxious input into the central nervous system from supersensitive receptor organs (nociceptors) and hyperreactive control systems at internuncial pools. Furthermore, trauma to a healthy nerve is usually painless or only briefly painful, unless there is preexisting neuropathy. Some pain syndromes in muscle (eg, trigger points and myofascial pain syndromes) and nerve (eg, causalgia and diabetic neuropathy) that may be related to denervation are discussed.

PMID: 6247768 [PubMed - indexed for MEDLINE]

### **MeSH Terms**

### **LinkOut - more resources**



**The Gunn Approach to the Treatment of Chronic Pain****Intramuscular Stimulation for Myofascial Pain of Radiculopathic Origin****C. Chan Gunn, MD****Clinical Professor, Multidisciplinary Pain  
Center****University of Washington Medical  
School, Seattle, WA, USA****Churchill Livingstone, 1996****NEUROPHYSIOLOGY**

What is not well known is that "when a nerve is below par and is not functioning properly, it becomes supersensitive and will behave erratically. This principle is fundamental and universal, yet is not at all well known or credited." This is known as Cannon's and Rosenblueth's:

**Law Of Denervation Supersensitivity**

# **Mechanoreceptors**

PubMed

**Display Settings:** Abstract

Full text links



Science. 1965 Nov 19;150(3699):971-9.

**Pain mechanisms: a new theory.**

Melzack R, Wall PD.

PMID: 5320816 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms

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## The Mechanoreceptors

Melzack and Wall's Gate Theory of Pain was published in 1963 and 1965. Dr. Korr's article on proprioceptors was published in 1975. Dr. Kirkaldy-Willis' article on manipulation and the Gate Theory of Pain was published in 1985.

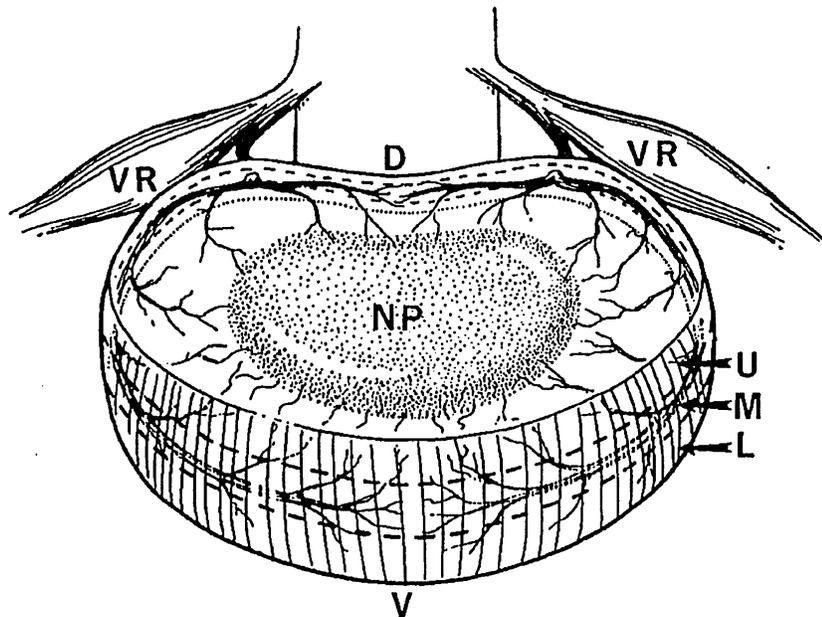
In 1992, the journal *Spine* published a study titled (Mendel):

### "Neural Elements in Human Cervical Intervertebral Discs"

The authors document that the human cervical intervertebral disc is innervated with mechanoreceptors. They state:

**"The presence of neural elements within the intervertebral disc indicates that the mechanical status of the disc is monitored by the central nervous system."**

**"The location of the mechanoreceptors may enable the intervertebral disc to sense peripheral compression or deformation as well as alignment."**

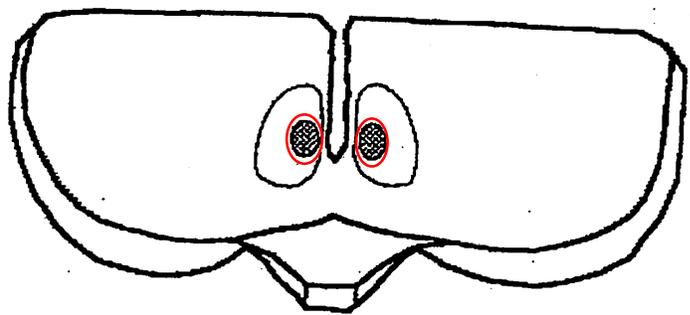


Key points from this study include:

- The intervertebral disc is innervated with mechanoreceptors, perhaps as deep as to the nucleus pulposus.
- These mechanoreceptors communicate to the central nervous system.

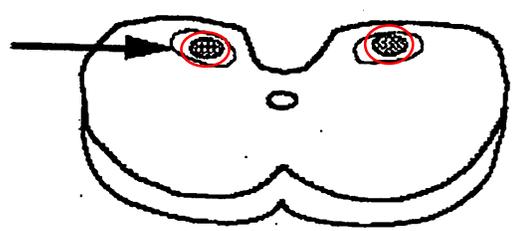
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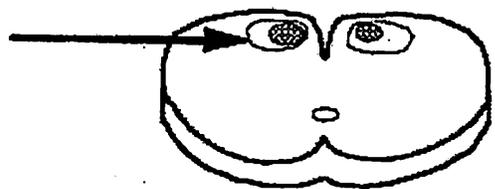
Thalamus

Vestibular nucleus

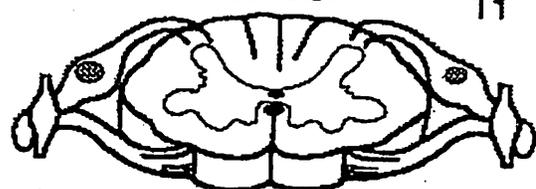


Pons

Nucleus cuneatus



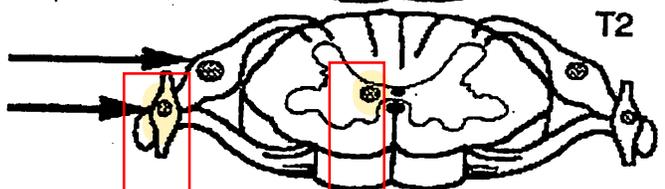
Medulla



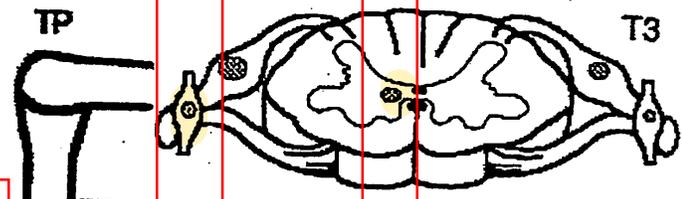
T1

Dorsal root ganglion

Sympathetic ganglion

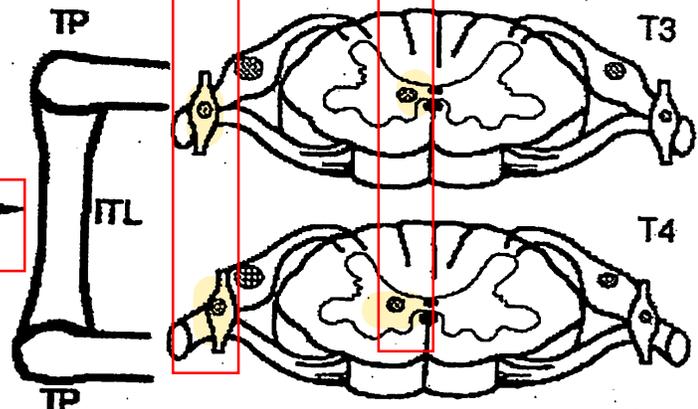


T2

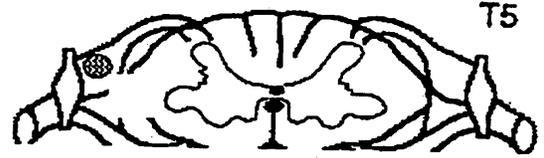


T3

Mechanical Stimulation



T4



T5

Right

Left

**Original Article****A hypothesis of chronic back pain: ligament subfailure injuries lead to muscle control dysfunction****European Spine Journal****July 27, 2005**Manohar M. **Panjabi**From the Department of Orthopaedics and Rehabilitation, **Yale** University School of Medicine

FROM ABSTRACT:

A new hypothesis, based upon the concept that subfailure injuries of ligaments (spinal ligaments, disc annulus and facet capsules) may cause chronic back pain due to muscle control dysfunction, is presented.

The hypothesis has the following sequential steps:

- 1) **Single trauma or cumulative microtrauma causes subfailure injuries of the ligaments and embedded mechanoreceptors.**
- 2) The injured mechanoreceptors generate corrupted transducer signals, which lead to corrupted muscle response pattern produced by the neuromuscular control unit.
- 3) Muscle coordination and individual muscle force characteristics, i.e. onset, magnitude, and shut-off, are disrupted.
- 4) This results in abnormal stresses and strains in the ligaments, mechanoreceptors and muscles, and excessive loading of the facet joints.
- 5) Due to inherently poor healing of spinal ligaments, accelerated degeneration of disc and facet joints may occur.
- 6) The abnormal conditions may persist, and, over time, may lead to chronic back pain via inflammation of neural tissues.

THIS AUTHOR ALSO NOTES:

70–85% of the population in industrialized societies experience low back pain at least once in their lifetime.

30% of the population has low back pain at any given point in time.

The total cost of low back pain in the US is more than \$50 billion per year.

“Abnormal mechanics of the spinal column has been hypothesized to lead to back pain via nociceptive sensors.”

With ligament injury, the mechanoreceptors generate corrupted transducer signals [altered afferent mechanical input to the spinal cord], and motor control mismatch, simultaneously firing both the agonist and antagonist muscles, stabilizing the spine and minimizing intervertebral motions. This muscle response may become chronic.

“The subfailure injuries of ligaments are incomplete injuries, which may range between tearing of a few fibers to a nearly complete rupture of a ligament.”

ALSO:

- 1) Functional spinal units have many ligament structures that may sustain a wide range of injury, depending upon the magnitude and mode of the trauma.
- 2) The density of the mechanoreceptors imbedded in the various ligament structures varies greatly.
- 3) Therefore, seemingly similar injury-causing events can produce a wide spectrum of corrupted muscle response patterns.
- 4) These altered muscle response patterns may result in muscle atrophy and weakness due to disuse, aggravating the spinal system dysfunction.
- 5) “As the muscles participate in the feedback loop via the mechanoreceptors in the form of muscle spindles and golgi tendon organs, their disruption could further corrupt the muscle response pattern.”

Injured muscles heal relatively quickly due to abundant blood supply and therefore are not the main cause of chronic back pain. **[Important]**

In contrast, ligament injuries heal poorly and therefore lead to tissue degeneration over time.

“Thus, the ligament injuries are more likely to be the major cause of the chronic back pain.” **[Very Important]**

The corrupted transducer signals [altered afferent mechanical input to the spinal cord] may be the result not only of the ligament injury, but also due to ligament fatigue and viscoelastic creep stretch [as from chronic altered posture].

“If the corrupted muscle response pattern becomes permanent, then it may result in abnormal posture, disturbed intervertebral motion pattern, altered gait, and, in general, a less efficient system to perform every day spinal functions.”

“The incoming corrupted transducer data may never become normal, even though the ligaments, incorporating the injured mechanoreceptors, may heal/scar over time.” **[The Fibrosis Of Repair]**

## CONCLUSIONS

A new hypothesis of chronic back pain based upon muscle system dysfunction due to ligament injuries.

“Subfailure injuries of the ligaments and embedded mechanoreceptors generate corrupted mechanoreceptor signals.”

“Consequently, the neuromuscular control unit produces corrupted muscle response pattern, resulting in excessive loading and, possibly, injuries of the spinal structures, including additional injuries of the mechanoreceptors.”

In the whiplash patient, this new hypothesis for back pain accounts for both the decreased motion in active testing and the increased motion in passive-relaxed testing.

“The hypothesis proposes that the dysfunction of the muscle system over time may lead to chronic back pain via additional mechanoreceptor injury, and neural tissue inflammation.”

### KEY POINTS FROM DAN MURPHY

- 1) The spinal ligaments, disc annulus and facet capsules are innervated with mechanoreceptors.
- 2) Degenerative spinal disease, single trauma, or cumulative microtrauma causes subfailure injuries of the spinal ligaments, disc and facet capsules, causing abnormal firing of the embedded mechanoreceptors.
- 3) There is increased nerve ingrowth into diseased intervertebral discs.
- 4) Subfailure injury of spinal ligaments is defined as an injury caused by stretching of the tissue beyond its physiological limit, but less than its failure point. **[IMPORTANT: This is the classic definition of a whiplash injury].**
- 5) Chronic whiplash patients have decreased active neck range of motion, but an increase in passive neck range of motion.
- 6) Injured muscles heal relatively quickly due to an abundant blood supply and therefore they are not the main cause of chronic back pain. **[Important]**
- 7) Ligament and disc injuries heal poorly and therefore lead to tissue degeneration over time.
- 8) “Thus, the ligament injuries are more likely to be the major cause of the chronic back pain.” **[Very Important]**
- 9) The subfailure ligament injuries may heal with scar tissue over time, resulting in long-term or permanent mechanoreception. **[The Fibrosis Of Repair]**

Dear Dr. Panjabi:

Congratulations on your article "A hypothesis of chronic back pain: ligament subfailure injuries lead to muscle control dysfunction" European Spine Journal, July 27, 2005.

The hypothesis you presented is consistent with the perspective offered within the chiropractic community for decades. In the parlance of the chiropractic profession you have expertly and vividly described what is referred to as a vertebral subluxation. The chiropractic community has been studying, writing about and modifying its perspective on the phenomenon you articulated for more than a century.

Our present hypothesis suggests that the altered mechanoreceptive afferent driven motor mismatch can be corrected by the firing of the mechanoreceptors of the facet joint capsules which are activated by means of a chiropractic adjustment (1). The hypothesis you articulated, explains why chiropractic spinal adjustments have proven to be more effective in treating chronic spinal pain when compared to medication, exercise, and needle acupuncture (2, 3, 4, 5, 6, 7, 8, 9).

Respectfully,

Daniel J. Murphy, DC  
Practice of Chiropractic  
Faculty, Life Chiropractic College West

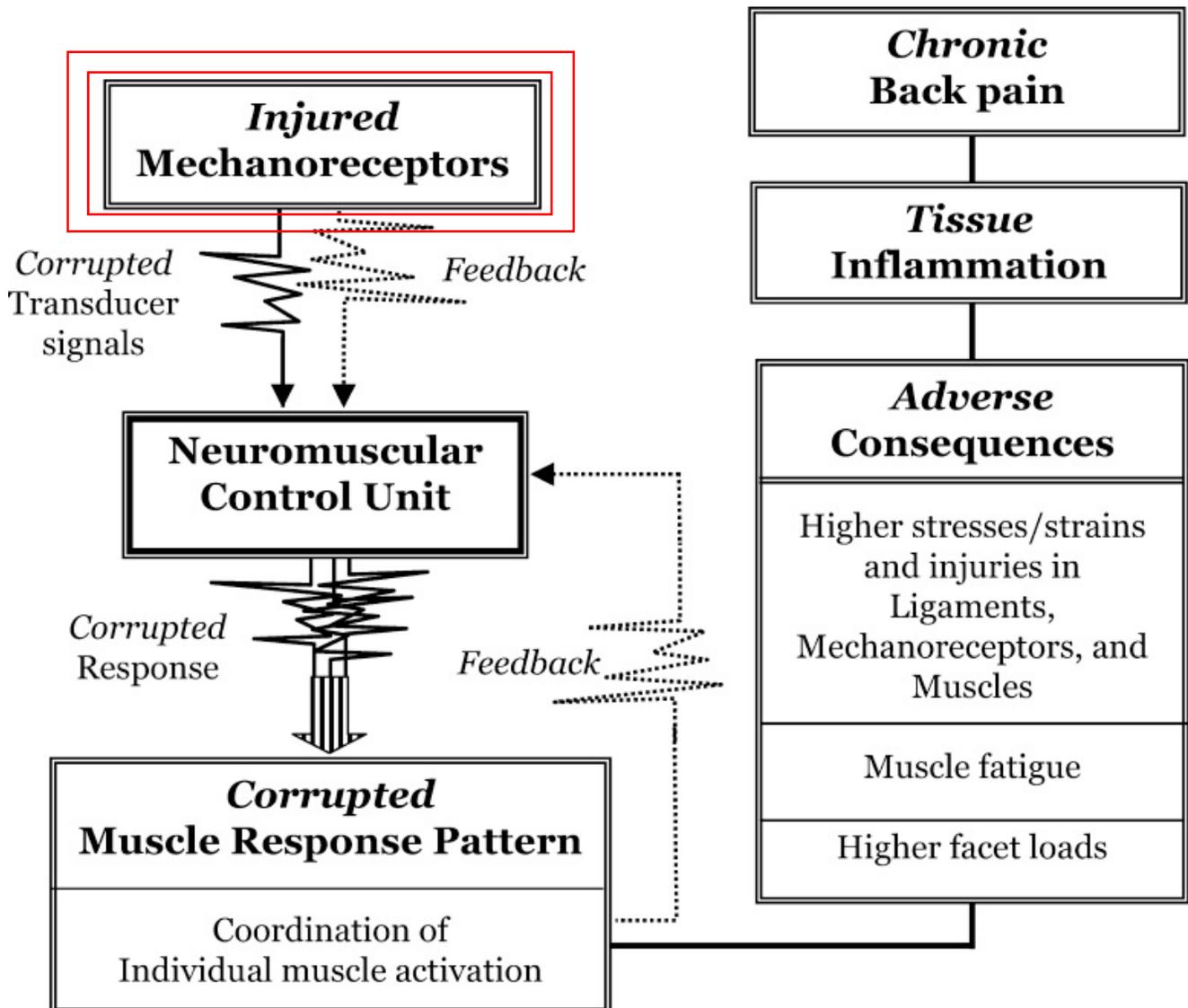
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**A hypothesis of chronic back pain:  
Ligament **subfailure** injuries lead to muscle control dysfunction**

**European Spine Journal**  
May 2006

**Manohar **Panjabi****  
Yale University School of Medicine



**Display Settings:** AbstractCan Fam Physician. 1985 Mar;31:535-40.

## Spinal manipulation in the treatment of low-back pain.

Kirkaldy-Willis WH, Cassidy JD.

### Abstract

Spinal manipulation, one of the oldest forms of therapy for back pain, has mostly been practiced outside of the medical profession. Over the past decade, there has been an escalation of clinical and basic science research on manipulative therapy, which has shown that there is a scientific basis for the treatment of back pain by manipulation. Most family practitioners have neither the time nor inclination to master the art of manipulation and will wish to refer their patients to a skilled practitioner of this therapy. Results of spinal manipulation in 283 patients with low back pain are presented. The physician who makes use of this resource will provide relief for many patients.

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# Whiplash, Real or Not Real? A Review and New Concept

# 46

David Vallez Garca, Rudi A.J.O. Dierckx, Andreas Otte,  
and Gert Holstege

## Contents

46.1	Introduction.....	948
46.2	Biomechanical Context of the Whiplash Trauma.....	949
46.2.1	Pathological Considerations.....	950
46.2.2	Facet Joint and Capsular Ligament.....	951
46.2.3	Ligaments and Intervertebral Disk.....	951
46.2.4	Dorsal Root Ganglion.....	952
46.2.5	Neck Muscles.....	952

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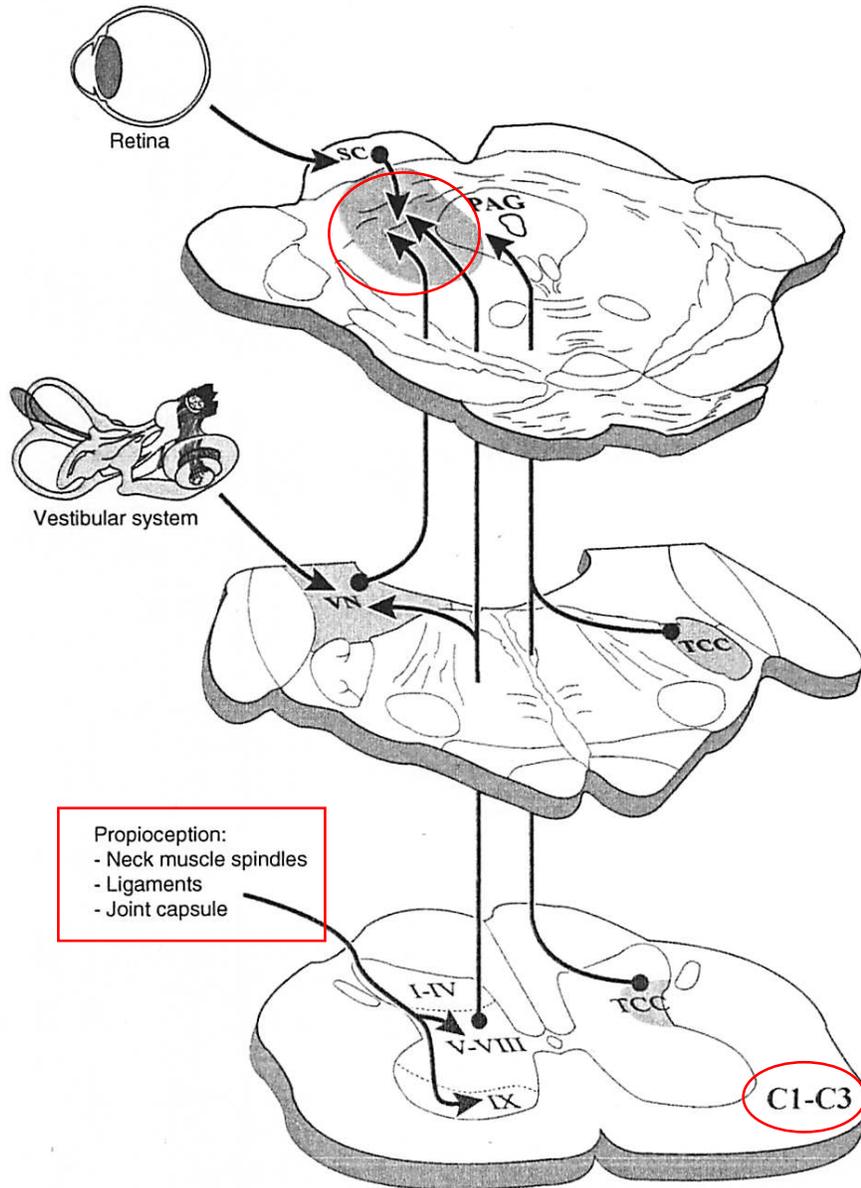
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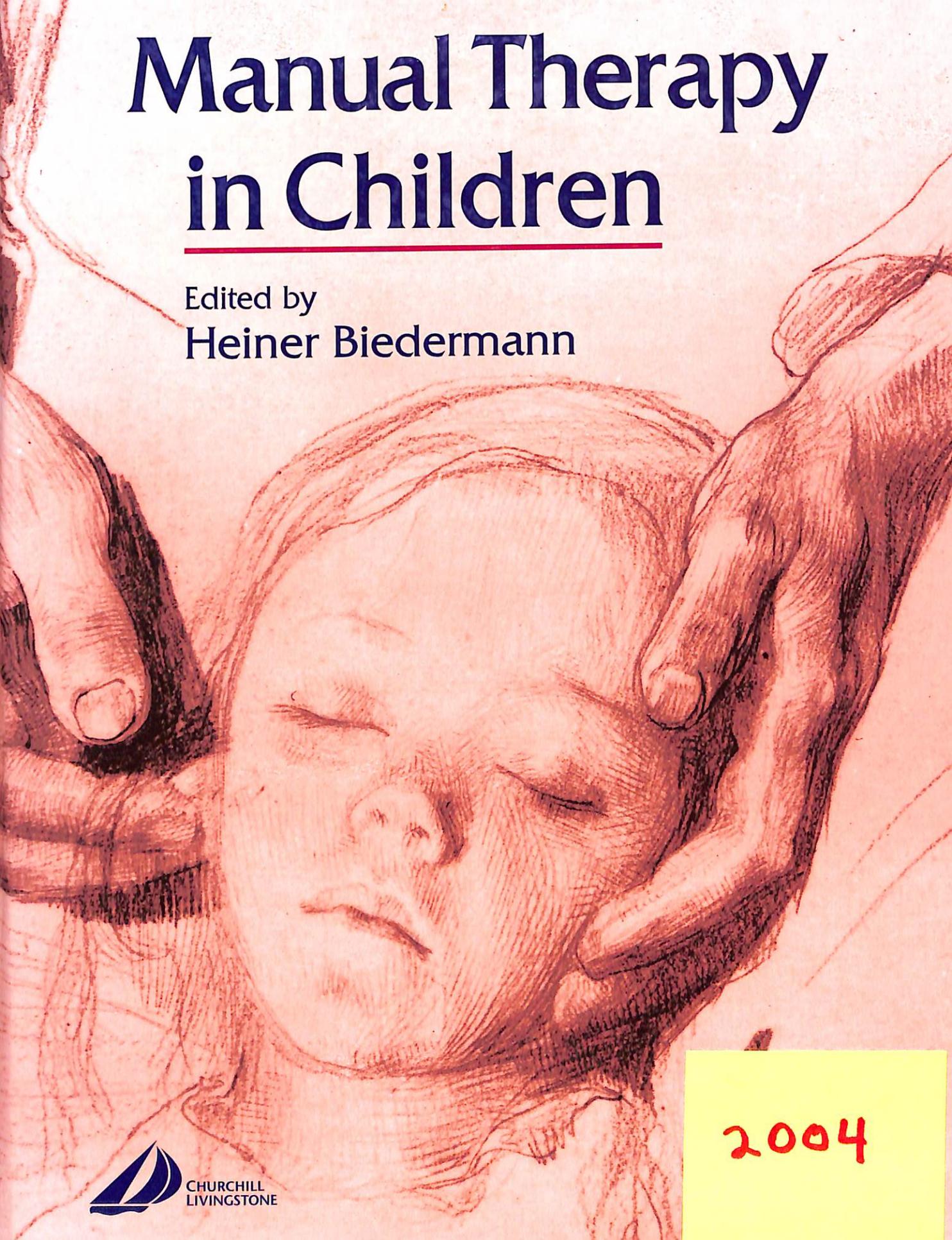


**Fig. 46.5** Ascending afferents from the upper cervical segments (C1–C3) to the periaqueductal gray and its adjoining regions. *TCC* trigemino-cervical complex, *VN* vestibular nuclei, *PAG* periaqueductal gray, *SC* superior colliculus

The involvement of the PAG and adjoining areas in the pathophysiology of WAD can explain the alterations in pain perception, but also depressive-like symptoms (Northoff et al. 2011). The relation of the trigemino-cervical complex and the PAG can explain the headaches and temporomandibular pain symptoms in many WAD

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# **The Autonomic Nervous System in Health and Disease**

**David S. Goldstein**

*National Institute of Neurological Disorders and Stroke  
National Institutes of Health  
Bethesda, Maryland*



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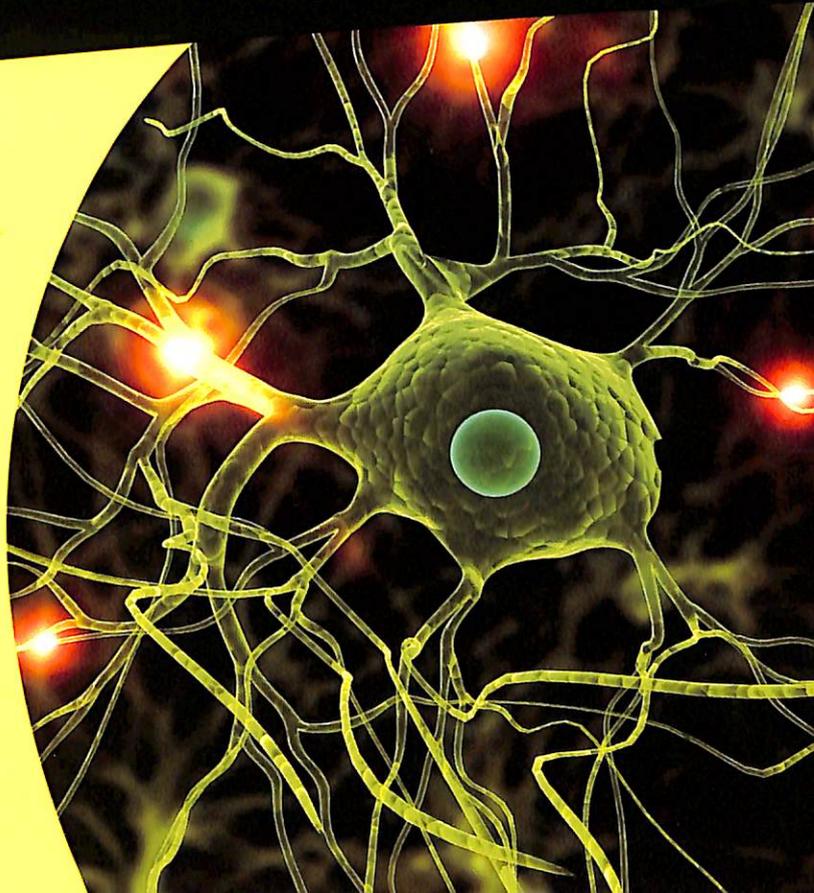
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## *Crossing signals: When the autonomic nervous system goes awry*

Sympathetic fight-or-flight responses divert the body's resources from necessary homeostatic mechanisms like digestion to enable rapid and prolonged voluntary muscular exertion. If this diversion is constant and excessive, however, a price is paid. Chronic stress is a name typically given to continual over-activation of the sympathetic system. The specific physiological effects from chronic stress's over-activation of the sympathetic nervous system include

- ✔ Suppression of the immune system
- ✔ Reduced growth (due to suppression of growth hormones)
- ✔ Sleep problems
- ✔ Memory dysfunction

Many of these symptoms are associated with high circulating levels of cortisol released by the adrenal cortex.

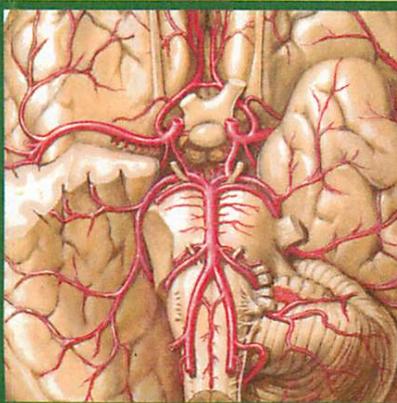
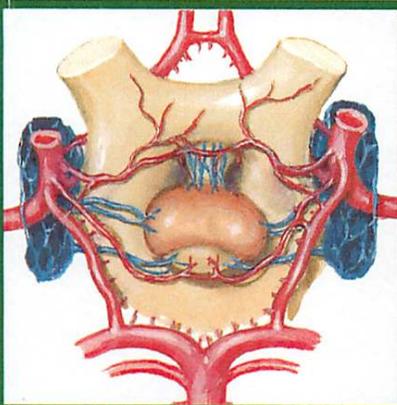
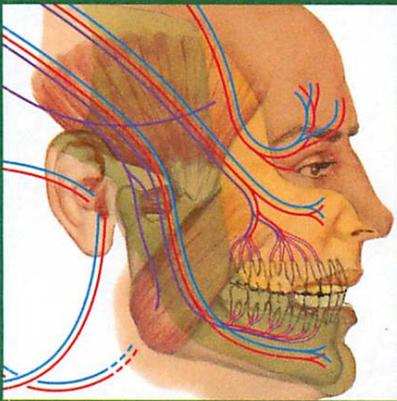
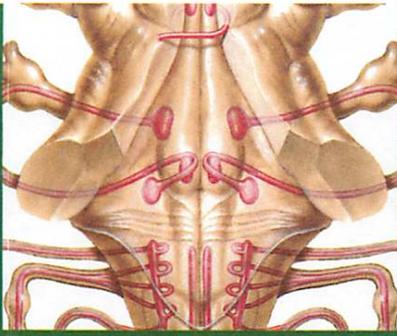
The response to chronic stress, both in form and amount, may differ considerably between individuals. In women, the accumulation of fat around the waist frequently accompanies chronic stress, while in men experience a reduction in sex drive and a risk of erectile dysfunction. Both sexes may experience depression, hair loss, heart disease, weight gain, and ulcers. Even alcoholism and fibromyalgia have been linked to chronic stress. These problems can occur even if no real threat is present in the environment. Excessive light or noise, feelings of entrapment, and social subordination can induce stress. Stress can also add to sleep and other health problems.

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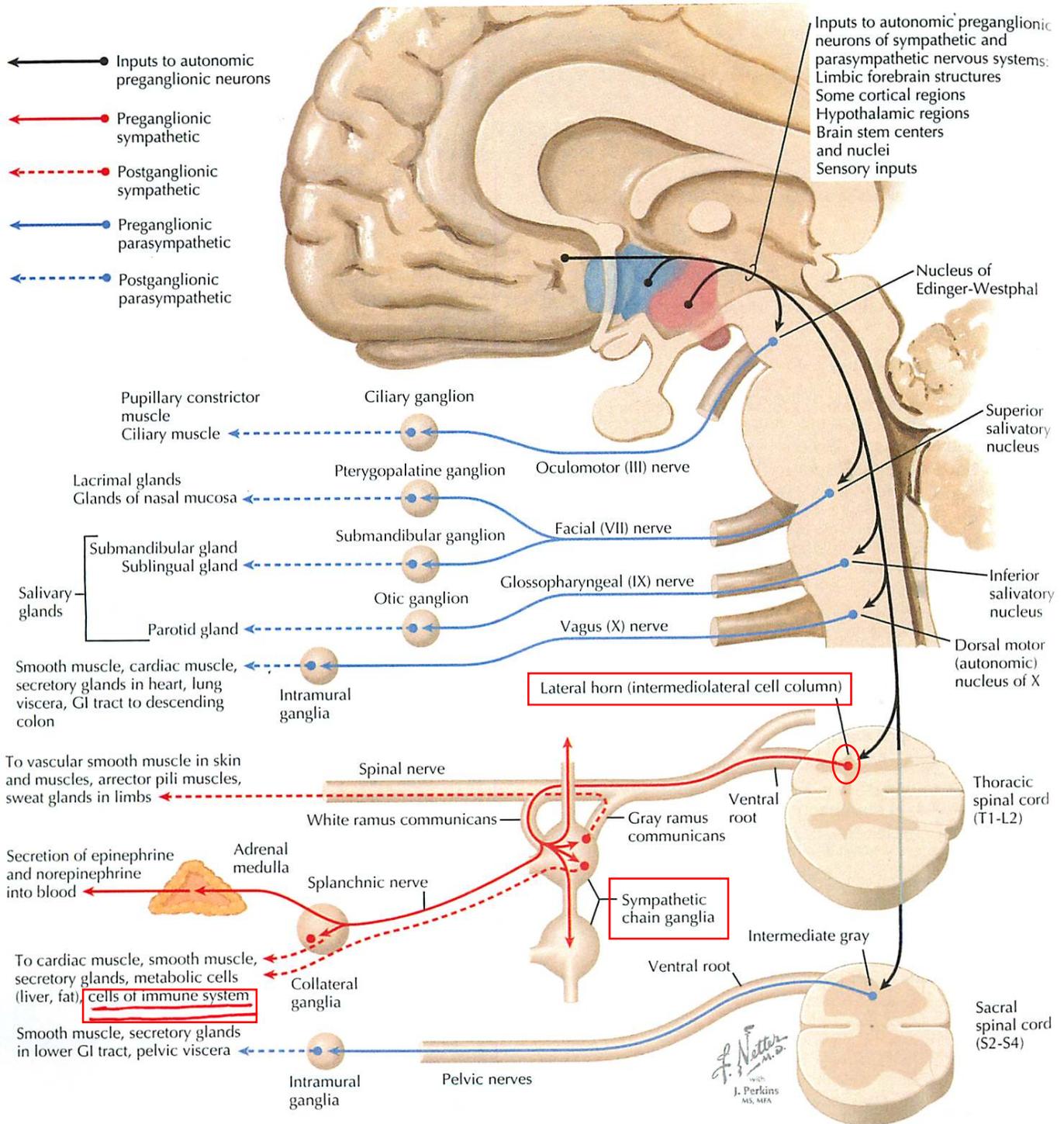
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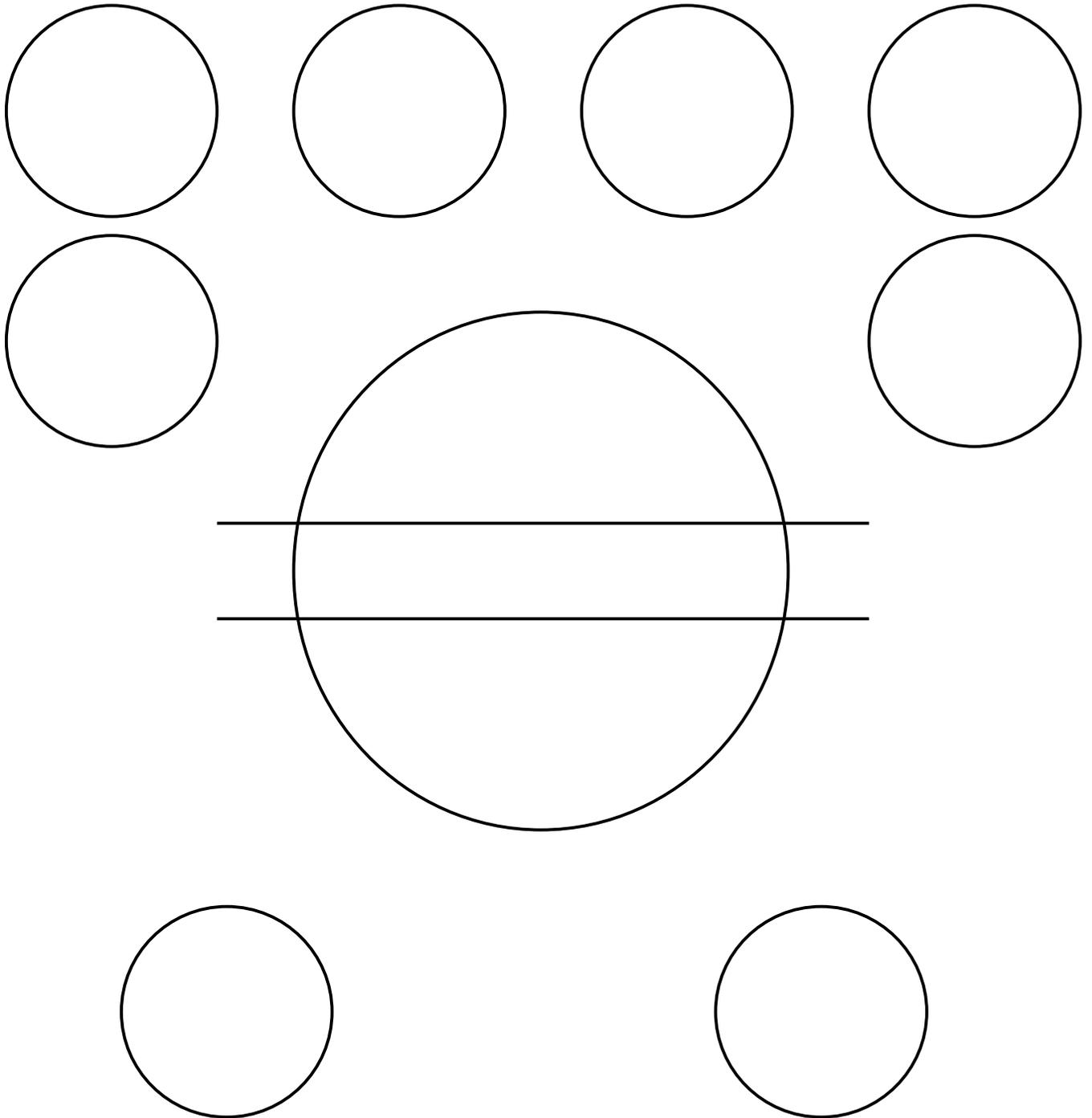


*F. Netter  
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General Organization of the Autonomic Nervous System

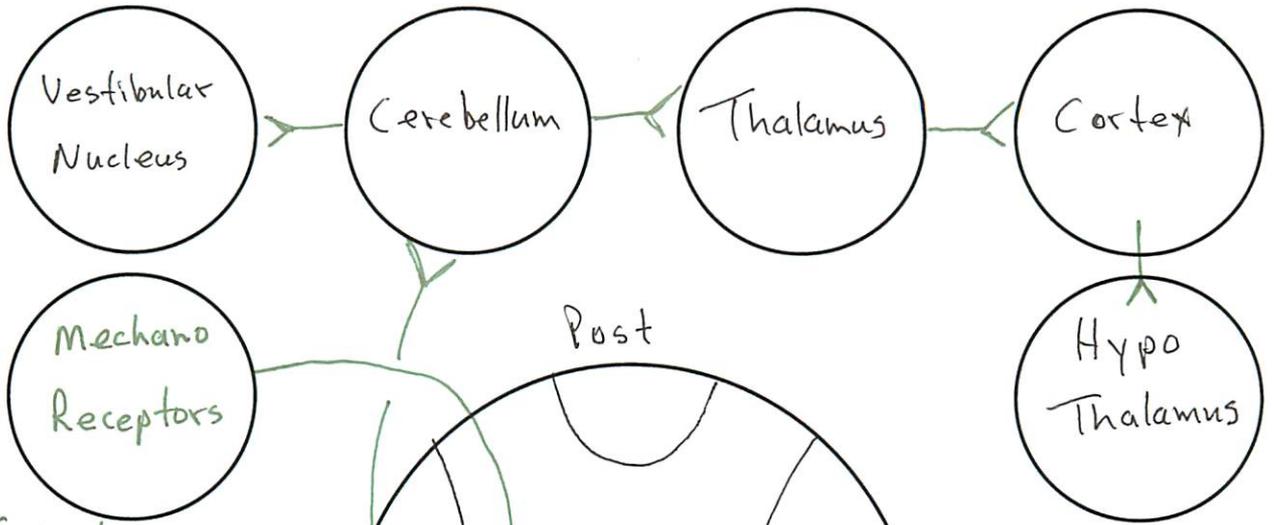
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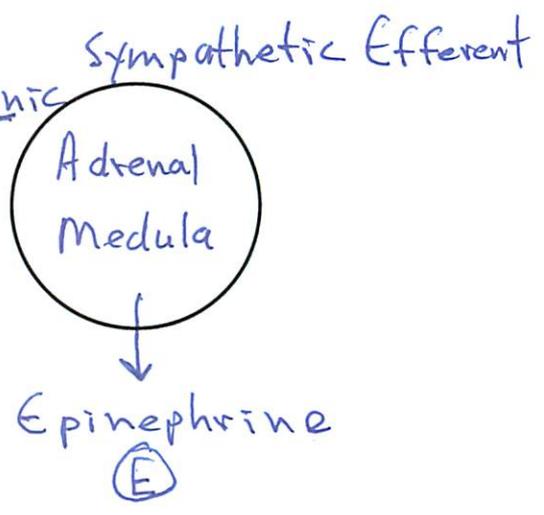
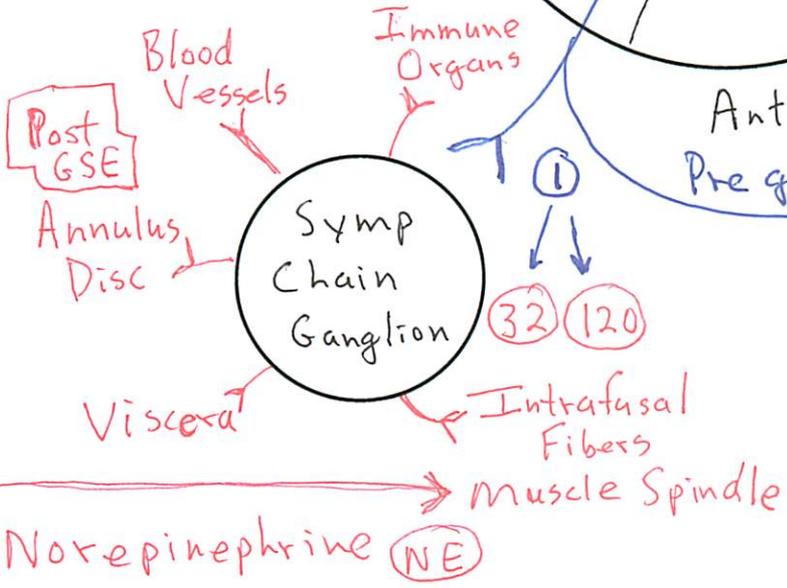
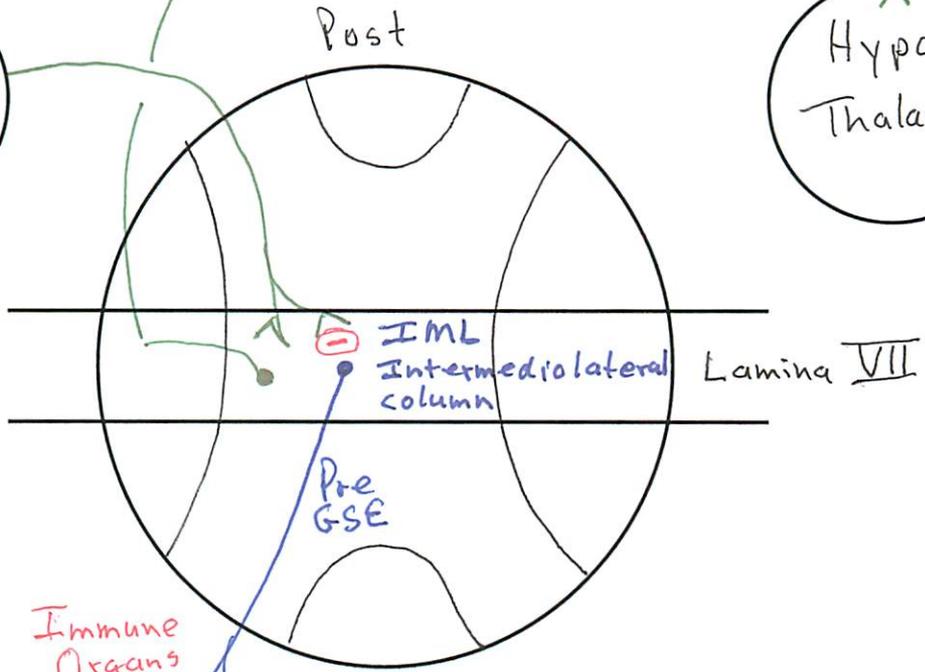
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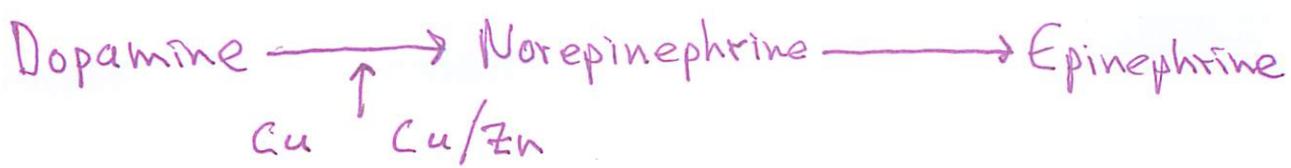


- Facet Capsules
- Annulus Disc
- Supra spinus Lig.
- Inter transverse Lig
- Muscle Spindle



**CATECHOLAMINES**

**BETA-ADRENORECEPTORS**



# PAIN AND THE SYMPATHETIC NERVOUS SYSTEM

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1990

Edited by  
Michael Stanton-Hicks

Current Management of Pain  
P. Prithvi Raj, Series Editor

pons, medulla, and lateral columns of the spinal cord extending from T<sub>1</sub> to L<sub>2</sub>. Peripherally, the sympathetic nervous system consists of preganglionic and postganglionic efferent fibers and afferent fibers that are responsible for visceral sensation and reflex information (figure 4-1). It is the peripheral portion of the sympathetic nervous system that is amenable to regional block techniques.

Structurally, the two paravertebral sympathetic chains or trunks are connected segmentally by preganglionic neurons whose cell bodies are situated in the lateral spinal cord from T<sub>1</sub> to L<sub>2</sub>, with exceptions in C<sub>7</sub>, C<sub>8</sub>, and L<sub>3</sub>, L<sub>4</sub>. Each preganglionic fiber may synapse with as many as 32 postganglionic fibers whose cell bodies are either in ganglia of the sympathetic chain or more distal prevertebral ganglia. These preganglionic fibers travel in the emerging spinal nerve roots before branching as small white rami communicantes, the small nerves connecting the sympathetic ganglia in the chain to each segmental spinal nerve. Some of the postganglionic neurons, as gray rami communicantes, return to the segmental nerve, while others proceed to viscera in the head, chest, and abdomen.

Of importance to regional anesthetic blocks is the arrangement of these sympathetic ganglia into two main groups: paravertebral and prevertebral. It is these former ganglia and interganglionic fibers that constitute the sympathetic trunks or chains. Any semblance to segmental specificity by those preganglionic axons traveling in a white ramus is lost once they enter their corresponding ganglia, since while some may end here, others travel varying distances before synapsing in other ganglia in the sympathetic trunk, or as already mentioned, by passing through without interruption to terminate in one or more prevertebral ganglia.

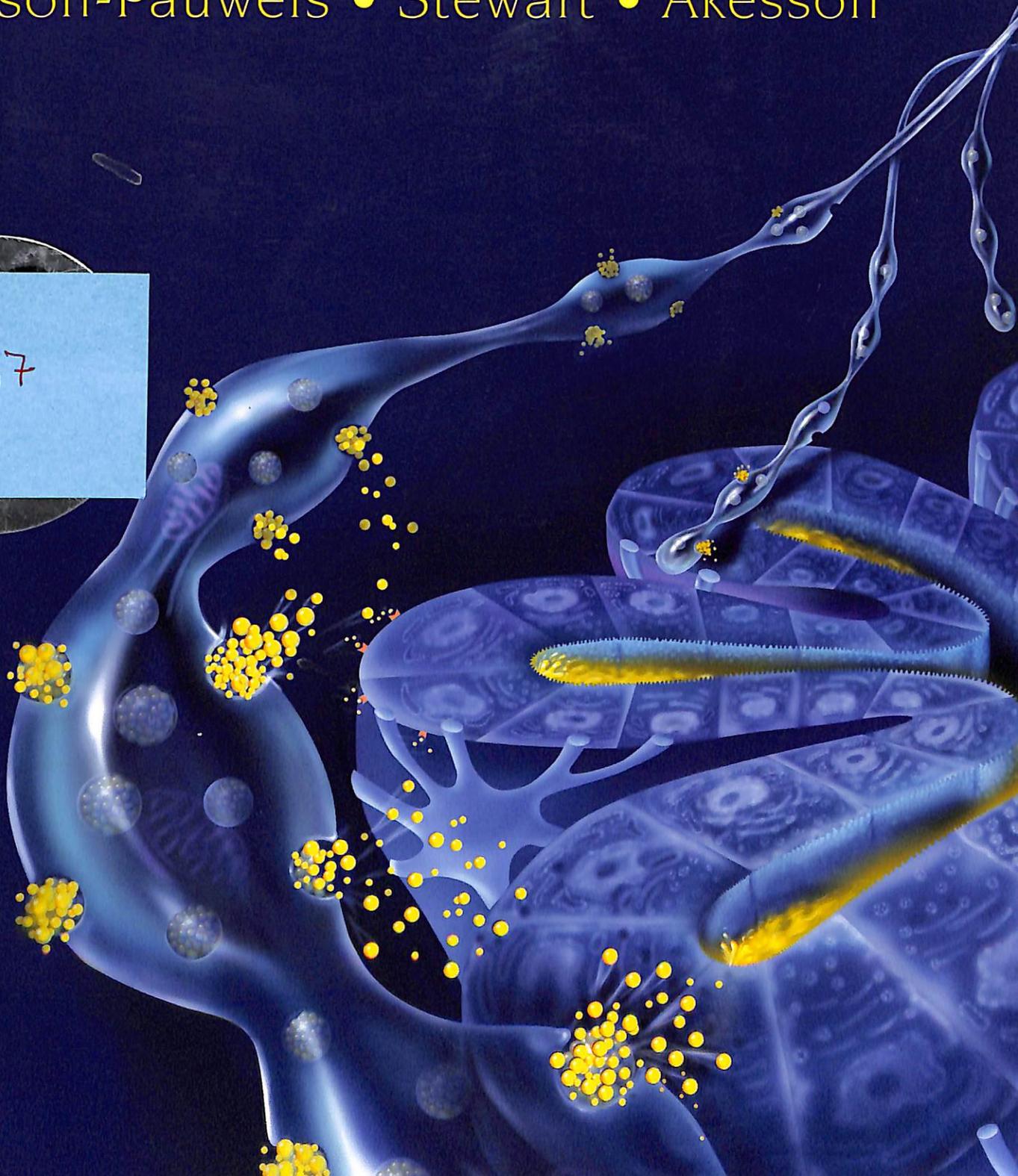
The sympathetic trunks extend from the second cervical vertebra to the coccyx. In the cervical region, the trunks are lateral to the vertebral column such that their ganglia lie ventral to the transverse processes; in the thoracic region the ganglia lie in front of the heads or necks of the ribs; in the lumbar region the sympathetic chain has moved to an anterolateral position with the ganglia lying on the vertebral bodies; and in the sacral region, the ganglia lie medial to the anterior sacral foramina. Both sympathetic trunks merge together in front of the coccyx to form the ganglion impar. At the opposite, cephalad, end, each trunk divides into a number of fine nerves termed the internal carotid nerves that envelop the right and left carotid arteries. The paravertebral ganglia occur segmentally such that in the thoracic region there are 10 to 12, lumbar 4 to 5, and sacral 5. In the cervical region they coalesce to form 3 ganglia termed superior, middle, and intermediate ganglia, the inferior ganglion tending to fuse with the first thoracic ganglia as the stellate ganglion in some 80 percent of subjects.

Prevertebral sympathetic ganglia are amenable to regional blocking techniques only in the celiac region, psoas muscle, and hypogastric plexus. With the exception of the celiac plexus, it is more common to block the sympathetic

# AUTONOMIC NERVES

Wilson-Pauwels • Stewart • Akesson

1997



2. Somatic motor neurons, whose cell bodies reside in the motor nuclei of the brain stem and in the anterior horn of the spinal cord, project directly to their target cells, whereas autonomic motor neurons form two-neuron chains: **preganglionic motor neurons**, whose cell bodies reside in the central nervous system (brain stem or spinal cord), and **postganglionic motor neurons**, whose cell bodies reside in autonomic ganglia.

This two-neuron arrangement has several advantages as follows:

- Firstly, a single preganglionic neuron synapses on large numbers of postganglionic neurons, thereby allowing for a small number of central neurons to influence large areas of the body. This is the principle of divergence of stimuli (Figure 1-3);
- Secondly, since sensory (afferent) axons course through the ganglia, a certain amount of sensory-motor integration can take place at the ganglionic level, thereby giving the autonomic nervous system a degree of autonomy from the central nervous system; and

4

Figure 1-3 The principle of divergence of stimuli is illustrated in the sympathetic nervous system. Preganglionic motor neurons in the spinal cord project to numerous postganglionic motor neurons in the coeliac ganglion. In humans, the ratio of pre- to postganglionic neurons averages 1:120. It is higher in sympathetic than in parasympathetic pathways.

5

Figure 5-2 Preganglionic axons project to a large number of postganglionic axons. This "divergence of stimuli" allows only a few neurons in the spinal cord to have widespread influence in the body.

77

Preganglionic axons branch extensively before they reach their target postganglionic neurons. In humans, the ratio of pre- to postganglionic neurons is more than 1 to 100. Preganglionic axons terminate in synaptic boutons that form synapses with the body and dendrites of the postganglionic neurons.

78

# **Cerebellum**

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Norman Doidge, MD  
2015

Thoughts, memories, perceptions, learning, skill, [humanism], are not encoded in specific neurons, or even in the connections between neurons, but in "the *cumulative electrical wave patterns* that are the result of all the neurons firing together."

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**The cerebellum "occupies only about 10 percent of the brain's volume, it contains almost 80 percent of the brain's neurons."**

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# The Cerebellum AND Cognition

EDITED BY

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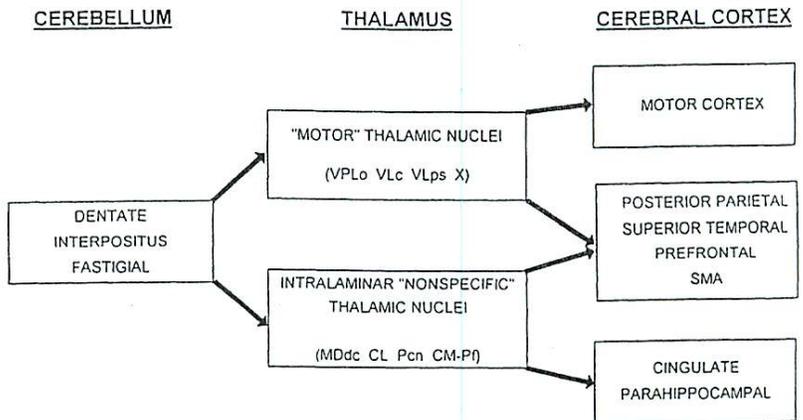
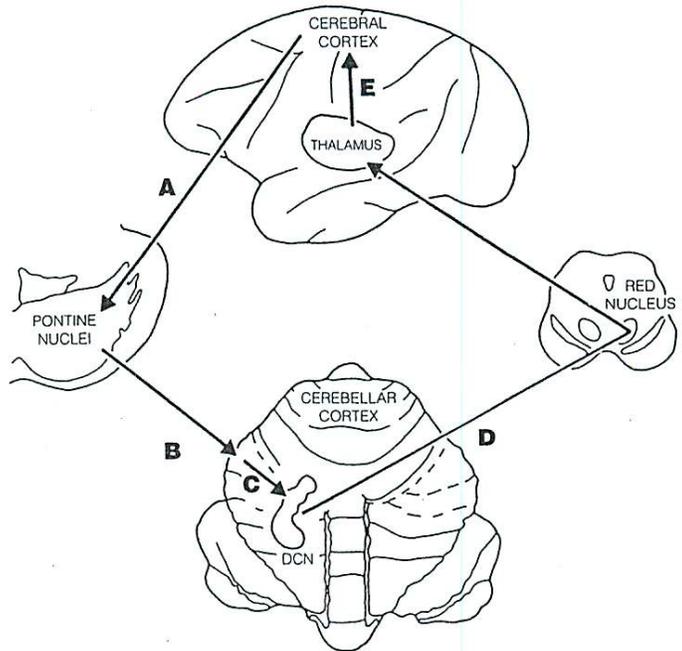
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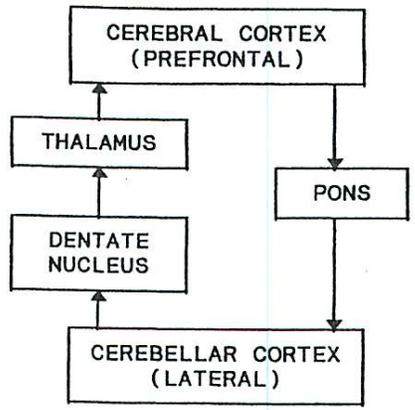
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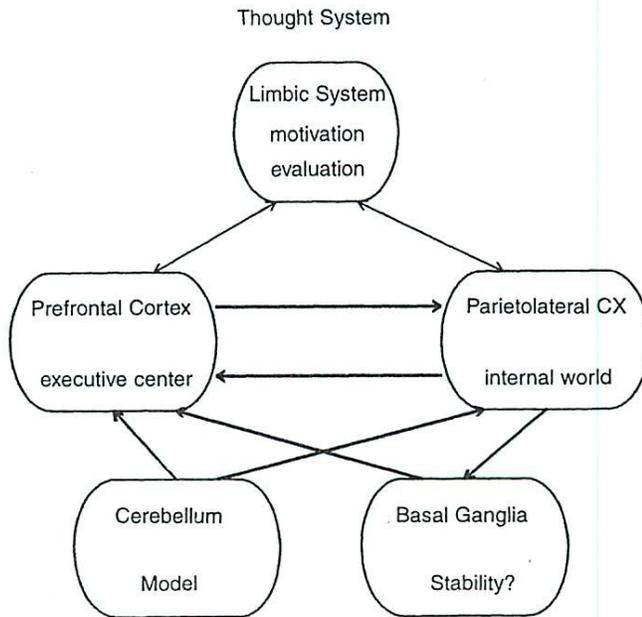
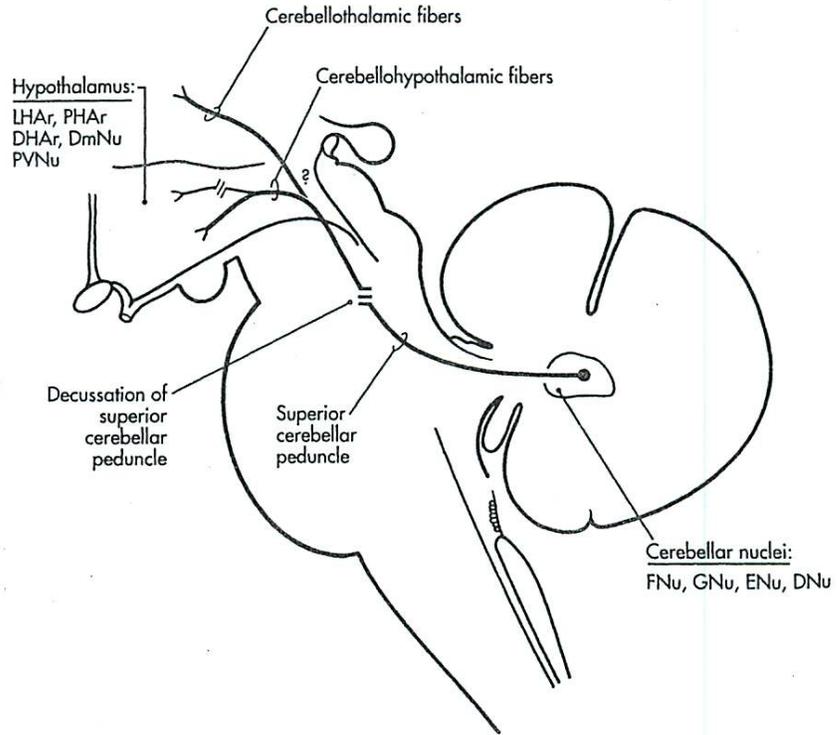
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“This complex neural input reflects the role of the **hypothalamus** as a regulatory center for many vital functions.”

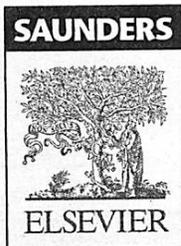
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ACTH = Adrenocorticotrophic hormone

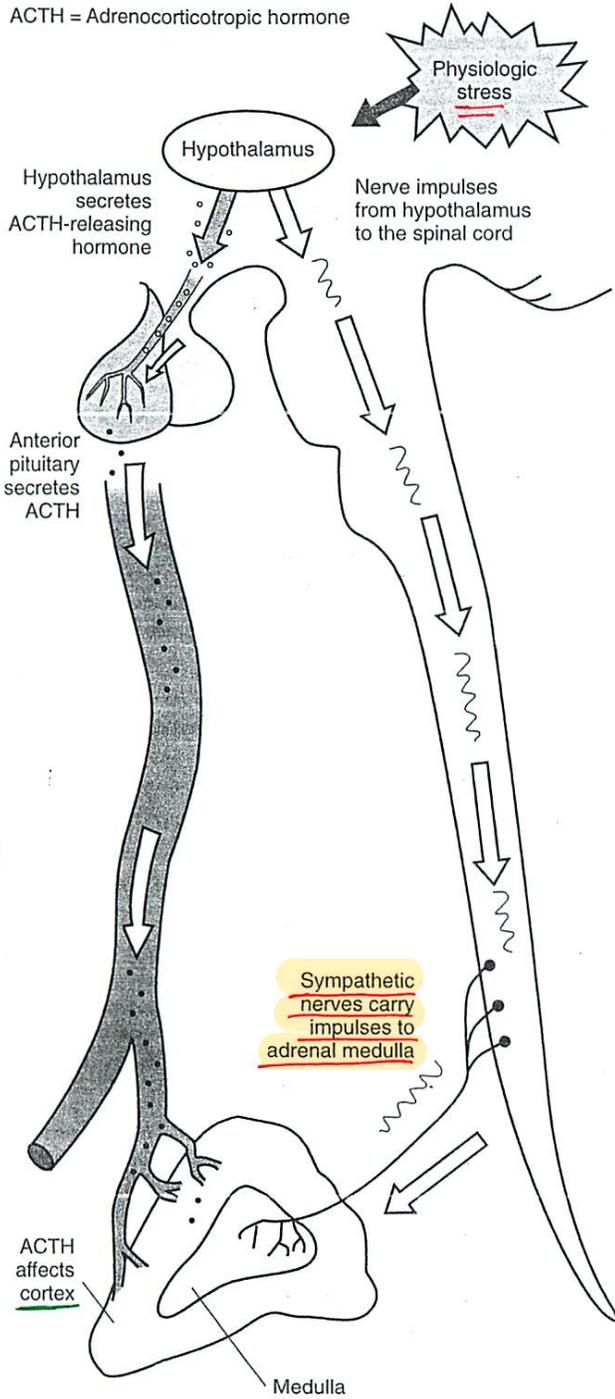


Figure 10-9 Hypothalamic control of the adrenal gland.

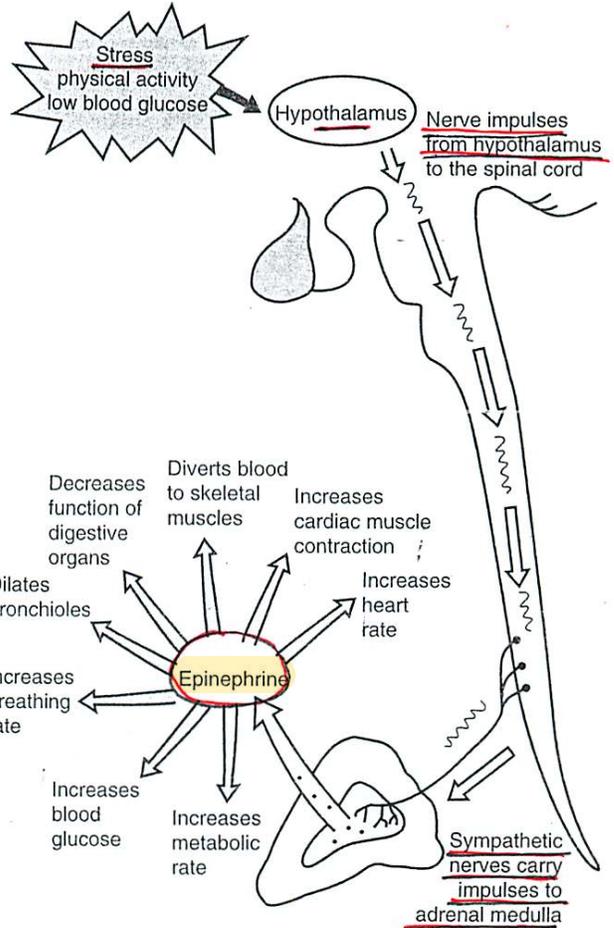


Figure 10-11 Epinephrine—its effects and control of its secretion.

# **Mechanobiology**

# ENERGY MEDICINE

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## THE SCIENTIFIC BASIS

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James L. Oschman

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Med Hypotheses. 2015 Dec;85(6):819-24. doi: 10.1016/j.mehy.2015.10.003. Epub 2015 Oct 14.

## Measurable changes in the neuro-endocrinal mechanism following spinal manipulation.

Kovanur Sampath K<sup>1</sup>, Mani R<sup>2</sup>, Cotter JD<sup>3</sup>, Tumilty S<sup>2</sup>.

### Author information

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- 2 Centre for Health, Activity, and Rehabilitation Research, School of Physiotherapy, University of Otago, New Zealand.
- 3 School of Physical Education, Sport and Exercise Sciences, University of Otago, New Zealand.

### Abstract

The autonomic nervous system and the hypothalamic-pituitary-adrenal axis have been shown to be dysfunctional in a number of chronic pain disorders. Spinal manipulation is a therapeutic technique used by manual therapists, which may have widespread neuro-physiological effects. The autonomic nervous system has been implicated to modulate these effects. A theory is proposed that spinal manipulation has the potential to be used as a tool in restoring the autonomic nervous system balance. Further, it is also hypothesised that through its anatomical and physiological connections, the autonomic nervous system activity following a thoracic spinal manipulation may have an effect on the hypothalamic-pituitary-adrenal axis and therefore pain and healing via modulation of endocrine and physiological processes. To substantiate our hypothesis we provide evidence from manual therapy studies, basic science and animal studies. According to the proposed theory, there will be measurable changes in the neuro-endocrinal mechanisms following a thoracic spinal manipulation. This has far-reaching implications for manual therapy practice and research and in the integration of spinal manipulation in the treatment of a wide array of disorders.

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Neurochem Res. 2015 Dec;40(12):2583-99. doi: 10.1007/s11064-015-1581-6. Epub



## The Glymphatic System: A Beginner's Guide.

Jessen NA<sup>1</sup>, Munk AS<sup>2</sup>, Lundgaard I<sup>2</sup>, Nedergaard M<sup>2</sup>.

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- 2 School of Medicine and Dentistry, University of Rochester Medical Center, 601 Elmwood Ave, Box 645, Rochester, NY, 14642, USA.

### **Abstract**

The glymphatic system is a recently discovered macroscopic waste clearance system that utilizes a unique system of perivascular tunnels, formed by astroglial cells, to promote efficient elimination of soluble proteins and metabolites from the central nervous system. Besides waste elimination, the glymphatic system also facilitates brain-wide distribution of several compounds, including glucose, lipids, amino acids, growth factors, and neuromodulators. Intriguingly, the glymphatic system function mainly during sleep and is largely disengaged during wakefulness. The biological need for sleep across all species may therefore reflect that the brain must enter a state of activity that enables elimination of potentially neurotoxic waste products, including  $\beta$ -amyloid. Since the concept of the glymphatic system is relatively new, we will here review its basic structural elements, organization, regulation, and functions. We will also discuss recent studies indicating that glymphatic function is suppressed in various diseases and that failure of glymphatic function in turn might contribute to pathology in neurodegenerative disorders, traumatic brain injury and stroke.

**KEYWORDS:** Aging; Astrocytes; Cerebrospinal fluid secretion; Neurodegenerative diseases; Perivascular spaces; Sleep; The glymphatic system; Traumatic brain injury; Virchow–Robin spaces

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# **The Longevity Paradox**

## **How to Die Young at a Ripe Old Age**

Steven Gundry, MD  
2019

### **Sleep and the Glymphatic System**

“The glymphatic system is most active during the specific stage of deep sleep that happens very early in the sleep cycle.”

“The glymphatic system, just like your digestive system, requires a great deal of blood flow. This means that if you eat too soon before going to bed, your blood will all flow to your gut to aid in digestion and will not be able to reach your brain to complete the all-important brain wash.”

“If your glymphatic system cannot wash out your brain effectively, you end up with a building up of amyloid and other toxins, including lectins and LPSs, in the brain.”

“This wash cycle is probably the single most overlooked and misunderstood aspect of neurodegenerative diseases.”

The “simple solution: leaving as big a gap as possible between your last meal of the day and your bedtime.”

“The minimum amount of time between finishing your last meal and going to sleep should be four hours.”

## The Brain's Waste-Disposal System May Be Enlisted to Treat Alzheimer's and Other Brain Illnesses

### An Internal Plumbing System Rids the Brain of Toxic Wastes

#### Sleep is When this Cleanup Ritual Occurs

Scientific American

March 1, 2016

[modified]

Maiken Nedegaard and Steven Goldman: from the University of Rochester Medical Center and the University of Copenhagen

The human brain weighs about 3 pounds, or roughly 2% of the average adult body mass. Yet its cells consume 20-25% of the body's total energy. In the process, inordinate amounts of potentially toxic protein wastes and biological debris are generated.

Each day, the adult brain eliminates 7 grams of worn-out proteins that must be replaced with newly made ones, a figure that translates into the replacement of about half a pound of detritus a month and nearly 6 pounds, twice the brain's own weight, over the course of a year.

To survive, the brain must have some way of flushing out debris. It is inconceivable that an organ so finely tuned to producing thoughts and actions would lack an efficient waste disposal system.

Disturbances in waste clearance could contribute to cognitive problems encountered in neurodegenerative disease because the disruption would lead to the accumulation of protein debris in and around brain cells. The aggregates could impede the transmission of electrical and chemical signals in the brain and cause irreparable harm.

These authors found an undiscovered system for clearing proteins and other wastes from the brain—and this system is *most active during sleep*. The need to remove potentially toxic wastes from the brain may help explain the mystery of why we sleep.

### The Glymphatic System

In most regions of the body, a network of intricate fluid-carrying vessels, known as the *lymphatic system*, eliminates protein waste from tissues. Waste-carrying fluid moves throughout this network between cells. The fluid collects into small ducts that then lead to larger ones and eventually into blood vessels. This duct structure also provides a path for immune defense, because lymph nodes, a repository of infection-fighting white blood cells, populate ducts at key points throughout the network. Yet,

neuroscientists had believed that the lymphatic system did not exist in the brain or spinal cord.

*Astrocytes* are support cells that perform a multitude of functions for the interconnected network of neurons that relay signals throughout the brain. The astrocytes' extensions—*astrocytic end feet*—completely surround the arteries, capillaries and veins in the brain and spinal cord. The hollow, tube-like cavity that forms between the feet and the vessels remains largely free of obstructions, creating a *spillway* that allows for the rapid transport of fluid through the brain.

**Arterial pulsations might drive the CSF through the perivascular space.** From there, some of it could enter astrocytes through their end feet. Using astrocytes as conduits, the CSF then moved through the brain tissue, where it left the astrocytes and picked up discarded proteins.

The fluids exited the brain through the perivascular space that surrounded small veins draining the brain, and these veins in turn merged into larger ones that continued into the neck. The waste liquids went on to enter the lymph system, from which they flowed back into the general blood circulation.

The astrocytes play a critical role in the brain's counterpart of a lymphatic system.

The authors named this discovery the *glymphatic system*. They combined the words "glia"—a type of brain cell of which the astrocyte is one example—and "lymphatic," thus referencing this newly discovered function of the brain's glial cells.

In a healthy brain, Alzheimer's beta-amyloid is cleared by the glymphatic system. Other proteins implicated in neurodegenerative diseases, such as the synuclein proteins that turn up in Parkinson's, Lewy body disease and multisystem atrophy, might also be carried away and could build up abnormally if the glymphatic system were to malfunction.

Many patients with Alzheimer's experience sleep disturbances long before their dementia becomes apparent. In older individuals, sleep becomes more fragmented and shallow and lasts a shorter time. Epidemiological studies have shown that patients who reported poor sleep in middle age were at greater risk for cognitive decline than control subjects when tested 25 years later.

Healthy individuals who are forced to stay awake exhibit symptoms more typical of neurological disease and mental illness—poor concentration, memory lapses, fatigue, irritability, and emotional ups and downs. The *sleep difficulties* of dementia might not just be a side effect of the disorder but *might contribute* to the disease process itself. If the glymphatic system cleared beta-amyloid during sleep at a higher rate than when awake, perhaps the poor sleeping patterns of patients with neurodegenerative disorders might contribute to a worsening of the disease.

CSF in the glymphatic system falls dramatically while awake. Within *minutes after the onset of sleep influxes of the fluid increased significantly*. The brain's interstitial space—the area between cells through which glymphatic fluid flows on its way to perivascular spaces around veins—rose by more than 60% with sleep. The flow of glymphatic fluid increases during sleep because the space between the cells expands, which helps to push fluid through the brain tissue.

**Norepinephrine appears to regulate the volume of the interstitial area and consequently the pace of glymphatic flow. Levels of norepinephrine rise when awake and are scarce during sleep, implying that sleep-related dips in norepinephrine led to enhanced glymphatic flow.**

### The Power of Sleep

The expansion and contraction of the interstitial space during sleep is important to both brain function and protein-waste clearance. The *waste clearance rate more than doubled with sleep*. The sleeping brain exports protein waste, including beta-amyloid, through the glymphatic transport system.

**Normal-pressure hydrocephalus, an illness typically seen in the elderly, is a form of dementia in which excessive CSF accumulates in the hollow central brain cavities, the cerebral ventricles. When a procedure called lumbar puncture removes the fluid by draining it out, patients often exhibit remarkable improvements in their cognitive abilities.**

Fluids moving through the glymphatic system may do more than remove wastes; they may deliver various nutrients and other cargo to brain tissue, including delivery of glucose to neurons to provide energy. The glymphatic system may deliver both nutrients and materials needed for maintaining the cells' structural integrity.

#### MORE TO EXPLORE

The Glymphatic System: A Beginner's Guide. Nadia Aalling Jessen et al.; *Neurochemical Research*; December 2015; Vol. 40; No. 12; pp. 2583–2599.



Review

# The Glymphatic System (En)during Inflammation

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**Abstract:** The glymphatic system is a fluid-transport system that accesses all regions of the brain. It facilitates the exchange of cerebrospinal fluid and interstitial fluid and clears waste from the metabolically active brain. Astrocytic endfeet and their dense expression of the aquaporin-4 water channels promote fluid exchange between the perivascular spaces and the neuropil. Cerebrospinal and interstitial fluids are together transported back to the vascular compartment by meningeal and cervical lymphatic vessels. Multiple lines of work show that neurological diseases in general impair glymphatic fluid transport. Insofar as the glymphatic system plays a pseudo-lymphatic role in the central nervous system, it is poised to play a role in neuroinflammation. In this review, we discuss how the association of the glymphatic system with the meningeal lymphatic vessel calls for a renewal of established concepts on the CNS as an immune-privileged site. We also discuss potential approaches to target the glymphatic system to combat neuroinflammation.

**Keywords:** glymphatic system; astrocytes; glia limitans; AQP4; ocular glymphatic system; inflammation; immune privilege; CSF; ISF; immune surveillance



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## 1. Introduction

The blood–brain barrier (BBB) is a critical component of the central nervous system (CNS) that dampens environmental perturbations in interstitial ionic and chemical concentrations, and thereby supports the stability of synaptic transmission. Long-distance neural networks require a protected environment with limited fluctuations of the concentrations of interstitial ions, neurotransmitters, essential metabolic intermediates, and toxic xenobiotics. The BBB also restricts the entry to the brain of peripheral inflammatory mediators and pathogens that might negatively impact neuronal activity. In the eye, the blood–retina barrier (BRB) similarly protects the environment of the neuroretina. The CNS lacks a parenchymal lymphatic vessel system that supports fluid homeostasis and provides a path for immune surveillance in the peripheral organs. The lack of lymphatic vessels in the retina and brain presented a conceptual challenge in understanding how fluid homeostasis and the export of waste products are obtained within the confines of the CNS [1]. With the discovery of the glymphatic system initially in brains of rodents [2–5], and later in human brain by magnetic resonance imaging (MRI) studies [6–10], a glial-associated functional homologue of the lymphatic system was established. More recently, the existence of an ocular glymphatic clearance system was demonstrated [11]. Astrocytes play a key role in the glymphatic system. Astrocytes create with their vascular endfeet the perivascular spaces that surround the cerebral vasculature. The perivascular spaces are utilized as “highways” for fast transport of cerebrospinal fluid (CSF) into deep brain regions.

The heterogenic nature and function of astrocytes in neurological diseases has been studied excessively at molecular and cellular levels. Many excellent reviews exist on this topic [12–14]. The existence of the glymphatic system provides, however, a novel perspective on the role of astrocytes in pathological processes: Astrocytes are not only



# The Craniocervical Syndrome and MRI

Editors

Francis W. Smith

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2015



**KARGER**

# Craniospinal Hydrodynamics in Neurodegenerative and Neurological Disorders

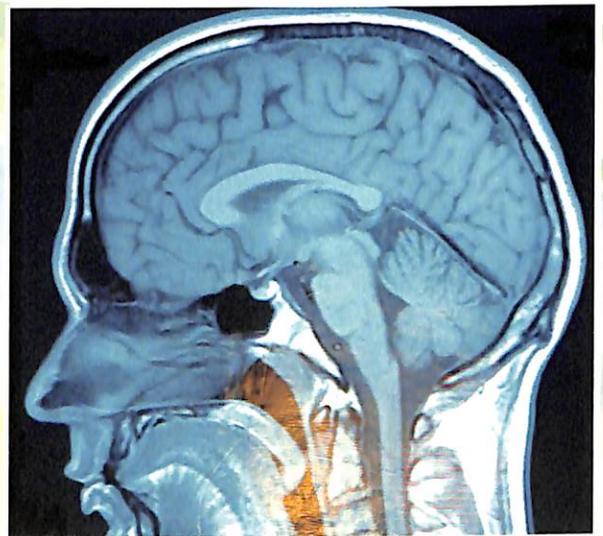


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Michael Flanagan

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# Sports



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Jim McMahon literally gets a feel for the green Tuesday while putting on the third hole in the Tahoe South Celebrity-Am at Edgewood Tahoe.

## Shoeless golf is perfect fit for McMahon

*Sacramento Bee*

Former Bears QB is still playing through pain at Edgewood Tahoe

7/21/2016

OPINION BY ANDY FURILLO



STATELINE, NEV.

The first thing you notice about Jim McMahon is the bare feet, which the management at Edgewood Tahoe would frown upon had they belonged to anybody other than the quarterback of one of the greatest teams in NFL history. "It's how I learned to play," Shoeless Jim said of his golf game - not football - at the conclusion of his round Tuesday in the Tahoe South Celebrity-Am. "I've got bad feet, and there's no rule that says you have to wear shoes." There aren't any in football, either, which has given rise to the barefoot kicker, although



Eli McKirgan, 9, of Ireland gets an autograph and photo with McMahon, who quarterbacked the 1985 Chicago Bears to the Super Bowl title.

you don't see many quarterbacks going without them. How'd his feet get to be so bad? Simple, McMahon answered: "Fat (fellows) stepping on them for 20 years." As one of the many front men on the 1985 Chicago Bears, McMahon directed an offense that lived off the fat of the land. The defense tore it up like Sherman did Georgia to simplify McMahon's work. He reveled in the physicality, banging heads

with his linemen in celebration. The team went 15-1 during the regular season, wiped out everybody in the playoffs, and contributed an important piece to our cultural landscape as a song-and-dance man in the "Super Bowl Shuffle" video. Now McMahon's feet are a wreck, and it doesn't get much better for him as you work your way upward. Twelve times, doctors oper-

SEE FURILLO, 5C



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Jim McMahon hits his approach shot on the third hole Tuesday at Edgewood Tahoe, where he's been a regular.

FROM PAGE 1C  
**FURILLO**

ated on his knees, a seven-five split in favor of the right side. Three times, they cut into his right shoulder. He'll never forget the time the Raiders ripped apart his kidney in 1984. Put him down for five broken ribs, too.

And who can forget one of the dirtiest plays ever inflicted by one football player on another in 1986, when Green Bay Packers linebacker Charles Martin body-slammed McMahon. The separated shoulder ended McMahon's season and probably did in the Bears' chances of repeating as Super Bowl champions.

Then there were the concussions - at least three McMahon said were fully diagnosed, along with an untold number of other blows to the head that were not. In McMahon's post-retirement

years, the pain got so bad he contemplated suicide. When painkillers did more harm than good, he turned to medicinal marijuana and moved to Arizona where he can grow his own.

McMahon signed on as one of the original plaintiffs in the concussion lawsuit that former players filed against the NFL. The list of plaintiffs grew into the thousands, and the league agreed in 2013 to a settlement that could be worth up to \$5 million to some players depending on the severity of their neurological damage. It could end up costing the league in the neighborhood of \$1 billion.

Although the appeals by a group of players unhappy with the deal appear to be winding down, "nobody's seen a dime, yet," McMahon said.

He sat in his golf cart with a can of Coors Light after an 18-hole scramble Tuesday, when his team competed against others headed by celebrities and

“  
**IT'S HOW I  
LEARNED TO PLAY.  
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THERE'S NO RULE  
THAT SAYS YOU  
HAVE TO WEAR  
SHOES.**

*Jim McMahon,  
on golfing while shoeless*

athletes such as Marshall Faulk, Eric Gagne, Bode Miller and Sebastian Janikowski.

Pain, McMahon said, still represents a line of demarcation in his life. On one side of it, he can still do the things that make life worth living, like playing golf along the deep blue waters of Lake Tahoe and breathing deeply the fresh air that whistles through the pines. On the other side of

the divide, there is abject immobility.

"I've got my good days and bad," McMahon said. "As long as I keep my neck and head in alignment, I'm fairly normal."

McMahon visits a chiropractor in New York City every two or three months to keep everything lined up.

"It keeps the spinal fluid flowing properly," he said. "But when it gets out of whack, all I want to do is lay down in a dark room."

Tuesday's scramble served as a prelude to this weekend's \$600,000 American Century Championship at Edgewood Tahoe. The 54-hole main event gets underway Friday, with 84 athletes and entertainers taking to the fairways. A-listers include singer-actor Justin Timberlake, two-time NBA MVP Stephen Curry, former 49ers coach and current Michigan head man Jim Harbaugh, Green Bay Packers quarterback Aaron Rodgers and retired soccer star and World Cup

**American  
Century  
Celebrity Golf  
Championship**

**When:** Friday through Sunday

**Where:** Edgewood Tahoe Golf Course

**TV:** Friday, NBCSN, 3 p.m.; Saturday-Sunday, Ch. 3, noon

champion Abby Wambach.

McMahon will be out there again Friday, competing in the charity tournament for the 27th consecutive year.

On Tuesday, it looked as if his game could use some work. He blasted deep on his drives and looked OK with the putter toward the end of his round, but he let loose with the expletives on several occasions when he hit it fat on the fairways or chipped them hot across the greens.

"I need to take a few days off," McMahon said. "This Sunday I'm going to be exhausted."

The self-directed anger of his flubs quickly dissipated. When he returned to his golf cart at the end of each hole, he patiently autographed shirts, caps and programs for dozens of fans. Want a selfie with No. 9? Step right up.

"The fans have always been great," McMahon said. "It's fun."

It's not always a frolic, though, for yesterday's heroes. You know they made plenty of money and that some of them are doing just fine. You also know that the pursuit of their craft came with great sacrifice to their minds and bodies, all the way down to their bare feet.

Andy Furillo: 916-321-1141, @andyfurillo

# Sporting Gr

SAN FRANCISCO CHRONICLE AND SFCHRONICLE.COM | Saturday, July 15, 2017 | Section B ★★★★★

AMERICAN CENTURY CHAMPIONSHIP *Jim McMahon*



Jeff Bayer/American Century Championship

Jim McMahon tees off during the opening round of the American Century Championship.

## Quarterbacking a gypsy lifestyle

Renewed outlook for former NFL star

STATELINE, Nev. — Not having seen Jim McMahon in several years, I'm not sure I can pick him out on the practice range at the

the announcer hails McMahon as "The grittiest NFL quarterback of all time!"

Now he might be the grittiest celebrity golfer

## GOLF

# McMahon sings praises of golf, new treatment

*Ostler from page B1*

he spits. "I enjoy playing, it just pisses me off."

After each day's golf, and after any tourney dinner or other obligation, McMahon retires to the motor home he parks in a corner of a vast casino parking lot, in a fenced-off compound flanked by snowplows. His own private asphalt Idaho on the shores of Lake Tahoe.

I want to talk to McMahon about his golf-gypsy lifestyle, but I'm hesitant. Five years ago, a Sports Illustrated story spotlighted his head problems. McMahon had been diagnosed with early-onset dementia, surely related to the football beatings of 15 NFL seasons. Unfortunately, his toes didn't absorb *all* the dents and dings.

The reports had McMahon in bad shape, in near-constant pain, wandering through life in a fog, frustrated and angry. He'd drive to an errand, phone his girlfriend and ask, like a lost child, "Where am I?"

A couple of his old football comrades with similar dementia issues opted for the six-gun exit. McMahon says he contemplated the same escape from the pain, confusion and unexplained hostility.

So I'm a bit surprised when McMahon agrees to meet at his motor

home and, one night later, is expecting me when I show up. If he's in a fog, he'd hiding it well. After a few minutes, I ask him how his head is.

He says it's good. After his woes became public in 2012, McMahon was contacted by a person who said he might be able to help him. A New York chiropractor named Scott Rosa, who was pioneering a non-invasive treatment for head, neck and brain disease, told McMahon he had neck-alignment problems related, in part, to an undiagnosed broken neck suffered somewhere along the NFL trail.

To simplify the medical stuff, the misaligned parts were short-circuiting the flow of cerebrospinal fluid up and down his brain stem and spine. Some adjusting, shaking and tweaking freed the flow, kind of like un-kinking a garden hose. Actually there were three separate kinks. The relief was instant and dramatic.

McMahon's says his short-term memory is much improved. The ice-pick headaches are gone. He's a functioning human being. Whenever symptoms return, he goes back for a tune-up and is good to go for another few months.

The NFL is officially skeptical of the treatments, but McMahon is officially skeptical of the NFL, which he believes



**A barefoot Jim McMahon**

is in league with Big Pharma, depriving suffering former players of relief from alternative approaches, such as marijuana.

Now McMahon tries to spread the word. He works with a foundation trying to convince the NFL that weed is sometimes a better treatment for pain. And he spreads the gospel of the unkinked garden hose.

"I tell all the guys I know," McMahon says. "A lot of guys get frustrated, they don't know what's going on. Some of

FULL TEXT LINKS



> [Brain Inj.](#) 2010;24(7-8):988-94. doi: 10.3109/02699052.2010.490512.

## A case-control study of cerebellar tonsillar ectopia (Chiari) and head/neck trauma (whiplash)

Michael D Freeman <sup>1</sup>, Scott Rosa, David Harshfield, Francis Smith, Robert Bennett, Christopher J Centeno, Ezriel Kornel, Ake Nystrom, Dan Heffez, Sean S Kohles

Affiliations

PMID: 20545453 DOI: [10.3109/02699052.2010.490512](https://doi.org/10.3109/02699052.2010.490512)

### Abstract

**Primary objective:** Chiari malformation is defined as herniation of the cerebellar tonsils through the foramen magnum, also known as cerebellar tonsillar ectopia (CTE). CTE may become symptomatic following whiplash trauma. The purpose of the present study was to assess the frequency of CTE in traumatic vs non-traumatic populations.

**Study design:** Case-control.

**Methods and procedures:** Cervical MRI scans for 1200 neck pain patients were reviewed; 600 trauma (cases) and 600 non-trauma (controls). Half of the groups were scanned in a recumbent position and half were scanned in an upright position. Two radiologists interpreted the scans for the level of the cerebellar tonsils.

**Main outcomes and results:** A total of 1195 of 1200 scans were read. CTE was found in 5.7% and 5.3% in the recumbent and upright non-trauma groups vs 9.8% and 23.3% in the recumbent and upright trauma groups ( $p = 0.0001$ ).

**Conclusions:** The results described in the present investigation are first to demonstrate a neuroradiographic difference between neck pain patients with and without a recent history of whiplash trauma. The results of prior research on psychosocial causes of chronic pain following whiplash are likely confounded because of a failure to account for a possible neuropathologic basis for the symptoms.

### LinkOut - more resources

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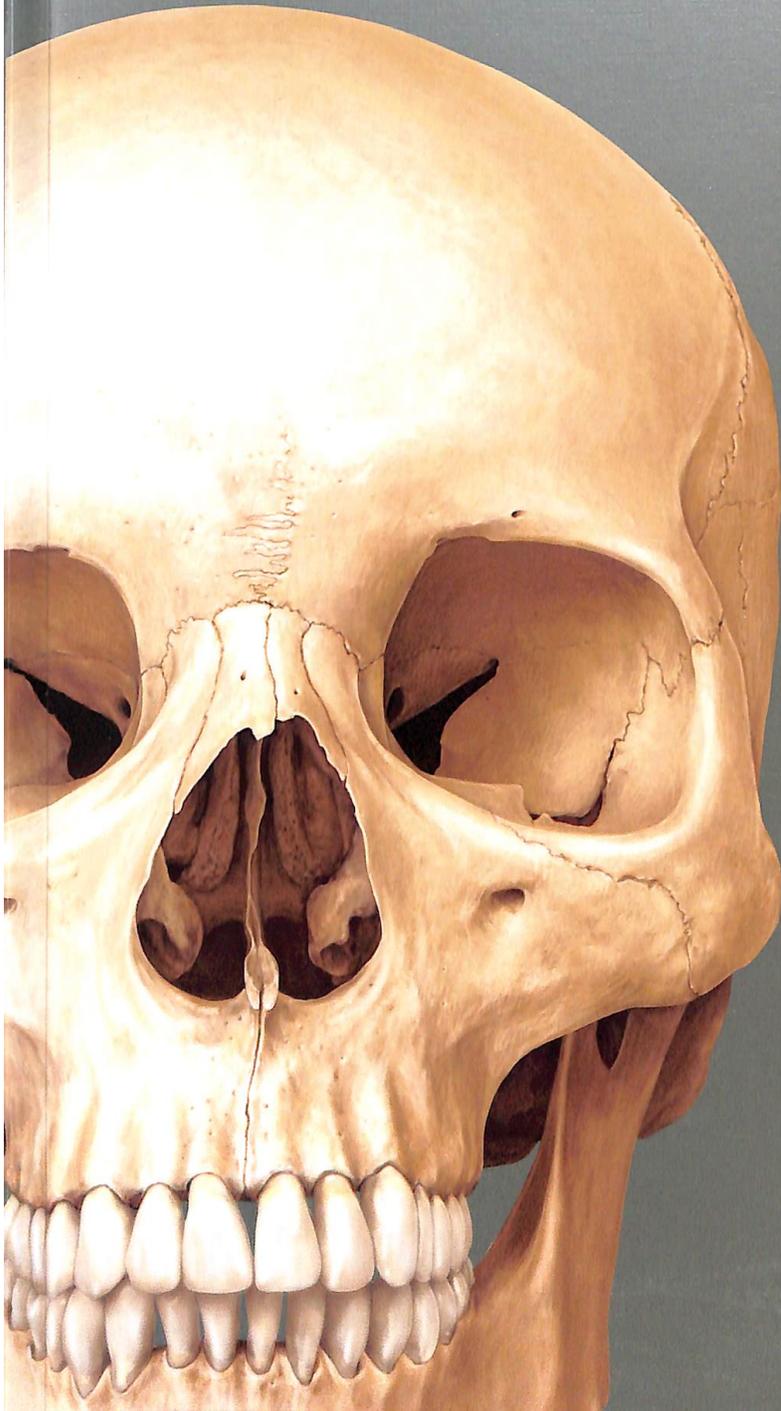
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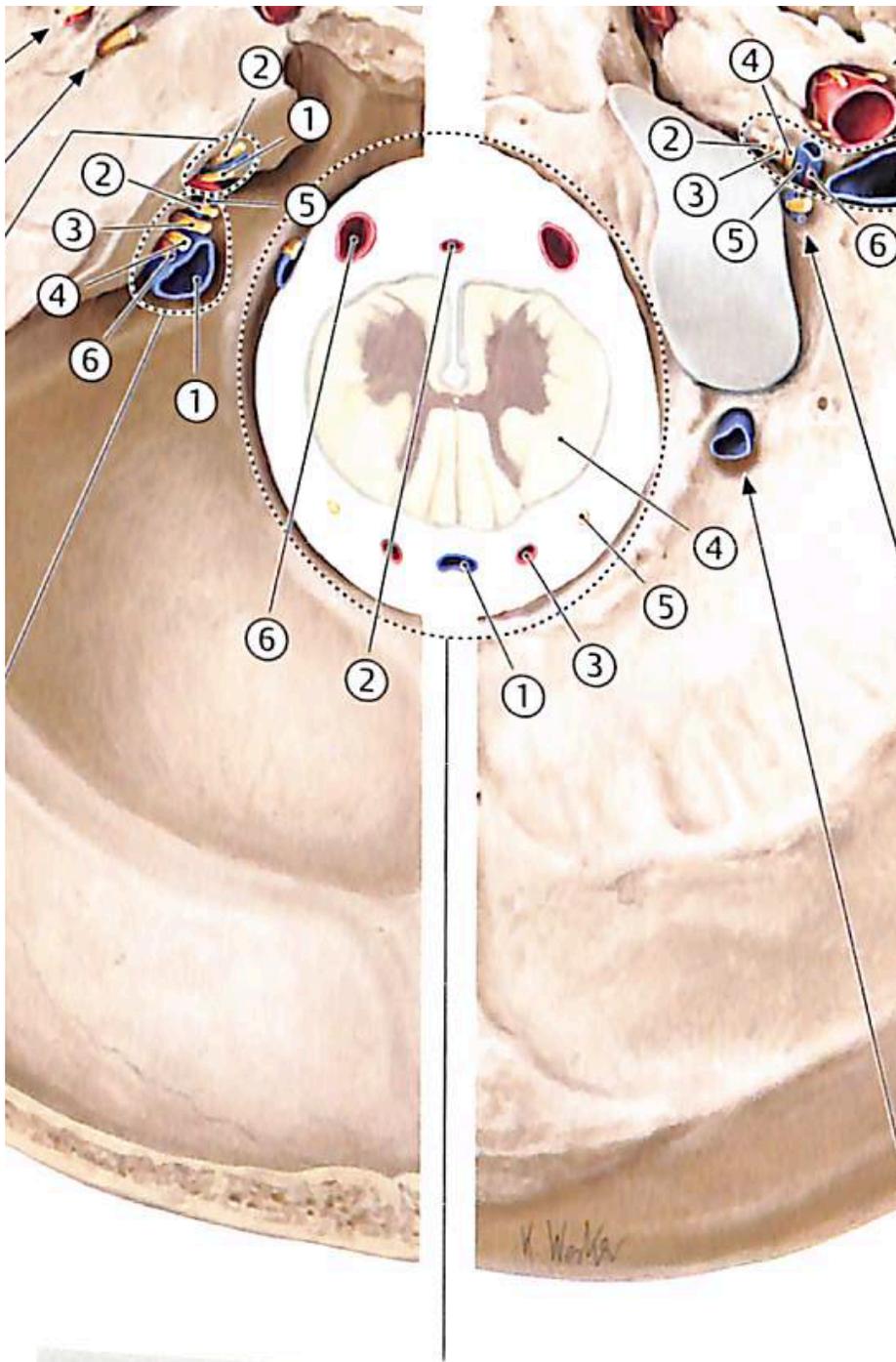
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# THIEME

## Atlas of Anatomy

Head and Neuroanatomy





**Foramen magnum**

- ① Spinal vein
- ② Anterior spinal artery
- ③ Posterior spinal artery
- ④ Spinal cord
- ⑤ Spinal root of accessory nerve
- ⑥ Vertebral artery

8/28/22

RAYMOND DAMADIAN

1936 - 2022

# Doctor Pioneered MRI Scanning

BY JAMES R. HAGERTY

Raymond Damadian, a young physician, had an audacious thought in 1969 while using magnetic-resonance equipment to analyze cells inside a test tube: What if the device could be made large enough to wrap around a human being?

That could give doctors a richly detailed view inside bodies and help them diagnose cancer and other diseases. Dr. Damadian and a small team went to work on that project, with meager funding, at a medical center in Brooklyn. In 1971, he published a paper in Science that established how a magnetic scan could be used to distinguish between cancerous and healthy tissue.

The next step was to cobble to-

**A pioneer of MRI scanning was furious when snubbed by a Nobel committee.**

gether a human-scale magnetic resonance imaging, or MRI, scanner, involving large magnets and radio signals to explore the body's interior. At one point, Dr. Damadian had to bring in jackhammers to blast through a granite floor to provide more vertical space in his lab. An early test fried a mouse to death. After the defect was fixed, a second mouse survived, as did a turkey and Dr. Damadian's first human subject, who nervously endured a scan in 1977.

It was a moment of triumph for Dr. Damadian, who died Aug. 23 at the age of 86. Yet struggles and anguish lay ahead.

Dr. Damadian obtained patents and in 1978 formed a company, Fonar Corp., to make commercial MRI scanners. These powerful new tools began showing up in clinics and providing far more de-

tail than X-rays could.

Giant competitors including Johnson & Johnson and General Electric Co. made their own scanners. Dr. Damadian filed lawsuits, alleging they had copied his patented technology. After years of litigation, a court judgment required GE to pay \$128.7 million to Fonar.

The biggest blow to Dr. Damadian came in 2003, when two other scientists, Paul Lauterbur and Peter Mansfield, shared a Nobel Prize in medicine for their contributions to the technology behind MRI scanning. Dr. Damadian was furious that the Nobel committee had snubbed him.

He and his supporters bought full-page newspaper advertisements denouncing a "shameful wrong that must be righted." Dr. Damadian continued to press the case. "If anybody deserved to get the Nobel Prize first, I did," he told The Wall Street Journal. "If defending yourself when you're mutilated is egocentricity, then I'm guilty."

In "Gifted Mind," a 2015 memoir written with Jeff Kinley, Dr. Damadian suggested that the Nobel committee may have shunned him because of his rejection of Charles Darwin's theory of evolution. "I hold to a literal six-day creation scenario as described in Genesis," he wrote. In any case, he credited his MRI discoveries to divine inspiration.

Raymond Vahan Damadian was born into a family of Armenian descent in New York on March 16, 1936. His father, an immigrant, was a photo engraver at a newspaper. His mother was an accountant.

He attended the University of Wisconsin on a scholarship and majored in mathematics. He earned his medical degree at the Albert Einstein College of Medicine.

Though he didn't win the Nobel, recognition for his discoveries came in the form of a National Medal of Technology, awarded by President Reagan in 1988.

## The Possible Role of Cranio-Cervical Trauma and Abnormal CSF Hydrodynamics in the Genesis of Multiple Sclerosis

(Click here to view the videos of the CSF obstructions of the MS patients)

**Raymond V. Damadian and David Chu**

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**Abstract:** UPRIGHT® Multi-Position™ MR scanning has uncovered a key set of new observations regarding Multiple Sclerosis (MS), which observations are likely to provide a new understanding of the origin of MS. The new findings may also lead to new forms of treatment for MS. The UPRIGHT® MRI has demonstrated pronounced anatomic pathology of the cervical spine in five of the MS patients studied and definitive cervical pathology in the other three. The pathology was the result of prior head and neck trauma. All eight MS patients entered the study on a first come first serve basis without priority, and all but one were found to have a history of serious prior cervical trauma which resulted in significant cervical pathology. The cervical pathology was visualized by UPRIGHT® MRI. Upright cerebrospinal fluid (CSF) cinematography and quantitative measurements of CSF velocity, CSF flow and CSF pressure gradients in the upright patient revealed that significant obstructions to CSF flow were present in all MS patients. The obstructions are believed to be responsible for CSF “leakages” of CSF from the ventricles into the surrounding brain parenchyma which “leakages” can be the source of the MS lesions in the brain that give rise to MS symptomatology. The CSF flow obstructions are believed to result in increases in intracranial pressure (ICP) that generate “leakages” of the CSF into the surrounding brain parenchyma. In all but one MS patient, anatomic pathologies were found to be more severe in the upright position than in the recumbent position. Similarly, CSF flow abnormalities were found to be more severe in the upright position than in the recumbent position in all but one MS patient. Images of the MS patient anatomic pathologies and CSF flow abnormalities are provided with comparison images from normal examinees in Figures 1–16.

**KEY WORDS:** Multiple Sclerosis, Cranio-Cervical Trauma, CSF Hydrodynamics, CSF Leaks, Intracranial Pressure, CSF Peak Velocity, CSF Pressure Gradient, CSF Flow

# The Possible Role of Cranio-Cervical Trauma and Abnormal CSF Hydrodynamics in the Genesis of Multiple Sclerosis

## Physiological Chemistry and Physics and Medical NMR

September 20, 2011; 41: 1-17

Raymond V. Damadian and David Chu  
FONAR Corporation

### KEY POINTS FROM THIS ARTICLE:

- 1) Eight MS patients and 7 normal volunteers were MRI scanned on a 0.6 T scanner with a quadrature head-neck combination coil to visualize the overall CSF flow pattern. The scans were performed in both the upright and recumbent positions using the FONAR UPRIGHT(R) Multi-Position™ MRI.
- 2) An important benefit of MRI technology is the ability to visualize the plaque lesions of Multiple Sclerosis.
- 3) The advent of phase coded MR imaging has made it possible to visualize and quantify the dynamic flow of the cerebrospinal fluid (CSF) within the cranial vault and spinal canal.
- 4) UPRIGHT(R) Multi-Position™ MR scanning has uncovered a key set of new observations regarding Multiple Sclerosis (MS), which observations are likely to provide a new understanding of the origin of MS.
- 5) "The UPRIGHT(R) MRI has demonstrated pronounced anatomic pathology of the cervical spine in five of the MS patients studied and definitive cervical pathology in the other three. The pathology was the result of prior head and neck trauma."  
**[KEY POINT]**
- 6) Seven of 8 MS patients in this study had a history of serious prior cervical trauma which resulted in significant cervical pathology. The cervical pathology was visualized by UPRIGHT(R) MRI.
- 7) "Upright cerebrospinal fluid (CSF) cinematography and quantitative measurements of CSF velocity, CSF flow and CSF pressure gradients in the upright patient revealed that significant obstructions to CSF flow were present in all MS patients. The obstructions are believed to be responsible for CSF 'leakages' of CSF from the ventricles into the surrounding brain parenchyma which 'leakages' can be the source of the MS lesions in the brain that give rise to MS symptomatology."
- 8) The CSF flow obstructions are believed to result in increases in intracranial pressure (ICP) that generate 'leakages' of the CSF into the surrounding brain parenchyma.

- 9) In 7 of 8 MS patients, anatomic pathologies and CSF flow abnormalities were found to be more severe in the upright position than in the recumbent position.
- 10) "Traditionally the symptom-generating lesions in the brain and spinal cord of Multiple Sclerosis (MS) patients are ascribed to tissue specific autoimmune interactions."
- 11) Abnormal CSF flows were found in all eight MS patients. "The abnormal CSF flows corresponded with the cranio-cervical structural abnormalities found on the patients' MR images.
- 12) "Every MS patient exhibited obstructions to their CSF flow when examined by phase coded CSF cinematography in the upright position."
- 13) "All MS patients exhibited CSF flow abnormalities that were manifest on MR cinematography as interruptions to flow or outright flow obstructions somewhere in the cervical spinal canal, depending on the location and extent of their cervical spine pathology. Normal examinees did not display these flow obstructions."
- 14) "Trauma may have a causative role in the onset of MS." **[Important]**
- 15) "All seven patients had distinct cervical anatomic pathology on their current MR images that corresponded with their trauma histories, thereby establishing that the historical trauma events contributed directly to their permanent pathologies of the cervical spine and that their cervical trauma histories were not immaterial."
- 16) "Four had received neck injuries in motor vehicle accidents, three of which were whiplash injuries, and the fourth a "reverse whiplash" (neck flexion preceding neck extension) injury. A fifth, patient was involved in a severe motor vehicle accident at age 2-3 that "totalled" the car in which she was riding without a seat belt or infant seat."
- 17) "In all but two of the patients the trauma preceded the onset of MS symptoms by more than 8 years."
- 18) "The abnormal CSF flow dynamics found in the MS patients of this study corresponded to the MR cervical pathology that was visualized." **[Key Point]**
- 19) "The findings raise the possibility that interventions might be considered to restore normal intracranial CSF flow dynamics and intracranial pressure (ICP)." **[Important]**
- 20) The elevated peak CSF velocities measured in the MS patients indicate elevated intracranial pressures (ICP) in these MS patients. The elevated ICP is the origin of the CSF "leaks" that appear in MS patients.

21) "The most important finding of this study is that cerebrospinal fluid 'leaks' from the ventricles of the brain into surrounding brain parenchyma, possibly secondary to trauma induced blockages of CSF flow and resulting increases in ICP, may be playing an important etiologic role in the genesis of Multiple Sclerosis."

22) Protein is the principal ingredient, other than water, of the cerebrospinal fluid. These authors suggest that the "leakage" of these CSF antigenic proteins, could be the source of the antigens generating the autoimmune reactions known to be the origin of MS lesions.

23) Trauma induced "leakage" of CSF antigenic proteins into the surrounding brain parenchyma is contributing to the formation of MS plaques.

24) "The findings further suggest that going forward, victims of Motor Vehicle Whiplash injuries with persisting symptoms, e.g., headache, neck pain, should be scanned by UPRIGHT(R) MRI to assure that their CSF hydrodynamics and cervical anatomy (C1-C7) are normal. Should their CSF hydrodynamics prove abnormal, they should be monitored by UPRIGHT(R) MRI to assure they are restoring to normal over time, or ultimately decompressed by expansion stenting or cervical realignment if they are not."

25) "In conclusion, the results of our investigation suggest that Multiple Sclerosis may be biomechanical in origin wherein traumatic injuries to the cervical spine result in cervical pathologies that impede the normal circulation of CSF to and from the brain." "The obstruction to CSF outflow would result in an increase in ventricular CSF pressure (ICP) which in turn could result in 'leakage' of cerebrospinal fluid and its content antigenic proteins (e.g., tau proteins) into surrounding brain parenchyma. The attachment of antigenic proteins to surrounding brain nerve fibers would stimulate the antigen-antibody reactions that produce the axon demyelinations characteristic of MS."

#### COMMENTS FROM DAN MURPHY:

This is an important article for chiropractors. These authors suggest that cervical spine trauma and malalignment obstructs the flow of cerebral spinal fluid. This obstruction of CSF flow increases intracranial pressure, causing cerebral spinal fluid to leak out, along with antigenic proteins. The immune system's response to these antigenic proteins cause the demyelination of multiple sclerosis.

These authors suggest that the improvement of spinal malalignment could improve cerebral spinal fluid flow, stopping the aforementioned cascade to MS. In fact, in one of the MS patients, the UPRIGHT MRI found a malalignment of C-1. This malalignment "was successfully treated by Dr. Scott Rosa, using the Atlas Orthogonal (AO) instrumentation." "The patient's symptoms, severe vertigo accompanied by vomiting when recumbent and stumbling from unequal leg length, ceased upon treatment." Objective improvements in obstructed CSF fluid was also noted "immediately following treatment with the AO instrument."

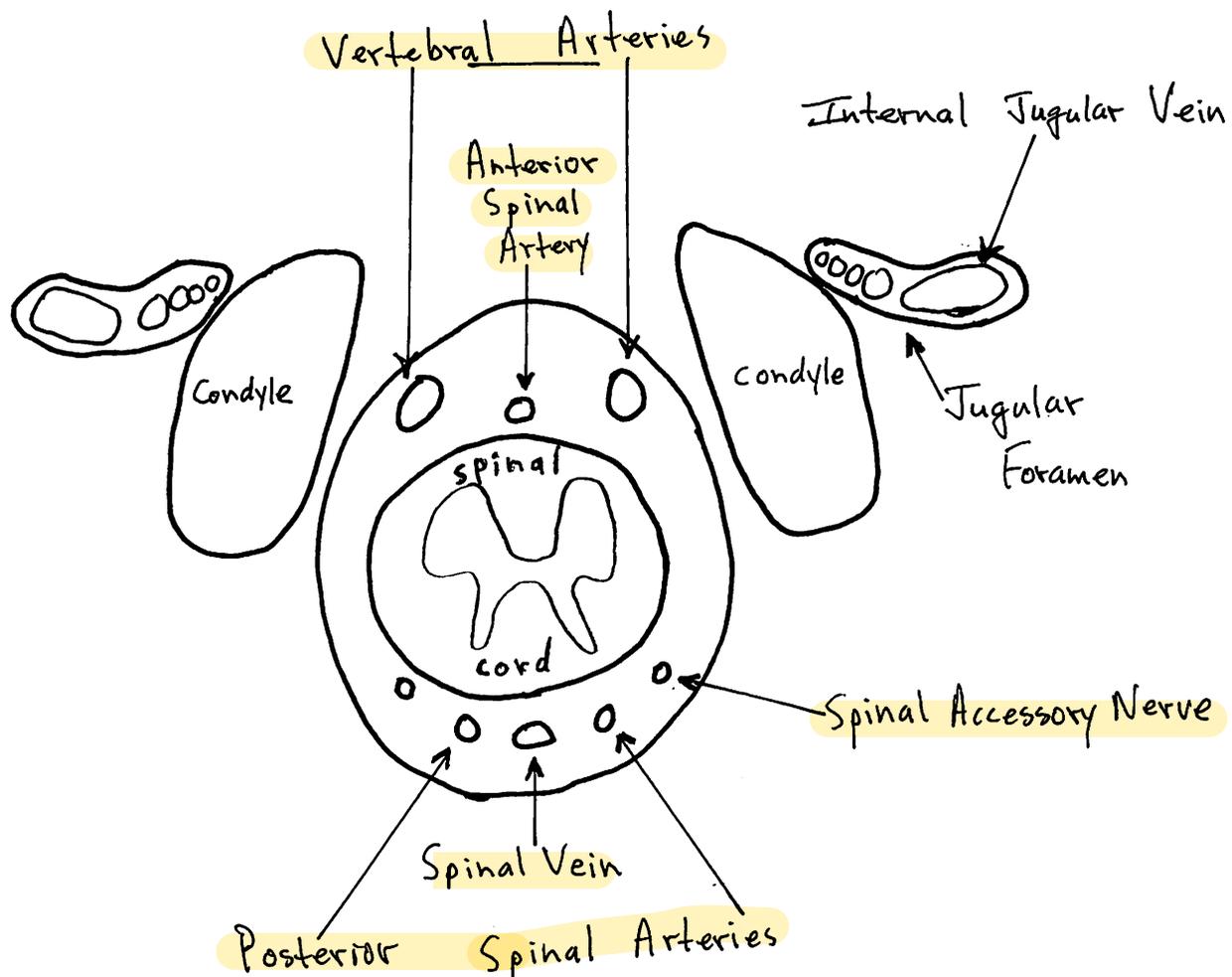
# The Role of the Cranio-cervical Junction in Cranio-spinal Hydrodynamics and Neurodegenerative Conditions

Neurology Research International  
November 30, 2015; [epub]

Michael F. Flanagan; This article has 257 references

BACKGROUND FROM DAN MURPHY

## Axial View of the Foramen Magnum and its Contents, from below:



A new model of the atlas subluxation is emerging: a misalignment between the atlas and occiput could compromise the venous drainage of the brain (spinal vein, internal jugular vein), compromise the flow of cerebral spinal fluid, and/or compromise the arterial supply (anterior and posterior spinal arteries, and vertebral arteries) to the brain. This article explores the probability and consequences of this occurrence.

9) "Misalignments of the CCJ [*atlas-occiput articulation*] can obstruct blood flow through the vertebral arteries and veins that can lead to chronic [brain/cranial] ischemia and edema." **[Key Point For Chiropractors]**

10) Chronic brain/cranial edema decreases arterial flow in the brain which can result in [*decreased ATP production*], increased oxidative stress, and brain atrophy.

11) "Blockage of blood and CSF flow due to malformations and misalignments of the CCJ may play a role in chronic [*brain/cranium*] ischemia, edema, hydrocephalus, and ventriculomegaly [*enlargement*]."

12) "The CCJ is a potential choke point for blood and CSF flow between the cranial vault and spinal canal that can cause faulty cranio-spinal hydrodynamics and subsequent chronic ischemia, edema, and hydrocephalus." **[Key Point]**

"Upright posture and motion of the cervical spine compound the strains and deformation of blood and CSF pathways of the CCJ further contributing to blockage of flow."

13) "Faulty cranio-spinal hydrodynamics may also play a role in neurodegenerative diseases such as Alzheimer's, Parkinson's, multiple sclerosis, dementia, and motor neuron diseases," as well as migraines, silent strokes, seizures, psychosis, depression, and mania. **[see the legal briefs by Judge Ponath and also the Kentucky Houses of Reform papers under the free-stuff tab on my webpage, [www.danmurphydc.com](http://www.danmurphydc.com)].**

14) The vertebral arteries provide about 20% of blood flow to the brain. [The vertebral arteries enter the skull through the foramen magnum.]

15) The internal carotid arteries supply about 80% of blood the flow to the brain.

16) The Subclavian Steal Syndrome occurs when:

- The proximal portion of the subclavian artery is obstructed (i.e. stenosis) resulting in decreased blood flow and pressure downstream in the vertebral and axillary arteries.
- This creates a pressure gradient that causes the arm to draw blood from the ipsilateral vertebral artery, which in turn gets its supply from the contralateral vertebral artery via their connection to the basilar artery.
- This may in turn steal blood flow from vessels of the brain including the ophthalmic (the first branches of the internal carotid artery) arteries of the eyes, resulting in hypoperfusion of the optic nerve head, causing impairment of vision.

17) Reduced posterior blood supply (vertebral artery) may cause migraines.

"The vertebral arteries also supply the medial temporal and occipital lobes.

Decreased blood flow to the medial temporal and occipital lobes may play a role in the déjà vu and aura symptoms associated with migraines." "Malformations, misalignments, and deformation of the CCJ and dura mater can obstruct blood flow

26) Cervical kyphosis causes both strains of the dura of the CCJ and also causes the internal jugular vein to bend around the transverse process of the atlas, reversing its normal course, compressing the vein and increasing resistance to blood flow. **[Key Point]**

27) "Malformations and misalignments of the CCJ may play a role in chronic [brain/cranial] ischemia and edema, which may in turn lead to neurodegenerative processes and subsequent diseases."

28) Cerebral Spinal Fluid (CSF) is an extra-fine filtrate of the blood. The production of CSF uses hydrostatic pressure gradients. Changes in these pressure gradients alter the production of cerebral spinal fluid.

29) Trauma can cause dural tears resulting in CSF leaks and coning of the brain stem and cerebellum. Connective tissue disorders such as Ehlers-Danlos appear to be predisposed to CSF leaks.

30) Proper CSF volume is essential to the regulation of intracranial pressure.

31) There is a possible connection between cerebellar tonsillar ectopia and structural strains due to trauma. Other structural strains occur from an abnormal clivo-axial angle (cranio-cervical angulation), including retroflexed odontoid. "An abnormal clivo-axial angle or retroflexed odontoid can cause cervicomedullary kinking and compression of the ventral epidural space of the neural canal of the CCJ." **[Important]**

32) "Structural strains of the CCJ affect the dura mater, which can cause displacement (ectopia) of the brainstem and deformation of the neurovascular and CSF tunnels and pathways."

33) "Chiari malformations and coning of the brainstem cause blockage of CSF flow through the CCJ." "They also compress the epidural space which contains the vertebral veins that connect to the emissary veins and dural sinuses used to drain the brain during upright posture."

34) "Malformations, misalignments, and deformation of the CCJ compress the vertebral veins, which may affect CSF flow." "An increase in CSF volume in the brain can compress veins and decrease drainage."

35) CSF flows along cranial nerve roots, especially the olfactory and optic nerves. Enlargement of the optic nerve sheath is a sign of increased CSF volume.

36) The CCJ is a choke point for CSF flow between the cranial vault and spinal canal. **[Very Important]**

# Posture

## Sagittal Balance

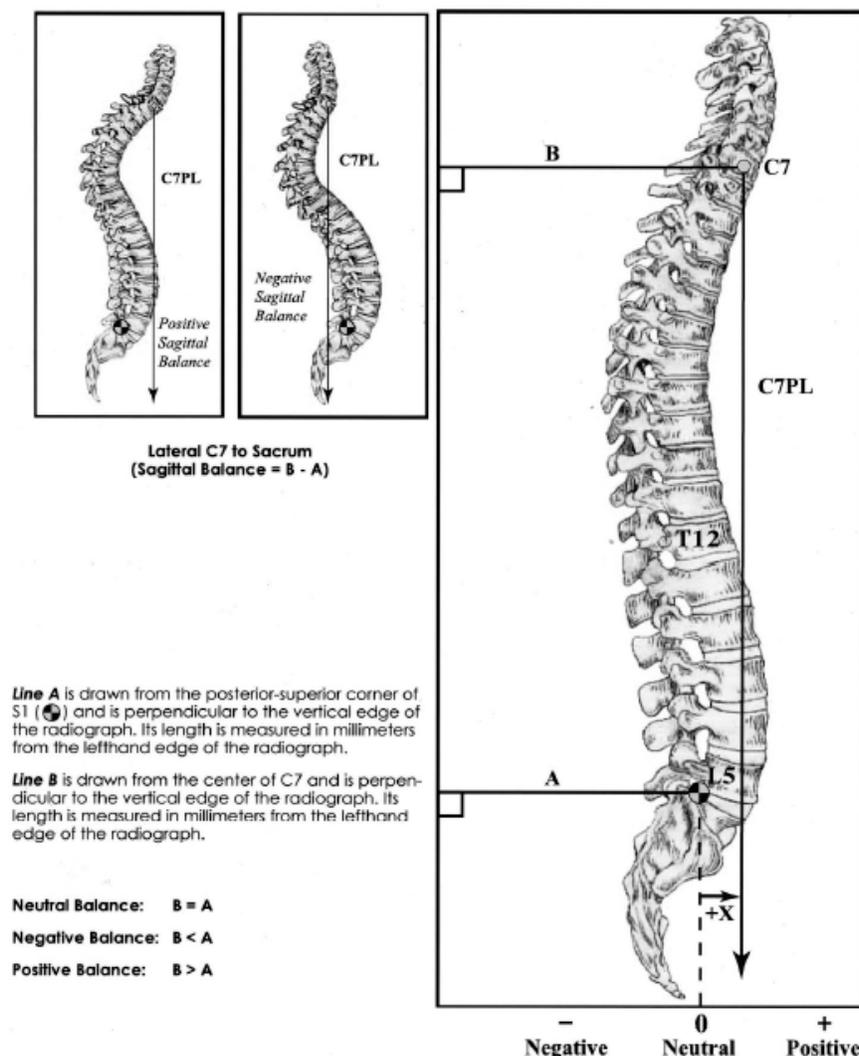


Figure 1. Technique for measurement of sagittal balance.

## "The impact of positive sagittal balance in adult spinal deformity"

### Spine

September 15, 2005;30(18):2024-9

Glassman SD, Bridwell K, Dimar JR, Horton W, Berven S, Schwab F.

"All measures of health status showed significantly poorer scores as C7 plumb line deviation increased [forward head / body]."[WOW!]

"There was a high degree of correlation between positive sagittal balance and adverse health status scores, for physical health composite score and pain domain."

"There was clear evidence of increased pain and decreased function as the magnitude of positive sagittal balance [forward head / body] increased."

"This study shows that although even mildly positive sagittal balance is somewhat detrimental, severity of symptoms increases in a linear fashion with progressive sagittal imbalance [forward head / body]."

## Abstract

Surg Technol Int. 2014 Nov;25:277-9.

# Assessment of stresses in the cervical spine caused by posture and position of the head.

Hansraj KK<sup>1</sup>.

## Author information

### Abstract

Preamble. Billions of people are using cell phone devices on the planet, essentially in poor posture. The purpose of this study is to assess the forces incrementally seen by the cervical spine as the head is tilted forward, into worsening posture. This data is also necessary for cervical spine surgeons to understand in the reconstruction of the neck.

PMID: 25393825 [PubMed - in process]

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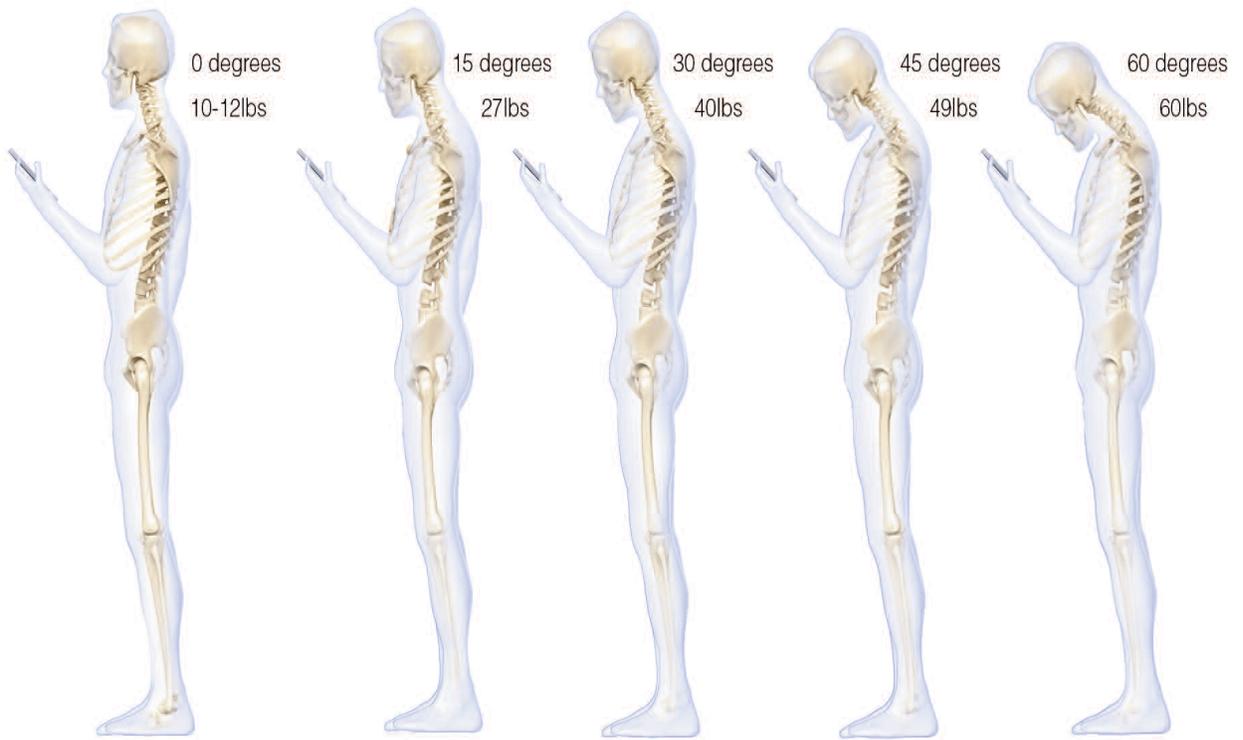
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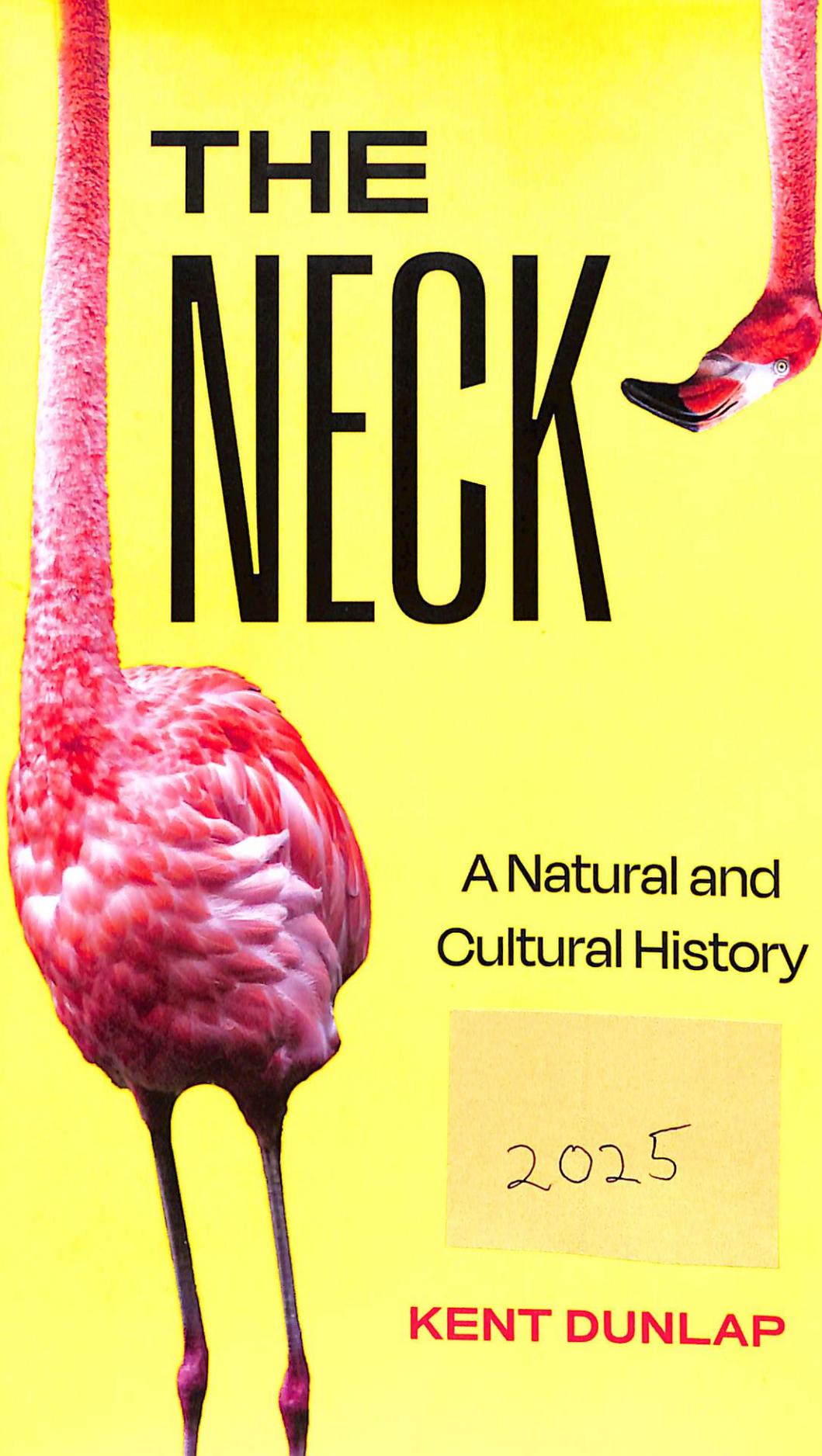
# Assessment of Stresses in the Cervical Spine Caused by Posture and Position of the Head

KENNETH K. HANSRAJ, MD  
CHIEF OF SPINE SURGERY  
NEW YORK SPINE SURGERY & REHABILITATION MEDICINE  
NEW YORK, NEW YORK

## ABSTRACT

**P**reamble. Billions of people are using cell phone devices on the planet, essentially in poor posture. The purpose of this study is to assess the forces incrementally seen by the cervical spine as the head is tilted forward, into worsening posture. This data is also necessary for cervical spine surgeons to understand in the reconstruction of the neck.





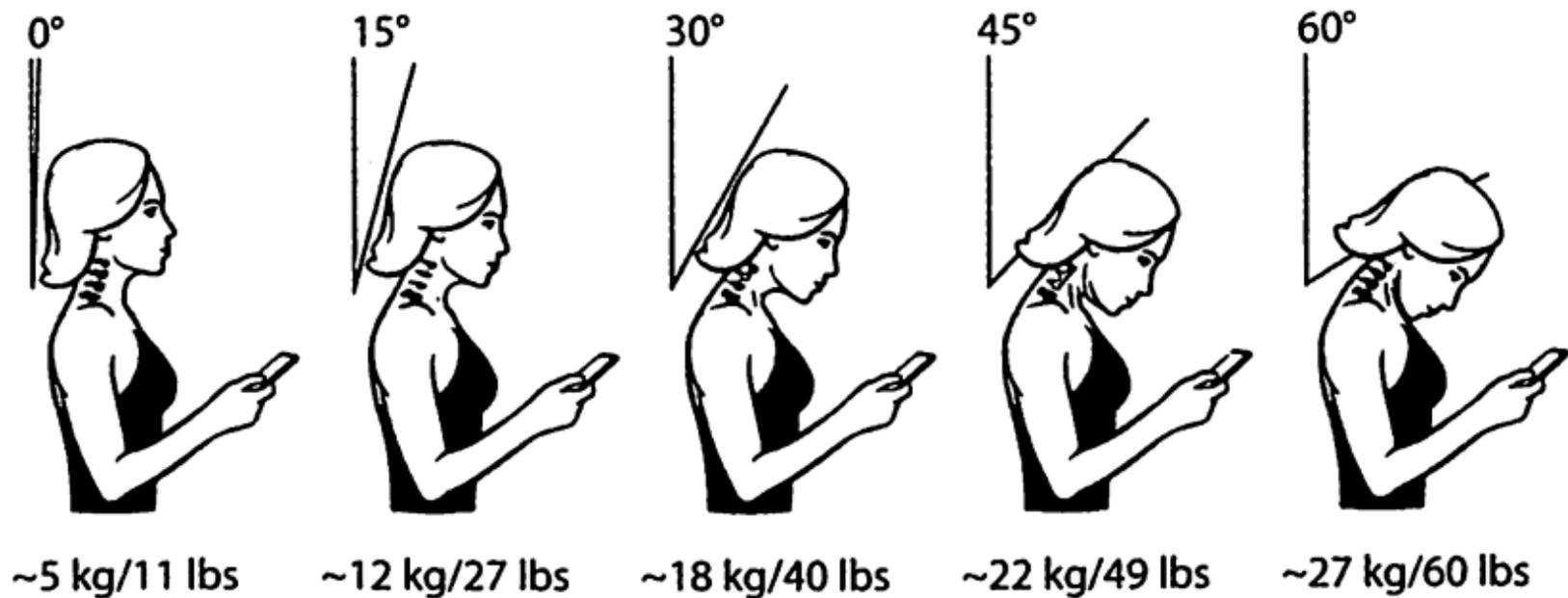
# THE NECK

A Natural and  
Cultural History

2025

**KENT DUNLAP**

## Head tilt



## Pressure on neck

Figure 1 The effect of operating a smartphone with different head angles

# **Vagus Nerve**

# Vagus Interactive Drawing



5 WAYS TO MAKE  
GERMS YOUR FRIENDS

WHY  
DIRT  
IS GOOD



2009

MARY RUEBUSH, PhD

## OPINION

## Covid and the 'Hygiene Hypothesis'

By Eran Bendavid

**M**aintaining good health is often a balancing act. Too much food and we develop obesity, diabetes and heart disease. Too little food and we see stunting and wasting. This kind of equilibrium applies to our interactions with bacteria, viruses, parasites and other microbes. Too much exposure to some microbes leads to disease, and so does too little.

**Measures like masking and social distancing may be doing long-term damage to our immune systems.**

The intensification of hygienic policies with the advent of Covid-19 was understandable. But long-term masking, deep cleaning, distancing and isolation can be harmful to health, especially for children, precisely because it reduces exposure to microbes. Hygiene practices have health risks as well as benefits.

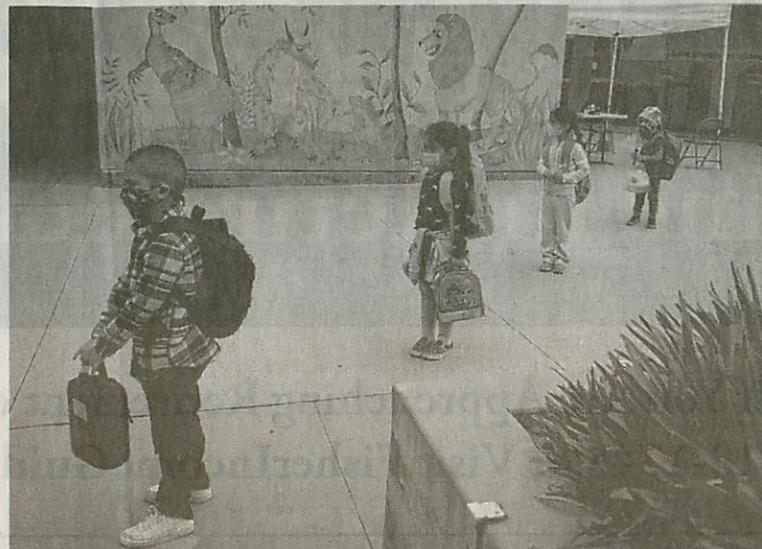
One of the greatest accomplishments of modern civilization has been the "great escape" from the threat of infectious disease. Clean drinking water, vaccinations, antibiotics and sanitation have helped tame pestilences such as tuberculosis, typhoid fever, polio and smallpox. But increasingly antiseptic populations also experience increasing rates of asthma, allergies, Type 1 di-

abetes, Crohn's disease and other diseases with a significant autoimmune component.

The idea that exposure to some infectious agents is protective against immune-related disorders isn't new and comes with significant scientific heft. The so-called hygiene hypothesis is constructed from epidemiologic evidence, laboratory studies and clinical trials that, put together, support the notion that an excessive emphasis on antiseptics is implicated in misalignments of the immune system that risk disease.

Allergic and autoimmune diseases are far less common in communities with less hygiene, and autoimmune disorders increase in children who migrate from areas with less emphasis on hygiene to areas with more emphasis. They are less common in agricultural communities, where exposure to dirt and animals is common, compared with neighboring communities with shared genetics but little farming. Children who attend daycare early in life—runny noses, colds and all—have less asthma and fewer allergies. Animal studies, laboratory experiments and small trials in humans all point in a similar direction: Avoiding exposure to some microbes prevents the immune system from training well and predisposes to autoimmune diseases.

The risk of untoward consequences from excessive hygiene is particularly striking for children. The immune system gets the most effective tuning during childhood, and reducing its ability to distin-



Schoolchildren in Los Angeles, April 2021.

guish disease-causing invaders from benign targets is a common mechanism proposed for allergies, asthma and immune-mediated bowel diseases, among others.

The hygiene hypothesis isn't a hard-proven theory, and its implications vary by context, but it fits with mainstream scientific knowledge about the development of our immune system and the role of exposure to a range of microbes—including viruses and parasites—in keeping the immune system tuned.

This isn't a paean to infections and poor hygiene but a reminder of the importance of balance. When I prescribe antibiotics, they have to be strong enough to treat my patient's infection. But if I overtreat, I run the risk of giving the patient

colitis (inflammation of the colon) without additional benefits. Current hygiene policies and practices need rebalancing.

This is particularly true for practices like deep-cleaning and contact restrictions that likely play a trivial role in limiting Covid-19 transmission. The evidence that masking reduces spread is stronger, but it also limits the exchange of other microbes, which may be deleterious, especially to children.

A related important balance that may be disrupted is our microbiome, the collection of microbes that live in our bodies and play crucial roles in regulating bodily functions. Loss of microbiome diversity in early life is associated with a host of adverse

health consequences. Many measures implemented to control Covid-19, including distancing, isolation, lockdowns, masking, travel restrictions and deep cleaning, are poised to reduce microbiome diversity in profound and lasting ways.

The consequences of these changes to our immune system and microbiome may not appear precipitously, and it is too early to see evidence of rising immune disorders. But the ubiquity of Covid-19 policies in schools and daycare facilities may herald meaningful harms for children.

The extreme concern for hygiene at the onset of Covid-19 was intuitive and understandable. The virus was spreading fast, information on routes of transmission was limited, and we as a society tried to protect one another from infection. But policies that were easy to support two years ago need re-evaluation. Distancing, deep-cleaning and masking aren't "more is better" kinds of goods.

On the other side of the balance, health risks from extended intensive hygiene are credible. As Omicron recedes and we internalize the paucity of Covid-19 benefits from some hygiene practices, we should balance those against the benefits we lose by shielding our immune systems from normal exposures—and the ones we withhold from children by preventing the exchange of microbes through play and smiles.

*Dr. Bendavid is an associate professor of medicine at Stanford.*

ASSOCIATED PRESS

# *Allergic*

## *Our Irritated Bodies in a Changing World*

*Theresa MacPhail*

*“The definitive  
biography of allergies.”*

*— Michael Moss*

2023

# New Scientist

THE HUNT FOR  
BLACK HOLE STARS

WHY CULTURE CAN  
HELP YOU LIVE LONGER

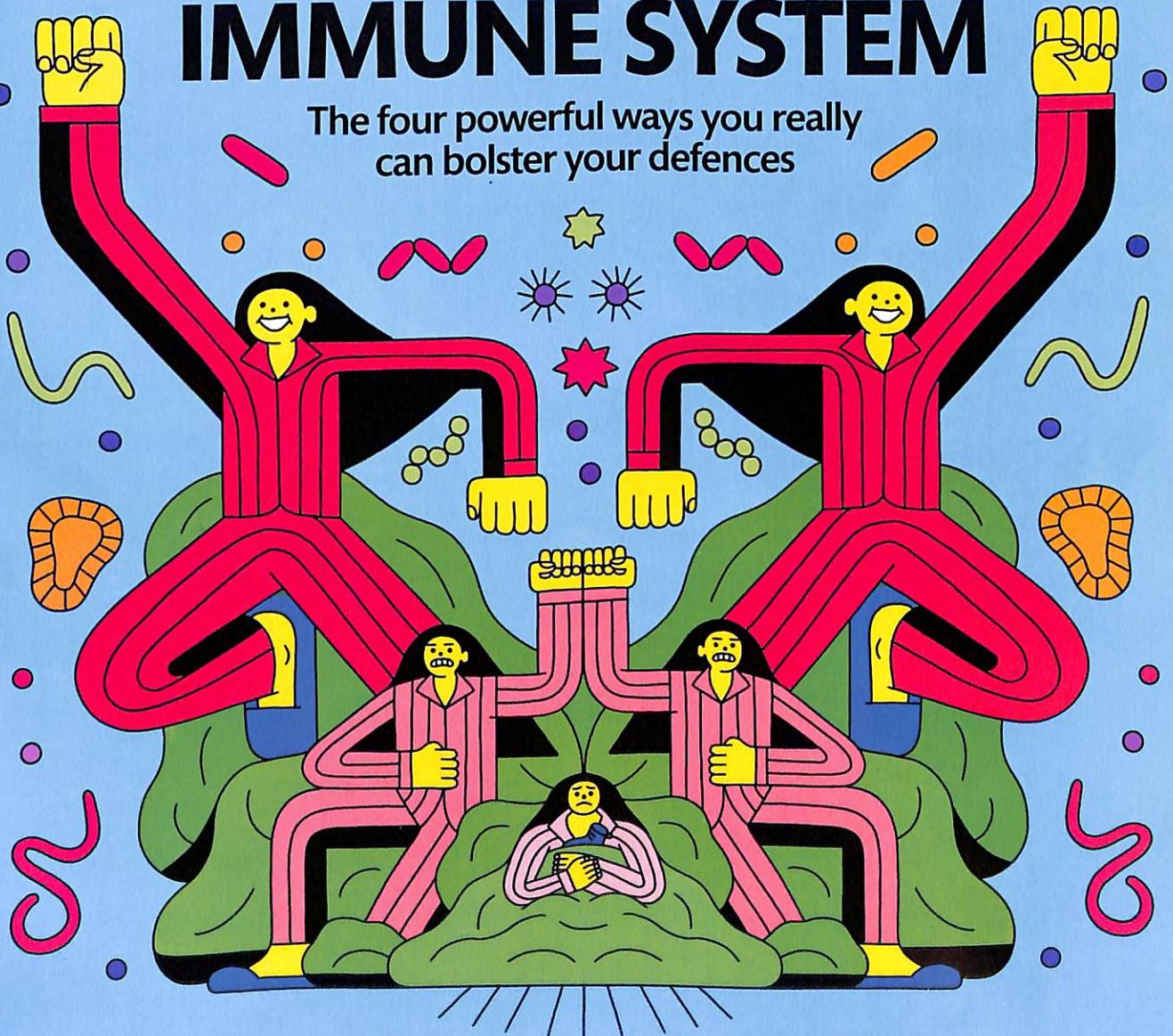
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## UPGRADE YOUR IMMUNE SYSTEM

The four powerful ways you really  
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# Improve your immunity

You can upgrade your immune system to help fight off infection, but not in the way you think, discovers **Helen Thomson**

I AM lying under a blanket, feeling rough, staring at a bowl of oranges. Every fibre of my being is urging me to devour the lot. I can hear my mum – and medical friends at university – insisting that a megadose of vitamin C will head off my oncoming cold.

The thing is, I know it isn't true. Despite the common belief, vitamin C doesn't prevent colds. At best, it may shave a few hours off your symptoms. Still, the myth endures, because who wouldn't want an easy way to supercharge their immune system?

Over the past weekend, friends have also suggested I drink ginger tea and gobble down some turmeric. It got me thinking: what, if anything, really helps strengthen the immune system to aid it in warding off potential invaders? To find out, I decided to take stock of my own immune health and find an evidence-based approach to improving it. Along the way, I learned how absent bacteria, the contents of my spice rack and even my outlook on life play a critical role in enhancing my immune defences – and uncovered the one thing that might harm immunity more than anything else.

We often talk about “boosting” our immune

system, but, taken literally, that would be a terrible idea. Immunity isn't a dial you can just turn up, says immunologist Daniel Davis at Imperial College London.

Your immune system is made up of a diverse network of cells, proteins and organs that must be powerful enough to attack invaders but restrained enough not to target healthy cells or harmless molecules – overreactions that underlie autoimmune conditions and allergies. “You don't want to boost your immune system. You want to help it respond appropriately,” says Davis. “That's a lot harder to do.”

But before I start tinkering with my immunity, I need some idea of what shape it is in. According to immunologist Jenna Macciochi at the University of Sussex, UK, a rough gauge is simply counting your colds. “An average person experiences a few mild illnesses a year,” she says. “More frequent or severe illness can indicate an underlying immune dysfunction or heightened susceptibility.”

By that measure, my immune system is worse than average: I had a couple of colds at the beginning of the year, plus a recent



CRISTINA SPANCO

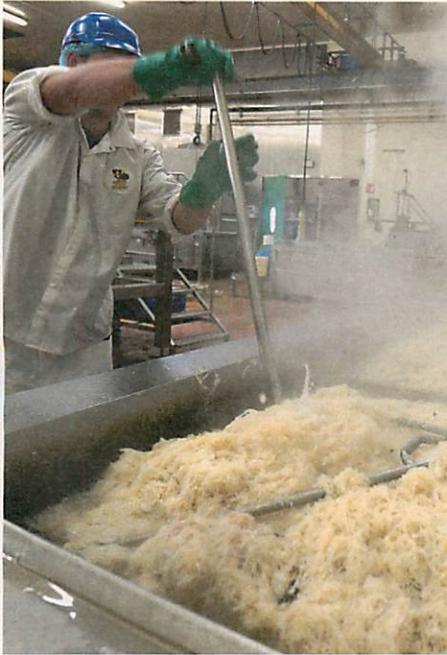


throat infection and a bout of covid-19 in the past three months.

A more sophisticated assessment comes from Sunil Ahuja at the University of Texas Health Science Center at San Antonio, who has developed an “immune grade” that reflects your immune resilience – the ability to neutralise threats while minimising collateral tissue damage.

When immune resilience is low, you get increased inflammation, the immune system’s brute-force response to any kind of threat. Immune cells also become senescent – where they stop dividing but don’t die. The accumulation of senescent cells causes the release of chemicals that accelerate ageing processes, independent of chronological age. “Low immune resilience opens the door for disease states,” says Ahuja.

To find out your immune grade, you need a T-cell test sometimes called a lymphocyte subset test, which in the UK costs around £199 (it is generally a little cheaper in the US). This measures two types of immune cell: CD4 “helper” T-cells, whose job it is to coordinate immune responses, and CD8 “killer” T-cells, which destroy infected cells. >



Sauerkraut and fresh ginger are tasty ways to help your immunity

A high CD4 count is good: it means plenty of generals to organise any potential immune battle. High CD8 is helpful if you are currently fighting an infection, but chronically high levels indicate an overactive immune system and increased inflammation, which is linked with several serious health problems. CD8 levels increase with age and with lifestyle factors like smoking, heavy drinking and lack of physical activity.

### Making the immune grade

These numbers are inadequate on their own. Instead, you need to work out their ratio by dividing CD4 by CD8. A ratio above 1 suggests CD8 levels are being kept in check, or "restrained", as Ahuja calls it. A ratio below 1 suggests they are "unrestrained", something you want to avoid. Combine this result with your CD4 level, which ideally should be above 800 cells per microlitre, and you have your grade (see "Immunity score", right). My ratio was 2.66, meaning my CD8 levels are being kept in check, but my CD4 count was 691 per  $\mu\text{L}$ , which translates to a grade of 2a. Respectable, but could do better.

Immune grade is a meaningful measure: over the past decade, Ahuja's team has tracked the immune grade of more than 10,000 people. Those with better scores respond well to vaccines, are less susceptible to infections and have lower rates of hospitalisation from infections. "During the pandemic, we found that 80-year-olds with a good immune grade were less likely to be hospitalised with covid-19 than people of any age with the lowest

**"For long-term immune power, we must look to our microbiome"**



### Immunity score

For a high immune grade, you need good levels of CD4+ cells, and you also need your CD8 cells to be kept in check, or "restrained"

	Score	CD4+ T-cells (cells/mm <sup>3</sup> )	
Immune Health Grades	I	≥800	Restrained
	IIa	≥500 <800	
	IIb	>200 <500	
	IIc	≤200	
	III	≥800	Unrestrained
IVa	≥500 <800		
IVb	>200 <500		
	IVc	≤200	

immune grade," says Ahuja. Having a bad grade also puts your mortality on the fast track: 40-year-olds with grade 4 – the weakest grade – face the same mortality risk at that age as healthy 55-year-olds with a grade 1 result.

So, how do I move from 2a towards grade 1? I don't smoke, which has a negative impact on almost every type of immune cell studied, so my first instinct is diet.

Here, our mass ignorance about vitamin C is a cautionary tale – particularly as we live in a world where inaccurate health advice spreads so easily on social media. This myth actually began in the 1970s with Nobel prize-winner Linus Pauling, whose book *Vitamin C and the Common Cold* spread the message that high doses could prevent colds. "He was always on TV, always on the radio, everyone was listening to him," says Davis. Later analyses suggested that his data was flawed and cherry-picked, but the message stuck.

There is something that might give me a quick fix, however. A 2013 review concluded that 75 milligrams of zinc taken daily within 24 hours of getting your first sniffle reduced the duration of a cold, with significantly fewer people still experiencing symptoms on day 7 than those who took placebos.

For long-term immune power, though, we need to look to our microbiome. The trillions of bacteria inhabiting our gut influence the action of all the main cell types in our immune army. Vitally, they maintain the integrity of the gut lining, preventing leakiness and inflammation, and churn out beneficial chemicals such as short-chain fatty acids, which can modify T-cells' response to viruses like influenza or HIV.

The simplest way to build a healthy microbiome is to ensure microbial diversity by feeding them plenty of whole foods, plus at least 30 grams of fibre per day. Another easy intervention is gardening. Healthy soil is teeming with beneficial bacteria that get transferred directly from our hands to our guts and are linked to better immune health. Amish communities who farm manually, for instance, tend to have stronger immune systems than similar Hutterite groups who use industrialised farming.

Then there are probiotics – live microorganisms – that you can drink or consume through fermented foods like natural yogurt, kimchi or kefir. During the covid-19 pandemic, Tim Spector, co-founder of the nutrition app Zoe, and his colleagues

## “Your immune system must be powerful enough to attack invaders but not target healthy cells”

surveyed almost half a million people and found those taking probiotics or eating fermented food regularly had less severe covid-19 symptoms than those taking vitamin C, zinc, garlic or nothing.

Of course, correlation isn't causation, but other studies add to its weight. In a 2021 trial, 36 people were randomly assigned to eat five to six daily portions of fermented foods or a high-fibre diet for 10 weeks. The fermented food group saw bigger shifts in immune cells and a significant decrease in inflammatory proteins in just a few weeks, compared with the fibre group.

I have recently started eating around three portions of kefir and the like each day. The Zoe researchers tell me that fewer servings of fermented food should still be beneficial, though specific doses haven't been tested. For the sake of my immune system, I am motivated to try more. Five to six servings of fermented food a day sounds excessive, but each serving doesn't need to be large, it is about 300 calories altogether, says Christopher Gardner at Stanford University in California, who led the trial. “[It] isn't as much as it might sound.”

While it also seems a little excessive to delve much deeper into your microbiome, I recently happened to be approached by researchers at

DENNIS KUNDEL MICROSCOPICSCIENCE PHOTO LIBRARY



**Bifidobacterium in the gut helps prevent over-inflammation**

**Gardening can expose you to more beneficial bacteria**

the Functional Gut Clinic in London, the first microbiome clinic in the UK, with the offer of being their first patient to receive a full gut MOT. So, over a few days, I took a battery of stool, breath and glucose tests. Alongside some interesting revelations about bad bacteria that had taken up residence in my small intestine, giving me insight into some recent health issues, the results also offered a surprising window into my immune health. It turned out that my gut was completely devoid of four types of beneficial bacteria that are normally a significant part of the adult gut microbiome.

Their absence was concerning. For instance, one of the missing bacteria, *Bifidobacterium bifidum*, supports immune health by preventing over-inflammation and boosts the activity of immune cells that kill pathogens, as well as increases the production of certain antibodies. Anthony Hobson, clinical director at the Functional Gut Clinic, suggests that it could be my childhood dairy intolerance that led to these helpful bacteria – which are often consumed first through breast milk, then in other dairy products – failing ever to find a niche.

Most people with a healthy, balanced diet shouldn't need to take probiotic supplements – or, for that matter, spend £900 (\$1180) on advanced microbiome tests unless they have significant gut issues. But armed with this information, I have refocused my diet and now take daily probiotics to feed my gut its missing microbes. Reseeding the microbiome is challenging after the first five years of life, but I'm hoping that topping up with bacteria-rich foods will help my immune health in the long run.

### Spice up your diet

As I cast a thankful eye on some homemade sauerkraut in need of burping, I consider what else might earn its space in my store cupboard. I drink fresh ginger and turmeric tea daily, vaguely aware of supposed immune benefits. But is this, like vitamin C, largely wishful thinking?

Perhaps not. A recent review suggests that ginger does have anti-inflammatory properties, triggering the release of chemicals called cytokines that help regulate immune responses. “I do recommend people eat ginger in order to improve the health of their immune system,” says Fitriyono Ayustaningwarno at Diponegoro University in Semarang, ➤



MINT IMAGES/UNLIMITED/ALAMY



Indonesia, lead author of the review. He adds, however, that its anti-inflammatory properties will only be effective when consumed in adequate amounts. "The best way to get the bioactive compounds in the ginger is by eating it fresh," he says.

Turmeric also has a wealth of research on the immune benefits of its active compound, curcumin – in animals at least. The molecule that gives the spice its distinct orange colour protects against pneumonia by regulating immune responses and dampens inflammation. It also boosts the immune system's ability to fight a range of cancers.

In humans, however, results are limited. Curcumin may improve symptoms of rheumatoid arthritis by influencing the activity of macrophages, immune cells that digest pathogens, and there are trials

testing whether it can improve the efficacy of chemotherapy. But strong evidence is severely lacking. The problem – and it's a big one – is its bioavailability. When we eat turmeric, barely any curcumin is actually absorbed.

Researchers are currently exploring ways around this. Taking curcumin alongside piperine, found in black pepper, prevents the body from metabolising it so quickly, for example, and other formulations are being developed to improve absorption.

"You wouldn't use curcumin to prevent getting the flu or other infectious disease," says Claus Schneider at Vanderbilt University in Nashville, Tennessee. But he says there is good evidence that its breakdown products can act on pathways crucial for regulating immune response and inflammation. He points to a small study of people on haemodialysis,

which showed that 2.5 g of turmeric added to a daily fruit juice for three months reduced inflammatory proteins in their body compared with a placebo.

So my fresh ginger and turmeric tea is no miracle cure, but it is probably doing more good than harm.

While diet is a powerful but complex modulator of immune health, exercise is more straightforward. A wealth of evidence shows that moderate, regular physical exercise is one of the most effective ways to improve your immune system.

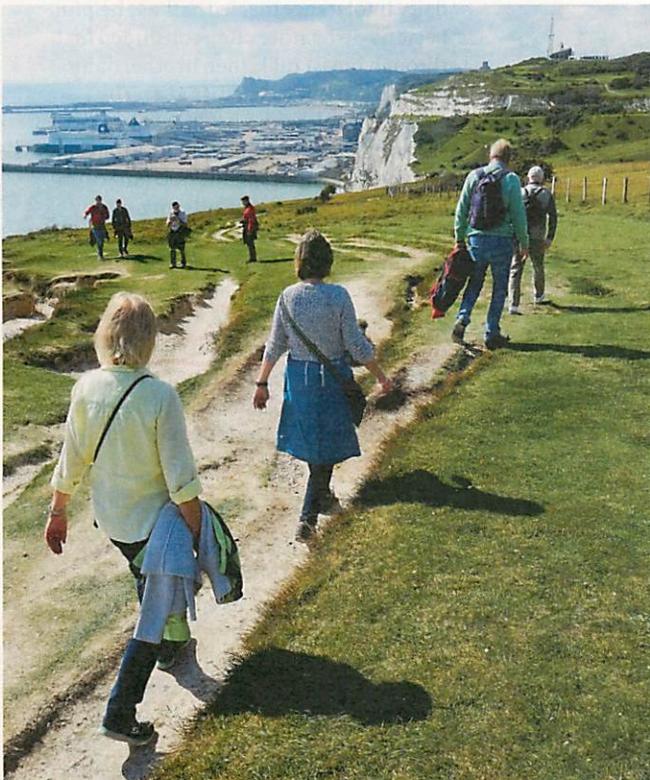
Moderate exercise is anything that raises your heart rate and makes you a bit sweaty: brisk walking, swimming, gentle running. These activities improve immune surveillance – increasing the number of circulating immune cells that scan for abnormal cells and pathogens – boost antibody production and help the body return to normal after an immune response. In July, Yang Li at Beijing Normal University in China and her colleagues performed a large-scale review of all the evidence of exercise on the immune system and their conclusion was frank: "Exercise minimises the chance of becoming sick... Exercise is considered a naturally built-in immune booster."

But more isn't always better. High-intensity training can raise levels of the stress hormone cortisol, which temporarily suppresses our immune system. When mice infected with a parasitic infection swam for 60 to 90 minutes, five times a week, it exacerbated symptoms by 50 per cent, whereas those that did so for 30 minutes, twice a week boosted helper T-cells and improved clearance of the parasite. In people with depression, spending 40 minutes walking, four times a week has been found to lower markers of inflammation in the brain by up to 25 per cent, whereas more intense exercise increased them.

Because of this, some advice has warned against daily exercise, arguing it could have negative effects on immune function. In 2018, however, John Campbell and James Turner at the University of Bath, UK, disproved this idea, showing that daily exercise increased T-cell production by up to 25 per cent and decreased inflammatory markers by up to 35 per cent.

So, how much is too much? Li and her colleagues concluded that negative effects on immune health are particularly noticeable in athletes who engage in high-intensity interval training, which involves short

A brisk walk is one way to raise antibody production



MICKAY ANDY/MILLENNIUM IMAGES, UK

**"Exercise is considered a naturally built-in immune booster"**



CHRIS STEELE/PERKINS/MAGNUM PHOTOS

**“The thing that has the most clearly proven impact on our immune health is long-term stress”**

**Your daily commute could be increasing your levels of inflammation**

bursts of exercise that raise your heart rate to 80 to 90 per cent of its maximum rate, followed by short recovery periods. Proper rest, appropriate nutrition and stress management can mitigate these risks, they say.

But given the majority of us don't train at such punishing levels every day, it is unlikely we will experience the negative side of exercise. So, if you are serious about boosting your immune health, moderate daily exercise is probably the sweet spot.

## Attitude check

And keep in mind that consistency is key: in unpublished work, Ahuja's team gave adults a regular exercise regime for 24 weeks and showed that everyone's immune grade had improved by the end. But after just two weeks of no exercise, their grades slid back to baseline. “We sit on our asses and it's not good,” says Ahuja.

Ahuja reminds me that, alongside diet and exercise, there is a third pillar of immune health that we often overlook: the brain.

“What do all these 100-plus-year-olds, sitting there smoking, drinking, have in common?” he asks. “They have a great attitude to life!” \*

He points to a study published in *Nature* in July that showed we can influence our immune system simply by the way we think. In the study, volunteers were exposed to virtual-reality avatars displaying clear signs of infection as they moved close to them.

Merely anticipating contact with infected avatars activated brain changes that altered immune cell activity in the participants' blood, in ways that mirrored what is seen when the body encounters a real infection.

It is a vivid demonstration of how powerfully the brain affects our immune health. And it isn't just the thought of being ill that can trigger the response: being on edge in general affects the state of our immune health. “The thing that has the most clearly proven impact on our immune health is long-term stress,” says Davis. One of the reasons we are so confident in stating this is because we have a molecular level understanding of what happens when we are stressed, he says.

When the body senses a threat, it releases hormones such as adrenaline and cortisol to initiate a fight-or-flight response. This response triggers signalling pathways aimed at promoting survival, temporarily increasing inflammation and certain immune cells in preparation for injury or infection. Meanwhile, it suppresses things like digestion – no need to digest your lunch when you are facing a tiger.

But when cortisol levels remain high due to chronic stress, these signalling pathways are impaired, weakening your immune system, making you more susceptible to infections and autoimmune diseases, and reducing your response to vaccines. When human immune cells are mixed with virus-infected cells, those that have cortisol added to the blend are weakest at responding, says Davis.

Of course, telling yourself to be less stressed to improve your immune health is easier said than done. At the very least, says Davis, knowing that negative cognitive states have real impacts on your immune system might motivate you to take steps to seek support and solutions that help you decompress.

If only there were a tablet that could do all of this for us, I thought. “That's what everyone wants,” says Ahuja, a magic pill that supercharges the immune system. He wonders whether in time, GLP-1 drugs like Wegovy or Mounjaro might prove to be something of a contender for this role, given their effects on metabolism and mood. But that is still speculation.

For now, as I burrow deeper under the covers, I am glad I have discovered that zinc, rather than oranges, might help me recover a little quicker. But it is the slow fixes that will make a difference over the long term: nourishing my microbes with fermented foods, challenging myself to daily workouts and finding ways to keep long-term stress in check. It isn't a magic pill, but if it nudges my immune grade towards a 1, perhaps I will be less of a target for whatever challenges next year brings. ■



Helen Thomson is a science journalist specialising in life sciences, health and biotech

# THE PLANT PARADOX



THE HIDDEN DANGERS IN "HEALTHY"  
FOODS THAT CAUSE DISEASE  
AND WEIGHT GAIN

STEVEN R. GUNDRY, MD

# **The Plant Paradox** **The Hidden Dangers in "Healthy" Foods that Cause Disease and Weight Gain**

Steven Gundry, MD  
2017

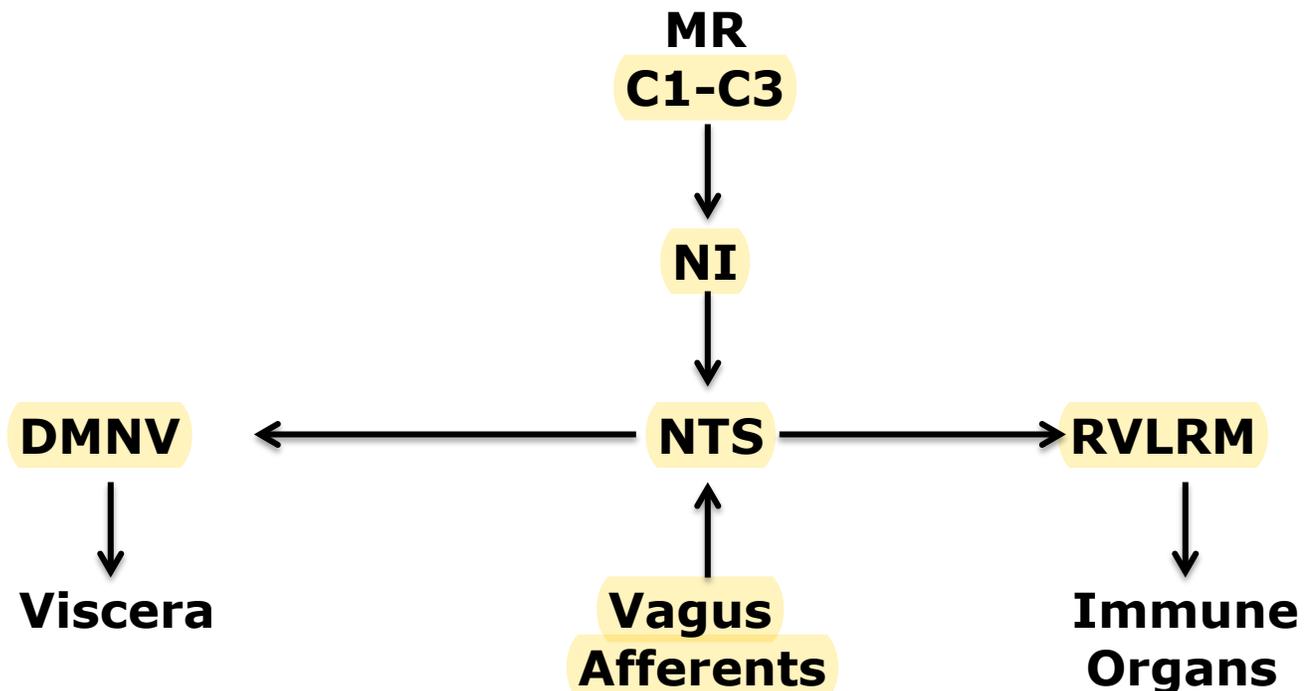
The vagus nerve, also called the parasympathetic nervous system, is the largest nerve coming from the brain to the gut.

It communicates orders to all the various organs in your body.

Exciting studies have shown that lectins reach the brain not only through the blood but, shockingly, also by climbing the vagus nerve from the gut into the brain.

It turns out that for every fiber leading from the brain to your heart, lungs, and your abdominal organs, there are nine times as many fibers leading up to the brain from the gut.

Unlike what I and most other doctors were taught in medical school, the vagus nerve exists to get information to the brain from the gut not the other way around.



“With a ‘wow’ on every page, *Gut Check* is an essential manual for what to eat and why to eat it. I learned so much from this book.”

—JAMES NESTOR, AUTHOR OF THE *NEW YORK TIMES* BESTSELLER *BREATH*

# GUT CHECK

UNLEASH THE POWER OF YOUR MICROBIOME  
TO REVERSE DISEASE AND TRANSFORM YOUR  
MENTAL, PHYSICAL, AND EMOTIONAL HEALTH

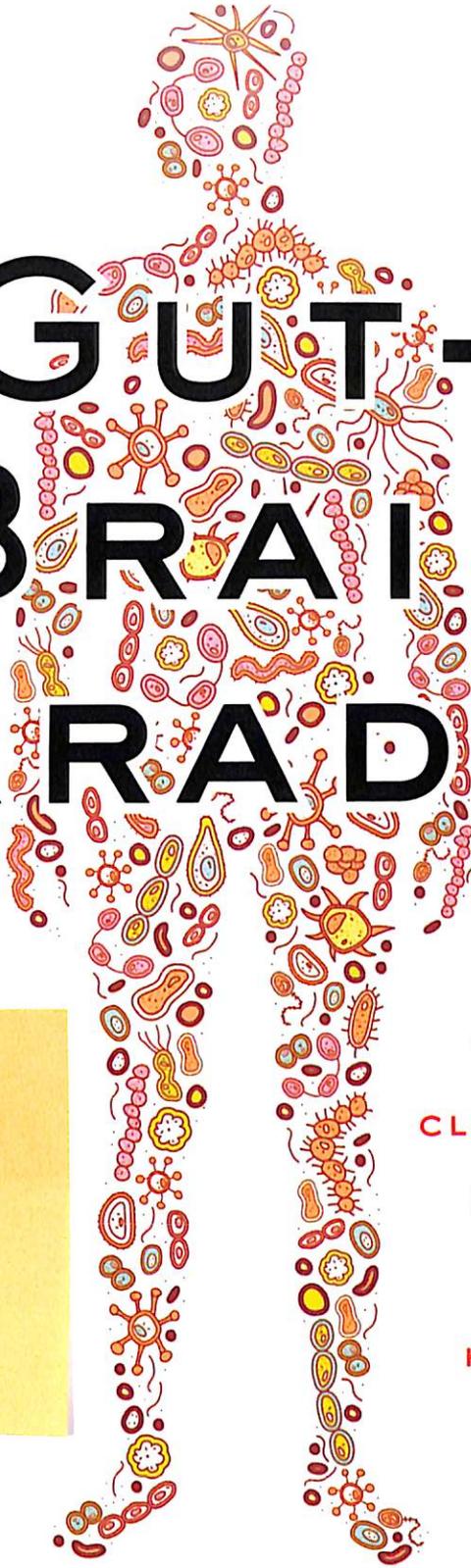


2024

STEVEN R. GUNDRY, MD

NEW YORK TIMES BESTSELLING AUTHOR OF  
*THE PLANT PARADOX*

# THE GUT- BRAIN PARADOX



IMPROVE  
YOUR MOOD,  
CLEAR BRAIN FOG,  
AND REVERSE  
DISEASE BY  
HEALING YOUR  
MICROBIOME

2025

STEVEN R. GUNDRY, MD

NEW YORK TIMES BESTSELLING AUTHOR  
OF THE PLANT PARADOX

# The Neurochemically Diverse Intermedius Nucleus of the Medulla as a Source of Excitatory and Inhibitory Synaptic Input to the Nucleus Tractus Solitarius

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Sensory afferent signals from neck muscles have been postulated to influence central cardiorespiratory control as components of postural reflexes, but neuronal pathways for this action have not been identified. The intermedius nucleus of the medulla (InM) is a target of neck muscle spindle afferents and is ideally located to influence such reflexes but is poorly investigated. To aid identification of the nucleus, we initially produced three-dimensional reconstructions of the InM in both mouse and rat. Neurochemical analysis including transgenic reporter mice expressing green fluorescent protein in GABA-synthesizing neurons, immunohistochemistry, and *in situ* hybridization revealed that the InM is neurochemically diverse, containing GABAergic and glutamatergic neurons with some degree of colocalization with parvalbumin, neuronal nitric oxide synthase, and calretinin. Projections from the InM to the nucleus tractus solitarius (NTS) were studied electrophysiologically in rat brainstem slices. Electrical stimulation of the NTS resulted in antidromically activated action potentials within InM neurons. In addition, electrical stimulation of the InM resulted in EPSPs that were mediated by excitatory amino acids and IPSPs mediated solely by GABA<sub>A</sub> receptors or by GABA<sub>A</sub> and glycine receptors. Chemical stimulation of the InM resulted in (1) a depolarization of NTS neurons that were blocked by NBQX (2,3-dioxo-6-nitro-1,2,3,4-tetrahydrobenzo[*f*]quinoxaline-7-sulfonamide) or kynurenic acid and (2) a hyperpolarization of NTS neurons that were blocked by bicuculline. Thus, the InM contains neurochemically diverse neurons and sends both excitatory and inhibitory projections to the NTS. These data provide a novel pathway that may underlie possible reflex changes in autonomic variables after neck muscle spindle afferent activation.

**Key words:** posture; neck; cardiovascular; respiration; medulla oblongata; autonomic

## Introduction

Reflex changes in cardiorespiratory variables during body movements rely on interactions between the somatic and autonomic nervous systems. A prime example of such interaction is the somatosympathetic reflex, in which stimulation of thinly myelinated group III (A $\delta$ ) and unmyelinated group IV (C-fiber) limb muscle afferent fibers can reflexly increase cardiorespiratory output (Potts et al., 2000, 2003; Wilson, 2000). These reflexes are mediated via sensory afferent input to the spinal cord, which is then relayed to the nucleus tractus solitarius (NTS), a brainstem

site for cardiorespiratory integration (Potts et al., 2003). Cardiorespiratory changes can also be evoked by stimulation of neck muscle afferents (Bolton et al., 1998; Bolton and Ray, 2000), proposed to contribute to alterations in cardiorespiratory outflow in preparation for a change in posture (Bolton and Ray, 2000). In contrast to limb afferents, the sensory signals from these muscles appear to be mediated by group IA muscle spindle afferents (Bolton et al., 1998). However, the neural pathways that link these afferent signals to cardiorespiratory control are completely unknown.

One target for sensory information from neck muscles is the cervical spinal cord where terminations can be found in the dorsal horn (although sparse) and the central cervical nucleus (CCN) (Bakker et al., 1984; Pfaller and Arvidsson, 1988; Prihoda et al., 1991). The CCN projection is generally considered to underlie spinal somatic reflex circuits, such as those for the tonic neck reflex involved in postural control (Wilson et al., 1984; Brink et al., 1985; Hongo et al., 1988; Popova et al., 1995). There is also a strong direct neck muscle afferent projection to the medulla oblongata where fibers terminate in the external cuneate nucleus and a nucleus located at the lateral edges of the dorsal aspect of the hypoglossal motor nucleus (XII), referred to either as the

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\*I.J.E. and M.L.D. contributed equally and significantly to this work.

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This study shows a separation of the afferent inputs to the INTERMEDIATE NUCLEUS of the MEDULLA from those to the CENTRAL CERVICAL NUCLEUS and vestibular nuclei, indicating that the INTERMEDIATE NUCLEUS of the MEDULLA participates in discrete circuits with a distinct functional role.

“Activation of neck muscle spindle afferents via neck flexion can initiate an increase in heart rate, muscle sympathetic nerve activity, and arterial blood pressure.”

“This cervico-sympathetic reflex appears to originate from muscle spindles in the dorsal neck musculature, it is very likely that the suboccipital muscle group is involved in the reflex because these muscles have an extremely high muscle spindle content.” **[Very Important]**

“Additional evidence for the involvement of the suboccipital muscle group in the cervico-sympathetic reflex comes from changes in blood pressure associated with chiropractic manipulations of the C1 vertebrae, which would result in altering the length of fibers in the suboccipital muscle group.”

“The projection from the INTERMEDIATE NUCLEUS of the MEDULLA to the NUCLEUS TRACTUS SOLITARIUS identified in this study therefore places it in an ideal position to mediate cardiorespiratory changes to neck muscle afferent stimulation, because the NUCLEUS TRACTUS SOLITARIUS is a major integratory area for autonomic control circuits.”

“The results from this study and others reveal that the INTERMEDIATE NUCLEUS of the MEDULLA is neurochemically rich.”

This study is the first to investigate the neurochemistry of the INTERMEDIATE NUCLEUS of the MEDULLA, and show that the INTERMEDIATE NUCLEUS of the MEDULLA sends both excitatory and inhibitory projections to the NUCLEUS TRACTUS SOLITARIUS.

#### KEY POINTS FROM DAN MURPHY

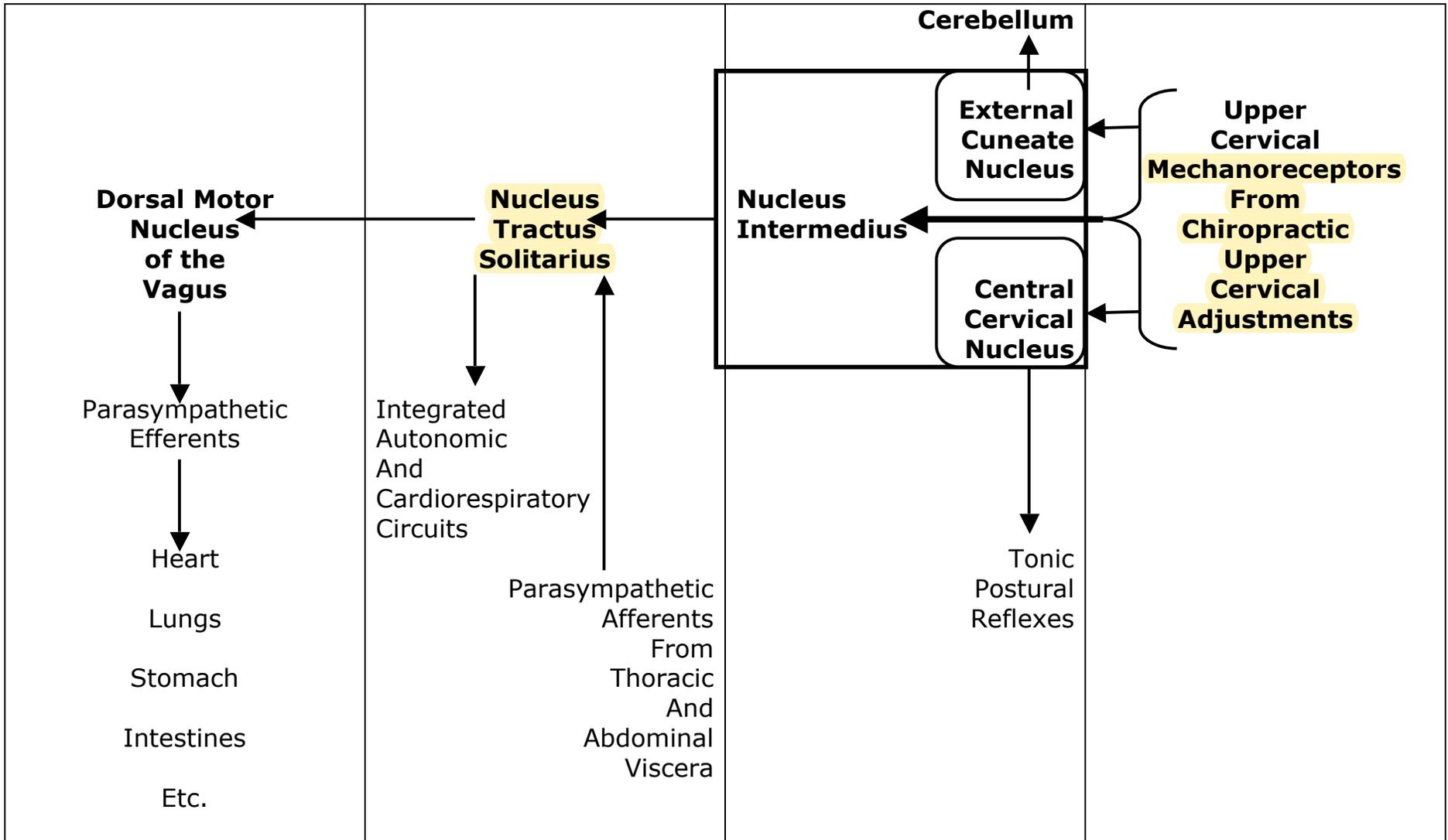
- 1) Sensory afferent signals from neck muscles are components of postural reflexes.
- 2) Sensory afferent signals from neck muscles influence central cardiorespiratory control.

**[This would suggest that if one could affect the sensory afferent from the neck muscles one could influence postural reflexes and cardiorespiratory control.]**

- 3) The INTERMEDIATE NUCLEUS of the MEDULLA is a target of neck muscle spindle afferents and is ideally located to influence both postural reflexes and cardiorespiratory control.
- 4) The INTERMEDIATE NUCLEUS of the MEDULLA sends both excitatory and inhibitory projections to the NUCLEUS TRACTUS SOLITARIUS.
- 5) In the "somatosympathetic reflex," muscle afferent fibers reflexly alter cardiorespiratory output. "These reflexes are mediated via sensory afferent input to the spinal cord, which is then relayed to the nucleus tractus solitarius (NTS), a brainstem site for cardiorespiratory integration."
- 6) "Cardiorespiratory changes can also be evoked by stimulation of neck muscle afferents."
- 7) Neck muscle afferents enter the CENTRAL CERVICAL NUCLEUS and its rostral continuation, the INTERMEDIATE NUCLEUS of the MEDULLA. "There is a strong direct neck muscle afferent projection to the medulla oblongata where fibers terminate in the external cuneate nucleus [accessory cuneate nucleus] and the INTERMEDIATE NUCLEUS of the MEDULLA."
- 8) There are monosynaptic excitatory and inhibitory projections from the INTERMEDIATE NUCLEUS to the NUCLEUS TRACTUS SOLITARIUS.
- 9) The INTERMEDIATE NUCLEUS of the MEDULLA receives afferent inputs from neck muscles.
- 10) "Neck muscle afferent stimulation is involved in postural reflexes such as the cervicocollic reflex and interacts with information from the vestibular system to maintain posture."
- 11) "This cervico-sympathetic reflex [that can alter heart rate and blood pressure] appears to originate from muscle spindles in the dorsal neck musculature, it is very likely that the suboccipital muscle group is involved in the reflex because these muscles have an extremely high muscle spindle content." **[Very Important]**
- 12) "Additional evidence for the involvement of the suboccipital muscle group in the cervico-sympathetic reflex comes from changes in blood pressure associated with chiropractic manipulations of the C1 vertebrae, which would result in altering the length of fibers in the suboccipital muscle group." **[Very Important]**
- 13) "The projection from the INTERMEDIATE NUCLEUS to the NUCLEUS TRACTUS SOLITARIUS identified in this study therefore places it in an ideal position to mediate cardiorespiratory changes to neck muscle afferent stimulation, because the NUCLEUS TRACTUS SOLITARIUS is a major integratory area for autonomic control circuits." **[Very Important]**

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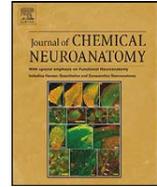
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## Review

# The intermedius nucleus of the medulla: A potential site for the integration of cervical information and the generation of autonomic responses

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### ABSTRACT

The **intermedius nucleus of the medulla** (InM) is a small perihypoglossal brainstem nucleus, which **receives afferent information from the neck musculature** and also descending inputs from the vestibular nuclei, the gustatory portion of the nucleus of the solitary tract (NTS) and cortical areas involved in movements of the tongue. **The InM sends monosynaptic projections to both the NTS** and the hypoglossal nucleus. It is likely that the InM acts to integrate information from the head and neck and relays this information on to **the NTS where suitable autonomic responses can be generated**, and also to the hypoglossal nucleus to influence movements of the tongue and upper airways.

Central to the integratory role of the InM is its neurochemical diversity. Neurones within the InM utilise the amino acid transmitters glutamate, GABA and glycine. A proportion of these excitatory and inhibitory neurones also use nitric oxide as a neurotransmitter. Peptidergic transmitters have also been found within InM neurones, although as yet the extent of the pattern of co-localisation between peptidergic and amino acid transmitters in neurones has not been established.

The calcium binding proteins calretinin and parvalbumin are found within the InM in partially overlapping populations. Parvalbumin and calretinin appear to have complementary distributions within the InM, with parvalbumin being predominantly found within GABAergic neurones and calretinin being predominantly found within glutamatergic neurones.

Neurones in the InM receive inputs from glutamatergic sensory afferents. This glutamatergic transmission is conducted through both NMDA and AMPA ionotropic glutamate receptors.

In summary the InM contains a mixed pool of neurones including glutamatergic and GABAergic in addition to peptidergic neurones. **Neurones within the InM receive inputs from the upper cervical region, descending inputs from brain regions involved in tongue movements and those involved in the co-ordination of the autonomic nervous system. Outputs from the InM to the NTS and hypoglossal nucleus suggest a possible role in the co-ordination of tongue movements and autonomic responses to changes in posture.**

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### Contents

1. Introduction .....	167
1.1. Nomenclature .....	167
1.2. Insights into function .....	167
2. Neurotransmitters .....	168
2.1. Amino acids .....	168
2.2. NOS .....	170
2.3. Peptide transmitters .....	170
3. Calcium binding proteins .....	171
3.1. Parvalbumin is predominantly found in inhibitory neurones .....	171
3.2. Calretinin is found within inhibitory and excitatory neurones in the InM .....	171
4. Receptors .....	171
4.1. Glutamate receptors .....	171

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“Changes in the positioning of the head relative to the trunk, or sensory information arising from the neck musculature, have been clinically implicated in the control of heart rate and blood pressure.”

When the sternocleidomastoid muscle loses (denervation) its normal proprioceptive input into the vestibular nucleus and/or NTS, there is an exaggerated vagal response subsequent to stimulation of the carotid sinus.

“The InM acts to integrate information from both the neck musculature and the vestibular system before relaying this information on to the NTS.”

This pathway from the neck musculature to the NTS might be behind the “changes in heart rate and blood pressure observed following upper cervical chiropractic manipulations and autonomic disturbances observed in whiplash patients.”

“Both excitatory and inhibitory neurones from the InM project to the NTS providing scope for the InM to evoke differential responses within NTS neurones according to the sensory information that it receives, rather than simply acting as a relay.”

“InM neurones are strongly targeted by afferent fibres projecting via the upper cervical DRG,” and this “information can manifest as changes in autonomic variables.”

“The InM is a little investigated nucleus in the brainstem which has surprisingly diverse neurochemistry. It is possible that this complex nucleus plays a role in the generation of autonomic responses to movements of the head, especially as it is monosynaptically connected with both the NTS and hypoglossal nuclei.”

#### KEY POINTS FROM DAN MURPHY

- 1) The intermedius nucleus of the medulla (InM) [nucleus intermedius] is in the medulla. It receives afferent information from:
  - A)) The neck musculature
  - B)) The vestibular nuclei
  - C)) The gustatory portion of the nucleus of the solitary tract (NTS)
  - D)) Cortical areas involved in movements of the tongue
  
- 2) The nucleus intermedius sends monosynaptic projections to:
  - A)) The nucleus of the solitary tract (NTS)
  - B)) The hypoglossal nucleus
  
- 3) The nucleus intermedius integrates information from the head and neck and relays this information on to the nucleus of the solitary tract where suitable autonomic responses are generated.

- 4) The nucleus intermedius also communicates with the hypoglossal nucleus to influence movements of the tongue and upper airways.
- 5) Nucleus intermedius neurones receive inputs from sensory afferents that use glutamate as a neurotransmitter. **[Some excitotoxin experts insist that dietary glutamate {MSG, hydrolyzed protein, etc.} will adversely influence the function of glutamatergic neurons]**
- 6) Outputs from the nucleus intermedius to the nucleus tractus solitarius and hypoglossal nucleus suggest a role in the co-ordination of tongue movements and autonomic responses to changes in posture. **[Very Important: the nucleus intermedius co-ordinates autonomic responses to postural changes]**
- 7) The nucleus intermedius has a spinal cord component called the "central cervical nucleus" or the "medullary portion of the central cervical nucleus" or the "intercalated nucleus" or the "nucleus intercalatus of Staderini."
- 8) The spinal cord component of the nucleus intermedius (central cervical nucleus) is "located lateral to the central canal at the border of the dorsal and ventral horns."
- 9) Sensory fibers from the upper cervical dorsal root ganglion (DRG) directly enter the nucleus intermedius. **[Very Important]**
- 10) Sensory nerves from the suboccipital muscles, the sternocleidomastoid muscle and the longus capitis muscle project to the nucleus intermedius via the upper cervical spine dorsal root ganglion. **[Very Important: the sensory projections from these muscles are mechanoreceptors and proprioceptors; alterations of mechanical afferent input from these muscles alters the input to the nucleus intermedius, then to the nucleus tractus solitarius and to subsequent autonomic responses]**
- 11) "These projections from the cervical DRG to the nucleus intermedius have been proposed to be proprioceptive, which suggests that activity within the nucleus intermedius is heavily influenced by the position of the head relative to the trunk." **[Very Important]**
- 12) "Chemical or electrical stimulation of the nucleus intermedius causes monosynaptic excitatory and inhibitory postsynaptic potentials in the nucleus of the solitary tract (NTS)."
- 13) The authors suggest that the greatest influence of the nucleus intermedius is to the "autonomic circuits relating to the cardiovascular system."
- 14) Nucleus intermedius neurones are "under the influence of information arising from the neck region, in particular the dorsal neck muscles."

15) One of the functions of the nucleus intermedius is to elicit autonomic responses to movements of the head to complement those triggered by the vestibular system.

16) The vestibular system regulates cardiovascular autonomic (sympathetic) responses to head movements.

17) Innocuous mechanical stimulation of the neck of humans that does not activate the vestibular system evokes changes in heart rate and blood pressure, perhaps through the nucleus intermedius.

**[This is like saying that altered mechanical afferent input from the neck {innocuous mechanical stimulation} subsequent to the chiropractic subluxation alters the neurological influence to the nucleus intermedius, in turn influencing the autonomic control of heart rate and blood pressure. Recall that the study in the *Journal of Human Hypertension*, March 2007, showed that specific upper cervical chiropractic adjustments (NUCCA) significantly reduced blood pressure, and the outcomes remained stable during an 8 week follow-up period]**

18) Low threshold stimulation of the nerves entering the C1 and C2 DRG can elicits changes in the activity of both sympathetic and respiratory nerves.

**[Very Important: supports chiropractic adjustments influencing sympathetic neurology]**

19) Proprioceptive information can play a role in modulating the autonomic nervous system. **[Very Important: this is a central theme to chiropractic clinical approaches to many non-musculoskeletal syndromes]**

20) "Neurons in the nucleus intermedius are under the influence of sensory afferent information arising from the neck region." **[Very Important]**

21) The nucleus intermedius receives afferent input from the vestibular nuclei. **[Important because the vestibular nucleus also receives monosynaptic inputs from upper cervical spine afferents]**

22) The nucleus intermedius also receives descending inputs from the prefrontal cortex and the amygdala. **[This explains some of the emotional influences on the autonomic neurological activity]**

23) Upper cervical DRG afferent fibers project to the nucleus intermedius, and these fibers are "proprio- and mechano-ceptive afferents" and not nociceptors. **[This is very important because it implies that non-painful aberrant mechanical afferent input from the upper cervical spine can alter autonomic function. In the study from the *Journal of Human Hypertension*, March 2007, which showed a significant reduction of blood pressure with specific upper cervical chiropractic adjustments, the authors noted that none of the patients were suffering from neck or back pain]**

24) The authors suggest the primary afferents influencing the nucleus intermedius are from the upper cervical muscles “adding weight to the theory that the nucleus intermedius is under the influence of cervical muscles.”

25) “The InM is a surprisingly complex nucleus which receives sensory inputs from the neck region via the upper cervical DRG.”

26) “Changes in the positioning of the head relative to the trunk, or sensory information arising from the neck musculature, have been clinically implicated in the control of heart rate and blood pressure.”

**[Very Important: the upper cervical chiropractic subluxation is a change in the “positioning of the head relative to the trunk, or sensory information arising from the neck musculature”]**

27) “The nucleus intermedius acts to integrate information from both the neck musculature and the vestibular system before relaying this information on to the nucleus tractus solitarius.”

28) This pathway from the neck musculature to the nucleus tractus solitarius might be behind the “changes in heart rate and blood pressure observed following upper cervical chiropractic manipulations and autonomic disturbances observed in whiplash patients.” **[Very Important: these authors acknowledge the ability of upper cervical chiropractic adjustments to influence heart rate and blood pressure, both autonomic functions]**

29) “The nucleus intermedius neurones are strongly targeted by afferent fibres projecting via the upper cervical DRG,” and this “information can manifest as changes in autonomic variables.”

30) The nucleus intermedius “plays a role in the generation of autonomic responses to movements of the head,” especially as it is monosynaptically connected with the nucleus tractus solitarius.

#### COMMENTS FROM DAN MURPHY

This is a very important article for chiropractors. It explains the neuroanatomical relationship between upper cervical spine subluxation (a mechanical problem) and visceral autonomic neurology. The authors use chiropractic adjustments of the upper cervical spine influencing cardiac function as support for their neuroanatomical findings. This study supports the 115 years of clinical observations of chiropractors. It shows the “biological plausibility” of the influence of chiropractic adjustments on non-musculoskeletal syndromes.

I would be unable to share this information with so many were it not for the efforts of ICA Board Member Dr. George Curry, an excellent chiropractor and scholar.

**The intermedius nucleus of the medulla:  
A potential site for the integration of cervical information and the  
generation of autonomic responses**

**Journal of Chemical Neuroanatomy  
November 2009**



**Proprioceptors / Mechanoreceptors  
from**

**Sternocleidomastoid  
Muscle**

**Suboccipital  
Muscle**

**Longus Capitus  
Muscle**

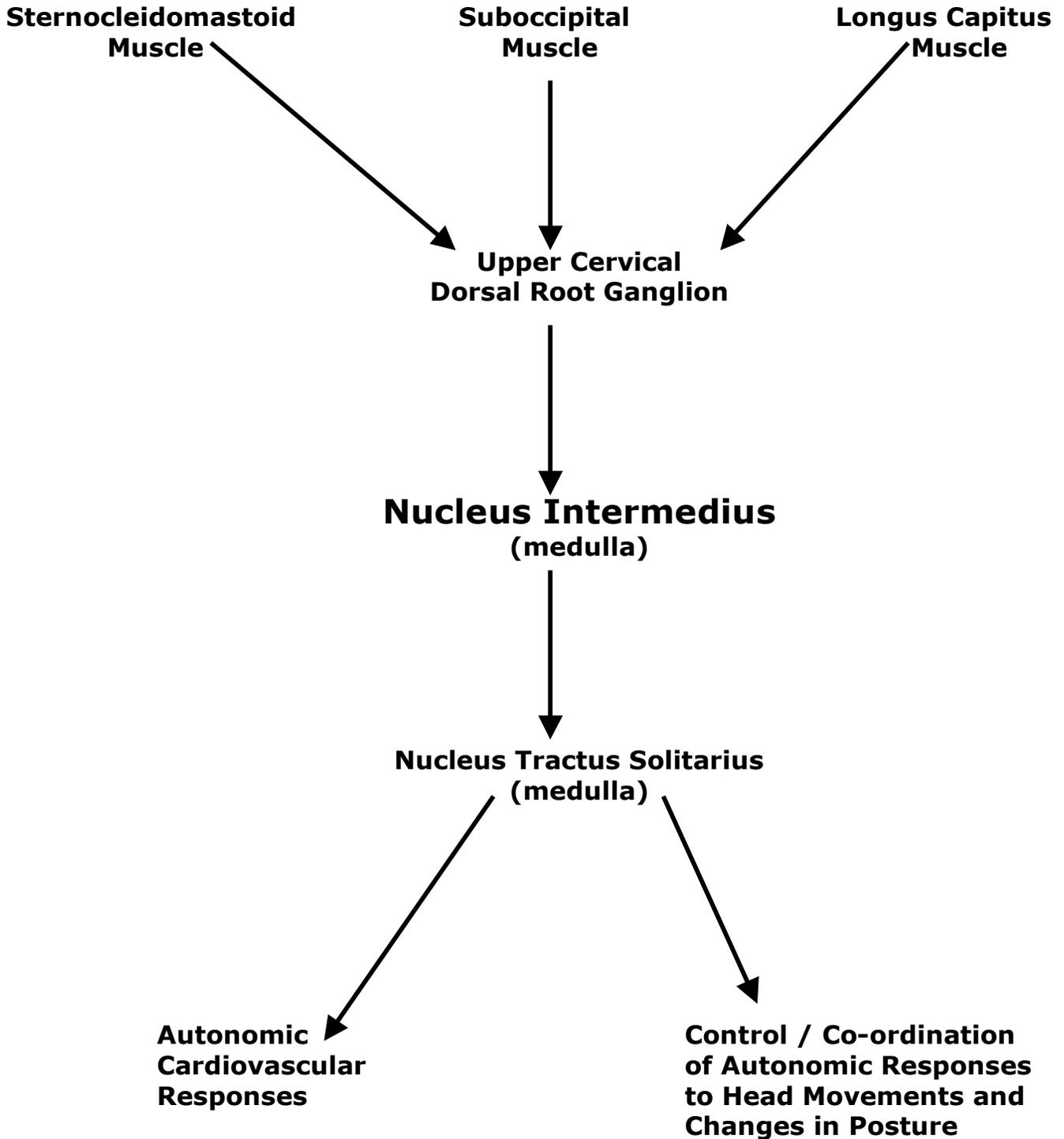
**Upper Cervical  
Dorsal Root Ganglion**

**Nucleus Intermedius  
(medulla)**

**Nucleus Tractus Solitarius  
(medulla)**

**Autonomic  
Cardiovascular  
Responses**

**Control / Co-ordination  
of Autonomic Responses  
to Head Movements and  
Changes in Posture**



## Neck muscle afferents influence oromotor and cardiorespiratory brainstem neural circuits

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**Abstract** Sensory information arising from the upper neck is important in the reflex control of posture and eye position. It has also been linked to the autonomic control of the cardiovascular and respiratory systems. Whiplash associated disorders (WAD) and cervical dystonia, which involve disturbance to the neck region, can often present with abnormalities to the oromotor, respiratory and cardiovascular systems. We investigated the potential neural pathways underlying such symptoms. Simulating neck afferent activity by electrical stimulation of the second cervical nerve in a working heart brainstem preparation (WHBP) altered the pattern of central respiratory drive and increased perfusion pressure. Tracing central targets of these sensory afferents revealed projections to the intermedius nucleus of the medulla (InM). These anterogradely

labelled afferents co-localised with parvalbumin and vesicular glutamate transporter 1 indicating that they are proprioceptive. Anterograde tracing from the InM identified projections to brain regions involved in respiratory, cardiovascular, postural and oro-facial behaviours—the neighbouring hypoglossal nucleus, facial and motor trigeminal nuclei, parabrachial nuclei, rostral and caudal ventrolateral medulla and nucleus ambiguus. In brain slices, electrical stimulation of afferent fibre tracts lateral to the cuneate nucleus monosynaptically excited InM neurones. Direct stimulation of the InM in the WHBP mimicked the response of second cervical nerve stimulation. These results provide evidence of pathways linking upper cervical sensory afferents with CNS areas involved in autonomic and oromotor control, via the InM. Disruption of these neuronal pathways could, therefore, explain the dysphagic and cardiorespiratory abnormalities which may accompany cervical dystonia and WAD.

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**Keywords** Proprioception · Autonomic ·  
Immunohistochemistry · Electrophysiology

### Introduction

The intermedius nucleus of the medulla (InM) is a neurochemically diverse perihypoglossal nucleus (Edwards et al. 2007, 2009) with no known function. Furthermore, very little is known regarding the anatomical connectivity of the nucleus. We have previously identified a monosynaptic projection from the InM into the neighbouring nucleus of the solitary tract (NTS) using electrophysiology (Edwards et al. 2007), indicating a possible role in autonomic and/or respiratory control. Direct primary afferent input to the InM arises from upper cervical levels in a number of

- 7) "These results provide evidence of pathways linking upper cervical sensory afferents with CNS areas involved in autonomic and oromotor control, via the InM." **[Key Point]**
- 8) "Disruption of these neuronal pathways could, therefore, explain the dysphagic and cardiorespiratory abnormalities which may accompany cervical dystonia and whiplash associated disorders."
- 9) There exists a monosynaptic projection from the InM into the nucleus of the solitary tract (NTS), "indicating a possible role in autonomic and/or respiratory control."
- 10) There is direct primary afferent input to the InM from upper cervical levels.
- 11) "Studies are suggestive of a possible role for the InM in mediating autonomic/respiratory responses to sensory afferent signals arising from the upper neck."
- 12) "Physiological studies are consistent with the notion that cervical sensory afferents influence autonomic function." **[Key Point]**
- 13) In animal studies, low threshold electrical stimulation of the C2 or C3 nerve evokes activity in the hypoglossal nerve, abdominal nerves, and the splanchnic sympathetic nerves. **[Important]**
- 14) Experimental stimulation of proprioceptive afferents causes sympathetic cardiovascular and respiratory responses. **[Key Point]**
- 15) These findings reveal cardiorespiratory responses to neck muscle afferent stimulation.
- 16) The primary investigations in this study involved rats, antibody phenotype tracings, immunohistochemistry staining, confocal microscopic assessment, electron microscopy, nerve stimulation, and much more. The exact protocols are extremely sophisticated and complex.
- 17) The experiments showed:
- Cardiovascular and respiratory responses to C2 nerve stimulation.
  - "C2 muscle afferents terminate within the intermedius nucleus of the medulla (InM)."
  - There is also a direct pathway from the cuneate nucleus to the InM.
  - "Neurons in the InM send efferent projections to known CNS areas associated with cardiovascular and oromotor functions."

- The “efferent projections from the InM were bilateral with an ipsilateral predominance.”
- The InM neurons fired to (and significantly bilaterally):
  - Cranial Nerve XII
  - Cranial Nerve VII
  - the ventrolateral medulla, coursing through the intermediate reticular formation with terminals observed within the nucleus ambiguus
  - the nucleus tractus solitarius (NTS)
  - the caudal portion of the spinal vestibular nucleus
  - they showed medullary catecholamine immunoreactivity
  - the ventral horn motoneurons in the cervical spinal cord at levels C4–6, predominantly around the phrenic motoneurons
  - the pontine parabrachial nucleus
  - medullary sympathetic relays
  - “Efferent projections from the InM were observed within cardiovascular, respiratory and oromotor regions of the brainstem.”

18) “This study shows that stimulation of neck muscle afferents can influence behaviour of the cardiovascular and respiratory systems. This is due to unique neuronal pathways which exhibit specialized functions, the first stage of this signaling arising from neck muscles.”

19) “Neurophysiological and neuroanatomical experiments indicate that the [upper cervical] sensory input exerts its influence via the InM, which appears to act as an integratory center.”

20) “Neck muscle afferent input to the intermedius nucleus of the medulla (InM).”

21) “Neuroanatomical studies looking at the central targets of cervical sensory afferents have revealed a direct sensory projection to the InM from upper cervical but not lower cervical levels.”

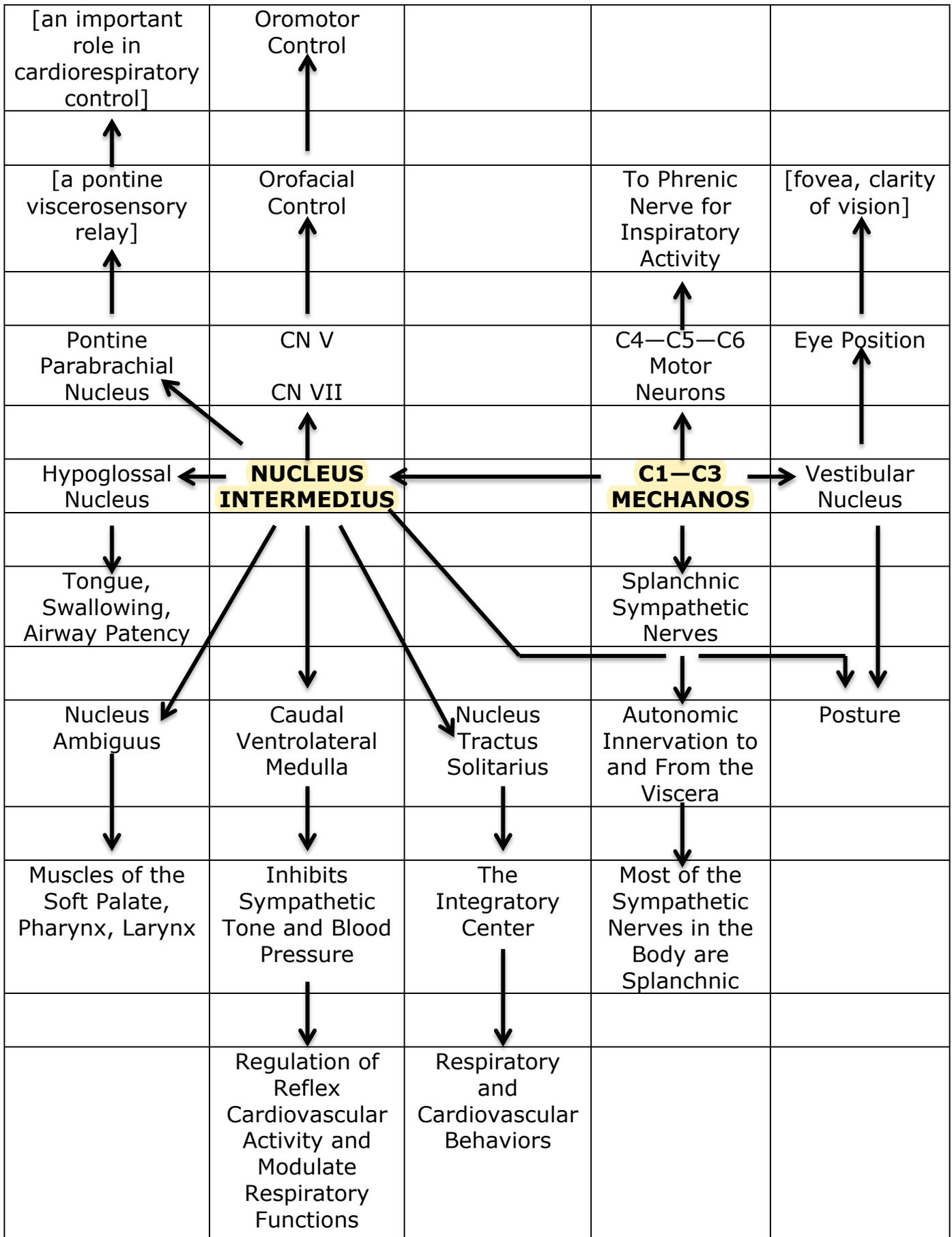
- 22) "The input to the InM is thought to be of a muscle origin [muscle proprioceptors/spindles] as when tracers are applied to the lesser occipital nerve, a pure skin nerve branch of C2, no terminal labeling is observed within the InM."
- 23) "The majority of the traffic to the InM through the C2 nerve is likely to be of a muscle origin." "Many of the primary afferent inputs to the InM arise from the musculature of the neck."
- 24) "The muscles supplying the upper cervical segments are particularly rich in muscle spindles."
- 25) Only afferents arising from C1–4 have been demonstrated to project to the InM. "The InM does not receive inputs from primary afferents caudal to C4."
- 26) There is a strong "role of InM in mediating specific actions of neck muscle afferents on oromotor, respiratory and sympathetic systems."
- 27) The InM may be acting as an upper cervical muscle sensory relay station.
- 28) The InM is a major source of input to the hypoglossal nucleus. "The InM appears to be in a prime position to integrate information from both the periphery and the CNS before influencing airway patency and tongue movements through the hypoglossal nucleus."
- 29) A main unique target of the "upper cervical sensory afferents is the InM."
- 30) The InM plays an integral part to upper cervical peripheral nerve stimulation.

#### COMMENTS FROM DAN MURPHY

I significantly simplified this article. The authors presented detailed, complex, sophisticated primary research showing the biological plausibility of how the proprioceptors of the upper cervical spine influence a wide variety of visceral responses. This supports more than a century of chiropractic anecdotal and clinical observations.

The basic premise is that upper cervical alignment influences the length and therefore the tone of the suboccipital muscles, thereby influencing the proprioceptive firing through the upper cervical spine nerve roots to the nucleus intermedius (InM).

The nucleus intermedius (InM) in turn influences the function of the lower 7 cranial nerves, including their parasympathetic functions, as well as medullary sympathetic relays. The biological plausibility is that the upper cervical spine mechanosensitive afferents have a major influence in the balance between the parasympathetic and sympathetic nervous systems, influencing whole body homeostasis and health. Please note the following schematic:





Concept Paper

# The Vagus Nerve Can Predict and Possibly Modulate Non-Communicable Chronic Diseases: Introducing a Neuroimmunological Paradigm to Public Health

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**Abstract:** Global burden of diseases (GBD) includes non-communicable conditions such as cardiovascular diseases, cancer and chronic obstructive pulmonary disease. These share important behavioral risk factors (e.g., smoking, diet) and pathophysiological contributing factors (oxidative stress, inflammation and excessive sympathetic activity). This article wishes to introduce to medicine and public health a new paradigm to predict, understand, prevent and possibly treat such diseases based on the science of neuro-immunology and specifically by focusing on vagal neuro-modulation. Vagal nerve activity is related to frontal brain activity which regulates unhealthy lifestyle behaviors. Epidemiologically, high vagal activity, indexed by greater heart rate variability (HRV), independently predicts reduced risk of GBD and better prognosis in GBD. Biologically, the vagus nerve inhibits oxidative stress, inflammation and sympathetic activity (and associated hypoxia). Finally, current non-invasive methods exist to activate this nerve for neuro-modulation, and have promising clinical effects. Indeed, preliminary evidence exists for the beneficial effects of vagal nerve activation in diabetes, stroke, myocardial infarction and possibly cancer. Thus, we propose to routinely implement measurement of HRV to predict such GBD in populations, and to test in randomized controlled trials effects of non-invasive vagal nerve activation on prevention and treatment of GBD, reflecting possible neuro-modulation of health.

**Keywords:** global burden of diseases; neuroimmunology; neuromodulation; vagal nerve; prediction; prevention

## 1. The Problem

Major non-communicable causes of death and of years of life lost today include coronary heart disease (CHD), stroke, cancer and pulmonary diseases [1]. Many risk factors (pollution, smoking, diet-driven cholesterol, insufficient exercise, etc.) explain a large proportion of major global burden of diseases—GBD (e.g., [2]). Furthermore, many of these diseases have common underlying biological causes, as we shall see below.

While modernization has brought many positive developments (e.g., transportation, huge improvements in disease detection and treatment, immense improvements in access to information via

# The Vagus Nerve Can Predict and Possibly Modulate Non-Communicable Chronic Diseases:

## Introducing a Neuroimmunological Paradigm to Public Health

Journal of Clinical Medicine

October 19, 2018; Vol. 7; No. 10; pii: E371

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BACKGROUND FROM DAN MURPHY:

Heart Rate Variability (HRV) is a measurement of the time intervals between adjacent heartbeats. It may be used to evaluate the balance between the sympathetic and parasympathetic divisions of the autonomic nervous system. "It is crucial to measure HRV for at least 5 min, to obtain both time and frequency domain HRV parameters in a reliable manner."

Analysis of beat-to-beat variability is a simple, non-invasive technique to evaluate autonomic neurological dysfunction. Heart rate variability data may be collected using:

- Electrocardiogram
- Plethysmograph

Spinal manipulation may alter heart rate variability.

The sympathetic nervous system uses the neurotransmitter *norepinephrine*.

- Norepinephrine is a *catecholamine*.

The vagus nerve is a parasympathetic nerve that uses the neurotransmitter *acetylcholine*. It descends from the brain stem and innervates most visceral organs. "The vagus nerve is a major branch of the parasympathetic nervous system."

●●●●●●●●

Global burden of diseases (GBD) includes non-communicable conditions such as cardiovascular diseases, cancer, and chronic obstructive pulmonary disease.

Cardiovascular diseases, cancer, and chronic obstructive pulmonary disease share 2 important behavioral risk factors:

- Smoking
- Diet

Cardiovascular diseases, cancer, and chronic obstructive pulmonary disease share 3 important pathophysiological contributing factors:

- Oxidative stress
- Inflammation
- Excessive sympathetic nerve activity **[Important Point]**

This article introduces a new paradigm to predict, understand, prevent, and possibly treat such diseases based on the science of neuro-immunology and specifically by focusing on *vagal* (parasympathetic/acetylcholine) neuro-modulation.

This study cites 80 references.

#### KEY POINTS FROM THIS ARTICLE:

- 1) Neuro-immunology is the science that investigates the interplay between the nervous and immune systems.
- 2) High vagal nerve activity alters homeostasis. It is key for neuro-modulation.
  - "HRV, the vagal nerve index, could be used to predict onset and prognosis of major global disease burdens."
  - "Vagal nerve activity predicts the risk of and prognosis in many major GBD."
  - High HRV predicts reduced risk of overall mortality.
  - "Higher HRV significantly predicts longer survival in cancer."
  - "HRV is inversely related to insulin resistance and to levels of HbA1C."
- 3) Vagal nerve activity (parasympathetic/acetylcholine) is related to frontal brain activity.
  - Frontal brain activity also "regulates unhealthy lifestyle behaviors."
- 4) High vagal activity predicts *reduced* risk of global burden of diseases (GBD) and better prognosis in global burden of diseases. **[Important Point]**
  - High vagal activity is measured by *greater heart rate variability (HRV)*. **[Important]**
- 5) "Biologically, the vagus nerve inhibits oxidative stress, inflammation and sympathetic activity (and associated hypoxia)." **[Key Point]**
- 6) Several non-pharmacological and non-invasive methods exist for activating the vagus nerve for neuro-modulation:

- “Evidence exists for the beneficial effects of vagal nerve activation in diabetes, stroke, myocardial infarction and possibly cancer.”
- “Physical activity increases HRV.”
- Transcutaneous vagus nerve stimulation devices have been developed.
- “Various forms of meditation and yoga also increase HRV.”

7) Modernization has brought heavy deleterious environmental, occupational, and lifestyle consequences, “with vast health implications.”

- Modernization leads to more air pollution, to a more sedentary lifestyle with reduced physical activity, and more job stress, “all having immense and adverse health consequences.”

8) With the escalation of the global burden of diseases, there is one factor that is epidemiologically related to major causes of death, which is related to behavioral risk factors contributing to these diseases, and which is related to their common underlying pathophysiological causes. It is the “vagus nerve hypothesis for global public health, reflecting a neuro-immunological paradigm.” **[Important]**

- These authors focus on three pathophysiological causes of many major health problems:
  - Oxidative stress
  - Inflammation
  - Excessive sympathetic activity **[The Key To Chiropractic]**

9) “Higher vagal activity predicts reduced risk of major chronic diseases.” **[Key Point]**

10) Oxidative Stress and Chronic Diseases:

- “Oxidative stress occurs when the body has more pro-oxidants than anti-oxidants.” This damages molecules such as DNA.
- Hypoxia can drive oxidative stress.
- “Pollution-induced oxidative stress is linked to cardiovascular diseases and cardiac death.” Air pollution is also a risk factor for dementia.
- “Pollution also causes inflammation to induce oxidative stress and subsequent DNA damage, obvious contributing factors in carcinogenesis.”
- Stress (psychological stress, job stress) is also associated with higher oxidative stress.

- Chronic stress is related to reduced telomere length, “which predicts diseases and earlier mortality.”

#### 11) Inflammation and Chronic Diseases:

- “Inflammation reflects recruitment of immune cells (mostly innate) due to various danger signals (e.g., injury, infection, cell damage).”
- “Inflammation contributes to all stages of carcinogenesis from escape from apoptosis and tumor onset, to angiogenesis and metastasis.”
- Inflammation contributes to multiple stages of atherogenesis, plaque rupture and thrombosis.
- “Inflammation is also a major contributing factor to insulin resistance, the main factor underlying diabetes.”
- Psychosocial stress is related to elevated pro-inflammatory cytokines and to reduced anti-inflammatory cytokines.
- “Inflammation, the over-reaction of the immune system to danger signals, underlies multiple non-communicable chronic diseases.”

#### 12) Excessive Sympathetic Nervous System Activity and Chronic Diseases:

- “Excessive sympathetic nervous system (SNS) activity is related to cardiovascular diseases by inducing greater oxygen demand from the heart and by inducing vasoconstriction, which can induce ischemia.” **[Key Point]**
- High SNS activity affects the direction to which cancer cells will metastasize.
- “Excessive sympathetic activity was found in diabetic patients to predict increased risk of cerebral and cardiovascular events.”
- “Job stress is associated with higher SNS activity.”
- Driving in peak traffic is associated with elevated *catecholamines* and sympathetic neuro-hormones.
  - Increasing wealth causes the constant global increase in traffic congestions and elevates *catecholamines* and sympathetic neuro-hormones.
- “The prevalence and possible impact of increased SNS activity on health are expected to rise in the future.” **[Critical Point]**

13) Physicians and health policy makers should use HRV “routinely for prediction and possible prevention of major diseases in the population.” **[Key Point]**

14) The Vagus Nerve Inhibits Oxidative Stress, Inflammation, and Sympathetic Activity:

- “Vagus nerve stimulation (VNS) reduces oxidative stress.”
- “The vagus plays a key neuro-immune mediator and modulator between peripheral immune signals and the brain.”
- The vagus inhibits inflammation through two mechanisms:
  - “Via activation of the hypothalamic pituitary adrenal axis which results in systemic cortisol secretion which reduces inflammation.”
  - Via the vagus to the spleen activates splenic T-cells (via adrenergic receptors), “resulting in the inhibition of synthesis of inflammatory cytokines.”

15) “Activity of the vagus nerve, being a major part of the parasympathetic nerve system, inhibits sympathetic activity.” **[Key Point]**

16) “An important parasympathetic role of the vagus is vasodilation.”

- “This anti-hypoxic role is crucial for reducing risk of CHD, stroke and even also cancer since many tumors flourish in hypoxic conditions and hypoxia is prognostic in cancer.”
- “There is evidence that hypoxia (related to excessive sympathetic vasoconstrictive activity), oxidative stress and inflammation are causally related in a vicious circle manner.” **[Key Point]**
- “The vagus nerve inhibits all three promoters of the major chronic diseases mentioned above.” **[Key Point]**

17) “Vagus nerve activity, indexed by HRV, is positively related to executive functioning.”

- Vagal nerve stimulation “increases executive control and emotional regulation, possibly relevant to ‘emotional eating’ and to greater frontal control of GBD behavioral risk factors in general.” **[Important]**
- “The vagus nerve reduces certain behavioral risk factors and inhibits three main pathophysiological factors which contribute to those diseases (oxidative stress, inflammation and excessive SNS activity).”

- “Higher HRV was associated with better self-control of craving for certain foods and with higher brain activity in the ventromedial prefrontal cortex, a region crucial in decision-making.”

18) “It is recommended to use HRV to estimate risk of major GBD.”

19) These authors “propose to routinely implement measurement of HRV to predict such GBD in populations, and to test in randomized controlled trials effects of non-invasive vagal nerve activation on prevention and treatment of GBD, reflecting possible neuro-modulation of health.”

#### COMMENTS FROM DAN MURPHY

These authors advocate the value of noninvasive methods to activate the vagus nerve. They appear unaware of the evidence that upper cervical chiropractic activates the vagus nerve through the nucleus intermedius:

Article Review 13-08:

**The Neurochemically Diverse Intermedius Nucleus of the Medulla as a Source of Excitatory and Inhibitory Synaptic Input to the Nucleus Tractus Solitarii**

Article Review 3-11:

**The Intermedius Nucleus of the Medulla: A potential Site for the Integration of Cervical Information and the Generation of Autonomic Responses**

Article Review 38-14:

**Neck Muscle Afferents Influence Oromotor and Cardiorespiratory Brainstem Neural Circuits**

Additional support include:

Article Review 48-13:

**Suboccipital Decompression Enhances Heart Rate Variability Indices of Cardiac Control in Healthy Subjects**

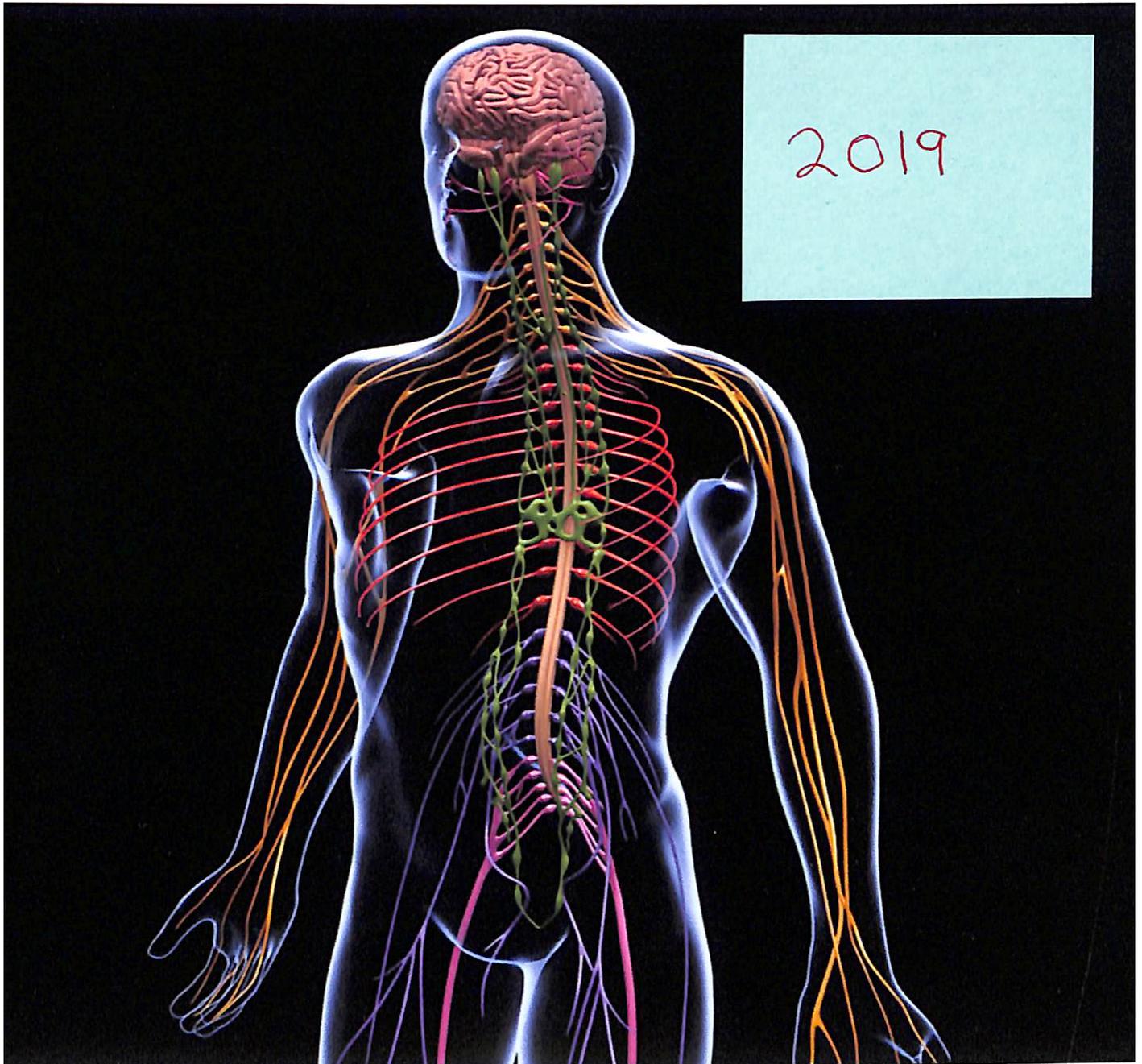
Most importantly, when these authors list several non-pharmacological methods for activating the vagus nerve, they do not list the review article on this topic by Chris Kent, DC, which was our Article Review 21-19:

**Heart Rate Variability to Assess the Changes in Autonomic Nervous System Function Associated With Vertebral Subluxation**

I will forward a copy of Dr. Kent’s review article to these authors.

COLD SPRING HARBOR PERSPECTIVES IN MEDICINE

# Bioelectronic Medicine



EDITED BY Valentin A. Pavlov  
Kevin J. Tracey

# Bioelectronic Medicine

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Every organ in the human body is innervated by the nervous system and communicates with the brain via electrical signals. Various devices can be used to modulate these electrical signals and elicit changes in organ function with the aim of treating injury or disease. This approach is the basis of the rapidly emerging field of bioelectronic medicine, which has the potential to diagnose and treat medical conditions more precisely and effectively than ever before.

# OPINION

THE WEEKEND INTERVIEW with Kevin Tracey | By Allysia Finley

## Electricity Is the New Medical Miracle

**K**elly Owens was a medical mystery, her teens and 20s blighted by a cascade of seemingly unrelated health problems that left her debilitated. For a decade and a half she was put on one medication after another—22 in all—to little effect. Then electricity saved her.

“I didn’t even remember how ‘healthy’ felt, since it had been 15 years,” Ms. Owens, 33, says. Now she and her husband are talking about having a child, something she had thought impossible. She credits Kevin Tracey, an innovative neurosurgeon she found through Facebook.

Ms. Owens was an athletic 13-year-old when she twisted her ankle tap-dancing. A few weeks later, her ankle was still swollen and she began experiencing severe nausea and diarrhea. A year or two later, her other ankle swelled up, though she’d never injured it. Then her knees grew inflamed.

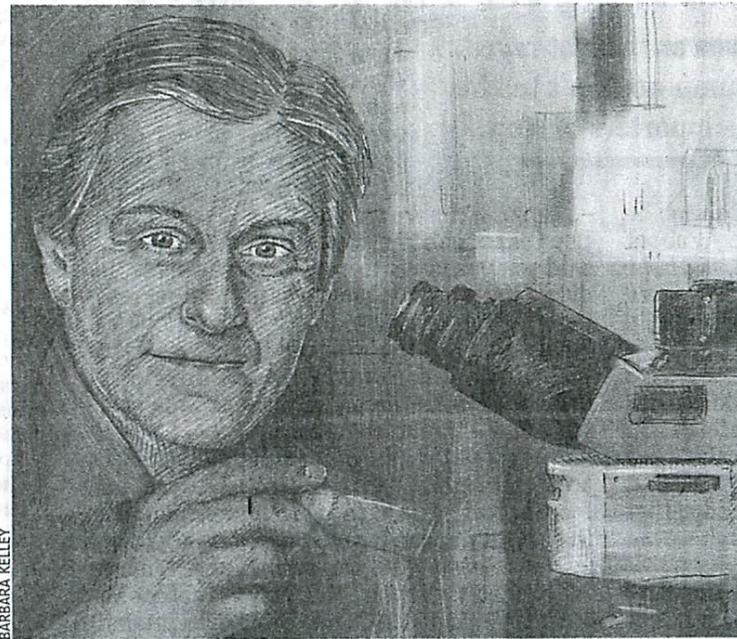
**Stimulating the vagus nerve can relieve arthritis, Crohn’s disease and other inflammatory conditions—perhaps someday even Alzheimer’s disease.**

family and friends, she and her husband moved to Amsterdam, one of the sites where the trial took place. The trial’s principal investigator was Geert D’Haens, a global expert in inflammatory bowel disease based at the Amsterdam University Medical Center.

SetPoint implanted a pace-maker-sized device in her chest cavity that sends stimulation to electrodes surgically placed on her vagus nerve. Her symptoms began to improve within weeks. Soon she was able not only to walk but to run. Two months after the device was implanted, doctors deemed her in clinical remission. Her ailments have remained at bay, and her doctors weaned her from steroids.

Scientists have long known that the vagus nerve carries signals between the brain and internal organs that regulate physiological processes such as digestion, breathing and heart rate. When you exercise, for instance, your heart speeds up. Then your brain sends a signal via the vagus nerve directing your heart to slow down so it doesn’t beat out of control.

Dr. Tracey’s breakthrough two decades ago was the discovery that the brain also controls the immune system through the vagus nerve. By using electrical stimulation to hack into neural networks, it’s possible to regulate the im-



BARBARA KELLEY

the molecule that killed Janice was made by her own immune system. It’s a molecule that’s known today as TNF—tumor necrosis factor.

TNF is a cytokine, a protein made by the immune system to send signals that can cause or reduce inflammation. But the discovery of TNF explained only part of the mystery behind sepsis. Questions remained, Dr. Tracey said: “What is it that controls the

can overproduce cytokines,” which can result in autoimmune conditions like rheumatoid arthritis and Crohn’s disease, Dr. Tracey says. Hence the treatment: “You can implant a device on the vagus nerve of humans, or animals, and by controlling the activity of the nerve with the nerve stimulating device, you can control the magnitude of the cytokine response.”

The vagus nerve is actually a

Eight of the 16 patients in Ms. Owens’s trial showed improvement after four months, and she and three others went into complete remission. SetPoint plans to conduct larger randomized controlled trials on patients who haven’t responded to biologic drugs. Such trials can take many years to complete, as they do for drugs, but the Food and Drug Administration has been helpful in supporting the innovation. Last year the FDA approved the technique to help people who have suffered damage to motor skills caused by strokes.

Vagus-nerve stimulation might also help some people suffering from “long Covid,” Dr. Tracey says, although he cautions more research is needed. A study earlier this year found that most long-Covid patients had signs pointing to vagus-nerve dysfunction, including diarrhea, dizziness and rapid heart rate. Many also showed signs of vagus-nerve damage on medical imaging.

Some patients may shudder at the idea of getting implanted with a device that sends electrical pulses up to their brains and back down to the body. “Some have been quick to say, well, vagus-nerve stimulation is invasive,” Dr. Tracey says. “Well, I would say that biologics are invasive too. They’re administered with needles.” He adds that the 150,000 or

year-old when she twisted her ankle tap-dancing. A few weeks later, her ankle was still swollen and she began experiencing severe nausea and diarrhea. A year or two later, her other ankle swelled up, though she'd never injured it. Then her knees grew inflamed.

## Stimulating the vagus nerve can relieve arthritis, Crohn's disease and other inflammatory conditions—perhaps someday even Alzheimer's disease.

After a colonoscopy and endoscopy, she was diagnosed with Crohn's disease, an inflammatory bowel condition. Blood tests and a physical examination revealed spondyloarthropathy arthritis, which attacked her spine, joints and organs. She developed blood clots and skin ulcers. By the time she finished college, she says, there wasn't a joint in her body that didn't hurt. Her myriad ailments made it difficult to walk and forced her to quit her job as a teacher. To control her joint inflammation, she was prescribed steroids, which made her bones as brittle as a 70-year-old woman's.

She was 25 when she stumbled on a Facebook video of Dr. Tracey, CEO of the Manhasset, N.Y.-based Feinstein Institutes for Medical Research, discussing how electricity could replace medication. Dr. Tracey, 64, pioneered research showing that electrical stimulation of the vagus nerve—the nervous-system “motherboard” that originates at the back of the neck, which connects the brain to the rest of the body—could suppress inflammation that causes chronic diseases such as Crohn's and rheumatoid arthritis.

She enrolled in a vagus-nerve stimulation trial by SetPoint Medical, a California-based biotech startup that Dr. Tracey co-founded in 2007. With financial help from

Scientists have long known that the vagus nerve carries signals between the brain and internal organs that regulate physiological processes such as digestion, breathing and heart rate. When you exercise, for instance, your heart speeds up. Then your brain sends a signal via the vagus nerve directing your heart to slow down so it doesn't beat out of control.

Dr. Tracey's breakthrough two decades ago was the discovery that the brain also controls the immune system through the vagus nerve. By using electrical stimulation to hack into neural networks, it's possible to regulate the immune response and perhaps someday cure inflammatory conditions such as multiple sclerosis, lupus and even Alzheimer's disease.

The story of this novel insight begins with Dr. Tracey's painful childhood. His mother died of an inoperable brain tumor when he was 5. That sparked his interest in neurosurgery. He wanted to develop treatments so that other children wouldn't have to suffer the way he and his two younger siblings had. He went to medical school and joined a New York hospital as a neurosurgery resident.

In 1985 he was caring for an 11-month-old girl named Janice. “She'd been crawling across the kitchen floor when her grandmother was cooking dinner. And grandma turned to drain boiling water in the sink and spilled the boiling water on her granddaughter,” Dr. Tracey recalls. “We didn't think she was going to survive. But she did—she survived for a month—and then inexplicably went into shock and died in my arms. And so I was haunted by her death. She died of septic shock.”

Septic shock occurs when a nonfatal injury or infection leads to organ failure and dangerously low blood pressure. Sepsis causes 1 in 5 deaths worldwide. In 1985 scientists didn't understand what causes the condition. Janice's death spurred Dr. Tracey to research sepsis' biological underpinnings: “What we discovered is that

the molecule that killed Janice was made by her own immune system. It's a molecule that's known today as **TNF**—tumor necrosis factor.

TNF is a cytokine, a protein made by the immune system to send signals that can cause or reduce inflammation. But the discovery of TNF explained only part of the mystery behind sepsis. Questions remained, Dr. Tracey said: “What is it that controls the amount of cytokines being produced? Why do some people, like Janice, make massive amounts of cytokines that can kill them?”

While testing an experimental drug that blocked TNF production in mice with strokes, his lab stumbled on a clue. The drug not only blocked TNF production in the rodents' brains, which helped the strokes heal; it also turned off TNF and other cytokines made in the rest of the body. That led to the discovery that “the brain communicates to these organs by sending signals through the vagus nerve.”

His lab performed two more experiments in mice that confirmed this hypothesis. “So now we knew the vagus nerve could transmit this off-switch to the immune system.” He postulated that “if there's an off-switch in the vagus nerve, there must be an on-switch, which is how a reflex works.” More experimentation and research proved his hunch true.

In the case of sepsis, bacteria activate white blood cells to produce cytokines, which can help heal wounds. An inflammatory condition like Ms. Owens's can also trigger the release of cytokines. Problems arise when the nervous system fails to regulate the production of cytokines. “If the nervous system doesn't control that response, the immune system

can overproduce cytokines,” which can result in autoimmune conditions like rheumatoid arthritis and Crohn's disease, Dr. Tracey says. Hence the treatment: “You can implant a device on the vagus nerve of humans, or animals, and by controlling the activity of the nerve with the nerve stimulating device, you can control the magnitude of the cytokine response.”

The vagus nerve is actually a network of some 160,000 nerve fibers, 80,000 on either side of the neck. Each fiber has a specific job—for instance, controlling heart rate. These fibers also deliver information to the brain, which processes them and sends signals back down the vagus nerve or to nearby structures such as the pituitary gland, which regulates hormone production.

How do doctors know which fiber or fibers to stimulate? Dr. Tracey explains a “cool trick called optogenetics,” which involves genetically engineering mice so that the fibers in their brain stem are stimulated to send signals to the body when activated by a laser beam. Researchers can then figure out which fibers control which processes by shining a laser on the neurons.

More than 100 trials world-wide are being conducted using vagus-nerve stimulation for an array of conditions. SetPoint has conducted three small trials on vagus-nerve stimulation for rheumatoid arthritis and Crohn's. “The same device implanted in the same location can be used for other diseases,” says CEO Murthy Simhambhatla. (Dr. Tracey resigned from the company's board in 2011 to spend more time in his lab after meeting the first rheumatoid-arthritis patient treated in a SetPoint clinical trial who experienced complete remission. He continues to work as a consultant for SetPoint.)

Search is needed. A study earlier this year found that most long-Covid patients had signs pointing to vagus-nerve dysfunction, including diarrhea, dizziness and rapid heart rate. Many also showed signs of vagus-nerve damage on medical imaging.

Some patients may shudder at the idea of getting implanted with a device that sends electrical pulses up to their brains and back down to the body. “Some have been quick to say, well, vagus-nerve stimulation is invasive,” Dr. Tracey says. “Well, I would say that biologics are invasive too. They're administered with needles.” He adds that the 150,000 or so epilepsy patients who have been treated with vagus-nerve stimulation over the decades have very rarely experienced side effects.

Some drugs also work by chemically stimulating the vagus nerve and may carry potential to treat conditions other than those for which they were originally developed. Dr. Tracey conducted a small trial that found famotidine (also known by the brand name Pepcid) can reduce the duration of acute Covid in patients with mild to moderate symptoms by activating the vagus nerve and suppressing the cytokine storm.

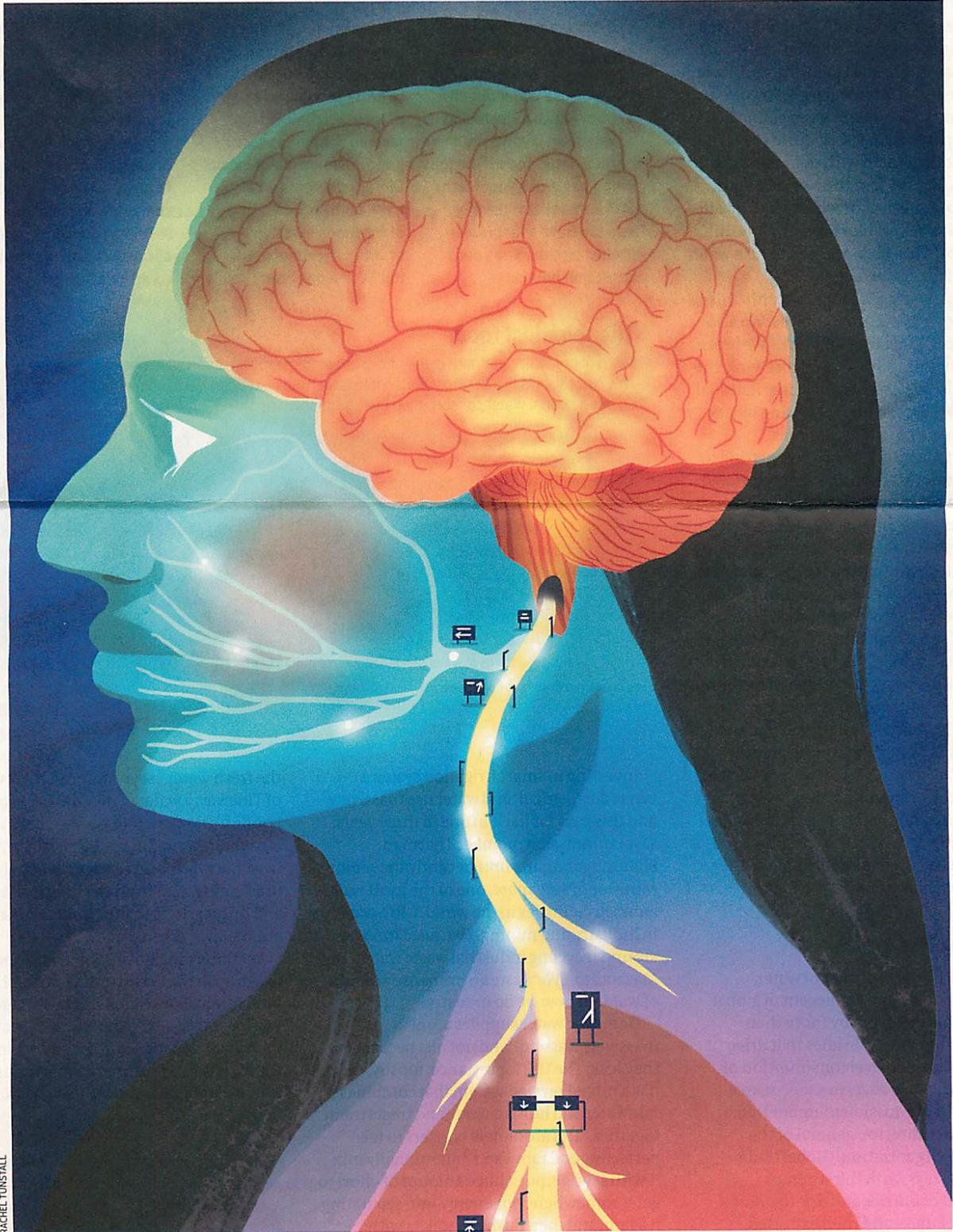
Healthy behaviors like exercise and meditation can also stimulate the vagus nerve, Dr. Tracey says, but they may not help patients whose nerve fibers are damaged or who have a genetic predisposition. The latter might have caused Ms. Owens's ailments.

Dr. Tracey is reluctant to say she's cured: “She might be. We don't know. How do you know if she's cured? No one wants to turn the device off.” But she feels like a normal, healthy 33-year-old, and she hopes her story will inspire others with similar conditions: “Patients really need to have hope.”

Ms. Finley is a member of the Journal's editorial board.



# Features



RACHEL TUNSTALL

**A**S I peered at its sinewy, tentacle-like tendrils, I thought the pale structure splayed on the table before me resembled a huge tapeworm, or perhaps a scrawny squid.

Its lacklustre appearance didn't match with the wonder of what I knew it to be: a human vagus nerve, the sensory superhighway that connects our brain to most of our vital organs and helps regulate everything from the movement of food through our intestines to the steady beating of our heart.

I was at the Feinstein Institutes for Medical Research in New York, viewing one of 30 vagus nerve samples being diced, sliced and imaged by Stavros Zanos and his colleagues. The goal? To create a detailed map of the roughly 160,000 nerve fibres along its structure.

This ambitious effort comes after recent research has revealed the vagus nerve's role in a wider array of processes than we ever realised – not only monitoring organ function, but helping discern facial expressions and even regulating mood. Most enticingly, we are starting to understand how it governs

inflammation, the immune response that runs rampant in conditions ranging from heart disease to Parkinson's.

Already, electrical devices called vagus nerve stimulators are used to treat epilepsy, depression, migraines and obesity. But they are limited by our rudimentary understanding of the nerve's complex structure. Now, efforts to untangle its mysteries are allowing us to map each of its branches and even discover specialised cell types we never knew existed. Not only might these insights enable us to control inflammation, they could open a whole new frontier for precision medicine.

The vagus nerve is a bundle of neural fibres that starts at the brain stem. It splits into two channels that run along either side of the neck, then rejoin at the heart before descending to the gut and other organs.

The earliest evidence of its crucial function dates back almost 2000 years to when the ancient Roman physician Galen accidentally severed a sheaf of nerves in a pig, stopping its squeals but not its squirms. It turned out he had sliced a branch of the vagus nerve

responsible for transmitting signals from the brain to the vocal cords.

Subsequent experiments revealed that the vagus nerve regulates functions of the heart, stomach, lungs, liver and more. But it wasn't until about three decades ago that we began to tap into it for medical treatments.

The earliest success was with epilepsy. In the late 1980s, J. Kiffin Penry and Joan Christine Dean, then at Wake Forest University in North Carolina, showed that implanting a vagus nerve stimulator reduces or even eliminates seizures for some people with the condition. Most of these stimulators use a pulse generator slightly larger than a poker chip, which is implanted under the skin on the chest. This sends electrical impulses via a wire to a cuff wrapped around the vagus nerve in the neck. The first such stimulator was approved by the US Food and Drug Administration (FDA) in 1997 for treating drug-resistant epilepsy.

Since then, the FDA has approved an implantable device for treatment-resistant depression, after trials showed that it lessened symptoms for about 40 per cent of people who had already tried four or more other treatments without success. A device called VBLOC has also been approved for treating obesity: people using it lost about 8 per cent more excess weight than those in a control group. Most recently, the FDA approved a stimulator for regaining upper body movement after a stroke. Research also indicates that stimulators can be used to regulate blood pressure and lower blood sugar.

Most tantalising is the role the vagus nerve plays in controlling inflammation. Hints of this first emerged in the 1990s, when Kevin Tracey, now at the Feinstein Institutes for Medical Research, and his colleagues developed an anti-inflammatory drug to block production of proteins called cytokines, which spur the body's immune response to infection or illness. In modest amounts, cytokines and the ensuing inflammation fend off foreign pathogens and heal injuries, but an overabundance of them has the opposite effect, damaging tissues and potentially causing chronic illness or even organ failure.

Tracey and his team injected their new drug into the brains of rats experiencing stroke from bacterial infections. As they hoped, it dampened inflammation in the brain. But to their surprise, the effect also extended throughout the rodents' whole bodies.

# YOUR BODY'S SECRET SUPERHIGHWAY

The vagus nerve influences everything from your heartbeat to your immune system. Unravelling its secrets could usher in a new era of medicine, finds **Grace Wade**

## You are electric

Listen to Sally Adee reveal how bioelectricity shapes your body and mind [newscientist.com/nsimag](https://www.newscientist.com/nsimag)

With drugs given orally or intravenously, you would expect widespread effects, but the researchers weren't anticipating this after injecting the medication directly into the brain. "For months, we agonised over what the mechanism could be," says Tracey. Eventually, they tried severing the animals' vagus nerves. "When we did that, the drug in the brain no longer turned off inflammation," he says. "Scientists don't say 'eureka' any more, they say 'holy shit', and that's what happened."

Tracey dubbed the vagus nerve's ability to mediate inflammation the inflammatory reflex. It kicks in when specialised neurons detect cytokines and send signals to the brain, which in turn relays messages to the spleen to start churning out white blood cells. The discovery suggested that we might be able to interrupt inflammation with an electrode, not just drugs, he says.

In 2012, a device using an electrode that Tracey designed while at SetPoint Medical, a biotechnology company in California, was tested in a small group of people with the chronic inflammatory condition rheumatoid arthritis. Of those, 70 per cent had at least a 20 per cent reduction in symptoms, and almost half saw a 50 per cent improvement.

The effect is similar to that of some drugs, but there is a major advantage: anti-inflammatory medications often severely suppress immune function, leaving people vulnerable to infection. Not so with this

**Cold water swimming is supposedly a way to enhance "vagal tone"**

UC  
 approach. Vagus nerve stimulation causes white blood cells to shut down cytokine production enough to avoid runaway inflammation, but not so much that our immune system is disarmed completely, says Tracey.

### Mysterious fibres

SetPoint Medical is now conducting a trial of the device in about 250 people. Tracey is hopeful that the FDA could approve the treatment for rheumatoid arthritis within a few years. Meanwhile, similar devices have also shown promise in treating conditions characterised by chronic inflammation, including inflammatory bowel disease, multiple sclerosis and Parkinson's disease.

"What diseases are affected by inflammation? Pretty much every chronic illness," says Zanos. "I'm not saying vagus nerve stimulation will work for every single one of them, but it makes sense to test it out in some way or another."

There is just one hiccup in all of this: how exactly these treatments work is largely a mystery. It is unclear which fibres the stimulators even target. Is it those closest to the electrode? The ones furthest away? The small ones? The large ones? We simply don't know. We just turn on the device and hope for the best.

With obesity, for instance, the stimulator is meant to work by mimicking signals that travel along the vagus nerve to tell the brain to stop eating when the stomach is full. In people with epilepsy, though, vagus nerve devices

may provide benefits by stimulating nerve cells that increase blood flow to a brain region called the thalamus, which processes information from most senses. It may also work in part by triggering the release of the neurotransmitter noradrenaline, which can reduce seizure symptoms. Boosting noradrenaline may be the way stimulation eases depression symptoms, too. But which particular nerve fibres play a role in this is unknown.

It is even trickier to pin down exact targets of devices that zap the vagus through the skin. Today, these transcutaneous stimulators can be purchased in many countries without a prescription from about \$200. They are often marketed as a way to boost "vagal tone", a supposed measure of vagal activity. But researchers say the concept isn't terribly scientific (see "What is vagal tone?", right).

Some transcutaneous stimulators have been rigorously tested, though. In 2018, the FDA approved one for treating chronic migraines and cluster headaches after research showed that it significantly lowered the number of days that people experience them. Tracey says it is important to talk with your doctor before using this kind of technology. These devices may not be suitable for some people with heart conditions, as they can affect heart rhythms.

Therein lies the problem. The extraordinary complexity of the vagus nerve is what makes it an avenue for improving so many aspects of health, but the lack of specificity in treatments also means they can have unintended side effects. It may also be why some applications simply fail.

"The way neuromodulation has been done for many years is creating an electrode and then placing it on a nerve or in the brain and hoping for the best," says Zanos. For more consistent results, and to expand the potential applications, we need a much more detailed understanding of what we are aiming for.

All of which explains how I find myself staring at the stringy tissue in Zanos's lab. He and his colleagues are embarking on a three-year, \$6.7-million project funded by the US National Institutes of Health to map the vagus in its entirety. That involves identifying every single nerve fibre and tracking its location along the structure's meandering pathway.

It is painstaking work, beginning with the process of extracting the vagus nerve from a cadaver. At points, it is thinner than a cotton thread, and researchers must carefully label



RON BINTANG/GETTY IMAGES

## What is vagal tone?

Contemplative activities, including yoga, tai chi and meditation, can slow respiration and, in turn, affect signals travelling along the vagus nerve. Extreme athlete Wim Hof, for example, swears by his daily dunks in ice-cold water and militant breathing routine to reduce inflammation by improving vagal tone, a supposed measure of electrical activity along the vagus nerve.

But what is vagal tone really, and is it actually something you can strengthen? When I ask Kevin Tracey at the Feinstein Institutes for Medical Research in New York, he cradles his head in his hands and groans. "It is a non-scientific term that is difficult to define, and because it is difficult to define, I think it is misappropriated," he says.

One issue is that it is almost impossible to directly gauge vagus nerve activity, so another measure called heart rate variability – or the variation in timing between heartbeats – is used as a stand-in. But research in rats shows heart rate variability doesn't correlate well with vagal output.

Even if people could reliably calculate the vagus nerve's firing capacity, it probably wouldn't do much good given the structure's dizzying complexity.

"People tend to think and talk about the vagus nerve like a single, solid copper wire," says Tracey. "But it's more like 160,000 wires, each of which can control a very specific function."

"Vagal tone implies that there is one function of the vagus nerve," says Stephen Liberles at Harvard University. But many fibres in the vagus have opposing effects (see main story). "So there is no vagal tone. It is a bit of a misnomer," he says.



GRACE WADE

Sections of the vagus nerve are encased in wax, then sliced thinly

what organs its many branches connect to.

The researchers then chop it into pieces that, at their thickest, resemble cannellini beans, which are moulded into blocks of wax. These are placed into what is essentially a deli meat slicer, where the encased nerve sections are shaved into slivers as thin as a human hair.

Finally, the team bathes the segments in staining solutions to reveal their inner complexity. Zanos shows me an image on his computer. What was once a rather dull, brown blob is now a motley of red, green and blue fluorescence. Each colour correlates to a different type of nerve fibre, yielding clues to its function, he says.

We can tell what types of signals neurons ferry based on their distinct anatomical features. Afferent neurons transmit sensory information towards the brain, while efferent neurons relay signals for controlling movement from the brain to our muscles. Fibres that are insulated in a fatty coating called myelin generally fire faster than those without it. "So, if it is myelinated and efferent, we know that most likely mediates muscle contractions," says Zanos.

Mapping the vagus nerve's anatomy won't only allow us to better predict the effects of placing an electrode anywhere along the nerve's structure, but could also lead to the creation of ultra-selective stimulators that act only on certain fibres, he says.

Zanos and his colleagues have already shown proof of this concept. After they mapped the vagus nerve of pigs, they developed an ultra-selective vagus nerve stimulator with 10 separate contact points. In research published earlier this year, they showed that, when implanted into live pigs, the device altered the animals' breathing while minimising effects on other organs.

Mapping the vagus nerve is just the first step, says Cristin Welle at the University of Colorado. "The next step is going to be, how do each of those fibre types then interact with the rest of the nervous system?" she says. She and her team are charting the vagus nerve in the opposite direction, identifying which brain regions it activates. Last year, they showed that vagus nerve stimulation targets neurons in the primary motor cortex of mice, enhancing the animal's ability to learn motor skills.

Stephen Liberles at Harvard University believes we can achieve even greater precision by elucidating the mechanisms of specific neurons with genetic sequencing. Of particular interest are sensory neurons, which constitute about 80 per cent of all nerve fibres in the vagus and use specialised receptors to detect changes in an environment. "Some of our landmark discoveries in the external senses were discovering odourant receptors or vision receptors," says Liberles. "We don't know the receptors for almost any internal organ sense."

### Conducting traffic

Already, he and his colleagues have identified previously unknown types of vagal neurons that mediate breathing, control blood pressure and detect nutrients in the gut. He believes we will eventually be able to develop drugs that act only on specific vagal cells. If the vagus nerve is our body's superhighway, such drugs would control the movement of individual cars, while vagus nerve stimulators would dictate general traffic flow across multiple lanes.

"When you understand how all these vital body-to-brain communication pathways operate, that will open the door to therapies by which you can toggle [these] different pathways with greater selectivity," says Liberles. Being able to modulate inflammation or other physical functions with this level of precision would be nothing short of game-changing for modern medicine.

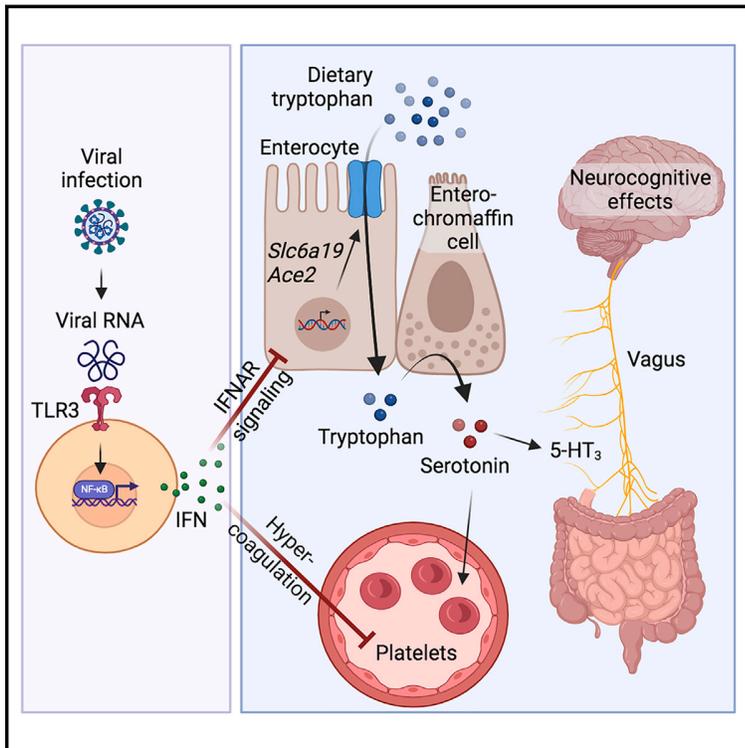
As I leave Zanos's lab, I steal a final look at the ribbon of white tissue, marvelling at its extraordinary potential – and the power of science to map it and manipulate it. ■



Grace Wade is a health reporter for New Scientist

# Serotonin reduction in post-acute sequelae of viral infection

## Graphical abstract



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## In brief

Post-viral syndromes are associated with serotonin reduction, which may contribute to the neurological and cognitive symptoms seen in individuals with Long COVID.

## Highlights

- Long COVID is associated with reduced circulating serotonin levels
- Serotonin depletion is driven by viral RNA-induced type I interferons (IFNs)
- IFNs reduce serotonin through diminished tryptophan uptake and hypercoagulability
- Peripheral serotonin deficiency impairs cognition via reduced vagal signaling

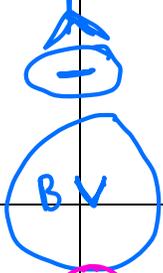


C1-C3

Nucleus Intermedius

Nucleus Tractus Solitarius

Dorsal Motor Nucleus Vagus



SCG

Postganglionic Sympathetic

x 120  
32

Pre-ganglionic Sympathetic



Nasal Specific → Sphenoid

Upper Cervical → Occiput/Atlas → Cork CSF

- \* Calming
- \* Vasodilation
  - ↓ B.P.
  - ↓ artery disease
- \* Immune Enhancing
- \* Longer Telomere

Acetylcholine

HRV

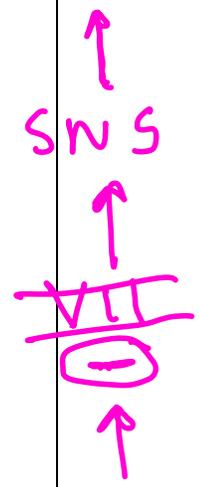
Stress  
Fight/Flight

↓

Vasoconstriction  
↑ BP  
↑ artery disease

Immune Suppression  
Shorter Telomeres  
Shrink Brain

Norepinephrine



Mechanoreceptors



The New Science of the  
*Vagus Nerve* and How to Harness  
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THE  
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*J Manipulative Physiol Ther.* 2016 Jan;39(1):42-53. doi: 10.1016/j.jmpt.2015.12.004. Epub 2016 Feb 1.

## Attenuation Effect of Spinal Manipulation on Neuropathic and Postoperative Pain Through Activating Endogenous Anti-Inflammatory Cytokine Interleukin 10 in Rat Spinal Cord.

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### Abstract

**OBJECTIVES:** The purpose of this study was to investigate roles of the anti-inflammatory cytokine interleukin (IL) 10 and the proinflammatory cytokines IL-1 $\beta$  and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) in spinal manipulation-induced analgesic effects of neuropathic and postoperative pain.

**METHODS:** Neuropathic and postoperative pain were mimicked by chronic compression of dorsal root ganglion (DRG) (CCD) and decompression (de-CCD) in adult, male, Sprague-Dawley rats. Behavioral pain after CCD and de-CCD was determined by the increased thermal and mechanical hypersensitivity of the affected hindpaw. Hematoxylin and eosin staining, whole-cell patch clamp electrophysiological recordings, immunohistochemistry, and enzyme-linked immunosorbent assay were used to examine the neural inflammation, neural excitability, and expression of c-Fos and PKC as well as levels of IL-1 $\beta$ , TNF- $\alpha$ , and IL-10 in blood plasma, DRG, or the spinal cord. We used the activator adjusting instrument, a chiropractic spinal manipulative therapy tool, to deliver force to the spinous processes of L5 and L6.

**RESULTS:** After CCD and de-CCD treatments, the animals exhibited behavioral and neurochemical signs of neuropathic pain manifested as mechanical allodynia and thermal hyperalgesia, DRG inflammation, DRG neuron hyperexcitability, induction of c-Fos, and the increased expression of PKC $\gamma$  in the spinal cord as well as increased level of IL-1 $\beta$  and

TNF- $\alpha$  in DRG and the spinal cord. Repetitive Activator-assisted spinal manipulative therapy significantly reduced simulated neuropathic and postoperative pain, inhibited or reversed the neurochemical alterations, and increased the anti-inflammatory IL-10 in the spinal cord.

**CONCLUSION:** These findings show that spinal manipulation may activate the endogenous anti-inflammatory cytokine IL-10 in the spinal cord and thus has the potential to alleviate neuropathic and postoperative pain.

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**KEYWORDS:** Ganglia; Interleukin-10; Interleukin-1beta; Nervous System; Pain; Spinal; Spinal manipulation; Trauma

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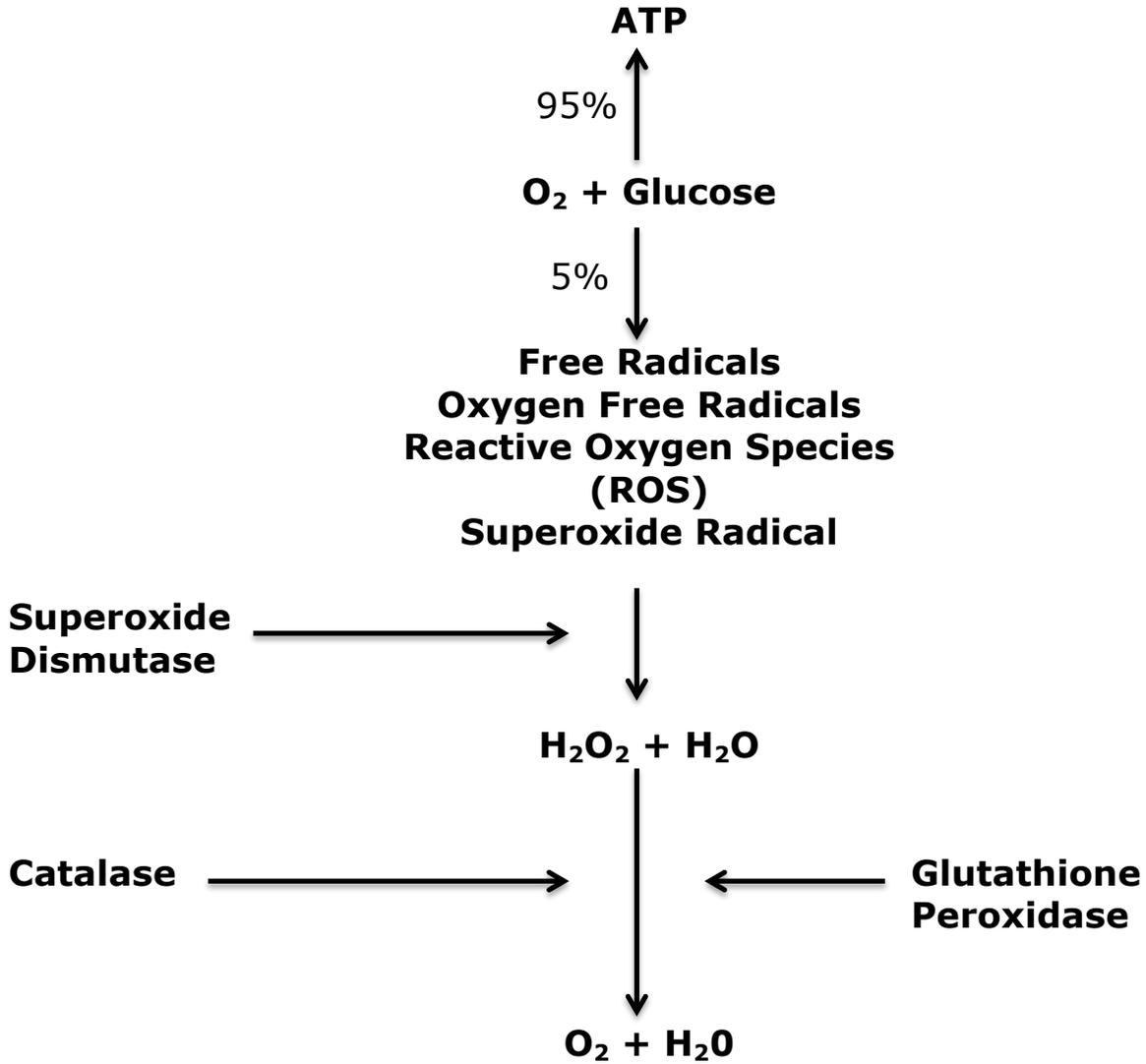
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## Endogenous Antioxidant Array



# PERIPHERAL OXIDATIVE STRESS BLOOD MARKERS IN PATIENTS WITH CHRONIC BACK OR NECK PAIN TREATED WITH HIGH-VELOCITY, LOW-AMPLITUDE MANIPULATION



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## ABSTRACT

**Objective:** The purpose of this study was to investigate oxidative-stress parameters in individuals with chronic neck or back pain after 5 weeks of treatment with high-velocity, low-amplitude (HVLA) spinal manipulation.

**Methods:** Twenty-three individuals aged  $38.2 \pm 11.7$  years with nonspecific chronic neck or back pain verified by the Brazilian Portuguese version of the Chronic Pain Grade, with a sedentary lifestyle, no comorbidities, and not in adjuvant therapy, underwent treatment with HVLA chiropractic manipulation twice weekly for 5 weeks. Therapeutic procedures were carried out by an experienced chiropractor. Blood samples were assessed before and after treatment to determine the activities of the antioxidant enzymes superoxide dismutase (SOD), catalase and glutathione peroxidase (GPx), and the levels of nitric oxide metabolites and lipid hydroperoxides. These blood markers were analyzed by paired Student *t* test. Differences were considered statistically significant, when *P* was  $< .05$ .

**Results:** There was no change in catalase but an increase in SOD ( $0.35 \pm 0.03$  U SOD per milligram of protein vs  $0.44 \pm 0.04$  U SOD per milligram of protein;  $P < .05$ ) and GPx ( $7.91 \pm 0.61$  nmol/min per milligram of protein vs  $14.07 \pm 1.07$  nmol/min per milligram of protein;  $P < .001$ ) activities after the treatment. The nitric oxide metabolites and the lipid hydroperoxides did not change after treatment.

**Conclusion:** High-velocity, low-amplitude spinal manipulation twice weekly for 5 weeks increases the SOD and GPx activities. Previous studies have shown a relationship between pain and oxidative and nitrosative parameters; thus, it is possible that changes in these enzymes might be related to the analgesic effect of HVLA spinal manipulation. (*J Manipulative Physiol Ther* 2015;38:119-129)

**Key Indexing Terms:** Antioxidant Enzymes; Oxidative Stress; Manipulation; Spinal; Manual Therapy; Chiropractic

The physiologic effects of vertebral manipulation may result from its effect on the flow of information to the central nervous system.<sup>1,2</sup> It is suggested that

the spinal biomechanical dysfunction known as vertebral subluxation disturbs the neurologic function by sensitizing paraspinal sensory afferents, especially the proprioceptors and nociceptors in joints and muscles.<sup>3-6</sup> This sensitization possibly leads to plastic changes in cells of the central nervous system.<sup>6</sup> On the other hand, high-velocity, low-amplitude (HVLA) spinal manipulation supposedly alters the central sensory processing by favoring a nociceptive modulation due to low-frequency stimulation of mechanonociceptors of paraspinal tissues, which contributes to analgesia.<sup>4</sup> This central modulation may also influence muscle and visceral reflex responses.<sup>1,2,6</sup>

The peripheral sensitization after activation of nociceptors and the subsequent central sensitization are associated with neuronal excitability and the presence of pronociceptive molecules locally.<sup>7,8</sup> In pain conditions, there is an increase in neural activity due to neuronal excitability, with more utilization of metabolic substrates and increased production of reactive oxygen and nitrogen species (RS).<sup>9,10</sup> RS, which include free radicals and peroxides, are normally formed in the cell respiration process and play an important role in both physiologic and pathologic conditions.<sup>11</sup>

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At moderate concentrations, the RS may act as important physiologic regulators in intracellular signaling pathways.<sup>12,13</sup> In the development of persistent pain states, as occurs in nerve injury or inflammatory insult, the increase in RS seems to be essential not only for the induction but also for the maintenance of central sensitization in the spinal cord.<sup>13-16</sup> It is thought that hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), nitric oxide (NO), and superoxide are the main RS involved in the central sensitization process.<sup>17</sup>

An overwhelming production of reactive oxygen species can generate oxidative stress, leading to deleterious effects on cellular function.<sup>18</sup> Oxidative stress occurs as a result of an imbalance between increased production and/or reduced degradation of oxygen reactive species. It may lead to damage to lipids, protein, and DNA.<sup>18</sup> To counteract reactive oxygen species-induced cell damage, biological systems have evolved endogenous mechanisms to protect themselves in normal physiologic conditions.<sup>19</sup> The cellular antioxidant mechanisms involve nonenzymatic compounds and enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx).<sup>19,20</sup> Superoxide dismutase is specific to superoxide-radical detoxification. Superoxide dismutase can rapidly dismutate the superoxide radical, yielding H<sub>2</sub>O<sub>2</sub> and oxygen.<sup>21</sup> Hydrogen peroxide is a diffusible reactive oxygen species that contributes to the development of pathologic pain states, not only by generating harmful reactive species but also by modulating synaptic plasticity.<sup>22</sup> The presence of H<sub>2</sub>O<sub>2</sub> apparently affects the release of intracellular calcium, leading to neuronal sensitization and pronociceptive patterns in interneurons in the spinal cord dorsal horn.<sup>15</sup> Catalase activity, in turn, converts H<sub>2</sub>O<sub>2</sub> to water.<sup>23</sup> Furthermore, GPx is an important enzymatic mechanism for the disposal of peroxides, producing water or alcohol and reduced glutathione.<sup>24</sup>

Nitric oxide may react with the superoxide radical and form peroxynitrite, a very deleterious nitrogen species, which may lead to lipid and protein peroxidation and damage.<sup>17</sup> In addition, NO has a modulatory role in pain states at both the central and peripheral levels.<sup>25,26</sup> Nitric oxide has been implicated in synaptic plasticity and multiple mechanisms involving central sensitization.<sup>26</sup> The involvement of NO in peripheral nociception is corroborated by data demonstrating the local release of NO by an inflammatory stimulus.<sup>27</sup> Nitric oxide plays a controversial role in pain modulation, that is, NO can mediate nociception or induce an antinociceptive effect.<sup>26</sup> The modulatory effect of NO may be related to neuronal excitability.<sup>25</sup>

In a previous study, we demonstrated a possible correlation between HVLA manipulation and oxidative-stress parameters. An increase in systemic catalase activity was demonstrated after 6 sessions of HVLA manipulation in 2 weeks of treatment.<sup>28</sup> Glutathione peroxidase activity, in turn, seemed to require a longer period of treatment (>2 weeks) because only a tendency to increased activity was found in the period considered.<sup>29</sup> These results led us to

hypothesize that the effects of HVLA spinal manipulation on antioxidant activity may depend on the treatment period. Therefore, to provide more information about this hypothesis, the purpose of this study was to assess RS in blood of patients with nonspecific chronic neck or back pain treated by HVLA spinal manipulation for 5 weeks, twice a week, to analyze the activity of the antioxidant enzymes SOD, catalase and GPx, the levels of NO metabolites, and the formation of lipid hydroperoxides (LOOHs), which are formed by the action of reactive oxygen species on polyunsaturated fatty acids,<sup>30</sup> in the blood of the patients before and after the treatment.

## METHODS

### Subjects

This study selected individuals with nonspecific<sup>31</sup> chronic neck or back pain as described by Guzman et al<sup>32</sup> and Lawrence et al,<sup>33</sup> respectively. The criteria for inclusion in the study were symptoms must be present for at least 90 days<sup>34</sup> and have an average intensity greater than 2 of 10 on a visual numerical pain scale.<sup>35</sup> The exclusion criteria were symptoms related to serious pathologies such as malignancy, infection, inflammatory disorder, or fracture. Patients were also excluded, when there were signs of lumbar or cervical spinal cord compromise or radiculopathy and/or a history of neck or back surgery. In addition, subjects were only eligible for trial inclusion if spinal manipulation was an appropriate therapy for their condition. The subjects had to be nonsmokers, not be on adjuvant therapy, and have a sedentary lifestyle because exercise can influence the biochemical parameters studied.<sup>36,37</sup>

### Experimental Procedures

Fifty subjects (18-60 years old) with chronic neck pain or back pain were recruited through advertisements in the local newspapers of Vale dos Sinos (free distribution, 13000 copies, May-July 2012; Jornal Bem Estar) and advertisements in public agencies (Agência do Sistema Nacional de Emprego e Fundação Gaúcha do Trabalho e Ação Social, June 2011-2012; and City Hall of Novo Hamburgo, August-December 2012). Each volunteer was identified by a code during the selection process; the same code was subsequently used to identify the records and blood samples. An inclusion/exclusion questionnaire was administered, and the history and a physical examination were used to screen the participants. The frequency, intensity, and disability of the symptoms were assessed by the Brazilian Portuguese version of the Chronic Pain Grade (CPG-Br), an adapted and validated version of the original graded chronic pain scale from Von Korff et al.<sup>38,39</sup> The CPG-Br evaluates self-perception of pain. The scale has 7 questions that assess pain intensity and disability. Six questions request numerical scores ranging from 0 to 10, including the pain intensity at the moment, in the worst phase, and the average pain intensity. An additional question

**Table 1. Demographic and Clinical Characteristics of Subjects**

	n = 23
Mean age $\pm$ SD, y	38.2 $\pm$ 11.7
Female/male	18/5
Mean body mass index $\pm$ SD, kilograms per square meter	24.9 $\pm$ 4.1
Patient complaints <sup>a</sup>	
Neck pain	45%
Low back pain	14%
Neck pain and low back pain associated	41%

<sup>a</sup> Distribution of patients according to the location of painful complaints.

### Characterization of Pain Symptoms

The demographic characteristics of the subjects are shown in Table 1. The characteristics of the pain of the neck or back were reported by the patients using the CPG-Br and are shown in Table 2. According to the CPG-Br, half of the patients had disabling pain, and of these, one-third had severely limiting symptoms and the others only a moderately limiting condition. Almost all of the remaining subjects had pain of high intensity but slightly limiting, and only 1 patient had pain of low intensity and not limiting. Overall, mean pain intensity was greater than 50% on a 10-point visual numerical pain scale, wherein the characteristics of pain at the moment, in the worst phase, and the average pain intensity were considered.

### Antioxidant Enzyme Activities

The SOD and GPx activities were significantly higher after 10 sessions of HVLA spinal manipulation for 5 weeks (SOD: pretreatment, 0.35  $\pm$  0.03 U SOD per milligram of protein, posttreatment, 0.44  $\pm$  0.04 U SOD per milligram of protein;  $P = .005$ ) (GPx: pretreatment, 7.91  $\pm$  0.61 nmol/min per milligram of protein, posttreatment, 14.07  $\pm$  1.07 nmol/min per milligram of protein;  $P < .001$ ; mean  $\pm$  SEM) (Fig 2). Considering the general average of the SOD and GPx activities of patients, the increase after the treatment was around 27% for SOD (Fig 2A) and more than 77% for GPx (Fig 2B) activities. The catalase activity, in these experimental conditions, did not show any significant change after the treatment (pretreatment, 3.72  $\pm$  0.19 pmol/min per milligram of protein, posttreatment, 4.25  $\pm$  0.35 pmol/min per milligram of protein;  $P > .05$ ) (Fig 2C).

### Nitric Oxide Metabolites

The NO metabolites (NO<sub>2</sub> + NO<sub>3</sub>) showed no significant change in the plasma from patients with nonspecific chronic neck or back pain treated by HVLA spinal manipulation (Fig 3A). The level of NO metabolites was 78.32  $\pm$  6.73  $\mu$ mol/L before treatment, whereas in posttreatment was 81.81  $\pm$  7.12  $\mu$ mol/L.

**Table 2. Classification on CPG-Br**

	n = 23
Grade 0 (no pain)	0%
Grade I (low intensity)	5%
Grade II (high intensity)	45%
Grade III (moderately limiting)	30%
Grade IV (severely limiting)	20%
Pain disability	
Low disability (grade I and II)	50%
High disability (grade III and IV)	50%
Pain intensity <sup>a</sup> (mean $\pm$ SD)	6.9 $\pm$ 1.3

Distribution of patients according to the classification on CPG-Br.

<sup>a</sup> Arithmetic mean of the reported pain at the moment, the worst pain, and the middle pain, according to CPG-Br.

### Lipid Hydroperoxides

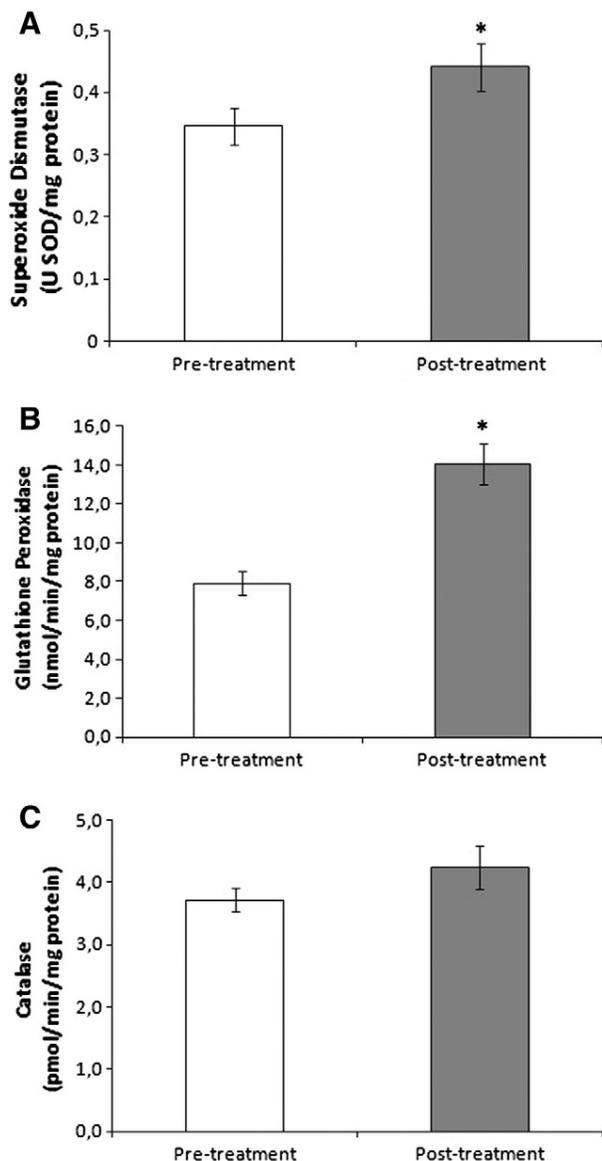
Similarly to NO metabolites, no significant difference was found in the LOOHs levels of the plasma from patients with nonspecific chronic neck or back pain treated by HVLA spinal manipulation (Fig 3B). The total amount of plasmatic LOOHs was 4.33  $\pm$  3.4 nmol/mg of protein in pretreatment and 5.89  $\pm$  5.0 nmol/mg in posttreatment.

### DISCUSSION

The present study demonstrated that treatment twice weekly for 5 weeks of individuals with nonspecific chronic neck or back pain by HVLA spinal manipulation increased SOD and GPx activities, with no significant changes in catalase activity, LOOHs, or NO metabolites in the systemic blood. In our previous study, in contrast, catalase activity increased after 6 interventions of HVLA spinal manipulation in patients with neck pain, whereas no significant change was observed in SOD and GPx activities. However, GPx activity showed a tendency to increase with a shorter period of treatment.<sup>28,29</sup> These results suggest that the effect of HVLA spinal manipulation on antioxidant enzyme activities may be affected by the length of time and the frequency of treatment.

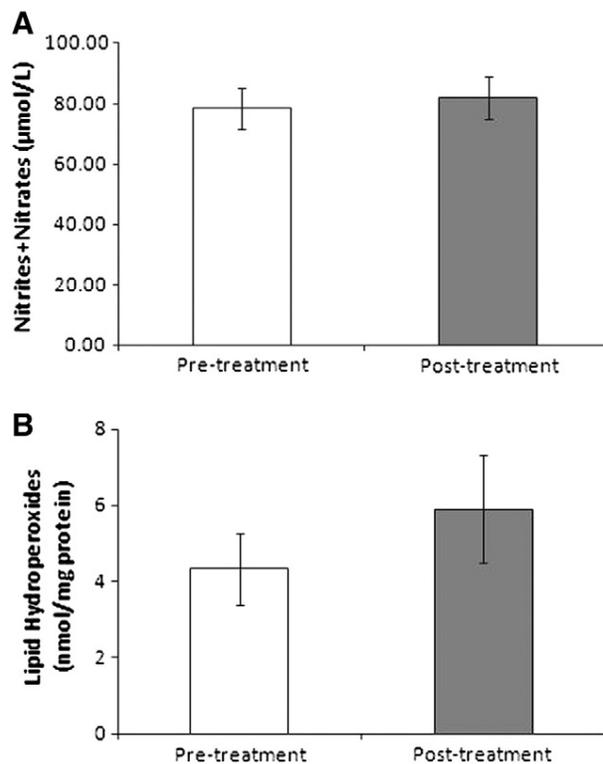
Before discussing our results, it is necessary to note some considerations. In the present study, no control group (a group without pain) was used. The absence of this group is because our pretreatment values for the SOD, catalase and GPx activities, and NO metabolites showed a similar range to that described in the literature for healthy individuals.<sup>52-54</sup> The choice not to include a control group also took into account previous studies that assessed oxidative parameters in blood, without a healthy control group.<sup>55,56</sup>

Our result showed no changes in the LOOH levels. It is possible that the lack of change in LOOHs may be due to the increase in antioxidant enzyme activities and the availability of NO metabolites. The presence of LOOHs causes oxidative stress-mediated damage by the action of peroxynitrites and hydroperoxides on polyunsaturated fatty acids.<sup>30</sup> The rise in SOD activity reduces the availability of the superoxide



**Fig 2.** Antioxidant activity of SOD (expressed units of SOD per milligram of protein) ( $n = 23$ ) (A), GPx activity (expressed as nanomoles per minute per milligram of protein) ( $n = 21$ ) (B), and catalase (expressed as picomoles per minute per milligram protein) ( $n = 23$ ) (C) in RBCs from patients with nonspecific chronic neck or back pain. Data are represented as mean  $\pm$  SEM. \* $P < .05$  (paired Student  $t$  test).

radical. This radical can react with NO, forming peroxynitrite, a harmful oxidant agent.<sup>17,57</sup> Glutathione peroxidase catalyzes the reduction of  $H_2O_2$  and organic hydroperoxides at the expense of glutathione. It also functions as a defense against peroxynitrite-mediated oxidations.<sup>58</sup> Thus, the increase in the SOD and GPx activities may be contributing to prevent the increase of peroxynitrite. Furthermore, it is known that in pain



**Fig 3.** Determination of NO metabolites ( $NO_2+NO_3$ ) (expressed as micromoles per liter) ( $n = 21$ ) (A) and LOOHs (expressed as nanomoles per milligram of protein) ( $n = 19$ ) (B) in plasma from patients with nonspecific chronic neck or back pain. Data are represented as mean  $\pm$  SEM. There was no significant difference after treatment (paired Student  $t$  test). SOD, superoxide dismutase.

processing or in injury to neural tissue, there is involvement of reactive species including superoxide, NO, and peroxynitrite.<sup>15,16,57,59</sup> Thus, the increase in SOD activity, which decreased the availability of superoxide, may be one contributing factor to the analgesic effect of the HVLA spinal manipulation treatment because no change was found in NO metabolites in our study.

However, the dismutation of superoxide radicals results in  $H_2O_2$  formation.<sup>21</sup> Hydrogen peroxide has a high damage potential and also contributes to central sensitization.<sup>16</sup> It appears to release intracellular stored calcium, and in this way affects synaptic activity in dorsal horn interneurons, leading to sensitization of these neurons and pronociceptive patterns.<sup>22</sup> However,  $H_2O_2$  does not have only deleterious effects. At moderate concentrations,  $H_2O_2$  can act as an intracellular messenger that modulates neurotransmitter systems.<sup>58</sup> Thus, it is important to maintain the intracellular concentrations within physiologic levels, restricting somewhat the increase of this molecule that would occur with the increase in antioxidant enzyme activity.

The enzymes catalase and GPx are important tools for the detoxification of  $H_2O_2$ .<sup>60</sup> An increase in the activity of these enzymes in any conditions indicates a decrease in  $H_2O_2$  levels. Our previous results demonstrated that catalase activity increased after the third session of HVLA spinal manipulation and was higher after 6 sessions.<sup>28</sup> However, we described only a tendency to an increase in GPx activity.<sup>29</sup> In the present study, HVLA spinal manipulation for 5 weeks did not induce a significant change in catalase but did increase GPx activity. These changes can regulate the concentrations of  $H_2O_2$  in erythrocytes. At moderate concentrations,  $H_2O_2$  maintains its beneficial intracellular functions.<sup>58</sup> The change in the activity of catalase and GPx in different periods after treatment by HVLA spinal manipulation appears to indicate that this treatment, directly or indirectly, induced these changes, although they appear to depend on the period of intervention.

It is possible that the effects on RS of the length of time and the frequency of the treatment by HVLA spinal manipulation may be related to the response of the immune system. Studies have demonstrated a close relationship between the oxidative stress balance and the immune system. Cytokines may induce SOD expression, which appears to protect the normal tissue from damage.<sup>61</sup> Some cytokines, such as tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) and interleukin 1 $\beta$  (IL-1 $\beta$ ) and some reactive-oxygen intermediates are involved in the process of signal transduction that leads to activation of the SOD gene.<sup>61,62</sup> Interleukin 6 (IL-6) may also indirectly favor SOD expression by enhancing IL 1 and TNF- $\alpha$ , which magnifies the effect of these cytokines on SOD expression.<sup>61</sup> The relationship between cytokines and SOD activity must be interpreted with caution because the gene expression of SOD and its enzymatic activity may be regulated by different factors and independently of each other.<sup>63</sup>

Some studies suggest an increase in proinflammatory cytokines in the blood of patients with neck or lower back pain of mechanical origin.<sup>64,65</sup> In turn, the treatment with spinal manipulation appears to decrease the proinflammatory cytokines.<sup>65-68</sup> Subjects treated with a single spinal manipulation therapy showed a time-dependent attenuation of lipopolysaccharide-induced production of the inflammatory cytokines TNF and IL-1 $\beta$ .<sup>68</sup> Chiropractic manipulation (activator method) for 2 weeks induced a tendency to reduction in IL-6 levels.<sup>65</sup> Interestingly, comparison between this and our previous results shows that the reduction of IL-6 coincided with the tendency to reduction in SOD activity.<sup>29</sup> Thus, it is possible that the lower SOD activity after the patients with neck pain who were treated by HVLA spinal manipulation for 2 weeks may be due to the reduction in proinflammatory cytokines, probably IL-6. It would be interesting to examine the relationship between proinflammatory cytokines and RS parameters in patients treated by HVLA spinal manipulation.

In tissue inflammation, not only the reactive oxygen species was increased but also NO production.<sup>17</sup> Nitric

oxide is a gaseous free radical that is synthesized from L-arginine and may act as an important regulator of vasoregulation, neuronal transmission, immune response, and cell apoptosis.<sup>69</sup> Excessive production of NO after induction of calcium-independent inducible NO synthase has been proposed as a major factor involved in tissue damage.<sup>69</sup> Interestingly, Mazzetti et al<sup>70</sup> found high levels of NO metabolites in chondrocytes stimulated with IL-1 $\beta$  and TNF- $\alpha$ , and these levels were higher in chondrocytes from patients with osteoarthritis than in those patients with rheumatoid arthritis. An animal model of joint immobilization showed reversible neurodegenerative changes, which were related, in part, to NO-mediated oxidative stress.<sup>71</sup> In addition, levels of NO metabolites were higher in individuals with mechanical neck pain compared with healthy controls, which are probably related to the activation of proinflammatory mediators.<sup>64</sup>

Despite the wider variation in values of the NO metabolites in our study, the values were similar to those found by Teodorczyk-Injeyan et al.<sup>64</sup> This study found levels from 12 to 106  $\mu\text{mol/L}$  in patients with pain, whereas our results ranged from 47 to 161  $\mu\text{mol/L}$ . However, we determined NO<sub>2</sub> plus NO<sub>3</sub> levels, whereas they determined only NO<sub>2</sub> levels. According to these authors, high levels of NO combined with neuronal sensitization could contribute to the genesis of the pain state. The vertebral manipulation response, in turn, could down-regulate inflammatory mediators.<sup>66-68</sup> Our data are consistent with the assumption that NO contributes to pain symptoms. However, it is interesting that no significant change was observed in NO metabolites after the HVLA spinal manipulation. In agreement with our findings, another study with HVLA spinal manipulation showed no alteration in plasma levels of NO in healthy subjects, either immediately or 2 hours after the intervention.<sup>72</sup> The same authors found only a correlation with the pain sensitivity at the pressure-pain threshold. These authors suggested that NO can be involved in pain sensitization but may not be a key element in the analgesic effects of spinal manipulation. Our results reinforce this hypothesis.

However, it is necessary to use caution in analyzing the relationship between NO and HVLA spinal manipulation. Our study showed that this treatment increases GPx activity. This enzyme catalyzes the reduction of  $H_2O_2$  and organic hydroperoxides at the expense of glutathione.<sup>24</sup> Some authors have considered glutathione as an additional cofactor required for maximum activity of NO synthase, the enzyme responsible for synthesis of NO.<sup>73</sup> An increase in GPx activity induces greater consumption of glutathione. Thus, it can be hypothesized that the relationship between NO, glutathione, and GPx has some role in the lack of changes in NO after treatment by HVLA spinal manipulation.

The maintenance of NO levels may explain in part why the increase in SOD activity was not as pronounced as the

increase in GPx because it has been demonstrated that SOD activity is inhibited in the presence of increases in NO formation.<sup>74</sup> Further studies demonstrating the relationship between NO formation and SOD expression will be necessary to clarify the relationship between these molecules in patients with pain treated by HVLA spinal manipulation.

High-velocity, low-amplitude manipulation may cause changes not only in neuronal excitability but also in other physiologic parameters.<sup>2,4-6</sup> We demonstrated again that the HVLA spinal manipulation affects the oxidative status by increasing the activity of the antioxidant enzymes SOD and GPx. In contrast to our previous studies that showed an increase only in catalase activity, the activity of this enzyme did not change in the experimental conditions used here. In addition, we observed no significant changes in LOOHs and NO metabolites. Because the main difference between the studies was the length of time and the frequency of interventions by HVLA spinal manipulation, our results reinforce our hypothesis that the length of time and the frequency of the HVLA treatment are the determinants for these changes in the antioxidant activity in patients with nonspecific chronic neck or back pain. It is possible that the combination of factors such as neuronal excitability, inflammatory response, and oxidative status may be responsible for the entire picture and possibly make some difference in pain attenuation. The most important aspect is that HVLA spinal manipulation increases the activity of antioxidant enzymes. Because the literature shows a relationship between pain and oxidative and nitrosative parameters, changes in these enzymes might be related to the analgesic effect of HVLA spinal manipulation.

### Limitations

This study was performed with HVLA spinal manipulation treatment for 5 weeks, twice a week, in subjects with nonspecific neck or back pain, without a control group. It would be more enlightening to have a healthy control group under the same experimental procedures and also to have a control group of a different therapeutic modality or sham manipulation. It is necessary to consider that this study was not blind, and some placebo effect may have occurred. In addition, it is important to consider the time of the blood collection. In this study, blood was drawn 1 day after the end of treatment. We suggest that future studies assess oxidative and nitrosative parameters in blood collected at different times, including during the interval of treatment, for example, after 1 session of HVLA spinal manipulation. It is also necessary to analyze the oxidative and nitrosative parameters in the serum. The determinations should also include cytokines. Data obtained for women and men require caution in the interpretation because of the systemic influence of female hormones on pain sensitivity. Finally, in future studies, the number of patients should be increased.

### CONCLUSION

Our study showed that SOD and GPx activity but not catalase activity of the RBCs of patients with nonspecific chronic neck or back pain increased after 10 sessions of HVLA spinal manipulation. This treatment did not induce significant changes in the LOOHs and NO metabolites in the plasma of these patients. Although it is too early to speculate on the role of oxidative and nitrosative species in HVLA treatment, the results of the present study support the hypothesis that the effects of HVLA spinal manipulation on oxidative and nitrosative species depend on the length of time and the frequency of treatment. Because previous studies have shown a relationship between pain and oxidative and nitrosative parameters, changes in these enzymes might be related to the analgesic effect of HVLA spinal manipulation. However, further studies on this topic are crucial for better understanding of the temporal relationship between oxidative and nitrosative parameters and HVLA treatment. This study provides preliminary data for a randomized control trial.

### FUNDING SOURCES AND POTENTIAL CONFLICTS OF INTEREST

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Design (planned the methods to generate the results): C.K., W.A.P.  
Supervision (provided oversight, responsible for organization and implementation, writing of the manuscript): C.K., W.A.P.  
Data collection/processing (responsible for experiments, patient management, organization, or reporting data): C.K., A.K., A.H., M.S.M., F.C.K.D., A.P.K.R., T.S., A.K.  
Analysis/interpretation (responsible for statistical analysis, evaluation, and presentation of the results): C.K., A.H., A.P.K.R., A.K.  
Literature search (performed the literature search): C.K.  
Writing (responsible for writing a substantive part of the manuscript): C.K., W.A.P.  
Critical review (revised manuscript for intellectual content, this does not relate to spelling and grammar checking): W.A.P.

# **Suprasegmental Pain Inhibition**

## Three Major Drivers of Inflammation Related to Pain Perception

<b>Omega-6/Omega-3</b>	<b>Inflammatory Cytokines</b>	<b>Systemic Inflammation</b>
Excessive Inflammatory Prostaglandins and Leukotrienes	TNF-alpha  Interleukin-6	<u>Leaky Gut</u> Lectins  <u>Chronic Infection</u> Lyme Herpes Molds Etc.

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Spine (Phila Pa 1976). 2017 Dec 1;42(23):1810-1816. doi: 10.1097/BRS.0000000000002218.

# The Prevalence, Patterns, and Predictors of Chiropractic Use Among US Adults: Results From the 2012 National Health Interview Survey.

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## Abstract

**STUDY DESIGN:** Secondary analysis of a national survey.

**OBJECTIVE:** The aim of this study was to investigate the prevalence, patterns, and predictors of **chiropractic** utilization in the US general population.

**SUMMARY OF BACKGROUND DATA:** **Chiropractic** is one of the largest manual therapy professions in the United States and internationally. Very few details have been reported about the use of **chiropractic** care in the United States in recent years.

**METHODS:** Cross-sectional data from the 2012 National Health Interview Survey (n=34,525) were analyzed to examine the lifetime and 12-month prevalence and utilization patterns of **chiropractic** use, profile of **chiropractic** users, and health-related predictors of **chiropractic** consultations.

**RESULTS:** Lifetime and 12-month prevalence of **chiropractic** use were 24.0% and 8.4%, respectively. There is a growing trend of **chiropractic** use among US adults from 2002 to 2012. **Back pain (63.0%)** and neck pain (30.2%) were the most prevalent health problems for **chiropractic** consultations and the majority of users reported **chiropractic** helping a great deal with their health problem and improving overall health or well-being. A substantial number of

# The Potential Mechanisms of High-Velocity, Low-Amplitude, Controlled Vertebral Thrusts on Neuroimmune Function: A Narrative Review

Medicina

May 27, 2021; Vol. 57; No. 6; pp. 536

Heidi Haavik, Imran Khan Niazi, Nitika Kumari, Imran Amjad, Jenna Duehr, Kelly Holt: This study cites 301 references. HVLA = High-Velocity Low Amplitude

“This review aims to elucidate the underlying mechanisms that can explain the HVLA controlled vertebral thrust–neuroimmune link and discuss what this link implies for clinical practice and future research needs.”

## KEY POINTS FROM THIS ARTICLE:

- 1) “The current COVID-19 pandemic has necessitated the need to find healthcare solutions that boost or support immunity.”
- 2) “There is some evidence that high-velocity, low-amplitude (HVLA) controlled vertebral thrusts have the potential to modulate immune mediators.”
  - 21 published papers were found that explored the impact of HVLA controlled vertebral thrusts on neuroimmune markers; 18 found a significant effect. **[Important] 18/21 = 86%**
  - “HVLA controlled vertebral thrusts influence the levels of immune mediators in the body, including neuropeptides, inflammatory markers, and endocrine markers.”
  - The mechanisms most for how HVLA manipulation could impact immune markers “are most likely due to the known changes in proprioceptive processing that occur within the central nervous system (CNS), in particular within the prefrontal cortex.” **[Key Point]**
    - “The prefrontal cortex is involved in the regulation of the autonomic nervous system, the hypothalamic–pituitary–adrenal axis and the immune system.”
- 3) “There are biologically plausible direct and indirect mechanisms that link HVLA controlled vertebral thrusts to the immune system, suggesting HVLA controlled vertebral thrusts have the potential to modulate immune function.” **[Key Point]**
- 4) Pain-related stress alters neuro-immune interactions.
  - Stress-induced sympathetic nervous system activity alters vertebral motor control.

12) “Adjusting [vertebral subluxation or joint dysfunction] problems in the spine alters the afferent input from the small paraspinal muscles around the spine and skull to the brain.” **[Key Point]**

- “This affects how the CNS processes and integrates all subsequent sensory input, such that the brain senses more accurately what is happening in and around the body, so there is improved brain–body awareness, adaptability, and coordination and therefore, better function.”
- “One of the keys to this proposed model is the proprioceptive role played by the small intervertebral muscles closest to the spine and skull.”
- “Maladaptive changes in neural function affect the way we respond to our internal and external environment, potentially leading to a lack of adaptability and resilience and the development of symptoms, diseases, and disorders.”
- “By adjusting [vertebral subluxation or joint dysfunction] problems, the associated rapid stretch of the deep paraspinal muscles enhances proprioceptive afferent input from these muscles; this is thought to improve brain–body awareness, adaptability, and resilience.”
- “It is quite clear that HVLA controlled vertebral thrusts can impact vital parts of the brain involved in creating internal and external schemas or maps of the internal and external environment.”

13) “There is evidence suggesting that chiropractic HVLA controlled vertebral thrusts have a significant effect on the prefrontal cortex.” **[Key Point]**

- “The prefrontal cortex is a high-level processing centre of the CNS and is described as the executive controller of the CNS.”
- “The prefrontal cortex is also known to be vital for proper immune system function.”
- “The prefrontal cortex is critically involved in regulating the autonomic nervous system, the endocrine system and therefore the immune system.”
- “The prefrontal cortex regulates the ANS, directly activates the vagal cholinergic anti-inflammatory system, and impacts the hormonal system, in particular the hypothalamus–pituitary–adrenal (HPA) axis.” **[Key Point]**
- “HVLA controlled vertebral thrusts influence the CNS, in particular the prefrontal cortex, which in turn has an impact on the ANS, HPA axis, and immune system, this provides a biologically plausible mechanism for how HVLA controlled vertebral thrusts may impact immune function.” **[Key Point]**

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## Measureable changes in the neuro-endocrinal mechanism following spinal manipulation.

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### Abstract

The autonomic nervous system and the hypothalamic-pituitary-adrenal axis have been shown to be dysfunctional in a number of chronic pain disorders. Spinal manipulation is a therapeutic technique used by manual therapists, which may have widespread neuro-physiological effects. The autonomic nervous system has been implicated to modulate these effects. A theory is proposed that spinal manipulation has the potential to be used as a tool in restoring the autonomic nervous system balance. Further, it is also hypothesised that through its anatomical and physiological connections, the autonomic nervous system activity following a thoracic spinal manipulation may have an effect on the hypothalamic-pituitary-adrenal axis and therefore pain and healing via modulation of endocrine and physiological processes. To substantiate our hypothesis we provide evidence from manual therapy studies, basic science and animal studies. According to the proposed theory, there will be measurable changes in the neuro-endocrinal mechanisms following a thoracic spinal manipulation. This has far-reaching implications for manual therapy practice and research and in the integration of spinal manipulation in the treatment of a wide array of disorders.

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[Indexed for MEDLINE]



Review

# The Potential Mechanisms of High-Velocity, Low-Amplitude, Controlled Vertebral Thrusts on Neuroimmune Function: A Narrative Review

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**Abstract:** The current COVID-19 pandemic has necessitated the need to find healthcare solutions that boost or support immunity. There is some evidence that high-velocity, low-amplitude (HVLA) controlled vertebral thrusts have the potential to modulate immune mediators. However, the mechanisms of the link between HVLA controlled vertebral thrusts and neuroimmune function and the associated potential clinical implications are less clear. This review aims to elucidate the underlying mechanisms that can explain the HVLA controlled vertebral thrust–neuroimmune link and discuss what this link implies for clinical practice and future research needs. A search for relevant articles published up until April 2021 was undertaken. Twenty-three published papers were found that explored the impact of HVLA controlled vertebral thrusts on neuroimmune markers, of which eighteen found a significant effect. These basic science studies show that HVLA controlled vertebral thrust influence the levels of immune mediators in the body, including neuropeptides, inflammatory markers, and endocrine markers. This narrative review discusses the most likely mechanisms for how HVLA controlled vertebral thrusts could impact these immune markers. The mechanisms are most likely due to the known changes in proprioceptive processing that occur within the central nervous system (CNS), in particular within the prefrontal cortex, following HVLA spinal thrusts. The prefrontal cortex is involved in the regulation of the autonomic nervous system, the hypothalamic–pituitary–adrenal axis and the immune system. Bi-directional neuro-immune interactions are affected by emotional or pain-related stress. Stress-induced sympathetic nervous system activity also alters vertebral motor control. Therefore, there are biologically plausible direct and indirect mechanisms that link HVLA controlled vertebral thrusts to the immune system, suggesting HVLA controlled vertebral thrusts have the potential to modulate immune function. However, it is not yet known whether HVLA controlled vertebral thrusts have a clinically relevant impact on immunity. Further research is needed to explore the clinical impact of HVLA controlled vertebral thrusts on immune function.

**Keywords:** high-velocity; low-amplitude thrust; HVLA; chiropractic; spinal manipulation; central nervous system; prefrontal cortex; immune system; endocrine system



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## 1. Introduction

The COVID-19 pandemic has resulted in significant global morbidity and mortality [1,2], especially amongst individuals who are immunocompromised, such as older people and those with underlying medical conditions [2,3]. The current pandemic and

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[Science](#). 1973 Mar 9;179(4077):1011-4.

## Opiate receptor: demonstration in nervous tissue.

[Pert CB](#), [Snyder SH](#).

### Abstract

Tritiated naloxone, a powerful opiate antagonist, specifically binds to an opiate receptor of mammalian brain and guinea pig intestine. Competition for the opiate receptor by various opiates and their antagonists closely parallels their pharmacological potency. The opiate receptor is confined to nervous tissue.

PMID: 4687585

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Candace B. Pert, Ph.D.

*Foreword by Deepak Chopra, M.D.*



1997

# Molecules of Emotion

THE SCIENCE  
BEHIND MIND-BODY  
MEDICINE

"Candace B. Pert . . . has managed to take the study of the emotional connection to the body . . . and present this information in not only an understandable manner, but an enjoyable one."

—Caroline Myss, Ph.D., author of *Why People Don't Heal and How They Can*

**Candace Beebe Pert** (June 26, 1946 – September 12, 2013) was an American neuroscientist and pharmacologist who discovered the opiate receptor, the cellular binding site for endorphins in the brain. In 1974 Candace Pert earned a Ph.D. in pharmacology from **Johns Hopkins University** School of Medicine, where she worked in the laboratory of Solomon Snyder and discovered the brain's opiate receptor.

•••••

Science; 1973 Mar 9;179(4077):1011-4.

**Opiate receptor: demonstration in nervous tissue.**

Pert CB, Snyder SH; John Hopkins

Tritiated naloxone, a powerful opiate antagonist, specifically binds to an opiate receptor of mammalian brain. Competition for the opiate receptor by various opiates and their antagonists closely parallels their pharmacological potency. **The opiate receptor is confined to nervous tissue.**

•••••

Science; 1977 Jul 8;197(4299):183-6.

**Pain relief by electrical stimulation of the central gray matter in humans and its reversal by naloxone.**

Hosobuchi Y, Adams JE, Linchitz R

Relief of intractable pain was produced in six human patients by stimulation of electrodes permanently implanted in the periventricular and periaqueductal gray matter. These results suggest that satisfactory alleviation of persistent pain in humans may be obtained by electronic stimulation. "periaqueductal gray pain"

**The Brain, The Last Frontier,**

Richard Restak, MD  
Warner Books, 1979

"Within the **periaqueductal gray**, a deep-seated brainstem area lying along the floor of the third ventricle, neurosurgeons at the University of California in San Francisco placed indwelling stimulating electrodes for pain relief in six patients afflicted with chronic, unremitting pain. Whenever the patients began to experience pain, they were able to shut it off via the activation of a battery-operated stimulator about the size of a pack of cigarettes. After activating the stimulator, all six patients—in accordance with earlier findings in other pain patients—experienced **dramatic, long-lasting, and repeatable pain relief.**"

"In order to test the hypothesis that pain relief was genuine and not just an example of a **'placebo response,'** one patient was outfitted with a stimulator containing a 'dead' battery. The patient, a fifty-one-year-old woman with severe back and leg pain caused by cancer of the colon, anxiously reported that her pain had returned and the stimulator 'wasn't working.' Replacement of a new battery led to immediate pain relief." pp. 341-342

## Descending Pain Inhibitory Control System

Descending pathways modify the activity of all ascending systems, including responses to noxious stimuli.

The best understood of these is the raphespinal tract, which arises from neurons in the raphe nuclei of the medullary reticular formation, mainly those of the nucleus raphes magnus, and use serotonin as a neurotransmitter.

The nucleus raphes magnus is itself influenced by descending fibers from the periaqueductal gray matter of the midbrain.

Electrical stimulation of the nucleus raphes magnus or the periaqueductal gray matter causes profound analgesia.

An electrode stereotaxically implanted into the periaqueductal gray matter enables a patient to relieve pain instantly when switching on an electrical stimulator. The analgesia often lasts for several hours after cessation of the stimulation.

Barr's The Human Nervous System, An Anatomical Viewpoint, John A Kiernan, Lippincott-Raven, 1998, pp351-352.

.....

Electrical stimulation (through implanted electrodes) of the periaqueductal gray of the midbrain causes analgesia so profound that major surgery can then be performed without the aid of an anesthetic.

Stimulation of the periaqueductal gray of humans can ameliorate intractable pain.

The periaqueductal gray receives inputs from the hypothalamus and several cortical areas. **[IMPORTANT]**

Efferents from the periaqueductal gray then project to one of the raphe nuclei (nucleus raphe magnus) of the rostral medulla and caudal pons, and to adjacent areas of the medullary reticular formation.

These areas in turn project to superficial laminae of the posterior horn via a pathway that travels through the posterior part of the lateral funiculus, suppressing the transmission of pain information by spinothalamic neurons.

Opium and its derivatives, especially morphine, have long been used for pain control, and one way they work is by activating the periaqueductal gray-raphe nucleus pain-control system at multiple levels.

Opiate receptors are found in abundance in the periaqueductal gray, nucleus raphe magnus, and superficial laminae of the posterior horn.

Serotonin-containing neurons of the raphe magnus, when stimulated by projection neurons of the periaqueductal gray, inhibit spinothalamic tract neurons either directly or by making excitatory synapses on inhibitory enkephalin containing neurons in the substantia gelatinosa (dorsal horn).

Microinjection of opiates at any of these three sites causes analgesia.

Opiate receptors are also found at a number of other sites in the CNS, accounting for some of the other effects of morphine and related drugs.

The system can be activated by inputs that stimulate the periaqueductal gray.

Serotonergic neurons are found at most levels of the brainstem, but are concentrated in the raphe nuclei.

Serotonergic projections from the rostral raphe nuclei reach the forebrain, providing a cortical innervation that is most dense in sensory and limbic areas.

Serotonergic neurons play a role in modulating the general activity levels of the CNS.

In addition, it seems clear that the serotonin system has at least one other important role, as part of the descending pain control system.

The Human Brain, An Introduction To Its Functional Anatomy, John Nolte, Mosby, 1999, pp. 270-271, p. 274.

.....

An even more potent counterbalance to nociception [other than segmental mechanoreceptor stimulation to close the segmental pain gate] has been found.

Stimulation of the periaqueductal gray region, produces a profound analgesia.

Periaqueductal gray neurons make excitatory connections with neurons of the rostroventral medulla, in particular with serotonergic neurons in the midline of the nucleus raphe magnus.

These serotonergic neurons in the midline of the nucleus raphe magnus project via the dorsal part of the lateral funiculus to the spinal cord and make inhibitory connections with neurons in the dorsal horn.

Stimulation of these neurons inhibits dorsal horn neurons, including neurons of the spinothalamic tract that respond to noxious stimulation.

Other descending inhibitory systems that suppress the activity of nociceptive neurons in the dorsal horn originate in the noradrenergic locus ceruleus and other nuclei of the medulla and pons.

These descending projections block the output of neurons in the dorsal horn by both direct and indirect inhibitory actions.

They also interact with endogenous opioid-containing circuits in the dorsal horn.

Opiates such as morphine and codeine are effective analgesic agents.

The periaqueductal gray region is the most sensitive sites for eliciting opiate (such as morphine) induced analgesia.

Morphine and other opiates produce analgesia by activating descending inhibitory pathways.

Opiates are endogenous peptides that cause powerful analgesia by acting directly on the central nervous system (rather than on pain receptors in the periphery).

There are three classes of endogenous opioid peptides, the best known are the enkephalins.

Morphine is a chemical that binds to opioid peptide receptor sites and causes powerful analgesia.

There are three major classes of opiate receptors: *mu*, *delta*, and *kappa*.

The muOR are highly concentrated in the periaqueductal gray matter, the ventral medulla, and in the dorsal horn of the spinal cord, all of which are important in the regulation of pain.

Opiates attach to opiate receptor sites (like muOR) and cause hyperpolarization of nociceptive membrane potentials, making them harder to depolarize (harder to reach excitation threshold and to fire an action potential).

Opiate receptors are found in many other sites of the central and peripheral nervous systems, which explains the many other physiological effects of systemically administered morphine.

Principles of Neural Science, Eric Kandel, et.al., 2000, pp. 482-485.

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An important aspect of nociception is that transmission along pain pathways is modulated by descending systems.

**Stimulation of the periaqueductal gray matter leads to a loss of sensitivity to painful stimuli.**

The mechanism for this effect is an inhibition of transmission along nociceptive pathways at the spinal level.

This finding led to the development of therapies for intractable pain that involved stimulating the periaqueductal gray with implanted electrodes. Such stimulation alleviates pain, but patients do not lose tactile sensitivity.

Descending modulation of pain sensitivity is mediated by the descending projections from the periaqueductal gray to two nuclear groups in the medulla: the raphe nucleus, which lies at the midline, and neurons in the lateral portion of the reticular formation.

These neurons in turn give rise to descending projections to the spinal cord that travel in the dorsolateral funiculus and terminate in the dorsal horn.

The axons from the raphe nucleus contain the neurotransmitter serotonin (5-HT); the descending axons from the reticular formation contain norepinephrine.

The descending circuits that modulate transmission along nociceptive pathways are thought to operate in part by using opioid peptides as their neurotransmitter.

When activated, these neurons release enkephalin near the synapses between the primary afferent and the second order neuron.

Enkephalin then inhibits transmission between the primary afferent and the second order neuron.

**It is thought that enkephalin acts both presynaptically and postsynaptically,** that is, by inhibiting release from primary afferent terminals and by exerting a postsynaptic inhibitory action on the second-order neurons of the nociceptive pathway.

Opiate-containing neurons in the periaqueductal gray and medulla activate neurons that give rise to the descending pathways.

**Functional Neuroscience,** Oswald Steward, Springer, 2000, pp. 218-219.

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# Wall and Melzack's Textbook of **Pain**

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**Fifth Edition**

**Edited by**

**Stephen B McMahon** FMedSci

Sherrington Professor of Physiology  
Director, London Pain Consortium  
King's College London  
London, UK

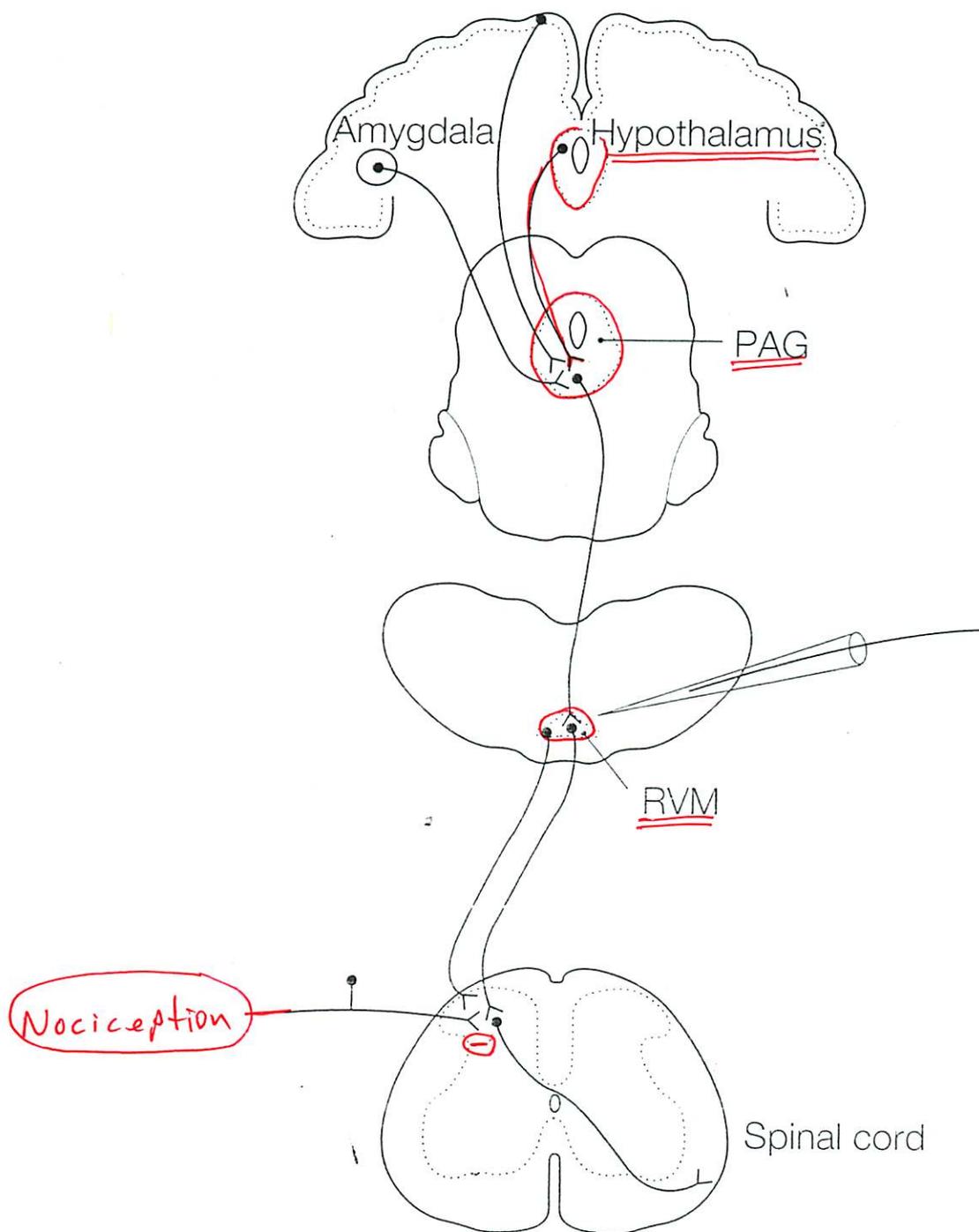
**Martin Koltzenburg** MD FRCP

Honorary Consultant Neurologist  
The National Hospital for Neurology and Neurosurgery  
Professor of Pain Research  
Institute of Child Health and Institute of Neurology  
University College London  
London, UK

2006



# Descending Pain Inhibitory System



## **The Initial Effects of a Cervical Spine Manipulative Physiotherapy Treatment on the Pain and Dysfunction of Lateral Epicondylalgia**

*Pain*; November 1996; Vol. 68; No. 1; pp. 69-74.

Bill Vicenzino, David Collins, Anthony Wright; University of Queensland

"A significant treatment effect beyond placebo or control was demonstrated."

"This study has demonstrated a clear hypoalgesic effect of a manipulative therapy technique in the period immediately following its application in a group of patients with lateral epicondylalgia."

"The beneficial effects of treatment [cervical manipulation] may continue after its application."

The author's theoretical model to explain their results involved manipulative therapy activation of the hypoalgesic effects of the endogenous supraspinal pain inhibitory systems.

"The [manipulative] treatment technique used in this study provided a non-noxious sensory input at the cervical spine which resulted in a reduction of elbow pain that outlasted the duration of its application." This is thought to activate the descending pain inhibitory system [DPIS] as a major component of their pain-relieving effects."

The DPIS is activated by stimulation of the periaqueductal grey (PAG).

"These findings indicate that manipulative therapy may constitute an adequate physical stimulus for activating DPIS."

A common finding in other studies "was the predominance of hypomobility at the lower cervical motion segments. It is feasible that part or all of the impairment in this study were "projected from the hypomobile cervical spine motion segment(s), and that the improvements gained following application of the [manipulative] technique resulted from treating the source of the pain."

"Manipulative therapy [may] recruit the DPIS, through which it exerts a portion or all of its pain relieving effects. That is, manipulative therapy applied to the cervical spine produces a sensory input which could be sufficient to activate DPIS."

"In a group of patients with LE, a manipulative therapy treatment technique applied to the lower cervical spine produced hypoalgesia at the elbow as manifest by increased pressure pain threshold, increased grip strength, improved neurodynamics and reduced pain over a 24 h period. This finding substantiates clinical observations that manipulative therapy is capable of producing improvements in pain and function immediately following application."

**The Role of the Descending Inhibitory Pain Mechanism in Musculoskeletal Pain Following High-Velocity, Low Amplitude Thrust Manipulation**  
**A Review of the Literature**

**Journal of Back and Musculoskeletal Rehabilitation**  
**2014; Vol. 27; No. 4; pp. 377–382**

Christos Savva, Giannis Giakas, Michalis Efstathiou

“The purpose of this review is to explore the role of the DIPM (descending inhibitory pain mechanism) in musculoskeletal pain following HVLAM (high-velocity, low amplitude thrust manipulation) as well as to identify the pain-relieving importance of this technique within clinical practice.”

KEY POINTS FROM THIS ARTICLE:

- 1) “Musculoskeletal pain is one of the most common complaints for which patients attend hospitals.”
- 2) “Musculoskeletal disorders often lead to chronic disability and increases the expenses of public health.”
- 3) “Patients who suffer from musculoskeletal pain often report difficulties and limitations to perform their daily activities and job tasks and often present impairments in their physical performance, loss of function and reduced quality of life.”
- 4) “Based on the kinetic chain principles that the upper and lower limb along with the spine is a kinetic chain of linked segments working together to perform daily movement and activity, the development of painful musculoskeletal disorders in these regions provoke muscle imbalances and alters the patient’s normal movement patterns.”
- 5) “HVLAM is an alternative treatment method and it is used as an analgesic modality for the rehabilitation of musculoskeletal dysfunctions including low back pain, neck pain, chronic ankle sprain, cervicogenic headache and dizziness etc.”
- 6) HVLAM “has been used by physiotherapists, osteopaths and chiropractors for more than 2000 years and it is recommended by the majority of international clinical guidelines due to its immediate analgesic effect on musculoskeletal pain.”
- 7) “The anti-nociceptive effect of high-velocity, low amplitude thrust manipulation (HVLAM) has been recognized by numerous systematic reviews.”
- 8) “Many studies have investigated the mechanism of hypoalgesia induced by the application of manipulation in humans and animals suggesting that, the excitation of the descending inhibitory pain mechanism (DIPM) might play the most important role for musculoskeletal pain relief.”

- 9) An increasing number of studies have suggested that HVLAM may excite the descending inhibitory pain mechanism (DIPM), which “might play the most important role for musculoskeletal pain relief.”
- 10) “Findings from current literature support that HVLAM has a profound influence on nociceptive stimulus via the possible activation of the DIPM.”
- 11) HVLAM “activates the periaqueductal gray region area of the midbrain, stimulates the noradrenergic descending system and at the level of the spinal cord, the nociceptive afferent barrage is reduced and mechanical hypoalgesia is induced.”
- 12) “The clinical importance of the activation of the DIPM should not be ignored since the resulted analgesic effect of this technique can provide a window of opportunity to restore impaired physical performance and disability.”
- 13) “Noxious stimuli generated by pathology of the musculoskeletal system are initially transferred to the dorsal horn of the spinal cord and then to the pain center located in the cerebral cortex of the brain.” **[1]**
- 14) “The PAG [periaqueductal gray] has been found to be an important component of the central nervous system with regard to post-manipulation hypoalgesia.” The DIPM projected from the periaqueductal gray region (PAG) of the midbrain to the dorsal horn of the spinal cord, has a profound role in regulating pain related signals at the spinal cord level. **[2]**
- 15) Activation of the DIPM inhibits the nociceptive afferent barrage at the level of the spinal cord and produces immediate analgesic effect on musculoskeletal pain.
- 16) From the PAG to the spinal cord, two different descending systems exist:
- The noradrenergic control system utilizes noradrenaline [norepinephrine] to inhibit pain. When this system is activated, it causes a *temporary excitation* of the sympathetic nervous system.
  - The serotonergic control system which uses the serotonin to increase the thermal nociceptive threshold. When this system is activated, it produces sympathetic *inhibition*.
- 17) HVLAM provokes an immediate activation of the PAG **[2]**, excites the noradrenergic [norepinephrine] descending system and produces pain inhibition along with a *period* of sympathetic excitation. “The mechanical hypoalgesic effect occurs within minutes of manipulation and is associated with an increase in pressure pain threshold.” “HVLAM does not modulate sensitivity to thermal pain suggesting that the serotonergic control system may not be stimulated.”

18) "Both mobilization and manipulation techniques induce hypoalgesia via the activation of DIPM." Both techniques produce hypoalgesia through the exact same mechanism.

19) The analgesic effect of mobilization and manipulation occurs within minutes as a consequence of sympathetic excitation, but the "evaluation of these techniques in the next few hours could reveal thermal hypoalgesia and sympathetic inhibition."

**[Important]**

20) "HVLAM used as an analgesic modality due to the possible activation of the DIPM can provide a window of opportunity to manage patients' symptoms and retrain the impaired motor function."

21) "When using HVLAM to produce pain inhibition, the patient is able to perform pain-free movements which were restricted due to pain."

22) To inhibit pain, HVLAM can be applied on the injured joint or on a joint proximal to the affected joint. **[Adjusting the precise painful joint is not necessary because adjacent joints are also capable of initiating the DIPM].**

23) HVLAM, through its immediate analgesic effect on musculoskeletal pain, can enable physiotherapists, osteopaths and chiropractors to "improve the limited joint mobility and restore the muscle imbalance around the area of symptoms."

24) "Activation of the DIPM might play the most important role with regard to post-manipulation hypoalgesia." **[Key Point]**

25) "HVLAM combined with conventional treatment such as strengthening, stretching and functional exercises can therefore contribute to improve range of motion, increase joint function and integrity and treat the altered proprioceptive input and movement patterns in order to restore impaired physical performance and disability."

COMMENTS FROM DAN MURPHY [[See Graphic Below](#)]

The key message from this study is that the pain reduction noted immediately after being adjusted *is not* primarily attributed to biochemistry/neurology changes at the adjusted joint, but rather are primarily attributed to activating the supra-segmental descending pain inhibitory control system, which involves the periaqueductal gray matter of the mesencephalon. This is very important because it is established that the periaqueductal gray is itself influenced by the hypothalamus. This adds to the evidence for explaining how spinal adjusting can influence a number of aspects of systemic physiology, as the hypothalamus controls whole body homeostasis, the pituitary gland, and the autonomic nervous system.

*"An important book."*

DAVID S. LUDWIG, MD, PHD, PROFESSOR, HARVARD MEDICAL SCHOOL;  
NEW YORK TIMES BESTSELLING AUTHOR

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***SUPERCHARGE YOUR BRAIN,  
REVERSE MEMORY LOSS, AND  
REMEMBER WHAT MATTERS MOST***

THE OFFICIAL PROGRAM OF THE AMEN CLINICS

**DANIEL G. AMEN, MD**

**“The prefrontal cortex (which is involved with focus, forethought, judgment, and impulse control) is the area of the brain most densely populated with mitochondria.”**

# THE BRAIN AND PAIN

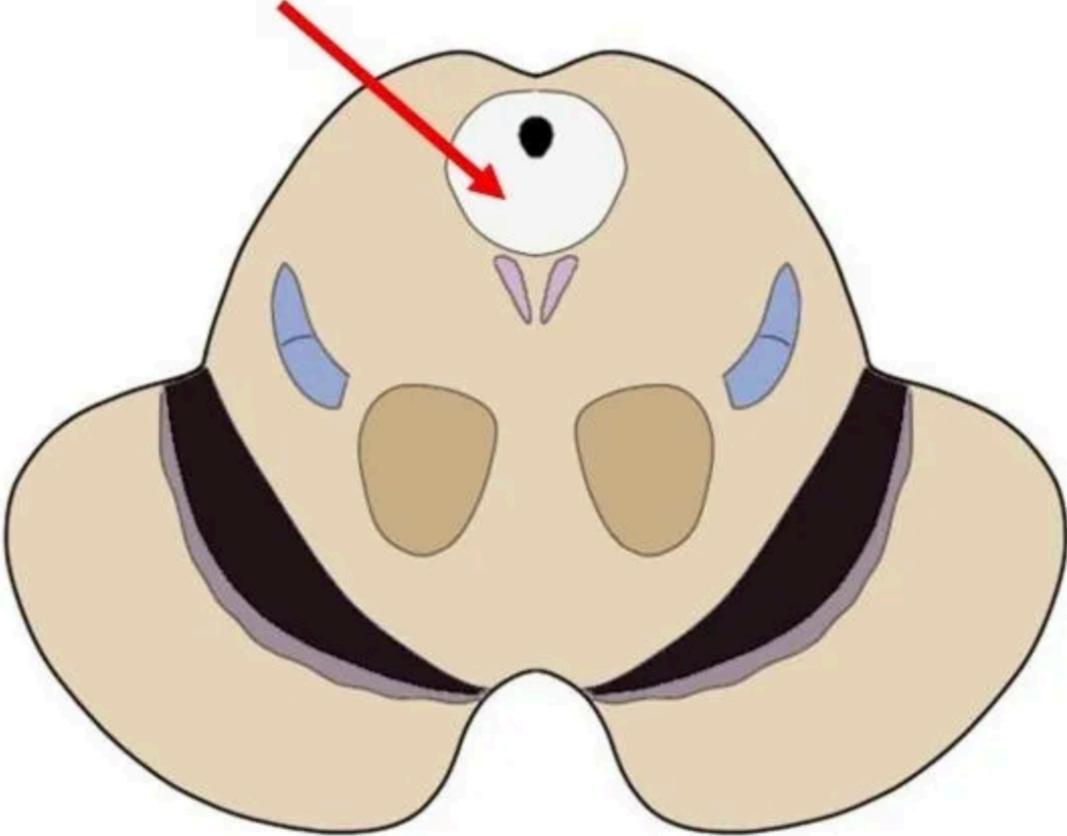
Breakthroughs in Neuroscience

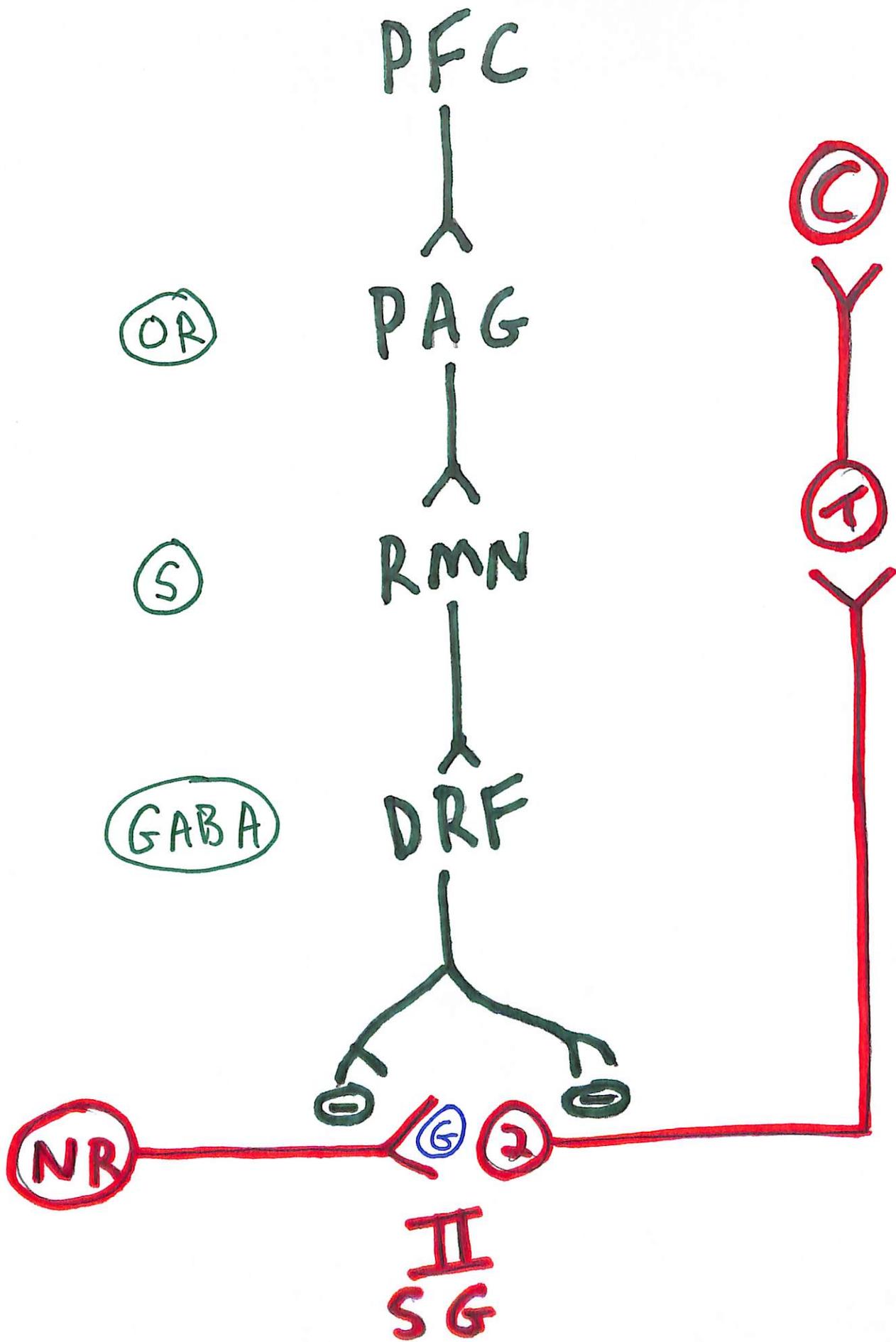


RICHARD AMBRON

Illustrated by Ahmet Sinav

PERIAQUEDUCTAL GRAY





## **Richard Ambron**

emeritus professor of pathology, anatomy, and cell biology at Columbia University

### **PAG = periaqueductal gray**

"Studies show that electrical stimulation of the PAG could diminish pain without interfering with touch, pressure, or temperature sensations."

The PAG is "placed" "as an essential center for the perception of pain."

The PAG blocks "synaptic transmission between the first and second-order neurons."

"Activation of neurons in the PAG results in the release of the endogenous opiates in the spinal cord that shuts down the nociceptive pathway to the thalamus."

"The suppression of injury-induced pain is most likely due to the activation of the opioidergic neurons in the PAG."

### **PFC = prefrontal cortex**

"The prefrontal cortex (PFC) comprises the cortical neurons found in the frontal region of the frontal lobe. Its functions are probably the most important for what separates us from other primates."

An increase in the activity of circuits in the PFC reduce responses to noxious stimulus.

Activation of circuits within the "PFC will have a significant impact on the experience of pain."

"The modulation of painfulness is associated with increased activity in the PFC."

"We know that there are connections between the PFC and the PAG."

"The activation of the PAG is controlled by circuits in the PFC."

"Inputs from the PFC to the PAG result in the activation of the opioidergic neurons whose axons descend to the spinal cord, where the release of opioids prevents synaptic transmission at the synapse between the first- and second-order neurons in the nociceptive pathway."

.....

"Only the cell body contains the genome and machinery for synthesis of proteins and other macromolecules."

## **Richard Ambron**

emeritus professor of pathology, anatomy, and cell biology at Columbia University

“*Glutamate* in the primary neurotransmitter for nociception.”

- It is the concentration of glutamate that matters.

“The entry of  $Ca^{++}$  [is] especially important because they initiate many events that are essential for pain.”

Glutamate opens the NMDA receptor. “The NMDA has a preference for  $Ca^{++}$ .”

The channel is blocked by the magnesium ion ( $Mg^{++}$ ).

Removal of the  $Mg^{++}$  blockade allows an influx of  $Ca^{++}$ .

Reduced  $Mg^{++}$  leads to chronic nociceptive central sensitization.

**"A bold and heroic work [that] will stand  
shoulder to shoulder with Rachel Carson's *Silent Spring*."**

—DAVID PERLMUTTER, MD, #1 *New York Times*  
bestselling author of *Grain Brain* and *Brain Wash*

# TOXIC LEGACY

HOW THE WEEDKILLER  
GLYPHOSATE  
IS DESTROYING OUR HEALTH  
AND THE ENVIRONMENT

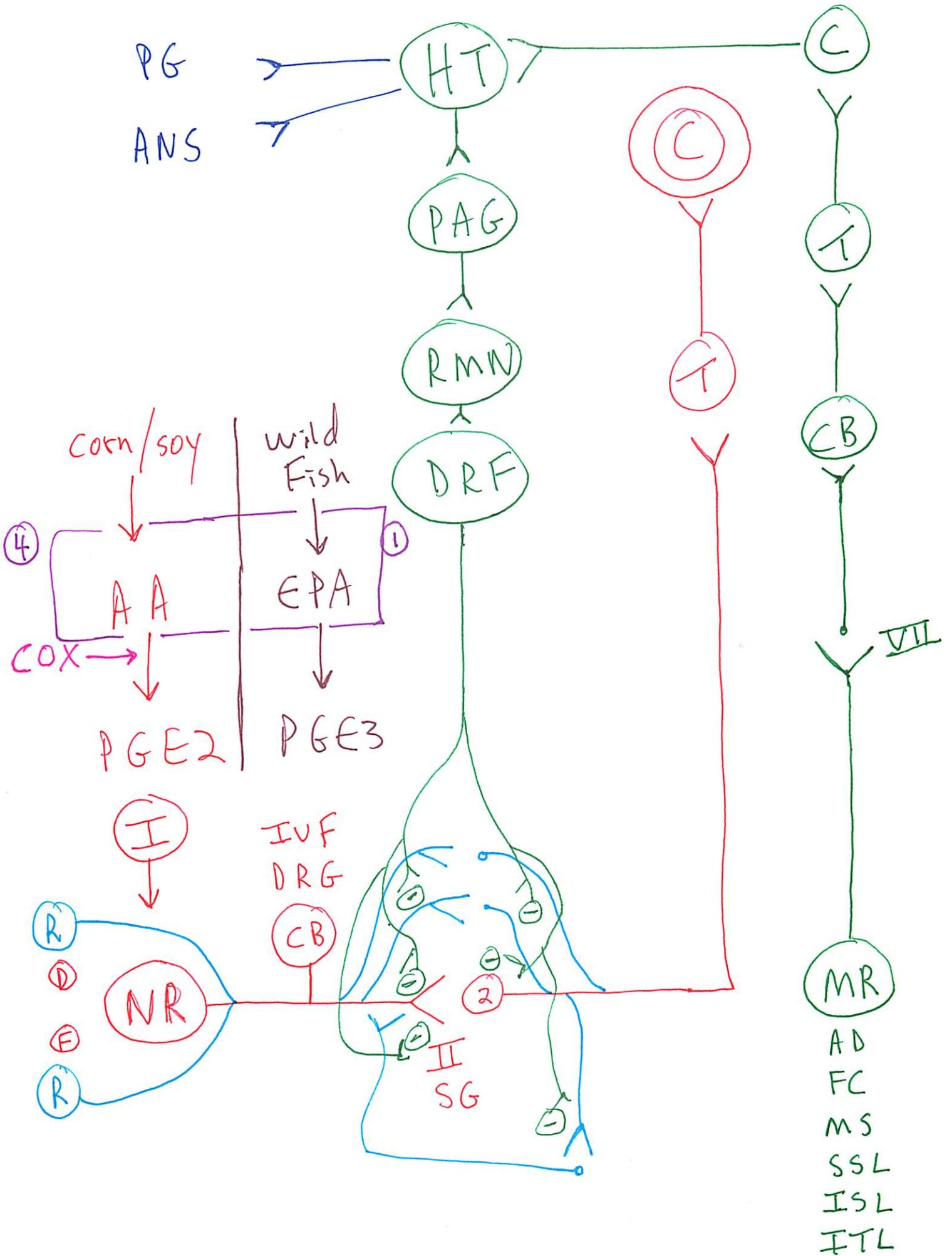
*One Scientist's Determined Quest to Reveal the Truth*

STEPHANIE SENEFF, PhD

2021



PG  
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# **Vestibular Nucleus**

# Neuroanatomy

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Duane E. Haines, Ph.D.

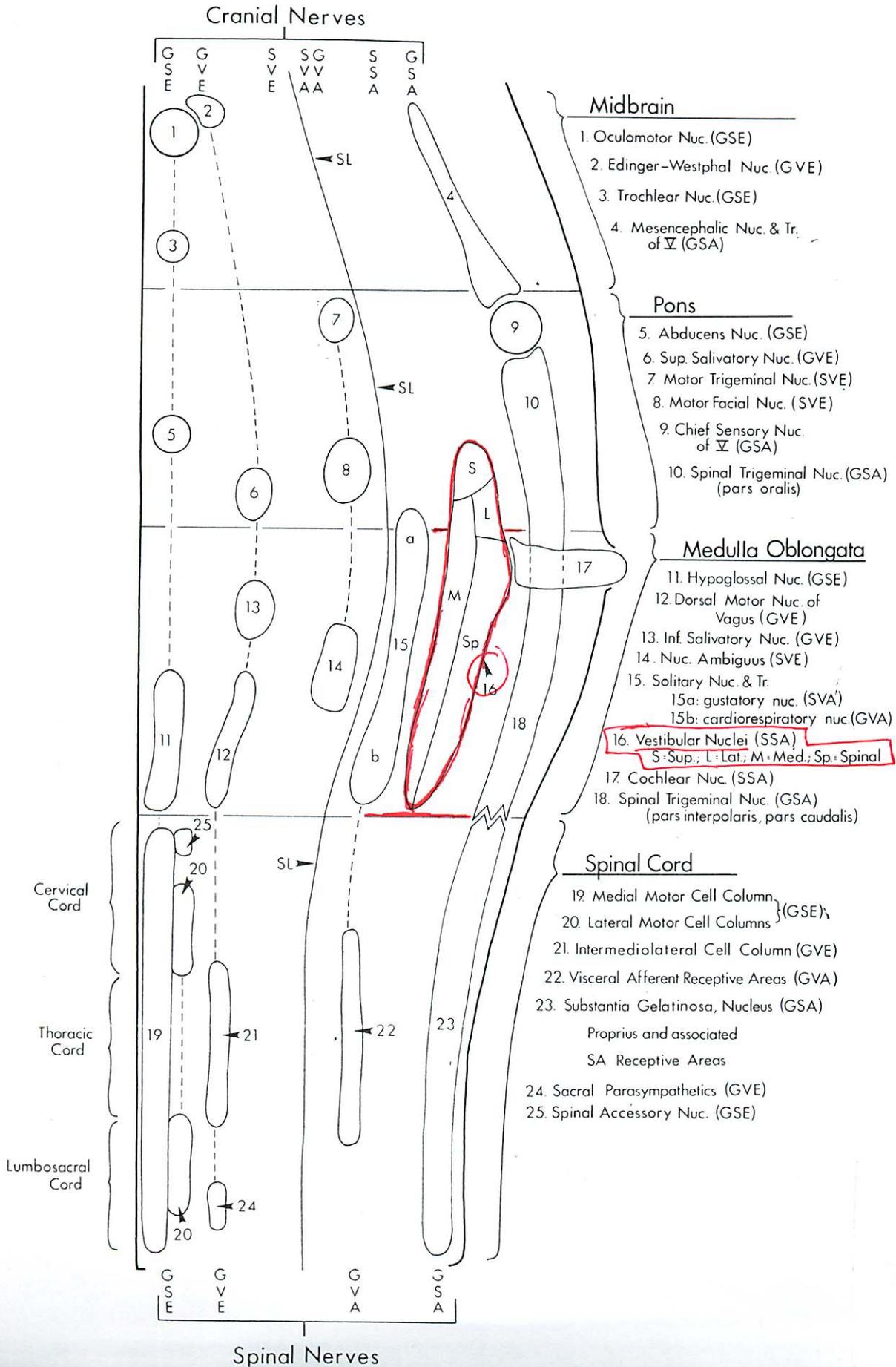
Professor and Chairman  
Department of Anatomy  
The University of Mississippi Medical Center  
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# BARR'S THE HUMAN NERVOUS SYSTEM

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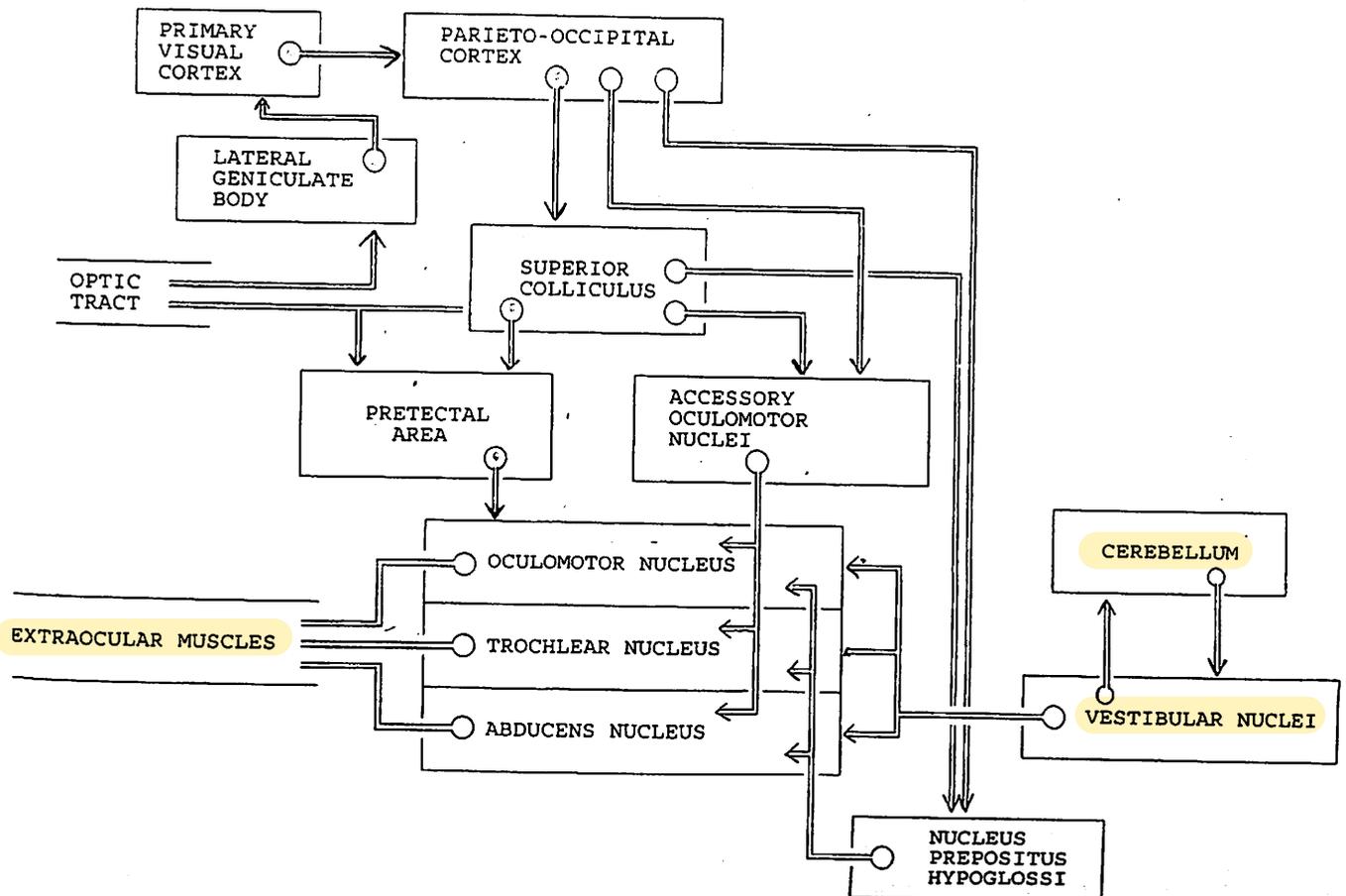
*Professor*

*Department of Anatomy and Cell Biology*

*The University of Western Ontario*

*London, Canada*

1998



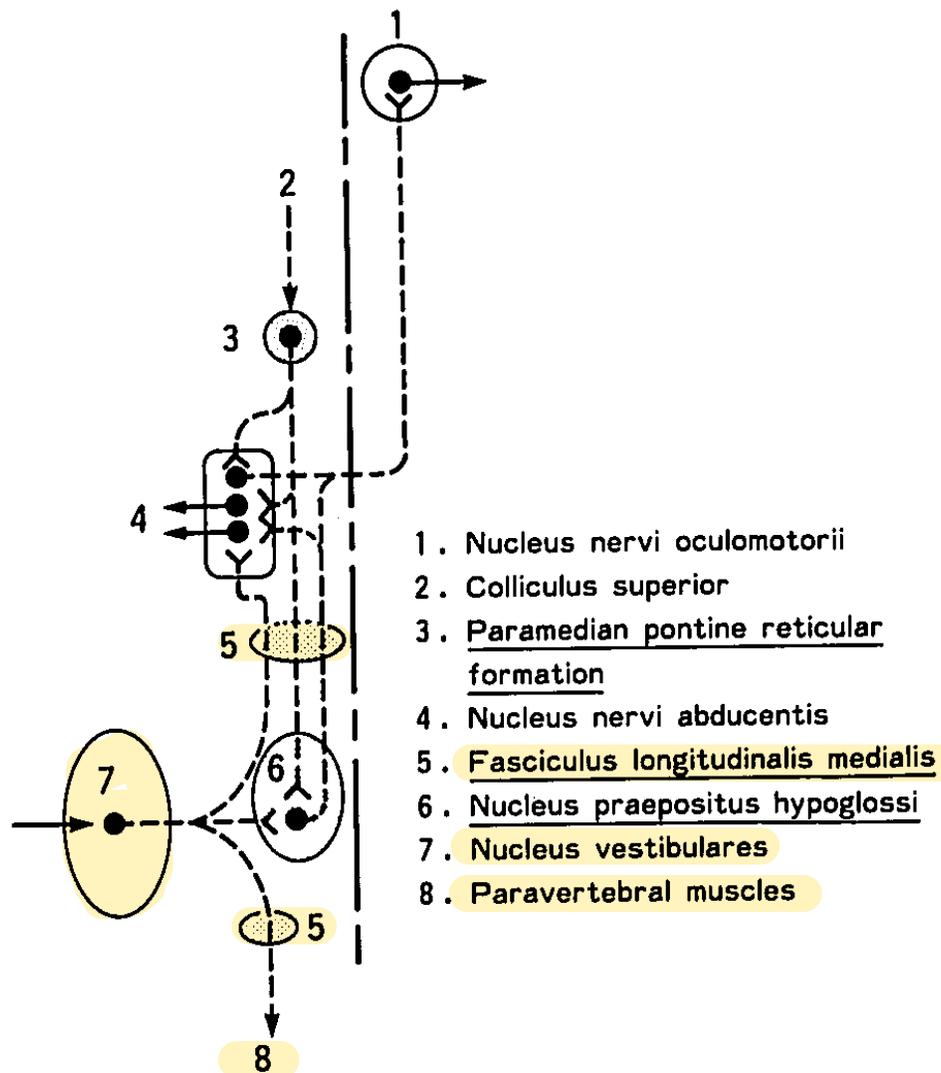
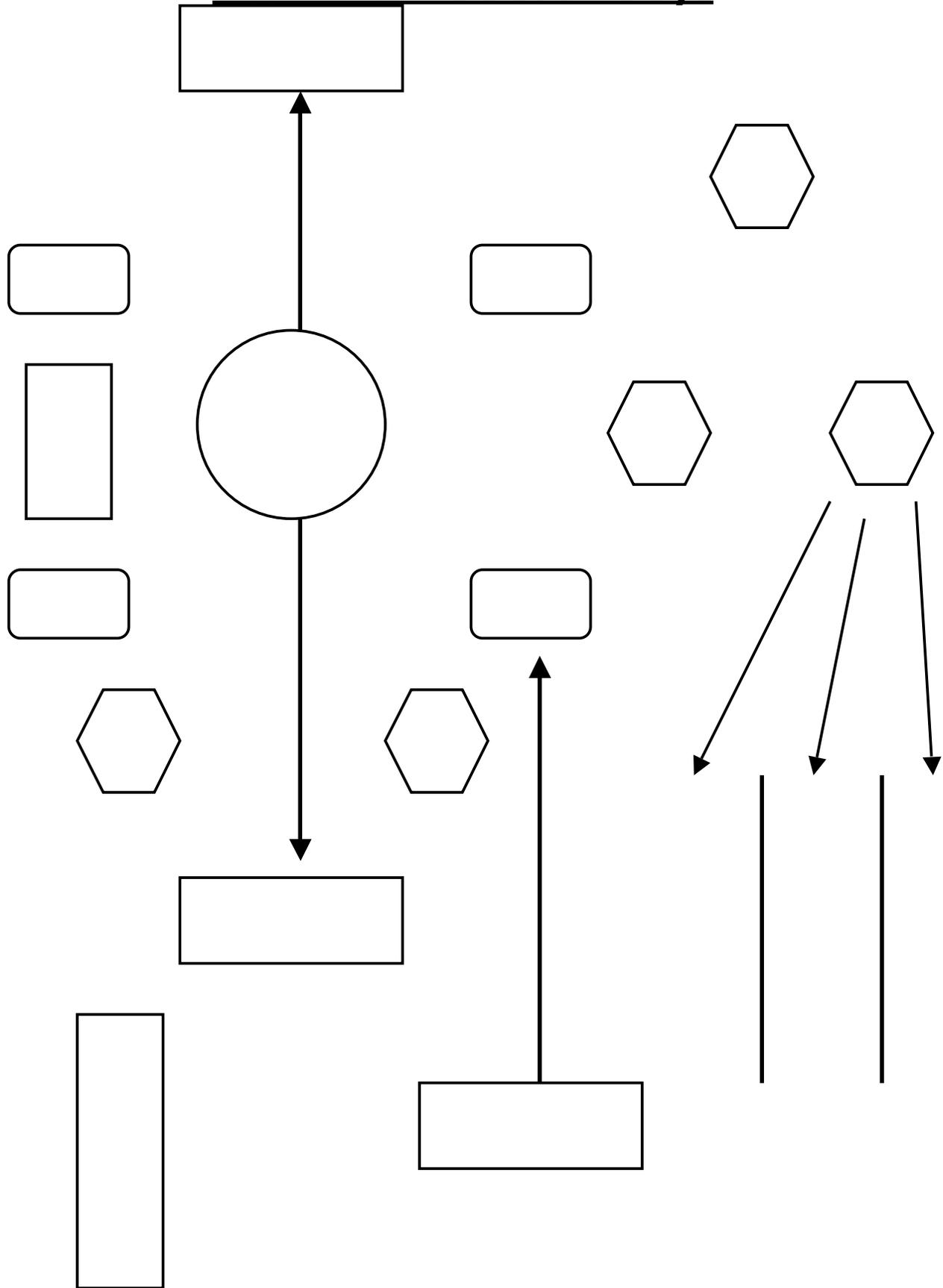


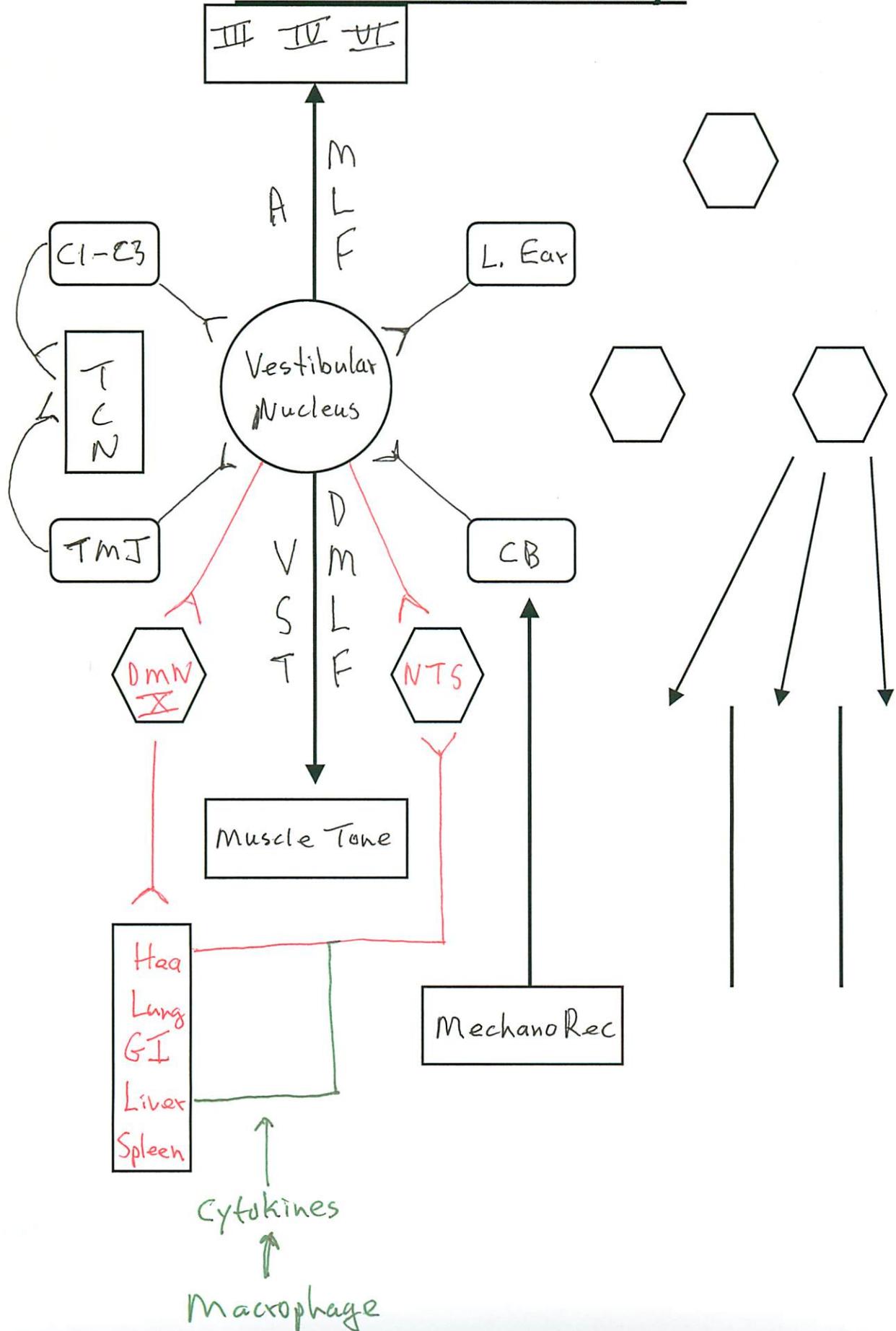
Figure 6. The neural connections between the vestibular, oculomotor, and preculomotor nuclei in the brain stem. Horizontal gaze movements are controlled by the paramedian pontine reticular formation and nucleus praepositus hypoglossi. The fasciculus longitudinalis medialis connects these nuclei among themselves and also connects the vestibular nuclei with the paravertebral muscles.

**Spine; 1993; pg. 2547**

# Vestibular Nucleus Relays



# Vestibular Nucleus Relays



## Neuro-Immunology Summary

The **mechanoreceptors** of the spine communicate with the **sympathetic** nervous system (Jiang, ***SPINE***, 1997).

The **sympathetic** nervous system controls the **innate immune response** (Elenkov, ***Pharmacological Reviews***, 2000; Nance, ***Brain, Behavior, and Immunity***, 2007).

The **innate** immune response controls the **adaptive** immune response (Sompayrac, ***HOW THE IMMUNE SYSTEM WORKS***, 2008), i.e. "The Innate System **Rules.**"

The primary cell of the innate immune response is the **MACROPHAGE** (Sompayrac, ***HOW THE IMMUNE SYSTEM WORKS***, 2008).

The best picture to date of the sympathetic nervous system communicating with the MACROPHAGE: (Mathias, ***AUTONOMIC FAILURE***, 2013).

The primary player of the innate immune response, the MACROPHAGE, activates the systemic immune response by using the sensory branches of the **vagus** nerve; these vagus afferents ascend to the **nucleus tractus solitarius** of the medulla (Tracey, ***Nature Reviews Immunology***, 2009).

The **nucleus tractus solitarius** is disynaptically post-synaptic from the mechanical afferents of the **upper cervical spine**: (Edwards: ***Journal of Neuroscience***, 2007; ***Journal of Chemical Neuroanatomy***, 2009; ***Brain Structure & Function***, 2015).

The sympathetic nervous system and the parasympathetic nervous system (nucleus tractus solitarius) interface in the brain stem for a **comprehensive** immunological response: (Tracey, ***Nature Reviews Immunology***, 2009).

This further supports the anecdotes and science of chiropractic neuro-immunity.

# **Misc. Studies**

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REALITY CHECK**

Dear Dan  
Hope you enjoy!  
Bob & Heidi

**DR HEIDI HAAVIK**

A quest to understand chiropractic  
from the inside out

2014

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# **Dan Murphy's**

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