



**The Most Important  
Molecule in Your Body**

**HYALURONAN**

**Douglas W. Kiburz, M.D.,  
Dalton Hermanson,  
& Linda A. Landon, Ph.D.**

*Hyaluronan: The Most Important Molecule in Your Body* is an informative, accessible, data-derived book describing an important health-related molecule that everyone should know about.

Orthopedic surgeon, Douglas W. Kiburz, MD, mines peer-reviewed clinical and basic science research to describe health benefits of hyaluronan.

- Improve muscle strength
- Improve joint function by decreasing pain and stiffness
- Increase quality of life by naturally decreasing pain
- Support bone healing
- Reduce processes leading to osteoporosis
- Contribute to healthy functioning of the immune system
- Protect the respiratory system from allergy and inflammation
- Contribute to healthy microbiome
- Improve objective and subjective signs of healthy, youthful skin
- Decrease dry eye.

Dr Kiburz's real-life patients describe their experiences with hyaluronan and how they believe that hyaluronan has improved their health. Dr. Kiburz has used what he has learned about hyaluronan to develop a high quality, high molecular weight, over the counter hyaluronan product, HA-TOPSHELF that he feels comfortable recommending to his patients.

Dr. Kiburz is an animal lover who owns cats, dogs, and award-winning American Quarter Horses. Hyaluronan is an important molecule for all mammals: Dr Kiburz gives hyaluronan to his animals to improve their lives.

Testimonials for  
“Hyaluronan: The Most  
Important Molecule in Your Body”

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Excellent compilation of facts and science on hyaluronic acid. I've followed the evolution of our biochemical knowledge of this miracle molecule, and this manuscript documents the most current understanding of its ubiquitous functions. My family and pets will be taking daily doses of HA!

— Dennis L. Johnson, M.D., Ph.D.

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I enjoyed the book and found it very informative and easy to follow.

— Jean Camden, Biomedical Researcher

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A fascinating review of the scientific literature supporting the use of high molecular weight hyaluronan supplements.

— Laurence E. Dahners, M.D.

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I told my long time friends, fellow Missourians Doug Kiburz and Don Grove, with whom I ran track with at Glendale High in Springfield in the '60's, that I was leery of any substance touted as a miracle. I read their heavily researched book on hyaluronan, replete with peer-reviewed studies from the scientific literature. Quite honestly, I was blown away by the supporting evidence for something I had never even considered to maintain my own personal health (edited for length).



— John Howard  
Three-time Olympic cyclist  
Gold medalist, 1971 Pan American Games  
Winner, 1981 Ironman Triathlon World Championship

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The owners of the American Quarter Horses that I train have made a significance investment of time and money in their horses. This book provides further scientific evidence that their horses will benefit from taking a hyaluronan supplement.

— Mike Camden, Professional Horse Trainer  
Owner, Mike Camden Quarter Horses

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The Most Important Molecule in  
Your Body

Douglas W. Kiburz, M.D.,  
Dalton Hermanson, &  
Linda A. Landon, Ph.D.



## DEDICATION

To Annie, Stony, and Marlin for playing a pivotal role in discovering the health benefits of HA that led to HA-TOP SHELF being developed.



## Hyaluronan: The Most Important Molecule in Your Body

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## WHY HAVE WE WRITTEN THIS BOOK?

### **Hyaluronan improves health. It is that simple!**

Dr. Douglas Kiburz, is an orthopedic surgeon. He is devoted to the well-being of the people in his life—his family and his patients. Even though surgery and prescription medications are the tools of his profession, he always looks for ways to help his patients solve musculoskeletal problems that do not involve surgery or prescription medication. He co-developed the over the counter hyaluronan (abbreviated as HA) supplement, HA-TOPSHELF, because of his commitment to people’s health. HA is a profoundly important molecule for nearly every cell in our bodies.

In addition to being an orthopedic surgeon, Dr. Kiburz is a dog, cat, and horse owner. Several years ago, he observed that veterinary preparations of HA benefited his animals. (Stay tuned for more on Dr. Kiburz’s beloved animals.) Based on his



Dr. Kiburz, Connie Kiburz, Marlin the Alaskan sled dog (a rescue dog), and Stony the Australian Terrier. (Used with permission.)

observations in his animals, Dr. Kiburz began to investigate whether HA also would be a safe and efficacious over the counter dietary supplement for his human orthopedic patients. Here's the cat's meow (or woof or whinny, depending on your favorite pet): HA is a beneficial supplement for all mammals, so you, your mother, your favorite great-aunt, and your pets will all benefit from adding HA to their diets.

Dr. Kiburz has used peer-reviewed scientific and clinical evidence to develop and produce an over the counter HA product that he feels confident recommending to his patients. In his research, he discovered that high molecular weight (1.6 to 1.8 megadaltons, abbreviated MDa) HA is more beneficial than lower molecular weight (1.4 to 1.6 MDa) HA. For example, in the world's longest-lived mammal, the naked mole-rat, high molecular weight HA is believed to contribute to their long lives by protecting the mole-rats' cells from stress-induced cell death, which is believed to be a major contributor to aging (Cyphert, et al., 2015; Takasugi, et al., 2020). (We will tell you more about these interesting animals, later.) In the immune system, there are indications that high molecular weight HA contributes to controlling both the beginning and ending of immune responses (Safrankova, et al., 2010).

Dr. Kiburz also learned about how to formulate a high-quality HA product. HA products must be stabilized somehow to prolong their shelf lives. Neutral pH and colloidal silver, which has anti-bacterial effects, increase the stability of the high molecular weight HA. Colloidal silver is the preferred preservative for HA compared to another commonly used preservative, sodium benzoate, which has been associated with cancer. Also, powdered HA products have longer shelf lives than HA products that are in solution at the time of purchase.



The purer the HA, the greater will be the health benefits. There is no reason to dilute HA with gluten, soy, yeast, artificial flavors and colors, GMO substances, and sugar. These unnecessary substances add nothing to the benefits or stability of HA products. HA products that lack these unnecessary molecules also are preferred for people who are sensitive to or want to avoid these ingredients.

Unfortunately, after learning all these lessons, Dr. Kiburz was not able to find an existing HA product that satisfied all his quality specifications, so he created his own product. Working with a team of physicians, pharmacists, and chemical engineers (the “HA Team”,<sup>1</sup> as we’ve come to call ourselves), Dr. Kiburz has developed HA-TOPSHelf, to help his orthopedic surgery patients to heal and maintain wellness. He also gives the product to his family and to his horses, cats, and dogs. To provide the best quality HA product for his patients, family, and animals, the HA Team deliberately developed the product to contain a powdered, high molecular weight HA that is stabilized with neutral pH and colloidal silver. The product is free of gluten, soy, yeast, artificial flavors and colors, GMO substances, and sugar. Each bottle’s label provides directions for adding water to make our HA solution into the “freshest” HA product available.

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<sup>1</sup> Meet the HA Team. Besides Douglas W. Kiburz, M.D., the team that developed HA-TOPSHelf includes Don Grove, Jr., who is a registered pharmacist and owns J&D Pharmacy in Warsaw, MO, and Don Jessup, who has earned two Ph.D.’s (pharmacology and holistic nutrition) and owns “Nature’s Extra” in Campton, KY. Our three founders bring more than 160 years of medical and scientific experience to ensuring the quality and effectiveness of the product.

After reading this book, the HA Team would be pleased if you would consider purchasing and trying HA-TOPSHELF.<sup>2</sup> However, it is more important to us that you understand why high molecular weight HA is so important to your health. If you decide to add an HA product to your health regimen, we'd like you to have objective information to use make an informed selection of your HA product.

The purpose of this book is to describe the scientific and clinical evidence that supports our conviction that high quality, high molecular weight HA is an essential health supplement that will benefit peoples' health. In this book, we focused on only those claims of benefits that we could substantiate with peer-reviewed clinical and basic science research reports. Along the way, we have included some human-interest case studies (a case study is an evidence-based story) stories to illustrate how real people (and their pets) have benefitted from HA.

Read on for more information...

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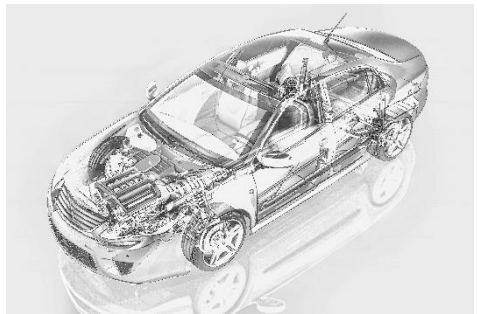
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<sup>2</sup><https://ha-topshelf.com/>

## YOUR BODY IS MADE UP OF ORGAN SYSTEMS

**The systems in your body are not all that different from the systems in your car.**

Like your body, your car is a collection of systems: The lubrication system, the braking system, the fuel system, and the chassis. Some systems are mechanical. In the engine, moving parts harvest energy from fuel to move the car forward. Other systems, like the fuel and lubrication systems, are pumps that move fluids from one place in the car to another to allow the car to function and to be lubricated appropriately. The exhaust system is designed to eliminate waste materials. If the exhaust system has holes or blockages, the heat and exhaust generated by the engine cannot escape.



Your body's organs systems are not that different from your car's systems. (Purchased image used under an end user license agreement.)

Finally, a car requires a support system to give it structural strength and to hold the other systems in the correct configuration to allow them to function in unison. That is the job of the chassis,

sometimes called the frame. If the chassis is damaged, both systems, the structural integrity of the car and its ability to function are impaired.

Your car requires constant care to run well. All a car's systems must be kept in tip-top shape. Sometimes, this upkeep is taking the car to a mechanic for new brakes. Other times, it is making sure that the fluids are replaced. When a car's fluids are changed, it is important to replace the fluids with the correct type and quality of fluids. Diesel cannot be added to a gasoline engine because diesel fuel will clog a gas engine. Add diesel to a gasoline engine and you will be buying a new gasoline engine for your car. Your car requires a specific type and grade of motor oil to lubricate the moving parts of the engine so it can run efficiently over the long haul. Most of us trust our mechanics to put in the correct weight but our owner's manuals also tell us what type of motor oil is best.

The human body also is made up of systems. Some of them are mechanical systems, like the cardiovascular system where the heart pumps fluids through arteries and veins to transport oxygen and nutrients to the cells in your body. Your muscles generate mechanical force to allow you to move, walk, and run. Your gastrointestinal system (stomach and intestines) functions like a hybrid of the car's fuel and exhaust systems. The gastrointestinal system is where fuel is added, and wastes are transported out of the body. The skeleton functions like a car's chassis to support and protect the body's organs. If you break a leg, your body will not be able to move. Without treating the break, your body eventually will start to fail.

Just like our cars, our body's systems—our joints and other moving parts—require high quality lubrication, too. High molecular weight HA is your joints' high quality "motor oil".

Dr. Kiburz sees many joints in his practice. Dr. Kiburz uses an apt analogy in the clinic with his patients. He tells his patients that their joints require a specific amount of sufficiently high grade “synovial fluid”, which is medical speak for “high quality motor oil for your joints”. (Believe it or not, Dr. Kiburz carries a grease zerk fitting in his lab coat to use as a prop to illustrate his analogy!) As we age or when we develop arthritis, our joints start to produce low quality lubrication. Our synovial fluid begins to degrade from “10W40 weight” synovial fluid to lower grade synovial fluid. Low grade synovial fluid is not what our bodies’ owner’s manuals calls for! Having enough high-grade synovial fluid is important. The articular cartilage (the cartilage in our joints that allows our joints to bend and twist) has no direct blood supply. The only nutrition that articular cartilage obtains to stay healthy is provided by synovial fluid. Too little or low-quality synovial fluid allows joints to degrade due to poor nutrition. Dr. Kiburz tells his patients that high molecular weight HA is high-quality “motor oil” for our bodies. Adding a high molecular weight HA helps to correct the viscosity of our joint fluid and sustain the nutrition of the cartilage.

Your body’s systems are made up of biological molecules and require other biological molecules to remain intact and to function appropriately. HA is one of the most important biological molecules that your body needs to remain intact and to function well. This book discusses how and why HA is important to various body systems.

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## HA IS IMPORTANT IN MANY ORGAN SYSTEMS

Turn to the next page for a diagram of the organs of your body in which HA might be important.

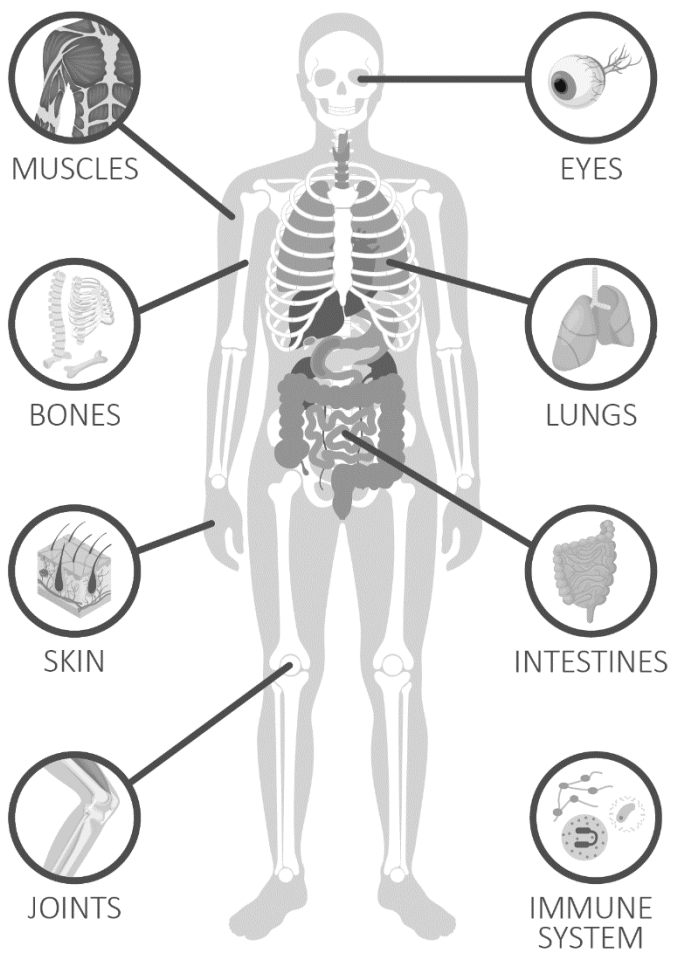
**Naturally-occurring and exogenously-added HA are important in many organ systems.**

In the next few sections, we are going to discuss specific organ systems in your body where peer-reviewed clinical and scientific research suggests that HA exists naturally and where HA might play important roles in maintaining good health.

In many of these systems, research indicates that HA taken orally or added to the body in other ways might be important to helping to maintain health or to prevent illness.

On the next page, we have included a handy diagram for you to use as a reference to remind yourself of where these organs are located in your body.







## ORTHOPEDIC PATIENTS, DOGS, & HORSES

### **A doctor learns a thing or two from horses and dogs.**

How did Dr. Kiburz become interested in HA as a beneficial molecule in the first place?

For that answer, we must turn to dogs, cats, and horses. Dr. Kiburz and his wife, Connie, own dogs, cats, and horses. Horses are a Kiburz family obsession: The Kiburzes have raised, ridden, and shown award-winning American Quarter Horses for 35 years. Dr. Kiburz' daughters, Alice and Beth, have won state, regional and world championships at horse shows. The Kiburz also work with a local trainer to train their dogs.

Dr. Kiburz loves his animals. Several years ago, to improve his animals' health and mobility, Dr. Kiburz began to administer a veterinary HA product to his animals. HA is safe and effective for all mammals. He observed, with a physician's eye for health-related



Connie Kiburz and her horse, Annie, at an American Quarter Horse Association show. (Used with permission.)

research, that HA-TOPSHELF benefitted his animals by improving their health and their ability to move and rebound after activity.

A valuable characteristic of studying the effects of oral supplements in animals is that animals do not distinguish an oral supplement from everything else they eat so they have no prior expectations for how they will be affected by the oral supplement. The prior expectation that a human patient has for how an oral supplement will affect them is called “placebo effect”. Placebo effect is an important problem to be overcome in clinical studies in humans. However, because animals do not experience placebo effect, researchers can see the true effect of an oral supplement without placebo effect. This is why research studies of supplement and drug effects in animals are important: These studies allow researchers to achieve unbiased results, which may not be achievable in human studies.

Dr. Kiburz’ observations that his animals—dogs, cats, and horses—benefit from taking HA are free of placebo effect. The animals really did benefit from the HA supplement. Independently of Dr. Kiburz’s observations and without knowing that the animals had been taking HA, the trainers who work with his dogs and the farriers (people who change the shoes on horses) who work with his horses have echoed Dr. Kiburz’s observations of his dogs’ and horses’ improved mobility and flexibility.

The benefits of HA that Dr. Kiburz observed in animals got him to thinking: Would HA be beneficial for the health and mobility of his patients, too? His review of the peer-reviewed scientific and clinical literature suggested that his patients would benefit greatly from a high quality, high molecular weight HA product. Unfortunately, he was unable to find an available HA product that met his quality specifications.

What is a physician to do? If you are Douglas Kiburz, you develop your own high-quality HA product, HA-TOPSHELF, that you are confident will be safe and effective for your patients, your family, and your animals. Dr. Kiburz and his wife, Connie, take HA-TOPSHELF, themselves. They give it to their other “family” members—feline, canine and equine. The dog trainer who trains the Kiburz’s dogs, was so impressed with the improvement in Dr. Kiburz’s dogs and the quality of HA-TOPSHELF, that he started giving HA-TOPSHELF to his own dogs. That is a pretty good product endorsement!

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## HYALURONAN IS AN ESSENTIAL BODY MOLECULE

### **Taking responsibility for our health.**

Our health and wellness are our personal responsibility. We cannot change our genetic makeup, but we can control some aspects of our health by making informed choices. Good health and wellness begin with understanding our family medical histories, screening for treatable diseases, and making early decisions on diagnosis and treatment plans.

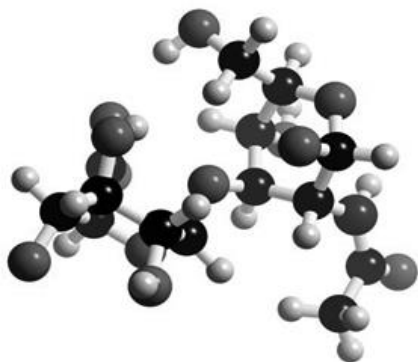
Prevention is very important to maintaining good health and preventing illness. Prevention choices that improve our health include exercising regularly, drinking enough water, avoiding smoking, drinking alcohol moderately, avoiding risky activity (Listen up, men!), managing stress, getting regular checkups and vaccinations, getting adequate sleep, and using medications and supplements appropriately.

Good health also depends on proper nutrition. Dr, Andrew Weill, an authority in holist, integrative medicine, suggests making food

choices that contribute to controlling inflammation.<sup>34</sup> Additional peer-reviewed scientific research shows that HA supplements can be part of a well-balanced, anti-inflammatory diet that contributes to controlling inflammation and to achieving a balanced microbiome in our gut (Jiang, et al., 2011).

## Hyaluronan.

HA is a profoundly important molecule for nearly every cell in our bodies. In science terms, HA is a “dynamic glycosaminoglycan”. Glycosaminoglycans<sup>5</sup> are long chains of molecules linked together. “Dynamic” means that enzymes in the body are constantly adding molecules to HA and subtracting molecules from HA in response to changes in health and environment. This helps our body to maintain optimum health.



HA's chemical structure.  
(Karl Harrison. [3DChem.com](http://www.3dchem.com),  
<http://www.3dchem.com/Hyaluronan.asp>.  
Image used under a Creative Commons  
Attribution license.)

HA was discovered nearly 100 years ago (Gupta, et al., 2019). Since then, peer-reviewed scientific research, conducted over decades, has shown that HA is a crucial contributor to the health and longevity of many parts of

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<sup>3</sup>Andrew Weil, MD. Healthy Lifestyle Brands, LLC. Used for informational purposes, only. HA-TOPSHelf is not associated in any way with Andrew Weil, MD or Healthy Lifestyle Brands, LLC. For additional information on Dr. Weil's teachings and products, visit his website:

<https://bit.ly/37U2zMM> and <https://bit.ly/2TYyzcC>.

<sup>4</sup>Whole Health: Change the Conversation. Advancing Skills in the Delivery of Personalized, Proactive, Patient-Driven Care. The Anti-Inflammatory Diet Clinical Tool. <https://bit.ly/314uSqd>

<sup>5</sup>See the YouTube video at <https://bit.ly/3fHFdMT> for more information on dynamic glycosaminoglycans.



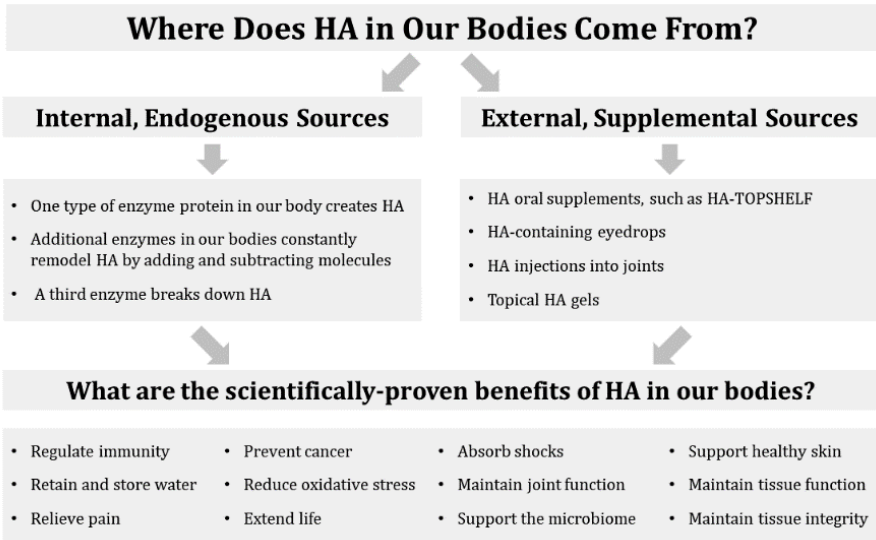
our bodies, including our joints, bones, eyes, spine, and skin, just to mention a few.

HA has not always been considered important to health by clinicians who practice western-style medicine. However, appreciation of HA's benefits is growing because of a growing awareness in the United States medical community of integrative medical techniques to improve overall human health (Gannotta, et al., 2018). Integrative medicine is "care that is patient centered, healing oriented, emphasizes the therapeutic relationship, and uses therapeutic approaches originating from conventional and alternative medicine" (Maizes, et al., 2009). Integrative medicine focuses on making all body systems function together harmoniously. For example, research indicates that the health of the gut, brain, and skin are linked (Salem, et al., 2018; Galland, 2014). One of the benefits of HA is that it promotes holistic health by improving hydration and maintaining healthy gut microbiome (the bacteria that naturally live in the gut) and leads to overall feelings of well-being (Bellar, et al., 2019; de la Motte & Kessler, 2015; Fallacara, et al., 2018; Gupta, et al., 2019; Jensen, et al., 2015). A healthy body shows in our outward appearance, as well, by improving the look and feel of our skin (Göllner, et al., 2017).

A good indicator of whether there is interest in whether a drug or other biologically active molecule, such as HA, improves human health is the number of human clinical trials being conducted to research using that substance. For a substance to be approved to be used in a human clinical trial, there must be solid preliminary evidence from studies conducted in cultured cells and in increasingly complex animal models that the substance is safe and has demonstrated potential to improve human health. On the United States registry of current and former clinical trials,

ClinicalTrials.gov, 866 current or former clinical studies have investigated using HA<sup>6</sup> (or the closely related hyaluronic acid or sodium hyaluronate) to improve human health. This is a relatively low number of clinical studies compared to the 3347 clinical studies of treatments for dementia<sup>7</sup> or 7984 clinical studies of treatments for hypertension,<sup>8</sup> but 866 clinical trials are sufficient to indicate that the medical community is aware of HA as being important to human health.

HA lubricates our joints and relieves joint pain; supports a healthy, functioning immune system; helps us to have healthy, comfortable eyes; fights the oxidants that cause cancer and damage to our skin and tissues; helps us to maintain a healthy microbiome in our gut; and helps wounds to heal. The list of the processes and parts of the body that HA protects and renews is endless.



<sup>6</sup>ClinicalTrials.gov. <https://bit.ly/2YIqnPk>. Retrieved June 13, 2020

<sup>7</sup>ClinicalTrials.gov. <https://bit.ly/2AwmW6t>. Retrieved June 13, 2020

<sup>8</sup>ClinicalTrials.gov. <https://bit.ly/2UPakhA>. Retrieved June 13, 2020

HA is about as close to a wonder molecule as you ever will find. However, there is some bad news: Our bodies' supply of HA starts to decrease in our twenties. Starting in our 20's but noticeably in our 60's, HA has decreased to the point that "old age aches and pain" start to creep in due to having insufficient HA to keep our bodies healthy and supple. Also, HA in our body "turns over" one third of our endogenous HA daily and, because the degradation of HA exceeds the production of HA, there is a net loss of this vital molecule. (Gupta, 2019). Both these characteristics—age-related loss and rapid turnover—make it very important to supplement our diets with high-quality HA. Peer-reviewed scientific research has shown that taking HA orally is safe (Bellar, et al., 2019) and, as we will describe later in this book, research indicates that HA is effective to maintain the health of several organ systems.

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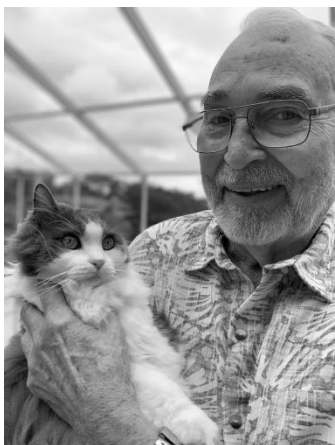
## BOB, OLYMPIA, & HA

**Bob is an 89-year-old man who has a beloved 18-year-old cat named Olympia.**

Bob and Olympia like to do all the things that a cat and her human like to do together. Olympia loves to sit on Bob's lap, and Bob loves to scratch her ears. Olympia adores getting her ears scratched.

However, both Bob and Olympia were getting older. They were slowing down. It was getting harder for both to move. Olympia could not jump up on Bob's lap anymore, and Bob had trouble bending down to pick her up.

Then, Bob found HA-TOPSHELF supplement, which is made of pure, high molecular weight HA. Bob was impressed that it was developed by a practicing orthopedic surgeon, who recommends HA supplement for his patients (and his animals). Bob read the Certificate of Analysis that came with the supplement and was reassured of the product's quality.



Bob and Olympia living their very best, active life.  
(Used with permission.)

Bob decided to buy HA-TOPSHELF to give it a try. Bob followed the directions for mixing, dissolving, and storing the product. Bob started giving himself 1 tablespoon and Olympia 1 teaspoon of the HA-TOPSHELF solution each day

Bob and Olympia have been rejuvenated. Olympia does not need to be picked up anymore because, since she has started taking HA-TOPSHELF, she can jump up onto Bob's lap on her own. Not only

that, Bob reports that she runs, dashes up and down stairs, and plays with her toys just like a kitten.

And Bob? Well, Bob does not sit all that much, anymore. Bob has become more active because he has less back pain and stiffness. He sleeps better. He can get up and down easier. He and Olympia still do their share of lap sitting and ear-scratching but now they do lots of other activities, too.

Here at HA-TOPSHELF, stories like this bring a tear to the eyes of the HA Team and make us want to work harder to bring the benefits of HA-TOPSHELF to more people

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## NAKED MOLE-RATS

### Unlocking the secret to HA & long-life.

The critter in the photo on this page is a female naked mole-rat.<sup>9</sup> Cute little gal, isn't she?

Naked mole-rats live in Africa and they are the source of a very important observation about the health benefits of HA. You see, naked mole-rats live for a very long time; up to 32 years “long” in captivity. That is a lot longer life than most rodents. Mice, for example, only live for about 2 to 3 years in captivity. Not only do naked mole-rats live long lives, but they almost never get cancer. So, they may not be pretty,<sup>10</sup> but naked mole-rats have a lot to teach humans. Scientists began to study naked mole-rats to discover their secret to happy, long, cancer-free naked mole-rat life.



Naked mole-rat.(Uploaded by Jedimentat44 on flickr /CC BY (<https://creativecommons.org/licenses/by/2.0>). [https://commons.wikimedia.org/wiki/File:Naked\\_mole\\_rat.jpg](https://commons.wikimedia.org/wiki/File:Naked_mole_rat.jpg)]

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<sup>9</sup><https://on.natgeo.com/3fj0515> and <https://nationalzoo.si.edu/webcams/naked-mole-rat-cam>

<sup>10</sup>"Who says we're not pretty?", asks the naked mole-rat.

Scientists quickly discovered that naked mole-rats have two characteristics that work together to give them long, cancer-free lives. These two characteristics combine to activate processes inside their cells that prolong cell life and that inactivate cellular processes that predispose cells to transforming into cancer cells (Deed, et al., 1997; Fisher, et al., 2015).

First, naked mole-rats have special enzymes that allow them to synthesize very high molecular weight HA molecules, ranging from 0.5 to 3 MDa (Fisher, et al., 2015). (Refer back to the “Hyaluronan is an essential bodily molecule” section for a reminder about molecular weight.) These high molecular weight HA molecules are thought to bind to cell proteins to modulate functions inside cells to increase how long a cell survives before being replaced (Tian, et al., 2013). Unfortunately, humans do not share this type of enzyme, so we must get our high molecular weight HA in some other way.

Second, naked mole-rats have a second set of special enzymes that affect a chemical process called oxidation (Lewis, et al., 2013). Oxidation is thought to be an important reason why people age and cells turn cancerous. The second set of special enzymes reduces oxidation (Takasugi, et al., 2020). This anti-oxidation effect, combined with the intracellular functions of extremely high molecular weight HA, give the naked mole-rat a long-life, anti-cancer benefit. Scientists think that both processes are must work together for the naked mole-rat to live long and be cancer-free (Lewis, et al., 2013).

So, what is the lesson that humans can learn from naked mole-rats? Humans cannot change the types of enzymes that our cells produce but we can imitate the effect of high molecular weight HA by supplementing our diets with high molecular weight HA. We also can reduce the oxidants produced by our bodies by eating an



antioxidant-rich diet. (Refer back to the “Hyaluronan is an essential bodily molecule” section for a reminder about an antioxidant diet.)

This is part of the scientific rationale that drove Dr. Kiburz to begin advising his patients to take an oral HA supplement and to develop HA-TOPSHELF, which contains high molecular weight HA and meets his quality standards. As you will see in the rest of this book, pure, high molecular weight oral HA supplements might contribute to helping people to replicate the naked mole-rat’s long-life and anti-cancer advantage.

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## STRONG MUSCLES

### **Muscles occur in surprising places in your body.**

When most people think of muscles, they see “Ah-nold” and his biceps in the Terminator movies. But did you know that muscles also occur in your blood vessels, heart, brain, and intestines? Biceps are important but some of these other muscles are more important than biceps. Scientists have good evidence that HA is important to health of those different types of muscles.

Healthy muscles require a delicate balance between building up and breaking down muscle. This delicate balance is partially dependent on a layer of supporting biomolecules. HA is an important component of this layer.

Starting during pregnancy, HA in the support layer allows embryonic muscle cells to grow in number and to migrate to their final place in the body (Leng, et al., 2019). Later in life, HA in the muscle-supporting layer plays an important role in maintaining healthy muscle.

When muscle is not broken down appropriately or grows in uncontrolled way, muscle cannot perform correctly. A good example of this is when the muscle in the heart overgrows its normal thickness. This weakens the heart and places people at risk

of dying because hearts with too much muscle cannot pump blood effectively. Scientists have evidence that HA being broken down too quickly into small fragments might contribute to overgrowth of the heart muscle by reducing the ability of the cardiac muscle support layer to maintain optimal muscle thickness (Calve, et al., 2012).

## MUSCLES

**There is little research about whether oral HA supplements are effective in maintaining healthy muscles:**

- Two clinical studies suggest that yogurt supplemented with HA improves the strength of muscles surrounding the knees in people with knee pain.

**However, numerous peer-reviewed clinical studies with injected HA\* support the importance of HA in muscle health.**

- In osteoarthritis, knee strength improves after HA injection.
- Injected HA improved hand grip strength in competitive racquet sports players after surgery to repair tendons.

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Kaux, et al., 2016

Maia, et al., 2019

Moriña, et al., 2018

Sánchez, et al., 2014

Wiig, et al., 2014

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\*HA-TOPSHELF is an oral, over the counter HA supplement. Do not use the product for injections. Injections always should be performed only by a qualified, licensed physician.

On the other hand, when muscles are damaged, the body acts to increase the amount of HA present because that helps the muscle to heal. There is evidence that HA might play a role in regenerating heart muscle after a heart attack (Missinato, et al., 2015; Wang, et al., 2019).

Strong muscles are important because strong muscles and strong joints go hand in hand. You cannot have one without the other. So, in the next sections, we will tell you two human interest case study stories about how HA benefits joints and then we will describe why HA is important to joint health.

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## GETTING BACK TO ACTIVITY

### **Strong knees: On the road & the ranch again.**

Our co-founder, Dr. Kiburz, has observed that patients with knee problems benefit from taking HA. One case study story tells of “Amelia”, a long-distance runner and biker. (Her name has been changed to protect her privacy.)



Amelia and her long-distance cycling friends. (Used with permission.)

Amelia is a 60-year-old athlete. She loves to run and bike. In her life, Amelia has run and biked more than 100,000 miles. (Yes, you read that right: 100,000 miles!) However, after all those miles, her knees have started to have issues. Her knees often hurt and become swollen. Her knees make strange clicking sounds. It is getting

harder and harder for Amelia to pursue her love of running and biking.

Eventually, Amelia had two knee surgeries, performed by Dr. Kiburz, to deal with her damaged joints. After the second surgery, Dr. Kiburz gave her a bottle of HA-TOPSHELF and asked her to try it as part of a comprehensive recovery plan.

At Dr Kiburz's recommendation, Amelia used HA-TOPSHELF. After following the comprehensive recovery plan for several months, Amelia perceived that HA-TOPSHELF and the strengthening exercises were improving her condition so much that she has continued to use HA-TOPSHELF to help her continue and maintain her improvement.

Amelia is on the road again! She is increasing her activity and able to do the things she loves to do. Another happy ending due to HA-TOPSHELF.

In another case study story of how HA-TOPSHELF benefits knees, one of Dr. Kiburz's patients, Amy (her name has been changed to protect her privacy), injured her knee in a ranch accident and required surgery. Adding HA-TOPSHELF to her recovery regimen allowed Amy to heal and resume her regular ranching activities within 4 months. Not too long ago, she helped put up 450 bales of hay on a hot summer afternoon. That is quite the recovery!

Stay tuned to learn more about our amazing joints and how HA helps our joints to stay strong and pain free.

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## JOINTS & ARTHRITIS

### **Joints are amazing biological mechanisms!**

Did you know that there are 208 bones and 360 joints in the human body? Somehow, we need to keep them all strong and healthy. Repairing all these bones and joints would be a major overhaul.

Joints perform work to transform energy into movement.<sup>11</sup> They accomplish this by generating power and torque. (Hmmm, sounds like an automobile engine.) Joints move. They twist. They allow us to move our fingers to type on a keyboard, like I am doing while I type this book. Joints let us dance for joy when something wonderful happens. Joints even distinguish humans and primates from other animals. Without our thumbs, which have 2 joints, and our opposing forefingers, which have 3 joints, we could not pick up coins or write with a pen.

However, because they move and twist, joints are susceptible to mechanical damage and are convenient targets for our immune systems in immunity disorders like arthritis<sup>12</sup>. We take our joints for granted until our knees hurt when we walk upstairs or our hips

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<sup>11</sup><https://www.niams.nih.gov/health-topics/kids/healthy-joints>

<sup>12</sup><https://www.nia.nih.gov/health/osteoarthritis>

hurt when we try to bend over to pick up something. Modern medicine has expended considerable energy to solve problems with joints.

### **Osteoarthritis.**

In certain circumstances when the immune system and joints meet, bad things might happen (Bowman, et al., 2018). Because of the wear and tear experienced by joints, sometimes body molecules from joints that should be hidden from the immune system become exposed to the immune system. This is a problem because body molecules that should be hidden from the immune system will be viewed as intruders by the immune system. This will activate the non-specific innate immune response. (We will talk in detail about the innate and adaptive immune systems in the section, “HA plays surprising—sometimes contradictory—roles in the immune system.”) There also are cases when these previously hidden body molecules resemble intruder molecules to which the adaptive immune system has already responded. The adaptive immune system cannot distinguish between highly similar molecules that originate from an invading pathogen versus molecules that originate from a previously hidden body site. When either of these events occur, the immune system begins to attack. This can happen anywhere in the body, but, because the previously hidden body molecules are concentrated in joints, the inappropriate immune response begins to damage the joints.

When the immune system attacks joints, various forms of arthritis can occur. There are over 100 different kinds of arthritis and arthritis-related conditions, but a common form of arthritis related to aging is “osteoarthritis”. Get ready, because, as we age, it is likely that all of us will experience osteoarthritic joints to some degree. People, like performance athletes, who place stress on their

joints are also at risk of osteoarthritis.<sup>13</sup> Luckily, oral HA has been shown to prevent arthritis in some, but not all, people and to improve arthritis symptoms in some other people. Osteoarthritis

## JOINTS & ARTHRITIS

**In peer-reviewed clinical studies, clinical researchers have observed that oral HA:**

- Improves quality of life (reduced pain, increased functioning, increased emotional well-being) for people suffering from osteoarthritis of the knee.
- Improves joint function and comfort (walking, stepping up and down, joint flexing, joint stiffness, joint swelling) for people suffering from osteoarthritis of the knee.
- Reduces the amount of breakdown products of joint cartilage in athletes.
- Reduces pain and use of pain medication
- Increases the work, power, and torque generated by the knee while improving joint structure and reducing pain.

Bowman, et al., 2018

Jensen, et al., 2015

Kalman, et al., 2008

Moriña, et al., 2018

Nagaoka, et al., 2010

Tashiro, et al., 2012

Sánchez, et al., 2014

Yoshimura, et al., 2012

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<sup>13</sup><https://mayoclinic.org/279Rmnp> and <https://www.niams.nih.gov/health-topics/osteoarthritis>

differs from osteoporosis, which is a distinct bone disorder that causes weakened bones.<sup>14</sup> We will talk about HA in osteoporosis in a later section.

Later in the “HA plays surprising—sometimes contradictory—roles in the immune system” section, we will talk about how HA binds to the surface of immune cells to modulate their function. One way that HA can modulate immune cell function is to reduce cellular processes that lead to excessive inflammation (Asari, et al., 2010).

HA has become a valuable tool for physicians to use to protect and to rescue our joints from damage (Bowman, et al., 2018). Do you remember earlier, in the “Hyaluronan is an essential bodily molecule” section, we discussed how having a substance used in human clinical studies is a good indicator that a substance can benefit human health? On ClinicalTrials.gov, clinical studies using HA (or the closely related hyaluronic acid or sodium hyaluronate) in joints were retrieved by using the keywords “joint” and “hyaluronan” in a search. Two hundred and thirty current or former clinical studies were found that focused on the clinical application of HA as a therapy for preventing or fixing joint damage.<sup>15</sup> Most peer-reviewed medical literature and practice focus on sterile HA that is injected into joints by physicians (Hermans, et al., 2019), either alone or mixed with other substances.<sup>16</sup> Injections have been shown in many clinical studies to be effective treatment for joint pain caused by arthritis and injury (Bowman, et al., 2018), but injections are painful, invasive, and expensive. Also, injections are intended to fix problems after they occur but not prevent problems from occurring in the first place.

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<sup>14</sup><https://bit.ly/2AXg1TN>

<sup>15</sup><https://bit.ly/2YFMTbF>. Retrieved June 13, 2020

<sup>16</sup>HA-TOPSHELF is an oral, over the counter HA supplement. Do not use the product for injections. Injections always should be performed only by a qualified, licensed physician.

Early in this book, we discussed the importance of preventative medicine. It would be much better for our joints if we prevented joint damage before it occurred. We can do that by taking care of our joints to prevent injury. We also can eat a diet intended to maintain joint health. Oral HA dietary supplements have been shown in peer-reviewed clinical studies to improve joint health and to help joints heal after damage (Moriña, et al., 2018; Tashiro, et al., 2012). Taking oral HA is less invasive, less expensive, and more convenient for patients. As osteoarthritis progresses, both the concentration and the molecular weight of HA remaining in arthritic joints decrease (Maheu, et al, 2016). Taking a high molecular weight HA supplement might be important to replace lost high molecular HA. It is unlikely that taking oral HA alone will prevent or solve all joint problems. However, oral HA is an important preventative health measure that is easy and convenient to apply to prolong the health of joints and to optimize other joint treatments, including exercise, surgery, and injections. That is a pretty good trade-off since an ounce of prevention is always better than an expensive, painful cure.

Oral HA has been shown to have many benefits for arthritis (Oe, et al., 2017; Sanchez, et al, 2014; Yoshimura, et al., 2012). One of the main difficulties that people with arthritis experience is chronic, sometimes debilitating, pain. A clinical study was conducted to observe whether oral high molecular weight HA relieved pain in people who had degenerative joint disease and other rheumatic conditions, including arthritis. People in the clinical study who took oral high molecular weight HA experienced more pain relief compared to people who took a placebo supplement. The extra pain relief lasted for 2 weeks. After 2 weeks, people in the treatment group started to become more active because they were pain-free. Physical activity is an important preventative health measure. The

added activity caused their pain to increase again, albeit not to the level that they had experienced prior to oral HA treatment. This study indicates that oral HA, especially high molecular weight HA, relieves chronic pain and reduces use of pain medication (Jensen, et al., 2015). Less pain can lead to downstream benefits, including increased physical activity. Interestingly, people who previously had taken oral HA were excluded from this clinical study because of the known pain-relieving effects of oral HA, which would have complicated analysis of the data.

A similar clinical study demonstrated that oral HA of unknown molecular weight, when combined with other substances not only relieved pain but also improved the quality of life for people with knee osteoarthritis (Kalman, et al., 2008; Maia, et al. 2019). A clinical study demonstrated that the combination of oral high molecular weight HA and therapeutic exercise was particularly effective in alleviating symptoms of osteoarthritis (Tashiro, et al., 2012). Importantly, studies have shown that the pain-relieving effects of high molecular weight HA are long-lived. Forty months after injection of HA into knees, more patients who received an HA injection in their knees reported pain relief compared to patients who received a placebo injection in their knees (Maheu, et al, 2016).

Knees and joints also contain a tissue called cartilage. In osteoarthritis, the immune system often damages cartilage (Kaux, et al., 2016). High molecular weight HA appears to protect cartilage cells from damage by modulating both immune cell function to reduce attacks on cartilage and by protecting cartilage cells from dying due to damage (Chiou, et al., 2018; Honda, et al., 2017; Kaux, et al., 2016). So, HA functions in many ways to keep joints healthy and pain free.

In the next sections, we will tell you a case study of how HA reduced joint pain and stiffness. Then, in “No bones about it: HA is important”, we will discuss how HA strengthens bones.

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## GETTING BACK TO NORMAL

### Love (and backs, ankles, and fingers) in the time of HA.<sup>17</sup>

All joints benefit from HA. We already told you the case studies of how HA-TOPSHELF helped Amelia's and Amy's knees to heal so they could get back to their activities. Did you know that our spines also are a long series of multiple joints and are particularly susceptible to damage? Dr. Kiburz's patients report to him that taking HA-TOPSHELF improves their back flexibility and reduces their back pain, which ultimately reduces their need for surgery.



Patients love HA-TOPSHELF!  
Dr. Kiburz tells the case study of

"Helen" loves her husband, but he will have to buy his own HA-TOPSHELF!  
(Used with permission.)

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<sup>17</sup>We just could not resist making this literary reference, even though it has nothing to do with HA. If you have not read *Love in the Time of Cholera* by Gabriel García Márquez, you should.  
<https://bit.ly/2C1cPlg>

Helen (her name has been changed to protect her privacy), a patient who added HA-TOPSHELF supplement to her diet to improve the flexibility of her spine, fingers, and other joints. After taking HA-TOPSHELF, Helen reported to Dr. Kiburz that her back, shoulders, elbows, and finger joints were less stiff and swollen and that she no longer had trouble getting out of bed.

Helen's experience has been echoed by others of Dr. Kiburz's patients. For example, Patty (her name has been changed to protect her privacy) also noticed a decrease in stiffness in her hands after taking HA-TOPSHELF for 1 month. Two weeks after she stopped taking HA-TOPSHELF, Patty began to notice that the stiffness in her fingers had returned. Patty told Dr. Kiburz that she intends to resume using the product.

There's a sweet ending to Helen's story. Helen told Dr. Kiburz that her husband was so impressed by Helen's improvement that he wanted to take some of her HA-TOPSHELF to help his stiff ankles to become more limber. But Helen was not about to share her HA-TOPSHELF, not even with her beloved husband, so she purchased a bottle just for him.

It appears that love means never having to say, "Here, have some of my HA-TOPSHELF!"

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## BONES & SKELETON

### **No bones about it: HA is important.**

On the 1960's science fiction TV show *Star Trek*, the doctor was nicknamed "Bones". The nickname was appropriate. Bones, the doctor, supported and protected the other characters, providing them with means and support to act and to keep the starship in tip-top shape so they could fight off the Klingons.

Like Bones, the doctor, the 208 bones in the human body support the muscles and organs of the body and give the body the ability to move and react. Bones give muscles an attachment point that allows the muscle to generate force that translates into movement. Bones, grouped together into the skeleton, protect the body's inner organs from damage. The most obvious example of this protective role is the skull protecting our brains from damage, which in turn preserves the structure and function of our brains and nervous system.

Bones have other important roles. In this section, we will talk about HA's role in general bone health. The next section describes a very important bone health role for HA that has not received enough interest from doctors and researchers: Using HA to prevent

and treat osteoporosis. Keep reading!

Bones are the place where blood cells, fat cells, and some types of cells that make up connective tissue are created and grow to maturity. Bones also regulate calcium levels in our bodies. Calcium has many important roles in the body. Bones themselves are partially made up of calcium. Calcium is an important ion that allows our heart to beat and is necessary for some glands in our body to secrete substances, such as saliva and tears.

## BONES

**The FDA has approved an injectable HA-based bone repair treatment for use in humans.<sup>2</sup>**

**In peer-reviewed dental clinical studies, dental clinical researchers have observed that HA gel:**

- Increases the amount of bone formed after tooth removal
- Improves the health of the surrounding tissue that supports the bone
- Improves bone healing in patients with diabetes

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Alcântara, et al., 2018

Asparuhova, et al., 2019

Casale, et al., 2016

Marin, et al., 2020

Bone is a tissue, and, like all tissues, bones require a support layer to be healthy. HA is an integral part of the support layer for other tissues. So, if HA also is an integral part of the support layer for bones, this suggests that oral HA supplements might contribute

indirectly to healthy bone. However, there is little scientific and clinical evidence to suggest that oral HA supplements improve human bone health (Lee, et al., 2014). In fact, there are very few studies of HA's direct role in human bone health at all.

Studies that use HA to target other drugs to bone cells or to support bone cells while other drugs do their work offer indirect suggestions that HA is important to bone health. One drawback of applying these studies to understanding how HA contributes to human bone health is that the studies have been conducted in cultured cells or animals rather than in humans. But we can use them to get a vision of where applications of HA in human bone health might go in the future after additional research is conducted.

Some animal studies suggest that HA gels or sponges in which building block molecules for bones are embedded help to hold the bone building block molecules in place so they are able to crosslink to build new bone or to repair bone after injury (Chang, et al., 2016; Huang, et al., 2017; Holloway, et al., 2014; Kim, et al., 2007; Kisiel, et al., 2013). This suggests that HA in the bone support layer contributes to maintaining bone by maintaining a constant supply of building blocks and by enhancing other molecules' ability to regulate the balance between bone breakdown and bone buildup (Hulsart-Billström, et al., 2013; Huang, et al., 2017; Chang, et al., 2016).

Additional hints that HA in the bone support layer contributes to maintaining bone come from animal studies that use HA to target drugs and bone building proteins to bone. Then, HA holds the drugs and proteins at the site where bone needs to be regenerated (Chang, et al., 2019; Fujioka-Kobayashi, et al., 2016; Rammel, et al., 2018). The anti-osteoporosis drug, bisphosphonate, has been delivered to bone by using HA to target bone cells (Hulsart-Billström, et al.,

2013; Kootala, et al, 2015). We will talk about osteoporosis in more detail in the next section. HA embedded in gels has been shown to promote growth of artificial bones to be used for bone grafts (Yeom, et al., 2014; Koca, et al., 2020). A magazine reported that the Food and Drug Administration, the United States government agency that approves drugs for use in the United States, has approved an HA-based preparation that is injected into voids in bone created by surgery or traumatic injury. The HA-containing bone filler helps new bone to grow to fill in the void.<sup>18</sup>

Currently, the best direct evidence for the importance of HA in human bone health comes from two sources. First, clinical trials suggest interest by the medical community in the medical benefits of HA-based treatments. Of the 25 clinical trials registered on ClinicalTrials.gov that were found in a search by using the keywords “bone” and “hyaluronan” (and the closely-related “hyaluronic acid” or “sodium hyaluronate”), six studies investigated using HA to regenerate bone after dental procedures.<sup>19</sup> The interest in HA in bone health is supported by numerous peer-reviewed dental practice articles describing the importance of HA in human bone health. These articles in dental journals describe how dentists successfully use non-invasive, topical HA gels after dental surgery and tooth extraction to help jawbone heal and regenerate (Eliezer, et al., 2019). Other dental clinical studies suggest that HA also is important to the health of the periodontal tissue that covers our jawbone. Healthy periodontal tissue is necessary for healthy jawbone and teeth (Ceccarelli, et al. 2017; Casale, et al., 2016).

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<sup>18</sup>ClinicalTrials.gov. <https://bit.ly/2MZVXme>. Retrieved June 13, 2020.

<sup>19</sup>ClinicalTrials.gov. <https://bit.ly/2MZVXme>. Retrieved June 13, 2020.

In the next section, we will discuss a very important bone disease, osteoporosis. The medical community is just beginning to understand how HA can be used to prevent and treat osteoporosis.

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## OSTEOPOROSIS & HA

### **Osteoporosis: HA's role in a "silent pandemic".**

During the year 2020, the COVID-19 pandemic was center stage in everyone's awareness. But there is another "silent pandemic" that has been occurring for years that affects the lives of millions of people, especially women. Osteoporosis, the loss of structural stability of the inner core of bones, has been called the world's "silent pandemic" because of the disease's negative quality of life, medical, and economic consequences. In an earlier section, we talked about osteoarthritis, an age- and immune-dependent joint disease. Osteoarthritis is a distinct disease from osteoporosis.

Every woman—and some men—should be worried about osteoporosis. Ten percent of people in the world and 30% of post-menopausal women suffer from osteoporosis. Osteoporosis is the main cause of bone fractures in elderly men and women (Bellar, et al., 2019). In the United States, 300,000 people aged 65 years old or older will experience hip fracture due to osteoporosis. Three-quarters of these fractures will occur in women because women more often have osteoporosis than do men.<sup>20</sup> Hip fracture is a major

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<sup>20</sup>National Institutes of Health. Osteoporosis and Related Bone Diseases National Resource Center. <https://bit.ly/2AXg1TN>

cause of death among the elderly. Thirty percent of elderly people with hip fracture will die within a year of fracturing their hip (Brauer, et al., 2009; Amin, et al., 2014).

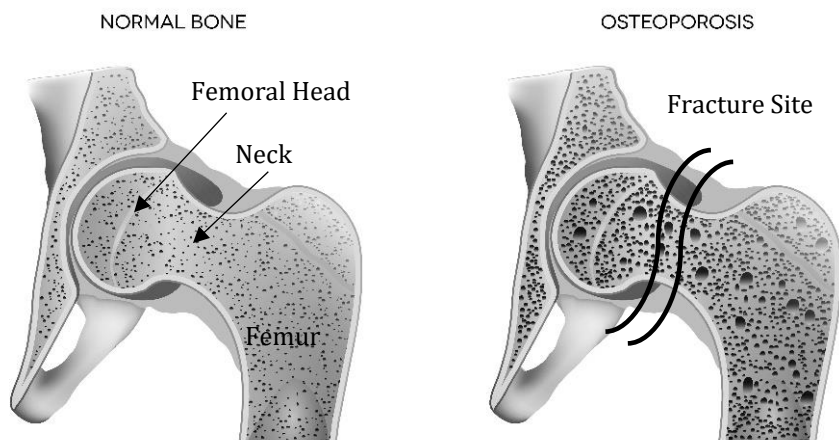
Each person's risk of developing osteoporosis is determined mostly by genetics, which is reflected in our family histories. However, risk of osteoporosis can be influenced by lifestyle choices. Osteoporosis risk is reduced by eating healthy, getting enough calcium (Dairy products like ice cream—yum—or calcium supplements), taking vitamin D supplements, and getting lots of weight-bearing exercise (gardening and walking are GREAT exercise). Osteoporosis risk is increased by lifestyle choices that weaken bones. These include drinking excessive alcohol, smoking, having an eating disorder, and taking illicit steroid drugs without physician supervision. Long-term exposure to high doses of prescription steroid drugs, such as prednisone, also can lead to osteoporosis, which is why it is so important to take all steroid drugs according to a doctor's prescription.

The way that hip bones are structured make hips highly susceptible to breaks in the elderly. The femoral head (the part of the hip bone that projects from the femur leg bone into the hip joint) is joined to the femur leg bone by a narrow neck. That narrow neck must be very strong to withstand the stress placed on it. Healthy internal bone structure is essential to that strength.

In advanced osteoporosis, the internal structure of bone becomes damaged, which severely weakens bone (see the pits and holes in the femur on the right in the hip joint image). Any weakened bone can break but hip fractures among the elderly are the most concerning because hip fractures often lead to disability, loss of independence, and even death.

Most hip fractures occur as the result of falls<sup>21</sup> but hip bones can become so weakened by osteoporosis that, even in the absence of a fall or other trauma, the femoral neck can spontaneously fracture and the femoral head will break away from the main body of the femur leg bone.<sup>22</sup> So, if your grandma says, “My leg just gave out and I fell.” and is later found to have broken her hip, she might be telling the truth. Start thinking about bone strength while you are young, because it is important to eat healthy, get plenty of exercise, and maintain calcium and vitamin D intake so this does not happen to you!

## OSTEOPOROSIS



Healthy hip bone (left). Weakened hip bone due to osteoporosis (right).  
(Purchased image used under an end user license agreement. Some annotations were added by the authors.)

Despite clinical evidence from dentistry and basic science evidence that HA helps to rebuild bone, very little basic science or

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<sup>21</sup>Centers for Disease Control and Prevention. <https://bit.ly/2XVNH6R>.

<sup>22</sup>Mayo Clinic. <https://mayoclinic/2YoeTR3>.

clinical research has been conducted to investigate HA in preventing or treating osteoporosis. A search of ClinicalTrials.gov using the keywords “hyaluronan” (or the closely-related “hyaluronic acid” or “sodium hyaluronate”) and “osteoporosis” returned no current or former clinical trials investigating HA in osteoporosis.<sup>23</sup> The lack of clinical trials combined with the paucity of basic science research reports about HA in osteoporosis suggests that the research and clinical communities are just beginning to comprehend the importance of HA in osteoporosis.

Thirty-six percent of Americans use integrative, alternative, and complementary medicine services. There is an oft-repeated pattern when integrative medicine treatments enter mainstream medicine: The positive benefits from what once were considered fringe medicine treatments become more widely known to clinical practitioners in their daily practices, possibly because their patients begin to ask their doctors about what they’ve heard or read about an integrative medicine technique. Then, as case study reports of the benefits of these integrative medicine practices start to enter the peer-reviewed clinical literature, additional practitioners as well as clinical researchers become aware of the techniques. Next, clinical researchers begin to design and conduct studies to determine if the reported benefits of the integrative medicine treatment are real. The awareness, validation, and acceptance of acupuncture<sup>24</sup> as a valuable and effective alternative well-being and curative therapy is an excellent example of this process (VanderPloeg & Yi, 2009; Mao & Kapur, 2010). This probably is the status of the clinical awareness and application of HA in preventing and treating osteoporosis.

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<sup>23</sup>ClinicalTrials.gov. <https://bit.ly/3hOD0B>. Retrieved June 13, 2020.

<sup>24</sup>Johns Hopkins Medicine. <https://bit.ly/2Y6zsCB>.

Examples of basic science research using HA osteoporosis include:

- In rats with artificially induced osteoporosis, oral HA decreased bone turnover leading to increased bone density (Ma, et al, 2013).
- In cultured cells, low molecular weight HA has been observed to reduce cell processes that contribute to osteoporosis, which suggests that oral HA might help to prevent and treat osteoporosis (Lee, et al, 2014).
- Some basic science studies investigate using HA's affinity for bone to target anti-osteoporosis drugs to bone. The anti-osteoporosis drug, bisphosphonate, has been delivered to bone by using the ability of HA to home in on and target bone cells (Hulsart-Billström, et al., 2013; Kootala, et al, 2015).

These studies are all conducted in animals or cultured cells and are too preliminary to predict whether oral HA is beneficial to prevent or cure human osteoporosis. However, the benefits of HA for osteoporosis suggested by these articles combined with the proven clinical benefits of HA for improving bone demonstrated in dental clinical studies provide an intriguing suggestion that adding HA to a healthy diet and exercise might help to prevent or treat osteoporosis.

In the next section, we will switch to a different organ system, the immune system. We have already discussed HA in osteoarthritis, which is partially an immune system-mediated disease. However, now it is time to delve deeply into the role of HA in the immune system. This is going to be an interesting and informative section.

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## HA & THE IMMUNE SYSTEM

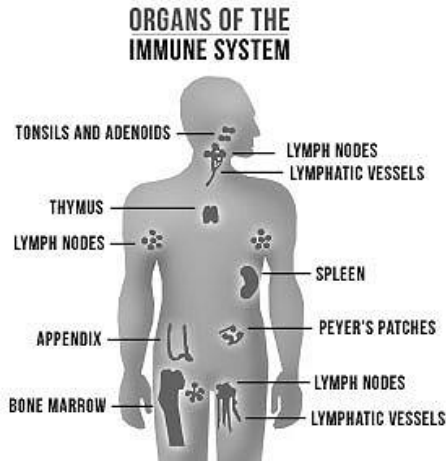
**HA plays surprising—sometimes contradictory—roles in the immune system.**

Did you know that the immune system is the largest and most highly distributed system in your body? The immune system is an amazing organ!

Most organ systems have a specific site in the body that you can point to and say, “There is the heart. It pumps blood through the body.” But the immune system is different. There is not just one organ that defines the immune system because parts and pieces of the immune system occupy many spaces throughout our bodies, including our bone marrow, thymus gland, spleen and lymphatic system and portions of our intestine.

The immune system is the white blood cells and antibody molecules that circulate in the blood to detect and fight off pathogens and other intruders. The immune system is the antibody-producing cells that live in the spleen and thymus. The immune system is pockets of immune cells that are clustered in patches spread throughout the lining of the intestine. The immune system is the marrow in the center of bones where new white blood cells are created and mature. Here is what is important: There is solid

clinical evidence that all these dispersed parts and pieces of the immune system require HA to be healthy and function well.



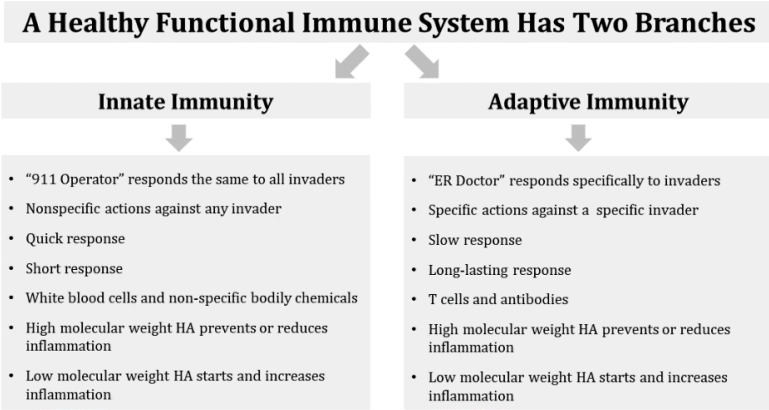
The immune system is dispersed in various organs throughout the body. (Organs of the immune system.jpg. By AIDS.gov - <https://www.aids.gov/hiv-aids-basics/just-diagnosed-with-hiv-aids/hiv-in-your-body/immune-system-101/>, Public Domain, <https://commons.wikimedia.org/w/index.php?curid=44689896>)

There are two separate functions in the immune system. The first immune function is innate immunity. The second immune function is adaptive immunity. Innate immunity responds first and quickly to a threat and is a short lasting response.<sup>25</sup> Adaptive immunity responds later and much more slowly to a threat but is a much longer lasting response (Chaplin, 2010). Both kinds of immunity are necessary for health, and both depend on HA to function well. A good way to think of the difference between the two types of

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<sup>25</sup>National Library of Medicine. National Center for Biotechnology Information. <https://bit.ly/2YEvlN7>





immunity is the differing roles in emergency medicine of 911 operators versus paramedics and emergency room doctors. The innate immune system is the 911 operator who sends an ambulance to everyone who urgently needs to get to the hospital for any reason. The adaptive immune system is the paramedic and the emergency room doctor at the hospital who provide the exact treatment a patient requires to survive the heart attack or severe injury they have experienced.

**HA in the innate immune system.**

The innate immune system’s main weapon against threats to health is inflammation (Cronkite & Strutt, 2018). You might think that inflammation is a result of an infection or other problem: “I got a cut, and it became inflamed.” However, inflammation really is a proactive mechanism the body uses to maintain balance: Inflammation is how the body gets rid of bacteria that could cause the cut to become infected and returns the body to normal. Inflammation is often portrayed as being bad and something to eliminate from your body, but this perception is flawed.

Inflammation is an important body defense. It is only when inflammation occurs without reason or runs out of control that it becomes “bad”.

Here is the plot of the innate immune system story:<sup>26</sup> Certain types of white blood cells continuously patrol our bodies looking for intruders. When these cells detect an intruder—like bacteria that have found their way into your cut—they set off an inflammatory cascade that serves to draw additional white blood cells, called neutrophils, to the site of the cut. Neutrophils are amazing little factories that produce and release enzymes and oxidants that can kill and break down bacteria. Neutrophils also release substances that encourage another type of white blood cell, called phagocytes, to come to the site of the cut. The recruited phagocytes eat the degraded bits of bacteria to remove the cause of inflammation from the body (Cronkite & Strutt, 2018; de laMotte & Kessler, 2015; Hato & Dagher, 2014; Kim & de la Motte, 2020).

HA is known to regulate the function of innate immune cells by using several mechanisms. For example, by binding to the surfaces of the white blood cells, HA activates the cells to play their role in immunity (Rayahin, et al., 2015; Safrankova, et al., 2010). One regulatory mechanism that is thought to activate inflammation is that the patrolling white blood cells, after detecting an intruder, release enzymes that degrade high molecular weight HA into small fragments. These small HA fragments appear to act as danger signals that encourage neutrophils and phagocytes to migrate to the wound or infection and to activate these cells to do their jobs (Cyphert, et al., 2015; Rayahin, et al., 2015).

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<sup>26</sup>National Library of Medicine. National Center for Biotechnology Information.  
<https://bit.ly/30K0eRb>

HA also is thought to play a role in ending inflammation when inflammation is no longer necessary. After the bacteria in your cut are degraded by neutrophils and the left over bits are eaten by the phagocytes, the reappearance of high molecular weight HA appears

## IMMUNE

**Injected HA is widely used in clinical practice (Kauz, et al., 2016) to reduce inflammation in joints.\* However, the efficacy and safety of oral and topical HA in reducing inflammation are beginning to be recognized. In peer-reviewed clinical studies, clinical and basic science researchers have observed that oral or topical HA:**

- Improves osteoarthritis caused by mast cells, a type of white blood cell
- Helps to reduce signs and symptoms of allergy and inflammation in the nose.
- Improves signs and symptoms of periodontitis by reducing inflammation.

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Bowman, et al., 2018

Casale, et al., 2016

Ciofalo, et al. 2017

Macchi, et al., 2013

Pignataro, et al. 2018

Safrankova, et al., 2010

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\*HA-TOPSHELF is an oral, over the counter HA supplement. Do not use the product for injections. Injections always should be performed only by a qualified, licensed physician.

to help to dampen down the inflammation by binding to molecules on the surface of the now-unnecessary white blood cells to cause them to go dormant and die (Chiou, et al., 2018; Cyphert, et al., 2015; Rayahin, et al., 2015).

So, you can see that both high and low molecular weight HA are important in regulating the innate immune system. The trick is to have the right amount of each size of HA in the right ratio at the right time. Having just enough low molecular weight HA at the right time and right place is required to start an innate immune response (Cyphert, et al., 2015; Rayahin, et al., 2015) but having too much low molecular weight HA is known to promote the spread of cancer cells (Kouvidi, et al., 2011). Having just enough high molecular weight HA at the right time and right place is required to stop an innate immune response (Cyphert, et al., 2015; Rayahin, et al., 2015) but having too much high molecular weight HA at the wrong time and in the wrong place is a problem, too. We will discuss an important instance of the detrimental effects of too much high molecular weight HA in a few paragraphs (Shi, et al., 2020).

Also, keep in mind that low molecular weight HA is created by degrading high molecular weight HA into smaller pieces (Gupta, et al., 2019) so not having enough high molecular weight HA indirectly can cause impaired innate immune responses (Cyphert, et al., 2015; Rayahin, et al., 2015). Mostly, we do not need to worry about having the correct balance of the high and low molecular weight HA because, when the human body is healthy, it has very strong mechanisms to govern the production and destruction of HA (Jiang, et al., 2011). Eating a healthy diet and making sure that our bodies have enough high molecular weight HA, such as by taking an oral supplement, is sufficient to support those mechanisms (Cyphert, 2015). However, as we will discuss in a later section, bacteria,

viruses, and some non-communicable diseases can subvert this system to cause serious, deadly illness (Mong, 2020; Jiang, 2011).

### **HA in the adaptive immune system.**

The other function of the immune system is adaptive immunity (Chaplin, 2010). The adaptive immune response differs from the innate immune response in that the adaptive immune system recognizes specific invaders and mounts a distinct response to each different invader.<sup>27</sup> The innate immune system does not care if the invader is a bacterium, a virus, or a splinter in your finger; it responds the same to all invaders. Like an emergency room doctor, the adaptive immune system takes the time to recognize that you have been infected with a specific pathogen and additional time to distinguish the chicken pox virus from the strep throat bacterium, for example. Then, the adaptive immune system activates a two-part immune response that involves, first, producing antibodies that specifically bind to and mark the pathogen for destruction and, second, causing cells to mature that specifically destroy the pathogen. The adaptive immune response is slower than the innate immune response due to the necessity to gear up synthesis of the specific antibodies and to create and activate the cells that attack the pathogen. The innate immune response provides just enough short-term, non-specific protection to give the adaptive immune response time to develop specific protection to fight off the invader.

As in the innate immune system, HA plays a role in the adaptive immune system. High molecular weight HA binds to a cell surface molecule on the outside of adaptive immune cells, specifically white blood cells called T lymphocytes (Asari, et al., 2010). T lymphocytes

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<sup>27</sup>National Library of Medicine. National Center for Biotechnology Information. <https://bit.ly/30Phk1Y>

(or “T cells” in medical and research parlance) are the cells that specifically recognize molecules from foreign invaders, distinguish those molecules from molecules that are part of the body, and then activate the adaptive immune response. Binding of HA to T cells helps to regulate and modulate the function of T cells to activate various immune functions, such as causing other immune cells to secrete antibody molecules to specifically target invaders.

### **HA and viral infections.**

There is some basic science, but not clinical, evidence that HA can protect cells from being infected with some, but not all, viruses (Cermelli, et al., 2011). Scientists do not quite understand how HA accomplishes this. However, having an understanding of how viruses infect cells offers some insight.<sup>28</sup> All viruses infect human cells by binding initially to the surface of cells and then moving inside the cells. Once inside the cells, viruses hijack the cells’ machinery to make more copies of themselves. When a certain number of offspring viruses are produced, the viruses start to exit from cells. In the process, viruses often kill the cells. In cultured cells (not in animals or humans), scientists observed that HA reduced the number of cells that were killed by different types of viruses and that HA was able to reduce the total number of offspring viruses produced. Scientists think that HA alters cellular function in a way that must interfere with viruses being able to bind to and enter cells or with viruses being able to hijack the cells’ machinery to make more viruses. It does not appear that HA directly interacts with the viruses; rather, it is HA’s effects on the cells that are important (Cermelli, et al., 2011).

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<sup>28</sup>St. John’s Health. Health & Medical Resources. <https://www.sjahs.org/virus-life-cycle/>

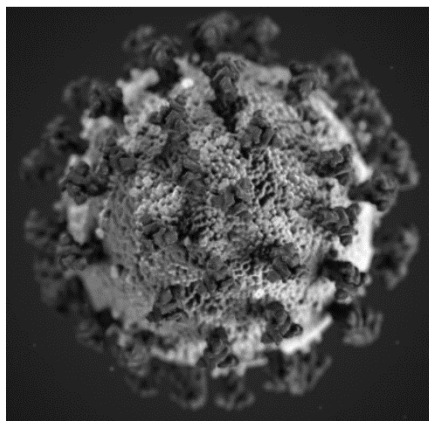
## **HA, COVID-19, and out-of-control innate immunity.**

One problem with the innate immune system and the processes that it uses to fight intruders, such as inflammation, is that these processes very easily can get out of control (Shi, et al., 2020). Going back to the car analogy at the beginning of the book, an out-of-control innate immune system is like a car speeding down the highway. The driver suddenly needs to stop but discovers that his brakes have failed, perhaps because all the brake fluid has drained out of the car. Bad things are going to happen to that car. Let us just hope that the driver is wearing a seatbelt! There's evidence that HA might be a component of the "brake fluid" that acts to keep the immune system's brakes functioning well.

Pathogens, like bacteria and viruses, can cause human disease and death by causing the innate immune system to lose control. The good news is that pathogens that cause the innate immune system to function uncontrollably most often are not very efficient at spreading between people because they tend to kill patients before patients can easily pass the pathogen to many other people (Engering, et al., 2013). So, while these pathogens do kill the people they infect, they are not transferred efficiently to enough people to cause epidemics (isolated outbreaks of disease) or pandemics (world-wide outbreaks of disease caused by many concurrent epidemics occurring in multiple places). But, every now and then, a scary pathogen emerges that efficiently can be transmitted from one person to many other people and can cause the innate immune system to roar out of control (Boulos & Gareghty, 2020; Mong, et al., 2020; Rothan, et al., 2020; Shi, et al., 2020; Song, et al., 2020). These types of pathogens cause epidemics and pandemics that result in

many people becoming sick and dying, and, thus, are important problems for public health to solve.

The 2020 COVID-19 pandemic was caused by such a pathogen, the SARS-CoV-2 virus. SARS-CoV-2 was able to move efficiently from one person to another by air droplets. The virus also had a long incubation period before illness occurred. This allowed people who were



SARS-CoV-2 Illustration  
(Open source from the Centers for Disease and Control Public Health Image Library.  
<https://bit.ly/2zBYJek>)

infected, but did not know they were infected, to spread the virus to many other people (Boulos & Geraghty, 2020). In some people, SARS-CoV-2 also was able to damage the brakes on the innate immune system, which allowed the immune system to roar out of control (Rothan, et al., 2020). Part of the way by which SARS-CoV-2 damaged the brakes was to interfere with normal synthesis and breakdown of HA (Bell, et al., 2019; Gupta, 2019).

In some, but not all, people who are infected with SARS-CoV-2, the virus causes a dangerous condition called “cytokine storm” (Shi, et al., 2020; Song, et al., 2020; Sun, et al., 2020). In a cytokine storm, the innate immune system loses control over production of cytokines, which are chemicals it uses to fight infection. Cytokines, when produced by the body in just the right quantities and at just the right time, are very effective to help our bodies fight off infection. However, during cytokine storm, extremely large quantities of these chemicals are produced in an unregulated manner, which causes the body to begin to shut down leading to



severe, irreparable organ damage (Shi, et al., 2020; Sun, et al., 2020, Song, et al., 2020). Cytokine storms happen very quickly and cause rapid death, sometimes within hours of onset. Often, there is nothing medical professionals can do to stop cytokine storm once it has started. It is always much better to stop cytokine storm before it happens than to treat it after it starts. In some COVID-19 patients, the SARS-CoV-2 virus causes a cytokine storm that leads to a nearly always fatal lung condition called acute respiratory distress syndrome (ARDS). Most deaths that occur in COVID-19 patients result from ARDS (Mong, et al., 2020; Shi, et al., 2020; Sun, et al., 2020, Song, et al., 2020).

If there was ever a doubt about how important HA balance is to the well-being of the body, that doubt should be ended once and for all by the integral role played by HA in COVID-19 ARDS. Elevated high molecular weight HA concentration in the blood was quickly recognized by doctors as a hallmark sign of SARS-CoV-2 infection in patients (Mong, et al., 2020). The elevated levels of HA result because some of the cytokines that are overproduced in SARS-CoV-2-induced cytokine storm unbalance the body's tight control over HA synthesis and destruction leading to over-production of high molecular weight HA (Cyphert, et al., 2015; Fallacara, et al., 2018). Over-production of HA results in far too much high molecular weight HA being present in the lungs (Esposito, et al., 2017; Mong, et al., 2020; Shi, et al., 2020; Sun, et al., 2020, Song, et al., 2020). ARDS develops because the high molecular weight HA absorbs water—sometimes up to 1000 times its weight in water (Jiang, et al, 2011). Ironically, the ability of high molecular weight HA to absorb water is a benefit of HA in the eye, which we will describe in a later section. However, in the lungs, all the water soaked up by the excess HA causes the supporting layer for air sacs to become very thick. Air sacs, or alveoli in medical terms, are where oxygen

breathed in from the air moves between the air sac cells and across the supporting layer below the air sac cells into the blood. This process must occur efficiently for adequate oxygen to enter the blood to keep organs healthy. If the supporting layer becomes too

# RESPIRATORY DISEASE

**In a peer-reviewed clinical study, clinical and basic science researchers have observed that HA:**

- High molecular weight HA injected just under the skin reduced the number of repeat infections in bronchitis patients.
- HA aerosolized and inhaled by infants with bronchiolitis slightly shortened the length of time the infants' needed to be hospitalized. Unfortunately, these authors did not identify the molecular weight of the HA used in the treatment.
- Treating adult asthmatics with a drug that inhibits the action of a specific kind of immune cell reduced airway inflammation, which was detected as an increase in HA concentration in the airway. Unfortunately, these authors did not identify the molecular weight of the HA.

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Ayars, et al. 2013

Nenna, et al., 2014

Venge, et al., 1996

Macchi, et al., 2013

Pignataro, et al. 2018

Safrankova, et al., 2010

thick and dense with water, as it does in ARDS, oxygen can't be exchanged efficiently, and the body starts to shut down organs due to damage caused lack of oxygen (Mong, et al., 2020; Shi, et al., 2020, Sun, et al., 2020; Song et al., 2020)

At the time of writing this book (mid-June 2020), it is too early in the SARS-CoV2 epidemic to describe clinically validated therapies for COVID-19 ARDS that are based on regaining control over HA metabolism. However, at least one group of clinicians who have treated ARDS caused by SARS-CoV-2 suggest that using drugs that inhibit HA synthesis can prevent buildup of excess HA to prevent ARDS from developing or using drugs that increase HA breakdown can destroy excess HA to restore lung function after ARDS has developed (Cantor, 2007; Shi, et al., 2020).

### **HA's anti-inflammatory actions in respiratory disease.**

In the previous section, we discussed how cytokine storm resulting from infection with the SARS-CoV-2 virus causes the fatal lung disease, ARDS by stimulating the body to overproduce high molecular weight HA in the support layer for the air sacs in the lungs. This is an example of how unregulated synthesis of HA in the body causes disease. In adults with chronic obstructive pulmonary disease (COPD), more HA of unknown molecular weight appeared in the blood in adults experiencing severe COPD attacks compared to adults not experiencing severe COPD attacks (Papakonstantinou, et al., 2019). It is unfortunate that the authors did not test the molecular weight of the HA because molecular weight is known to be important to HA's functions in the immune system. However, given what we have already read, we might hypothesize that the observed excess HA could be low molecular weight HA, which has been shown in other studies to contribute to inflammation.

If low molecular weight HA increases inflammation, it stands to reason that adding high molecular weight HA, which is anti-inflammatory (Garantziotis, et al., 2016a), to the airway might have the opposite effect to reduce airway inflammation. In fact, clinicians have observed that this is true (Cantor, 2007). In a laboratory model of bacterial pneumonia, isolated human lung cells were infected with bacteria (to mimic bacterial pneumonia). Treating the cultured human lung cells with high molecular weight HA reduced signs of inflammation (Garantziotis & Matalon, 2019; Liu, et al., 2019). Bronchitis patients who were injected with high molecular weight HA got fewer repeat infections (Venge, et al., 1996). In mice with chemically induced, asthma-like lung injuries, high molecular weight HA prevented the immune reaction leading to the asthma-like condition (Lazrak, et al., 2015). In an animal model of lung transplant, low molecular weight HA caused an immune reaction like the immune reaction that causes humans to reject transplanted lungs. Treating the mice with high molecular weight HA prevented the immune reaction that led to rejection of the transplanted lungs and the mice were able to continue to live (Todd, et al., 2014). Unfortunately, many researchers appear to be unaware of the apparent link between molecular weight of HA and its pro- or anti-inflammatory effects because many researchers do not describe the molecular weight of the HA used or detected in their studies.

In the next section, we will discuss HA in the gastrointestinal system. Surprisingly, the most important role of HA in the gut is HA's effect on the immune system. At the beginning of this section, we mentioned that part of the immune system occurred in patches distributed throughout the gut. Well, it turns out that the immune cells in those patches have wide-reaching effects throughout our body—the so called gut-skin-brain axis.

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## GUT & DIET

### **HA benefits in the gut.**

The benefits of a healthy gastrointestinal system extend beyond the gut to our overall well-being and health (Jiang, et al., 2011). Gut homeostasis is central to hydration, gut microbiome, and innate immunity (Salem, et al., 2018; Colgan, 2013; de la Motte, 2011; de la Motte & Kessler, 2015; Galland, 2014; Kim & de la Motte, 2020). HA promotes gut health by improving hydration, maintaining healthy gut microbiome, and leading to overall feelings of well-being by decreasing stiffness and pain (Bellar, et al., 2019; de la Motte & Kessler, 2015; Fallacara, et al., 2018; Gupta, et al., 2019). Oral HA acts both in the gut as well as being absorbed into the blood to be distributed to the body (Fallacara, et al., 2018) where HA can have positive effects in addition to those in the gut.

There is evolving evidence that HA plays a role in the gut-skin-brain axis (Salem, et al., 2018; Galland, 2014). The gut-brain-skin axis occurs because all these organ systems work together. Therefore, poor health of one system reduces the health of the other two systems. For example, there is some evidence that chronic fatigue syndrome, which is characterized by extreme tiredness, mental “fogginess”, and generally ill appearance, might be caused

by gut microbiome bacteria that enter the blood stream when the gut wall becomes too leaky. HA might be beneficial to support and improve the gut-brain-skin axis because HA contributes to a non-leaky gut, which prevents cells and chemicals from escaping into the blood (de la Motte & Kessler, 2015; Galland, 2014; Kim et al., 2018)

## Gut

**Clinical studies of HA in the gut have been limited to HA in treating gastroesophageal reflux disease and the safety of HA in healthy humans:**

- In ongoing clinical trials, HA is being investigated as a human therapeutic to prevent and treat gastroesophageal reflux disease.
- In healthy humans, low molecular weight HA (35 KDa) was found to be safe, without side effects, and did not affect healthy gut metabolic function, healthy inflammation, or healthy microbiome. In the future, these clinicians plan to extend this study to older patient and patients with gut illnesses.

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<https://bit.ly/2zlxpuQ>

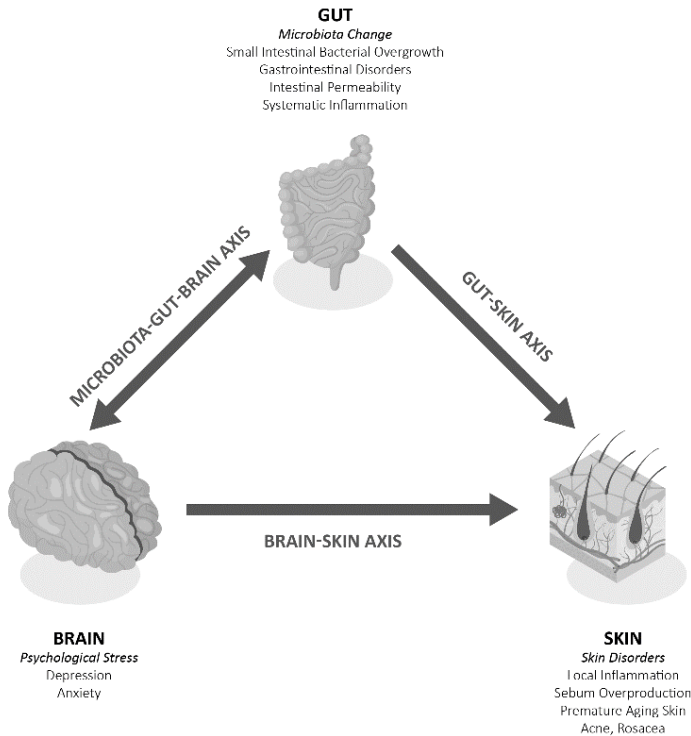
<https://bit.ly/3d7lMLX>

<https://bit.ly/3deFsNQ>

Bellar, et al, 2019

## Hydration.

In the immune system section, we described how COVID-19 ARDS resulted from excess HA in the lungs retaining excess water ultimately leading to the lungs being unable to transport oxygen across the tissue support layer to blood. This was an example of too much HA and too much water. However, the situation in the eye is exactly the opposite. Extra HA, in the form of sterile HA drops, that is added to eyes retains water in the eyes to relieve dry eye conditions. Later in the book, we will discuss HA in eyes in more detail.



The gut-brain-skin axis

In the gastrointestinal tract, the ability of HA to soak up water is required for health. In the gut, HA soaks up water and stores it until the body starts to run low on water. Then, HA starts to release its stored water. The support layer for gut cells, especially, requires the water-storing ability of HA to perform its role in gut and overall body health (de la Motte, 2011; de la Motte & Kessler, 2015; Kim & de la Motte, 2020). Most of the water absorbed into the body is absorbed from the gut. This water is then transferred to other parts of the body where it improves body function (Bellar, et al., 2019; de la Motte & Kessler, 2015; Fallacara, et al., 2018; Gupta, et al., 2019), including improving the look and feel of skin (Göllner, et al., 2017). The water absorbed into the gut support layer also assists in transporting ions and nutrients from the gut into the blood (de la Motte, 2011). Finally, a well-hydrated gut tissue support layer maintains the integrity of the gut so that pathogens can't gain entrance to the body and ensures that the immune functions of the gut occur normally (de la Motte, 2011; de la Motte & Kessler, 2015; Kim & de la Motte, 2020).

### **Microbiome.**

There is preliminary evidence that HA can stabilize and modulate the gut microbiome. A human clinical trial found that topical HA gel helped to maintain healthy microbiome in the mouth after dental implant surgery (Soriano-Lerma, et al., 2019). A clinical study in healthy people found that low molecular weight HA did not change the composition of the gut microbiome; however, this study did not look at high molecular weight HA, unhealthy humans, or humans with disturbed microbiomes (Bellar, et al., 2019). In mice that had experimental intestinal inflammation, a conjugate HA drug, in which HA was linked to another molecule, reversed the effects of inflammation both on the structure of the gut and on the general



well-being of the mice. Part of this effect was due to promoting a healthy microbiome in the mice (Lee, et al., 2020).

### **Inflammation.**

In an earlier section, we talked about the role played by HA in regulating innate and adaptive immunity. A main site where immune processes occur is in the intestinal lining (de la Motte, 2011; de la Motte & Kessler, 2015; Kim & de la Motte, 2020). HA is known to bind to the surfaces of gut immune cells to modulate their functions both in health and illness (de la Motte & Kessler, 2015). In mice, there are indications that HA's actions in the gut might be linked to preventing inflammation (Lee, et al., 2020).

Crohn's Disease is chronic inflammation of the gut. You might remember from our discussion of innate immunity earlier in the book, that one way the innate immune system sends out an alarm that there is an invader is by breaking down high molecular weight HA into HA fragments that act to attract innate immune cells. In Crohn's Disease, it appears that the normally healthy balance between building and breaking down HA is subverted to cause illness. Intestinal cells isolated from people with Crohn's Disease expressed excess amounts of a specific protein. One of the illness-causing actions of that protein is to break down high molecular weight HA into fragments inappropriately (Sorosh, et al., 2016). Just like in the innate immune system, these HA fragments called cells that contribute to inflammation to the gut; except, in this case, there is no need for those cells to come to the gut because there is no invader to which to respond.

In the next section, we will discuss how HA might affect longevity. We will use the story of Yuzuri Hara in Japan to illustrate a possible mechanism by which HA primes our bodies to live long, cancer-free lives.

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## THE “LONG-LIFE” VILLAGE

### **A link between HA and longevity.**

In 2000, Connie Chung reported on Yuzuri Hara (sometimes spelled “Yuzurihara”), Japan, a farming village in the hills of Japan.<sup>29</sup> Ms. Chung reported that the people of Yuzuri Hara lived very long lives and that many people in the village were 85 to 90 years old or older. The local village doctor believed that the villagers could attribute their longevity; low rates of cancer, diabetes, and Alzheimer’s; and their characteristic of having lovely, smooth skin to having high levels of high molecular weight HA in their bodies. The doctor believed that the purported high levels of HA resulted from Yuzuri Hara residents’ unique diets, which were high in specific, healthy carbohydrates derived from root vegetables (satsumaimo, a type of sweet potato; satoimo, a sticky white potato; konyaku, a gelatinous root vegetable concoction; and imoji, a potato root). In 2007, Bill Sardi, an HA enthusiast, visited Yuzuri Hara and corroborated the advanced age and spryness of the people of Yuzuri Hara’s residents.<sup>30</sup>

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<sup>29</sup><https://www.youtube.com/watch?v=Fgl-bW6txuw>

<sup>30</sup><https://bit.ly/30I574E>

The ABC News report has been routinely touted by HA enthusiasts as proof that high molecular weight HA causes long-life; however, neither the ABC News or the Sardi report have provided scientific, peer-reviewed evidence that the people of Yuzuri Hara actually do have high levels of high molecular weight HA in their bodies. The authors of this book have not been able to find peer-reviewed reports that directly substantiate that the Yuzuri Hara villagers' advanced age and good health were caused by or related to HA.

However, there are observations in the peer-reviewed literature that suggest indirectly that the Yuzuri Hara physician might be correct in his intuition that HA contributes to long life. Data-based observations in residents of Okinawa, another island in the Japanese archipelago (Willcox, et al., 2014) have shown that, like Yuzuri Hara residents, Okinawans also consume a nutrient rich, low energy diet that includes sweet potatoes (Drewnowski & R, 2013).<sup>31</sup> These data demonstrate that Okinawans experience significantly longer life expectancy and much lower rates of age-related disability compared to other cultures (Willcox, et al., 2014). Additional research suggests a data-based explanation for this phenomenon. Sweet potatoes are rich in a specific class of chemicals, polyphenols (Dini, et al., 2006). A specific type of polyphenol, anthocyanin, which is found in black currants and purple sweet potatoes, has been shown to correlate with increased anti-oxidant activity and increased hyaluronic acid content in cultured cells and in the skin of rats (Lim, et al., 2013; Nanashima, et al., 2018; Sugata, et al., 2015).

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<sup>31</sup><https://fdc.nal.usda.gov/fdc-app.html#/food-details/168482/nutrients>

So, perhaps the villagers of Yuzuri Hara are the proof that, if we eat the right foods and add oral HA supplements to our diet we can emulate our little buddy, the naked mole-rat, who has been shown by scientific research to have high levels of high molecular weight HA in his body, and to be cancer-free and long-lived (Lewis et al., 2013; Takasugi, et al., 2020. Peer-reviewed scientific research has shown that adding oral HA supplements to your diet is safe (Bellar, et al., 2019), and several clinical studies that we have described have shown that oral HA has specific clinically- and scientifically-proven health benefits (Gupta, et al, 2019)

In the next two sections, we are going to talk about HA in skin and eyes. These two sections highlight existing uses for HA in human health. HA has been applied extensively as treatments in both the skin and eyes by the medical community.

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# SKIN

## **Your skin is important to your health.**

We should never, ever take our skin for granted.

Skin is the first and most important barrier between us and the outside world and accounts for 50% of our total body HA. Skin helps us to retain the water that our bodies need to be healthy and function well. Nerve endings in intact skin help us to sense what is happening in the outside world so our bodies can respond appropriately. Our skin is the first part of us that people see. The character and tint of our skin can provide doctors with important clues to what disease processes might be occurring in our bodies. For example, patients with liver failure have skin with a characteristic yellow tint. The color of their skin is a telltale sign to doctors that something is very wrong with that patient.

If skin is damaged, our continued health will be severely compromised. One of the main causes of death in strong tornados, such as the 2011 EF-5 Joplin, Missouri tornado, is puncture wounds in skin. In the Joplin tornado, punctures in skin from people being hit with flying debris allowed fungus pathogens to enter the body and set up infections that indirectly killed more people than those who died directly in the tornado (Fanfair, et al., 2012). One of the

deadliest forms of cancer, melanoma, arises when excessive sun exposure damages skin cells.<sup>32</sup>

Clinical researchers have found that oral HA supplements can help to slow—possibly partially reverse—age related changes (Fallacara, et al, 2018; Pérez-Sánchez, et al., 2018). Scientists have various hypotheses about how HA accomplishes protects skin. In basic science research, HA has been shown to reduce antioxidant activity (McCall-Perez, et al., 2011; Braga, et al., 2015) and to protect from reactive oxygen species produced when skin is exposed to ultraviolet light (Penna, et al., 2019). Several clinical studies indicate oral HA supplements improve both objective and subjective characteristics of skin that has been damaged by sun and age (Papakonstantinou, et al., 2012).

So, no matter how you accomplish it, take good care of your skin. Protect it from trauma and too much sun. Also, eat a healthy, antioxidant diet, which will benefit your whole body. Finally, adding a high quality, high molecular weight HA supplement to your diet might add the protective benefits of HA to your skin care regimen.

Like the skin, HA drops have been extensively used in treating eye disease but, recently, understanding is rising that oral HA can be beneficial for eyes, as well.

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<sup>32</sup>United States National Library of Medicine. Genetics Home Reference. <https://bit.ly/3hNgfNT>



# SKIN

**In peer-reviewed clinical studies, clinical researchers have observed that oral HA:**

Improved objective signs of skin aging

- Decreased skin wrinkles
- Decreased skin roughness
- Increased skin elasticity
- Increased skin hydration

Improved quality of life by decreasing skin itching

Improved subjective perceptions of skin condition

- Improved skin luster
- Improved skin suppleness

Improved characteristics associated with photodamage of skin

- Improved “radiant complexion”
- Reduced wrinkling around the eyes
- Reduced skin roughness
- Reduced mottled pigmentation
- Reduced skin thickness

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Göllner, et al., 2017

Guaitolini, et al., 2019

Kawada, et al., 2014

Kawada, et al., 2015

Lubert, et al., 2019

Oe, et al., 2017

Schwartz & Park, 2012

Stephens, et al., 2016



## HA & EYE HEALTH

### **Eyes: It is all about the water.**

Eyes need water to be healthy and comfortable. The eye is 99% water (Gaffney, et al., 2009). However, something must hold water in the eye. That is where HA comes in. HA holds the water in the eye to lubricate and protect the eye. In fact, in 1934, HA was first isolated from the fluid inside eyes (Gupta, et al., 2019).

If there's not enough HA in your eyes, your eyes will start to lose water. One problem with maintaining sufficient HA concentration in the eye is that HA in the eye is replaced frequently (Gaffney, et al., 2009). Consequently, a large amount of continuously replenished HA is required to maintain the water balance of the eye. If our bodies can't synthesize enough HA, then we have to supplement HA with eye drops or oral HA supplements.

Most often, HA supplements for eyes occur in the form of sterile ophthalmic HA drops.<sup>1</sup> There are a multitude of clinical studies that indicate that sterile ophthalmic HA drops are beneficial to eyes (Gaffney, et al., 2009). However, a recent clinical study suggests that oral HA supplements also improve dry eyes (Kim, et al., 2019). These clinicians observed that, in patients who also were using

sterile eye drops, supplementing the patients' diets with high molecular weight HA improved the symptoms of dry eye more than did using eye drops alone. This study suggests that the benefits of

## EYES

**In a peer-reviewed preliminary clinical study, oral supplementation of HA:**

- Increased healing of the eye better than did drops containing sterile, ophthalmic preparations of HA

**In peer-reviewed clinical studies, sterile, ophthalmic HA\* drops applied after medical procedures improved eye health.**

- HA retained water in tears to increase the natural lubrication of the eyes
- HA caused eyes to retain naturally produced tears longer
- HA reduced damage to the cornea (the clear membrane over the iris of the eye that we see through)
- HA decreased redness (visible red blood vessels) in the white of the eyes

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Groß, et al., 2018

Kim, et al., 2019

Labetoulle, et al., 2018

Molina-Solana, et al., (2020)

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\*HA-TOPSHELF is not a sterile ophthalmological-grade product. Do not apply HA-TOPSHELF to your eyes

adding a high quality, high molecular weight HA supplement do not rest solely in the eye of the beholder.

We have come to the end of our sections on the benefits of HA in specific organ systems. Believe it or not, there is more information out there that we have not included in this book. We encourage you to continue your study of the benefits of HA, but we strongly urge you to be vigilant about the quality and validity of what you read. Think critically about what you read. Insist on reading only data-based accounts of HA benefits. HA is very popular as an oral supplement right now. Anyone can say anything about HA without having to prove that what they say is accurate and based in science. In our discussions of HA and HA-TOPSHELF, the HA team has focused on only those claims of benefits that we could substantiate with peer-reviewed clinical and basic science research reports. We urge you to apply the same rigor and critical thinking to your own studies of HA and selection of an HA product.

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## WRAPPING IT UP

### **WHY THE HA TEAM RELIES ON DATA TO DEMONSTRATE THE BENEFITS OF HA AND TO IMPROVE HA-TOPSHELF.**

Remember Helen who bought her husband his own bottle of HA-TOPSHELF so she would not have to share her own? Helen's experience with HA has been echoed by others of Dr. Kiburz's patients as well. Take Carolyn (her name has been changed to protect her privacy), for example.

Carolyn experienced moderate arthritis pain and stiffness. She decided to look for a dietary supplement to relieve her pain and stiffness. However, being an analytical type, Carolyn was determined to keep records of her pain and stiffness before and after taking a supplement so she could determine objectively whether the supplement provided a benefit. Carolyn started recording her pain and joint stiffness daily on a 1 to 10 scale.

Then, she looked for an appropriate supplement. Her independent reading suggested that an HA supplement might be a safe and effective solution to her problem. Next, she looked for a pure, high-quality HA supplement, which was when she heard, during conversations with acquaintances, that Dr. Kiburz was developing a pure, high-quality HA supplement, HA-TOPSHELF. She

approached Dr. Kiburz, who provided a complimentary bottle of HA-TOPSHELF (a 30-day supply) to Carolyn.

After taking HA TOPSHELF for one month, Carolyn said in an email to Dr. Kiburz, “I kept a chart that showed that, before taking HA-TOPSHELF, my arthritis pain in knee, hip, ankle and shoulder was mostly in the 2 to 3 range on a 1 to 10 pain scale. After taking the product, except for a few days of extra ankle pain, I noted that my knee, hip, ankle, and shoulder were at a 0 to 2 on a 1 to 10 pain scale later the same month. I have read good things about HA and plan to continue taking the supplement.”

Here at HA-TOPSHELF, we are analytical types, just like Carolyn. We value customers like Carolyn who provide objective data about whether our product is safe and effective. We used data to develop our product, and we will continue to use data to help us to improve our product. In this book, we focused on only those claims of benefits that we could substantiate with peer-reviewed clinical and basic science research reports.

We welcome your feedback on your experiences with HA as a supplement and HA-TOPSHELF as a product.<sup>33</sup> At the time of writing this book, the HA Team has not gathered data indicating any problems with our product. However, good scientists and clinicians will tell you that data indicating problems are very important—sometimes more important than data indicating no problems—

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<sup>33</sup>If you use HA-TOPSHELF and want to provide feedback on your experience, please email your feedback to [HA-TOPSHELFtestimonial@outlook.com](mailto:HA-TOPSHELFtestimonial@outlook.com). Please include as much information and data as you feel comfortable providing. We do not need to know your name or other personally identifying information. We will not contact you unless you request that we contact you. However, if you would like to be contacted about your feedback or a solution to a problem you have experienced with our product, please provide an email address or phone number. We are committed to preserving your privacy and will not share your name, email address, data, or other information without your written permission.



because learning of a problem means we can solve a problem, which leads to continually improving our product.

We encourage you to improve your health by supplementing your healthy diet with high quality, high molecular weight HA. To achieve the health benefits offered by HA, the HA Team at HA-TOPSHELF would be pleased if you would consider purchasing and using our product.<sup>34</sup> However, as we said in the first section of this book, it is more important to us that you understand why high molecular weight HA is important to your health and, if you decide to add an HA product to your diet, to have objective facts to use to select an HA product.

Our goal in this book is to describe the scientific and clinical evidence that supports our conviction that high quality, high molecular weight HA is an essential health supplement. We hope you enjoyed learning about our team of physicians, pharmacists and chemical engineers and why he set out to provide a high quality, high molecular weight HA product to patients, families, and pets. We hope you also enjoyed reading the human-interest case studies of Bob, Olympia, Amelia, Amy, and Helen that illustrate how real people (and pets) have benefitted from HA.

Hyaluronan! To health and beyond!

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<sup>34</sup><https://ha-topshelf.com/>



## SUPPLEMENTARY MATERIALS

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## Certificate of Analysis.

### Certificate of Analysis

Product Name	Sodium Hyaluronate	Batch No.	██████████
Manufacture Date	██████████	Test Date	██████████
Standard	Enterprise Standard ██████████	Weight	███

Test Items	Specification	Test Results
Appearance	White Powder	White Powder
Glucuronic Acid (%)	≥45.0	47.1
Sodium hyaluronate, %	≥93.0	97.4
Transparency,(0.1%water solution)	≥99.0	99.5
pH(0.1%Water Solution)	5.0-8.5	6.8
Molecular Weight (Da)	As requirement	$1.83 * 10^6$
Protein, %	<0.05	0.046
Loss on Drying, %	≤10.0	6.7
Residue on Ignition, %	≤20	12.65
Heavy Metal(as Pb), ppm	<10	<10
Arsenic, ppm	<2	<2
Bacteria Count, CFU/g	<100	<10
Molds & Yeast, CFU/g	<10	<10
Staphylococcus aeruginosa	Negative	Negative
Pseudomonas aeruginosa	Negative	Negative
Hemolysis	Negative	Negative
Viable Hemolytical Streptococci	Negative	Negative
Other Indexes of Microorganism	Accord with The National Standard	
Shelf life	3 years at 4-8 °C	

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## **Disclosures.**

Douglas W. Kiburz, M.D. is co-owner of HA-TOP SHELF and profits from sales of the product. Dr. Kiburz collaborated with partners, Don Grove, Jr. and Don Jessup, to develop, produce, and market HA-TOP SHELF over the counter supplement. Dr. Kiburz identified the content, illustrations, and writing style of this manuscript and critically reviewed the entire document prior to publication. Dr. Kiburz is a practicing orthopedic surgeon at Bothwell Orthopedics & Sports Medicine, Bothwell Regional Health Center in Sedalia, MO.

Linda A. Landon, Ph.D. is a basic biomedical research scientist, molecular pharmacologist, data scientist, and medical writer. Dr. Landon was responsible for all background basic science and clinical literature research, review, and analysis; for writing, copy editing, and proofreading the text; for identifying, designing, and/or producing all figures; and for managing production of the print and digital versions of the book. Dr. Landon was paid for her work on this book. Dr. Landon is the founder and president of Research Communiqué, a research and communication firm, and is co-founder, co-CEO, and COO/CFO of Velocity DataTech, a data science firm.

Dalton Hermanson is a medical student in the accelerated six-year medical program at the University of Missouri – Kansas City School of Medicine. Mr. Hermanson is augmenting his medical

education by completing an unpaid internship with Dr. Kiburz and Dr. Landon. Mr. Hermanson contributed to the extensive background literature research and analysis of clinical trials and participated in writing, copy editing, and proofreading the text.

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