

# NUTRI NEWS



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## ALTERNATIVE THERAPY FOR RHEUMATOID ARTHRITIS – SIX CLINICAL TRIALS REVIEWING UNDENATURED TYPE II COLLAGEN

Andrew Halpner, Ph.D., with contributions from Dr. Bagchi (InterHealth Nutraceuticals)

Arthritis is one of the most prevalent chronic health problems in the United States, affecting nearly 43 million people. Although arthritis is often thought of as a disease that predominantly affects the elderly, it is the number one disability affecting those over the age of 15. In fact, more than half of those affected by arthritis are under the age of 65, and almost 300,000 of those affected are children. Each year arthritis is responsible for 44 million outpatient visits, almost one million hospitalizations, and is second only to heart disease in terms of its effect on disability from work. As might be imagined from these statistics, the toll that arthritis takes on the health care industry is substantial, costing the United States approximately \$65 billion each year in health-related expenses. Unfortunately, the prevalence of arthritis does not appear to be improving, and by the year 2020 the Centers for Disease Control predicts that almost 60 million Americans will suffer from some form of this disease.

While the term arthritis may bring to mind a simple condition characterized by painful joints and difficulty performing certain tasks, arthritis actually encompasses more than 100 different diseases. Of these different forms of arthritis, however, osteoarthritis (OA) and rheumatoid arthritis (RA) are among the most common.

**Osteoarthritis:** Osteoarthritis currently affects 15.8 million Americans and is a degenerative joint disease in which the cartilage covering the ends of bones deteriorates, resulting in pain, stiffness, and loss of movement. This form of arthritis generally begins after the age of 40, and develops slowly over many years. In contrast to RA, people usually report pain beginning in joints on only one side of their body. While inflammation may be present, this joint pain is typically not accompanied by the amount or severity of inflammation observed in those with RA. Weight-bearing joints such as the knee and hip tend to be more affected than non-weight-bearing joints such as the elbow or shoulder. A general feeling of sickness that can accompany other forms of arthritis does not usually accompany osteoarthritis.

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## INTRODUCING THE NUTRI NEWS TECHNICAL BOARD OF ADVISORS

With this issue of *NutriNews*, we are introducing our new Technical Board of Advisors. The *NutriNews* Technical Board is comprised of some of the finest clinical practitioners and nutritional experts in the industry. Each upcoming issue of *NutriNews* will contain informative articles from one or more Board members or guest contributors. Articles will be reviewed by Board members for content clarity and accuracy. Editorial topics will continue to focus on specific health conditions, providing the latest clinical data and in-depth technical information on the most effective nutritional supplements, leading to improving patient health.

Our Technical Board represents a diverse assortment of scientific and clinical professionals. This diversity provides a broad editorial knowledge base that combines the best of both worlds: nutritional research with the experience and application of the clinical practitioner. Many of these professionals have written pertinent books in their respected fields of expertise. See page 2 for brief biographies of the Technical Board members' experience and qualifications.

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**Rheumatoid Arthritis:** Rheumatoid arthritis is not a “new” disease. One of the first descriptions of a disease resembling RA can be found in the *Caraka Samhita*, a medical text from India, and dates back as far as 500 B.C. Another ancient reference to the disease dates to 100 B.C. in Rome when Scribonius Largus described a polyarthritic condition occurring mainly in elderly women that closely resembled what we now understand to be RA. Rheumatoid arthritis currently affects approximately two million Americans, and about one percent of the population worldwide. However, the pathology and progression of RA is somewhat different from that of OA.

Unlike OA, RA often develops suddenly, within weeks or months and generally begins between the ages of 25 and 50. Non-weight-bearing joints such as the shoulders and elbows are usually affected bilaterally, and a significant amount of redness, tenderness, swelling and inflammation is often present. This form of arthritis often results in a feeling of sickness, fatigue, and may be accompanied by weight loss as well as fever. Morning joint stiffness lasting for an hour or longer is relatively common. Subcutaneous nodules that form over bones may also be present. While the reasons are not completely understood, three times as many women compared

## NutriNews Technical Board of Advisors

### **Andrew Halpner, Ph.D.** – Editor In Chief



Dr. Halpner received his Ph.D. in Nutrition from Tufts University School of Nutrition Science and Policy. His extensive research and interests focus around antioxidant nutrients, including their interactions and abilities to prevent and treat age-related degenerative illnesses. Dr. Halpner is Director of Product Development and Technical Services for Douglas Laboratories.

### **Martin P. Gallagher, M.S., D.C.** – Advisor, Contributing Author

Dr. Gallagher is a chiropractic physician specializing in clinical nutrition and has been in practice for more than twenty years. He received his bachelor's degree in psychology from Wheeling Jesuit College, his master's degree in biology and nutrition from the University of Bridgeport, and his doctorate degree (D.C.) from Logan College of Chiropractic in St. Louis. Dr. Gallagher has served as a faculty member at several colleges, lectures internationally to chiropractors, medical doctors and osteopathic physicians and is the author of *Dr. Gallagher's Guide to 21st Century Medicine*. Currently, Dr. Gallagher and associates operate a multidisciplinary health facility, Medical Wellness Associates, outside of Pittsburgh, Pennsylvania.

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Nita Bishop practiced as an herbalist in Phoenix, Arizona before entering the Naturopathic program at Bastyr University where she is in her fourth year of medical school. Ms. Bishop holds undergraduate degrees from Pepperdine University in Biology and English. She has an extensive background in natural medicine and working with traditional healers and is actively dedicated to enthusiastically elevating the awareness and validation of herbal medicines via the lecture circuit.

with men are afflicted with rheumatoid arthritis. Some patients will experience a monocyclic course of the disease that may abate within two years, while others will experience a polycyclic, or progressive course. Of all the forms of arthritis, RA tends to be one of the most serious and disabling forms of the disease, with 16 percent of those who have had the disease for 12 or more years becoming completely disabled. Lifespan has also been shown to be shortened by approximately seven years in men and three years in women, which is equivalent to the increased mortality observed in those with diabetes and Hodgkin disease.

## Etiology

While RA is classified as an autoimmune disease, the exact causes that result in its development remain a mystery. What is known is that many different and complex factors are involved. Some cases of OA may be the result of years of “wear and tare” on joint structures, while other forms of OA can be traced to an injury, infection, or metabolic disorder. However, RA does not result from overuse of a joint or from injury, but rather from an autoimmune problem in which the body attacks and damages its own tissue. The damage that occurs in RA appears to be propagated by cytokines

### **Derek DeSilva Jr., M.D.**

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Dr. DeSilva is a practicing physician specializing in cardiovascular health. Dr. DeSilva is on the teaching faculty of JFK Medical Center and the Institute of Medicine and Dentistry in New Jersey. He hosts a daily nutrition- and supplement-oriented radio show titled *Ask the Doctor* and is a much-sought-after lecturer at trade conferences and conventions.

### **Brad Lichtenstein, N.D.**

#### **- Advisor, Contributing Author**

Dr. Lichtenstein is a naturopathic physician and a graduate of Bastyr University. He specializes in HIV care, body-centered psychotherapy and energetic medicine. Dr. Lichtenstein has supervised the Immune Wellness Clinic, providing naturopathic care for people afflicted with HIV. He lectures throughout the country on living well with HIV and other chronic diseases.

### **Mitchell J. Ghen, D.O., Ph.D.**

#### **- Advisor, Contributing Author**

Dr. Ghen received his osteopathic degree from Philadelphia College of Osteopathic Medicine and his doctorate in alternative and holistic health from the Union Institute in Cincinnati, Ohio. He is a world-renowned lecturer and sits on the editorial boards of numerous health journals. Dr. Ghen co-authored the *Ghen and Rains Physician's Guide to Pharmaceutical Compounding* and is Editor in Chief for *The Advanced Guide to Longevity Medicine*. He currently has medical practices in Atlanta, Georgia; and Columbia, Landrum and Rockhill, South Carolina.

### **James Wilson, Ph.D.**

#### **- Advisor, Contributing Author**

Dr. Wilson holds three doctoral degrees, including one in human nutrition and immunology. In addition to being in private practice for 23 years, he has been formulating nutritional products since 1981. He was one of 14 founders of the Canadian College of Naturopathic Medicine and is listed in the first *International Who's Who in Medicine*. Dr. Wilson is well known and respected as a lecturer at medical seminars throughout the United States.

(important regulatory chemicals within the body) secreted by T-cells of the immune system in response to certain autoantigenic stimuli within the joint. In other words, the body's immune system is, for some unexplained reason, identifying some component or components of the joint as containing antigens against which a response from the immune system should be carried out. Various immunological factors are involved, including, but not limited to, CD4/inducer lymphocytes, CD4 memory cells, macrophages, neutrophils, and tumor necrosis factor (TNF). One of the most likely candidates for this autoantigenic stimulus is the collagen component of cartilage, specifically type II collagen. Some researchers believe that an infection may trigger the initial inflammation in a joint, which in turn triggers the autoimmune response by the body. However, genetics and other factors, including stress, may also play a role.

To fully understand the deterioration that is occurring in arthritic conditions, it is important to have a basic knowledge of the structure and components of a joint. When bones meet at a joint, such as the hip or elbow, the ends of the bones are covered with cartilage. This cartilage allows for flexibility and motion as well as provides a cushion against the impact of various forces on the bone. The detailed structure of cartilage is complex, but can be simplified into two major components, collagen and proteoglycans. Proteoglycans are large protein molecules attached to large carbohydrate chains called glycosaminoglycans. These proteoglycans help to provide a matrix in which the collagen as well as water can reside. There are a number of different types of collagen, but type II collagen accounts for the majority of what is found in cartilage. Type II collagen is composed of three identical chains (termed  $\alpha$ -1 chains), which form a triple helix. This interconnected network of collagen and proteoglycans is crucial in order to maintain joint flexibil-

ity and resistance to stress and fracture. In RA, autoantigenic responses, most likely triggered by type II collagen, ultimately result in the progressive inflammation, pain, and deterioration characteristic of this disease.

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Regardless of the initial cause, a progressive degeneration of the structure and function of the joint takes place, making normal activities of life increasingly difficult. In the case of RA, the body is unable to recognize its collagen as normal tissue and in turn attacks it as if it was a foreign invader. A novel approach to the treatment of RA termed "oral tolerance," has been the focus of signif-

icant positive scientific research. Oral tolerance is a treatment in which small amounts of type II collagen (the material that the body is destroying) are presented to the gastrointestinal tract. What results is a down regulation of the body's ability to destroy its own collagen and a resulting improvement in the symptoms and progression of the disease. However, before we explore this treatment further, it is important to understand traditional treatment options.

### Current Treatment Options

Traditionally, treatment options for those with rheumatoid arthritis are non-steroidal anti-inflammatory drugs (NSAIDs) alone or in combination with what are known as disease-modifying antirheumatic drugs (DMARDs). As is well known, chronic use of NSAIDs, especially in the elderly is linked to numerous side effects including gastrointestinal bleeding, and renal malfunctions. Even the newer generation of COX-2 inhibitors such as Vioxx and Celebrex are not without their own problems. While these drugs do reduce inflammation, they do not address the under-

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lying cause of the arthritis and therefore cannot alter the progression of the disease. Also, prolonged use of these newer COX-II inhibitors in the elderly can result in side effects similar

## DR. DAVID E. TRENTHAM: RESEARCHER BEHIND UNDENATURED TYPE II COLLAGEN

At the forefront of research involving undenatured type II collagen and rheumatoid arthritis is a doctor with a long history and commitment toward the treatment of this debilitating illness. David E. Trentham, M.D. has been a leading researcher on undenatured type II collagen.

Dr. Trentham's involvement in Immunological and Rheumatological research spans more than two decades. Dr. Trentham is a 1970 graduate of the University of Tennessee's College of Medicine specializing in Immunology and Rheumatology. After internship and residency at Memphis area hospitals, Dr. Trentham served as a captain in the U.S. Army Medical Corps at Walter Reed Army Medical Center in Washington, D.C. After

military service the doctor participated in research fellowships at NIH, University of Tennessee Center for the Health Sciences and the Harvard Medical School.

Following his research fellowships, he began teaching at the Harvard Medical School in 1978 where he is an Associate Professor of Medicine. Dr. Trentham is a frequent lecturer and visiting professor on Immunology and Rheumatology at seminars and learning institutions all over the world.

Dr. Trentham has served, and continues to serve, as an attending physician at various hospitals and as a member of several Rheumatology clinics; including ten-years as Chief of the Rheumatology

Division at the Beth Israel Hospital, Boston, MA. He is also a consultant in Rheumatology and Immunology for the Brockton, VA Hospital and InterHealth Nutraceuticals.

Throughout his career, Dr. Trentham has participated on numerous major hospital, government and industry committees and currently sits on the editorial boards of Cellular Immunology and the Journal of Clinical Rheumatology. Dr. Trentham's work is widely-published and has appeared in numerous professional and technical journals. Some of his most recent reports involve clinical research on oral tolerance in collagen-induced arthritis.

to those seen with traditional NSAIDs. Disease-modifying antirheumatic drugs attempt to more fully address the underlying pathology of RA by slowing the progression of the pathology. One of the components of this disease in addition to inflammation is microvascular injury, coupled with the formation of new capillaries. Many of the DMARDs attempt to inhibit the formation of new capillaries as well as address the underlying inflammation, although many of the mechanisms by which they may work are not completely understood. This category of drugs includes azathioprine, corticosteroids, gold, hydroxychloroquine, methotrexate, sulfasalazine, and a number of newer medications such as leflunomide, etanercept, and infliximab. While these medications have been shown to offer clinical improvement to those with rheumatoid arthritis, they also can be associated with significant toxicity and side effects including myelosuppression, lymphoproliferative disorders, macular damage, thrombocytopenia, osteoporosis, hyperglycemia and hepatotoxicity. Another factor with respect to the newer med-

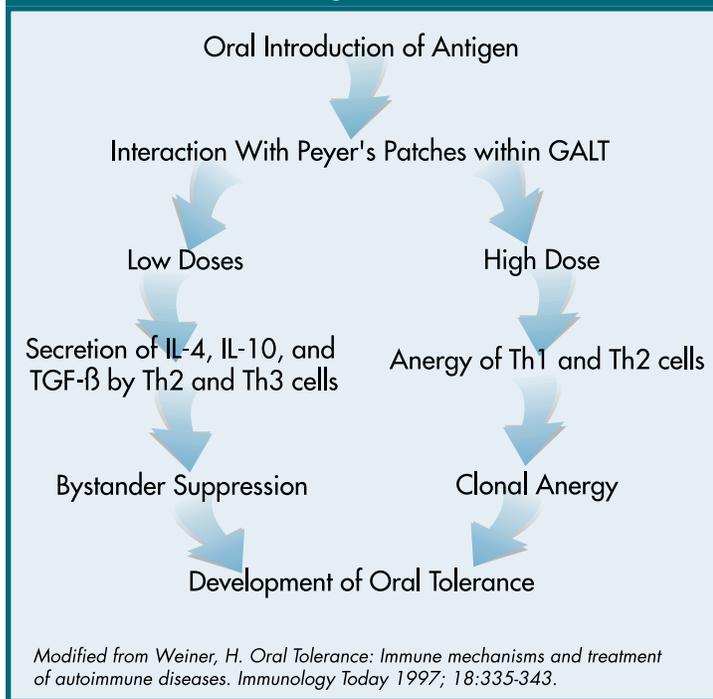
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ications that should be noted is cost. The monthly expense for etanercept and infliximab (both of which must be injected) can exceed \$1,000.

### Involvement of the Immune System and Oral Tolerance

When the immune system is functioning properly, it is able to recognize and identify foreign substances in order to help eliminate them from the body. One type of immune cell that is particularly important in this process is the T cell, a type of specialized white blood cell. T cells can be classified in a number of different categories depending on their function. "Helper" T cells have the function of releasing factors that help increase or decrease the immune response. These "helper" T cells have been further classified into Th-1 and Th-2 subsets. Th-1 cells amplify proinflammatory responses, while Th-2 cells limit such responses. "Killer" T cells have the function of attacking and destroying antigens. Another type of cell called the B cell is also crucial for the functioning of the immune system, as the B cell is responsible for the

**Figure 1**



**Mechanisms by which supplementation with an oral antigen can induce oral tolerants.**

production of antibodies. In a normal individual, the immune system does not seek out and destroy healthy tissue. This is in part due to the fact that T cells that have specificity for antigens on normal, healthy tissue are either suppressed or destroyed prior to being released into circulation. Unfortunately, in the case of rheumatoid arthritis, T cells with self-antigens for type II collagen are not properly destroyed or suppressed, resulting in the destruction that is a characteristic trademark of this disease.

**Oral Tolerance**

If one could decrease the activity of T cells that are releasing joint-destroying factors, one could improve the outcome for patients with RA. One such method to achieve this is termed "oral tolerance," and is a concept that may prove useful in the treatment of autoimmune diseases. Oral tolerance (OT) describes a state of immune hyporesponsiveness following the oral ingestion of a protein. In other words, OT is a method by which one is able to induce a peripheral immune tolerance (down regulation) to a particular antigen by presenting specific amounts of that antigen to the gastrointestinal system.

While this concept may at first sound "alternative" or "unproven," the concept of oral tolerance has existed since 1911, and the traditional medical literature is filled with papers describing this mechanism and how it might benefit those with autoimmune diseases.

Oral tolerance can be induced by two major mechanisms: Bystander Suppression, and Clonal Anergy, depending on the dose of antigen that is presented (Figure 1). Throughout the small intestine there are patches of lymphoid tissue termed gut-associated lymphoid tissue (GALT). Within the GALT can be found tissue that consists of nodules termed Peyer's patches. These Peyer's patches contain organized assemblages of T and B lymphocytes, macrophages, and dendritic cells, and are the primary area within the gastrointestinal tract where immune responses are generated. This immune tissue is designed to protect the host from ingesting pathogens as well as prevent the host from reacting to ingested proteins. In fact, scientists have attempted to use the GALT as a route for administering vaccines, but have been deterred by systemic hyporesponsiveness. Nonetheless, the generation of immune responses within the GALT is the primary mechanism by which orally ingested proteins can suppress systemic immunity.

*Bystander Suppression*

This form of oral tolerance is achieved by presenting small amounts of antigen to the GALT, which in turn generates a T cell response. After the antigen (in this case type II collagen) is consumed, regulatory T cells (specifically Th2 and Th3 cells), migrate from the GALT, through the lymphatic system, and then into the peripheral circulation. Once these regulatory T cells encounter an antigen within the body similar to what was ingested, they secrete cytokines including transforming growth factor beta (TGF-β), IL-4 and IL-10 that result in the down regulation of activated helper T cells (Th1 cells) (see figure 1). It is these activated helper T cells that are in part involved in producing the inflammation and destruction of collagen in RA. If this activity against healthy collagen can be decreased then the progression of the disease can be altered. It should be

noted that the oral antigen does not need to enter the systemic circulation in order to induce a response, as the regulatory T cells are induced as a result of the interaction between the antigen and the GALT.

### Clonal Anergy

Another mechanism by which an orally administered protein can induce a down regulation of an immune response is via a mechanism called clonal anergy. This situation results from the ingestion of high doses of an antigen, which in turn induces a state of unresponsiveness from overactive helper T cells (Th1 cells). The T helper cells are not deleted, but they are rendered incapable of responding to a specific antigen. In essence they are "turned off" or anergized, and will no longer recognize the antigen as a target for destruction.

### Clinical Studies

It is via the mechanism of oral tolerance that type II collagen has been studied for its ability to benefit those with RA. As previously stated, for those with RA, healthy type II collagen acts as an antigen against which the body's immune system is reacting. This makes sense, as type II collagen is the most abundant structural protein present in cartilage.

Numerous animal models of arthritis have demonstrated significant benefit from orally administered, native (undenatured) type II collagen. Oral collagen administration has been able to suppress almost all experimentally inducible forms of RA in animals, including antigen-induced arthritis, adjuvant arthritis, streptococcal cell-wall arthritis, and silicone-induced arthritis. These impressive results led to the investigation of native type II collagen supplementation in humans with RA. In 1993, the results of both an open-label, pilot trial as well as a phase II trial in humans were published in the prestigious journal *SCIENCE*. In a pilot trial, ten patients diagnosed with RA were taken off of their immuno-suppressive and disease-modifying drugs and were given 0.1 mg of native type II

collagen for one month, followed by 0.5 mg of native type II collagen for the next two months. Six of the ten subjects experienced a significant improvement (defined as > 50 percent compared with baseline) in swollen and tender joint counts, as well as morning stiffness, 15 minute walk time, grip strength time, and erythrocyte sedimentation rate (a measure of inflammation). One subject who was previously being treated with methotrexate experienced complete remission, which continued for 26 months. No adverse effects were noted. Given those exciting results, a placebo-controlled, phase II follow up trial was performed. This trial consisted of 60 subjects with severe, active RA. Participants were randomized to either native type II collagen or placebo for 90 days. At one, two, and three months, there was a significant improvement ( $P < 0.05$ ) in the number of swollen joints, the number of painful and tender joints, and 15 minute walking time (at two month's time  $P = 0.06$  for tender or painful joints). Four patients in the collagen group, compared with zero patients in the placebo group experienced complete remission of the disease. Again, one of

the most notable findings was the lack of side effects as a result of the treatment. This is important given the side effects that can be present with various DMARDs and NSAIDs.

Type II collagen has also been shown to be effective for those with juvenile RA, a disease affecting almost 300,000 children. Ten patients between the age of 8 and 14 years

who had active RA were treated orally with type II collagen for three months. Eight of the ten patients had a reduction in both swollen and tender joints at the end of three months. Similar to other studies, the authors reported the exciting finding that one patient achieved complete remission from their disease. It was concluded that oral treatment with native type II collagen may be a safe and effective form of treatment for juvenile RA.

At Harvard, a fourth study of native type II collagen supplementation in RA reported significant improvement in subjects who met Paulus criteria (morning stiffness, joint tenderness,

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use of denatured collagen in  
RA [treatment] ...**

joint swelling, and erythrocytes sedimentation rate). After 24 weeks, 39 percent of those taking type II collagen versus 19 percent taking placebo experienced significant improvement. While 19 percent may appear to be a large response in the placebo group, it is not unusual to observe this type of response in studies of arthritis. The impressive finding was the degree of improvement in the group treated with undenatured, type II collagen. An interesting observation in this study was that subjects with a presence of serum IgA and IgG antibodies to collagen at the beginning on the study had a significantly better response to treatment than those lacking such antibodies.

In a fifth double-blind, placebo controlled study out of Germany, 90 subjects with early RA were divided into those receiving 1 mg of collagen, 10 mg of collagen, or placebo. At the end of study three patients in the 10 mg, one patient in the 1 mg and no patients in the placebo group experienced marked improvement. While these results may not appear very impressive, the authors were surprised by the degree of benefit given the small subset of patients. In another German study, 1 mg and 10 mg of undenatured type II collagen resulted in reduced type II collagen antibody titres in patients showing a clinical response. This study also suggested that 10 mg was a more effective dosage than 1 mg. These studies provide the basis and rationale for the use of native type II collagen as a safe and effective modality of treatment for those suffering with rheumatoid arthritis.

### The Importance of a Native (Undenatured) Form of Collagen

One important variable in the ability of type II collagen to confer oral tolerance is the presence of **native** type II collagen. In other words, the collagen must be type II collagen, and must be present in its undenatured, three dimensional, triple helical structure. Unfortunately, many products on the market do not contain any type II collagen at all, and most products that do contain type II collagen have undergone harsh manufacturing procedures. This renders the collagen denatured and no longer able to illicit an immune response once ingested. In fact, no peer-reviewed studies exist to support the use of denatured collagen in RA, and one study has shown denatured collagen to have no impact of the severity of the disease. In order to insure that undenatured type II collagen is present, highly sensitive ELISA assays must be performed to confirm that the material will be biologically active.

### Dose

Dr. David E. Trentham, leading researcher in the field of RA at Harvard University, supports the use of native type II collagen and recommends a dose of 10 mg to be taken with water at bedtime on an empty stomach.

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