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HEALTHY AGING RESEARCH

The role of near-infrared light-emitting diodes in aging adults related to inflammation

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Abstract

Traumatic and non-traumatic injuries are common complications in the aging adult. Inflammation is related to aging in older individuals and may lead to an increased risk of mortality, reduced muscle strength, and decreased mobility. Unresolved inflammation could be related to the origin of many chronic diseases associated with aging such as autoimmune and neurodegenerative diseases or tumors. With any injury to the body there is initially a process of inflammation and wound healing that in large number of cases are related with pain that increases in the following days. On the other hand, chronic inflammation in high percentage of cases are related to chronic pain, very common symptoms in aging. Chronic inflammation is associated with normal and pathological aging. Surgery, orthopedic fixation, pharmaceutical therapies and physiotherapy can be used to the treatment of the pathologies and injured area. Here we review the use of gallium arsenide (GaAs)-based near-infrared light-emitting diodes (LEDs) as a coadjutant therapy to control inflammation and wound healing. GaAs-based near-infrared LED therapy can be used alongside surgery, orthopedic fixation and pharmaceutical treatments. Studies have shown it to be an effective therapy for the treatment of inflammation and to speed wound healing. This review of clinical observations highlights the capability of GaAs-based LEDs to accelerate wound healing and avoid inflammation.

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Introduction

An LED is an electronic device component that emits light when electricity passes through it. LEDs are mostly is monochromatic, occurring at a single wavelength. The LED light spectrum output can range from ultra violet to red. The ultraviolet and blue colors are about 400 nm, while the red color is about 700 nm. LED infrared emission can be greater than 830 nm and these types of LED devices are called Infrared Emitting Diodes (IRED). LEDs function by electroluminescence, a visible light production by an exposed substance to an electrical field with non-thermal energy generation. Gallium arsenide (GaAs) is a common semiconductor material used for near-infrared LEDs, but other semiconductors are also used. Aluminum gallium indium phosphide (AlGaInP) and other semiconductor compounds in groups III-V of the periodic table have also been utilized.

Low-level laser therapy and near-infrared LEDs have similar effects on inflammation and wound healing. Some studies have demonstrated that near-infrared LED is more efficient at speeding up wound healing compared to laser therapy [3-7]. Near-infrared (NIR) LED therapy has been shown to improve inflammation and accelerate wound healing, as well as

helping to control pain. NIR-LED devices for light therapy are affordable, portable and easy to use, unlike other light therapy sources, such as lasers or incandescent light. Furthermore, they have improved dramatically in quality since the late 1990s, when they had rather unstable power outputs and divergent wavelengths. Older generation NIR-LEDs were not able to produce a meaningful clinical reaction to tissues. A new generation of NIR LEDs, also called the "NASA LEDs", developed by Whelan *et al*., have a lower divergence and also a more stable power output [8].

For NIR-LEDs to be most effective it is important that they have an appropriate wavelength for the target cell. Recent literature suggests a wavelength of 830 nm for all aspects of wound healing, pain, anti-inflammatory treatment and skin rejuvenation. According to Kim *et al*., if the wavelength is incorrect, absorption will be suboptimal and, according to the Grotthus-Draper law of photobiology, there can be no reaction without absorption.

Photon intensity, or power density (W/cm2), should be sufficient for the retention of enough photons to achieve the desired result. If the intensity is too high, photon energy will be undesirably transformed into heat in the targeted tissue.

Finally, Kim *et al.* the fluency or dosage must be adequate (J/cm2). According to the Bunsen-Roscoe law of reciprocity, if the power density is too low, prolonging irradiation time to achieve an ideal energy density or dose will most likely not give a good final result [9].

Traumatic head and body injury, surgical procedure, and metabolic ulcers are common in the aging population. Each of these, and a variety of other conditions prevalent in the elderly, lead to a systemic response to injury. As aging progresses, the body's ability to respond to injury decreases. Inflammation in aging is characterized by increased inflammatory cytokines, decreased adaptation and defective tissue repair. Research into coadjutant therapies for pharmaceutical interventions needs to focus on enhancing the body's response mechanism and NIR-LEDs have shown positive results.

NIR-LED therapy has shown tremendous possibilities in anti-photo aging using non-thermal radiation. The radiation components in the NIR-LED device help improve the anti-inflammatory elements of cell rejuvenation treatments [10]. The mitochondria theory on aging states that oxidative stress, caused by mitochondria DNA mutations, is associated with decreased ATP production leading to cellular degeneration. An experiment conducted by Kokkinopoulos and his team show a significant mitochondrial shift in vitro using a 670nm light exposure and the result showed that aging related retinal inflammation can be reduced significantly with the application of light therapy of 670nm [11]. There are other NIR-LED therapy devices for anti-aging with the range of 940nm and above but more clinical research needs to be done on these devices.

Vascularized living tissue responds to injury (caused by infections, chemicals or physical agents, immune reactions and other methods) by becoming inflamed. Inflammation is intended to contain and isolate the damage, destroy microorganisms and inactivate toxins, and prepare tissues for repair and wound healing. Although inflammation is fundamentally a protective response, it can also be harmful since it can cause severe hypersensitivity reactions or an inexorable and progressive organic lesion by chronic inflammation and subsequent fibrosis. Inflammation can be modulated by different biological, chemical and physical agents. The wide variety of drugs used in the treatment of inflammation are well known, as well as physical agents, such as cold and light. The latter, in particular photomodulation through NIR-LEDs, has been demonstrated to have a positive effect in reducing inflammation and promoting the acceleration of wound healing and skin rejuvenation. NIR-LED therapeutic devices are non-coherent, which means the light intensity is consistent and can spread, covering larger areas of the tissue. NIR-LED therapies have short wavelengths and, based on our studies and literature cited, the shorter the wavelength the deeper the penetration of light to the tissues. NIR-LEDs are affordable, portable, easy to use, and continue to provide viable applications in medicine, for example, to reduce edema, the migration of inflammatory cells, and the production of inflammatory cytokines, as well as accelerating the regeneration of connective tissues. There are no known risk factors for addiction with this

type of treatment. The length of time the radiation therapy needs to be applied for optimal outcomes has yet to be determined.

Extensive review of the English and Spanish literature was performed using PubMed, BioMed, and Google Scholar scientific databases. The literature search included articles relating to light emitting diode, low level laser therapy in aging.

Inflammation and wound healing

The timeline for wound healing depends greatly on the level of inflammation. During 2009 1.8 million patients, in the United States, were discharged from hospitals for wound care and management [12] following a range of causes of injury including gait disturbances; decreased muscle mass; metabolic diseases; heart disease; and traumatic brain injury [13-29], Table 1 shows conditions that increase risks for injury in the aging. All of these may be common events in the aging population. Aging results in chronic low grade inflammation that is associated with increased risk for disease, poor physical functioning, and mortality.

Table 1. Potential causes for injury of the aging adult [13-29]

Exercise and fitness	Physical Abuse	Ataxia
Oncology	Metabolic diseases	Heart disease
Arterial Ischemia	Venous disease	Dementia
Polypharmacy	Traumatic brain injury	Traumatic spinal cord injury
Surgical wounds	Tooth extractions	Traffic collisions
Medical prosthesis rejection	Catastrophic Events	Warfare
Terrorism	Bone Fracture	Ligament strain
	Skin Infection	Orthostatic changes

Inflammation and tissue response to injury is characterized by acute and chronic phases. In the acute phase, changes in vascular caliber and permeability occur with the consequent migration of leukocytes, particularly neutrophils. Increased vascular permeability is induced in various ways, one of which is via chemical mediators such as histamine, interleukin (IL)-1, and tumor necrotic factor (TNF), as well as by the migration of leukocytes, and the release of reactive oxygen species (ROS) and proteolytic enzymes.

Both IL-1 and TNF facilitate increased vascular permeability and migration of lymphocytes, enabling the phenomena of acute inflammation and increased interstitial fluid. The application of near-infrared light on tissue in the acute phase of inflammation causes a decrease in the levels of both IL-1 and TNF-α [30,31].

During acute inflammation, the release of chemical mediators modulates vascular and cellular phenomena such as chemotaxis, leukocyte activation, phagocytosis and release of leukocyte products. An early mediator released in the area of injury is histamine, released primarily from mast cells, which causes vasodilation. Stimulation via near-infrared LEDs, or low-level lasers, has the ability to modulate the number of mast cell degranulations [32-34]. Leukocyte activation facilitates the release of pro-inflammatory molecules, such as the production of cytokines and metabolites of arachidonic acid. One of the key enzymes in the production of arachidonic acid derivatives, such as prostaglandins and thromboxanes, is cyclooxygenase-2 (COX-2). The activity of this enzyme can be decreased in areas of inflammation by stimulation with near-infrared light. Furthermore, the participation of neutrophils and macrophages in the acute stage of inflammation allows both phagocytosis to be initiated, and the release of products from phagolysosomes into the interstitial space, which can damage tissue [35,36].

Key products released primarily by macrophages are growth factors and ROS, which cause tissue damage and the inactivation of anti-proteases. Irradiation with near-infrared lasers has been shown to decrease the number of neutrophils and macrophages at the site of inflammation, and reduces ROS levels at both neutrophils and the damaged tissues [37-40]. Nitric oxide (NO) is a mediator that has some protective effects during acute phase inflammation. Some of these effects are to maintain vascular tone and reduce leukocyte recruitment. Studies have shown NO levels can be increased by stimulation with near-infrared light [41-43]. Finally, if the injurious agent can be

eliminated, the regulatory mechanisms of the inflammatory process can occur, leading to tissue regeneration. If the offending agent is not properly removed it can lead to chronic inflammation.

Chronic inflammation is a lengthy process of weeks to months, in which active inflammation, tissue destruction, and attempts at healing occur in a simultaneous manner. In contrast to acute inflammation, chronic inflammation is characterized by the infiltration of mononuclear inflammatory cells, tissue destruction, and attempts at healing by fibrosis and angiogenesis. Macrophages are the dominant and central cells in chronic inflammation; they are activated by clinical mediators such as interferon-γ, produced by T-lymphocytes. The application of near-infrared light significantly inhibits the expression of interferon-γ and IL-1β, and decreases inflammation by changing the expression of genes encoding inflammatory cytokines [44,45]. Macrophage activation produces chemical mediators that stimulate tissue repair; in turn, some of these mediators generate ROS, NO and proteases, which further cause tissue injury. The concentration of ROS, as well as metalloproteases, may be decreased in the damaged tissue by stimulation with near-infrared light. In addition, tissue repair mediators such as transforming growth factor (TGF)-β1 and platelet-derived growth factor (PDGF), can be modulated by light [40,46-48]. Finally, in chronic inflammation, infiltration of mononuclear cells into the tissues generates tissue destruction and attempts at healing tissue.

Aging is associated with various changes in the inflammatory response. As humans age there is an upregulation in the anti-stress responses, both cellular and molecular, that has been coined 'inflammaging'. Over time this leads to tissue damage that may lead to a decrease in effective function of the inflammatory response. Factors that may also lead to continuous low-grade inflammation in the elderly include smoking, subclinical disorders, and increased fat tissue [49]. Fat tissue may be linked to increased levels of macrophages, which are associated with cytokine production [50] Newer studies have found a correlation between infectious history and an increased risk of heart attack, stroke, and cancer [51] suggest that infections at early ages leave an imprint in the host and inflammatory mechanisms can become flawed, and lead to further diseases during later years. If an individual's body is adept in keeping inflammatory cytokines low, or anti-inflammatory cytokines high, they have a greater chance of attaining higher ages [52-54].

As humans age the functionality of the mitochondria decreases; both in effectiveness and by the increase of free radicals. Free radicals are known to increase pro-inflammatory signals that lead to cell death or uncontrolled cell growth has identified these mitochondrial deficiencies as a cause of chronic inflammation [55].

Diets high in red meat may also lead to an accumulation of antibodies for the Neu5Gc sugar molecule found in red meats, and enters human tissue after consumption. The human immune system sees this sugar as a foreign invader and creates antibodies. Over time, the combination of this foreign invader and the antibodies causes an inflammatory state that may become chronic [56].

Healing and tissue regeneration is the final process of tissue injury, and involves a large number of cells and chemical mediators. In tissue repair, it is known that various processes are activated to achieve tissue regeneration or healing, including the proliferation and migration of parenchymal cells of connective tissue, angiogenesis, synthesis of extracellular matrix (ECM) proteins, and tissue remodeling. The main connective tissue cells involved in tissue regeneration are fibroblasts. These cells, by stimulation with near-infrared light, can increase in activity and number. Their effects are modulated, in part, by increasing mediators such as TGF-β1 and PDGF [57-60]. It is also known that stem cells are involved in tissue regeneration; these can also be stimulated by near-infrared light, causing an increase in both number and activity [61,62]. One of the most important factors in the process of angiogenesis - a critical component of wound healing - is vascular endothelial growth factor (VEGF). Both VEGF and angiogenesis can be stimulated by near-infrared light [63]. Tissue continuity is rebuilt by fibroblasts and endothelial cells. Fibroblasts rebuild the matrix, while endothelial cells are needed for angiogenesis. Collagen, particularly Types I and III, is needed to ensure successful wound healing. As the repair progresses, fibroblasts synthesize and deposit collagen and other ECM proteins such as decorin. Levels of these

molecules can be increased by stimulation with light [64-66]. Collagen deposition and the composition of the ECM is remolded by metalloproteases. These enzymes generate a balance between the synthesis and degradation of molecules to achieve adequate regeneration and tissue healing. Metalloproteases can be modulated by near-infrared light [67,68].

Effect of lasers and LEDs on pathological conditions

In our experience, inflammation caused by tooth extraction, repetitive micro-injury to the tendons, shoulder pain caused by playing golf, acute tennis elbow pain, and chronic pain of the quadriceps tendon after swimming, all saw an improved range of motion and decreased pain after treatment with 940 nm NIR LEDs. Another study looking at patient recovery after surgical procedures in various locations (Achilles tendon, shoulder, wrist, etc.) showed that infrared light increased the rate of wound healing by 25-35% [69,70].

Chronic inflammation in aging is characterized by increased inflammatory cytokines, decreased adaptation, and defective tissue repair in response to injury. Many pathologies are related with aging process are mediated by the inflammatory process and, of these, osteoarthritis is among those affecting the highest number of patients. Oshima *et al.* observed that the application of NIR-LEDs to an osteoarthritis animal model increased Type II collagen expression and decreased TNF-α expression. This therapy can decrease levels of inflammation in the osteoarthritic joints [71]. A reduction in the number of polymorphonuclear cells and signs of inflammation was also observed in the treatment of joint inflammation using near-infrared light therapy [72].

Rheumatoid arthritis is another important illness that causes significant disability. Monocyte chemotaxis protein (MCP)-1 is a key chemokine in the inflammatory status of this disease. Kuboyama *el al.* demonstrated that NIR-LED irradiation significantly reduced MCP-1 gene expression in a rheumatoid arthritis rat model, thus reducing inflammation [73]. TNF-α and IL-6 are also important mediators in rheumatoid arthritis; studies in animal arthritis models have shown that stimulation with near-infrared light can reduce the levels of both [73,74].

Near-infrared light therapy may have potential applications as a noninvasive treatment. It has been suggested that low-level lasers and NIR-LED irradiation can modulate inflammatory processes, inhibiting edema formation, vascular permeability and hyperalgesia, and suppress inflammation in the synovial membrane [75,76]. In a recent study in an experimental tendinitis rat model, treatment with near-infrared LEDs once per day in the same location on the tendon, showed an increase in the amount of collagen Types I and III between days seven and 14. Increased collagen implies increased fiber organization and wound healing [77]. In a study of soccer players with second-degree ankle sprains, results showed that treatment with an 820 nm aluminum gallium indium phosphide (GaAlAs) diode laser, alongside conventional RICE (rest, ice, compression, and elevation), decreased edema after 24 and 48 hours with no recurrence. When range of motion in patients with tendinopathy was studied, patients treated with light therapy showed an average improvement of 32% compared to controls [78]. Xavier *et al.* studied the effects of NIR-LED therapy on Achilles tendinitis induced by collagenase in a rat model. The group treated with an 880 nm near-infrared LED showed fewer inflammatory cells arriving at the injury site, and reduced mRNA expression of IL-1β, IL-6, TNF-α, and COX-2 [79]. NIR-LED therapy may therefore have therapeutic benefits in reducing signs of inflammation in tendinitis. Near-infrared light therapy has also been shown to reduce the pain and increase the diminished range of joint motion typically seen in tennis elbow and epicondylitis, with no bony structure involvement [80]. The application of near-infrared light also accelerates healing following tenotomy of the tendon [81].

Some studies have shown that near-infrared light therapy can reduce inflammation in injuries of the nervous tissue. Moreira *et al.* (2009) studied the effect of near-infrared light in animal models with brain injury. They observed that, during the first few hours following brain injury, low-level laser phototherapy can modulate brain levels of TNF-α, IL-1β and IL-6. Along with other studies, this shows that stimulation with near-infrared light decreases inflammation in

injured brains while also stimulating reconnection of the injured areas [82,83].

In spinal cord lesions, it has been observed that the use of 810 nm light treatment in animal models can increase axonal numbers and decrease the activation of immune cells and cytokines [84]. Using an animal model to study a nerve lesion, NIR-LED phototherapy reduced edema, the number of mononuclear cells present in the inflammatory infiltration, and increased nerve regeneration [85]. Albarracin *et al.* found that near-infrared photobiomodulation in albino rats resulted in decreased retinal degeneration, presumably from reduced cell death, inflammation, and decreased microglia [86]. The sciatic nerve crush model was performed on mice while under anesthesia. Seven days after the operation, NIR-LED irradiation therapy (950 nm, 80 mW/cm^2, 2.5 J/cm^2) began - applied to the skin at the site of injury - and continued for 15 days. In both the spinal cord and sciatic nerve TNF-α levels decreased, but IL-1β and IL-10 levels did not change compared to the control [87]. Khalil et al. studied the role of free radicals and NO in delayed recovery in aged rats with nerve injury. The results suggest that ROS and neuronal NO contribute to delayed recovery of injured nerves in old rats. The results also raise the notion that possible interaction of free radicals with NO to form peroxynitrite might be responsible for such delayed recovery. In previous paragraphs we describe that ROS may be decreased in the damaged tissue by stimulation with near-infrared light and could be an interesting coadjuvant therapy in these types of lesions [88].

Cerebrovascular disease is the third leading cause of death and the leading cause of serious long-term disability in the Western hemisphere [89]. Endothelial dysfunction is characterized by a chronic alteration of inflammatory function and markers of inflammation and the innate immune response, including C-reactive protein, IL-6 and TNF-α are linked to the occurrence of myocardial infarction and stroke in healthy elderly populations [90]. Near-infrared light therapy is an emerging technology that could be used in combination with other therapies to treat cerebrovascular disease [91]. Moreira *et al.* (2011) observed the effects of phototherapy on wound healing following cerebral ischemia by cryogenic injury. They showed that the irradiated lesions lost less tissue than the control, had a significantly higher number of viable neurons, and the lesions of irradiated animals had fewer leukocytes and lymphocytes. They concluded that laser phototherapy was able to control brain damage, thus leading to wound healing following cryogenic injury [92]. Another study by Shen *et al.* investigated the effects of irradiation from a low-level laser applied to rat models with stroke. They observed the proliferation and differentiation of adipose tissue-derived stem cells in neuronal cells. The results of Western blot analysis indicated a significant increase in nestin and oligo-2, demonstrating that low-level laser irradiation exerts a positive effect on the differentiation of stem cells and can be employed to treat ischemic stroke to regain motor functions [93].

The inflammatory process plays an important role in some skin diseases. For some skin conditions NIR-LED therapy has shown bactericidal and anti-inflammatory effects [94-96]. As for other inflammatory skin diseases, a study performed in patients with psoriasis found anti-inflammatory effects when using 830 nm and 633 nm NIR-LED therapy [97]. In animal models of serositis it was observed that the application of near-infrared light therapy reduced inflammation in peritonitis and pleurisy by reducing inflammatory cell migration [98,99].

Near-infrared light therapy may accelerate cutaneous wound healing in different pathological conditions such as diabetes, and burned or injured skin. This accelerated process was observed in association with a photobiomodulation-related increase of healing mediators such as integrins, laminin, kinesin, TGF-β1 and matrix metalloproteinase-2. Photobiomodulation stimulated healing, relieved pain and inflammation, restored function of tissue, and helped to control secondary infection [100-106]. The wounds of patients treated with a 670 nm, 720 nm, and 880 nm near-infrared LED unit healed twice as quickly as their counterparts not treated with near-infrared. Following tissue injury, adequate inflammatory vascular responses are essential for subsequent tissue repair. Khodr *et al.* studied the role of ROS and age in modulating the inflammatory response in acute and chronic injury conditions and the implications of this modulation for tissue repair. The results showed that antioxidant treatment had no effect on the response during early and late phases of acute inflammation in

young rats. However in old rats, the vascular response was significantly attenuated (60%) or significantly increased (40%) during the early and late phases of acute inflammation, respectively. The results suggest that ROS have a paradoxical role exerting either a positive or negative effect on the inflammatory response with age. Related with this observation, the ROS can be modulated by NIR-LED as we observe previously in the text [107]. The potential for fracture and bone injury in the aging adult is high due to gait disturbances, daily activities, age more than 75, living alone, chronic pain, metabolic diseases, and nutrition/vitamin deficits. Bone healing has also been shown to benefit from light therapy [108,109]. Pinheiro *et al.* demonstrated that bone irradiated with near-infrared light showed increased osteoblastic proliferation, collagen deposition, and bone neoformation [110]. Rats given a ligature injury at the first mandibular molar were treated with NIR-LED irradiation, and histomorphological analysis revealed decreased bone resorption, lower neutrophil migration, and lower TNF levels [111].

Pharmacological therapy is widely used to modulate inflammation and wound healing, but NIR-LED GaAs therapy is emerging as a promising non-pharmacological coadjutant treatment for these conditions. Some studies have compared the effect of light therapy with that of the most commonly used drugs for inflammation and wound healing. De Almeida *et al.* compared the effects of the topical application of sodium diclofenac with low-laser therapy on morphological aspects and the gene expression of biochemical inflammatory markers. Compared to subjects given diclofenac, those receiving light therapy showed decreased expression of COX-2 and TNF-α, and improved morphological aspects of the tissue [112]. A similar study by de Paiva Carvalho *et al.* observed that, compared with the topical and intramuscular application of diclofenac, near-infrared light therapy more effectively decreased the levels of prostaglandin E2 during the treatment of acute muscle strain injury [113]. Viegas *et al.* observed that low-level laser therapy showed a higher degree of collagen fiber organization and maturation, and a better healing pattern than that seen with the use of meloxicam, but meloxicam more effectively decreased the intensity of polymorphonuclear infiltration and edema in rat wounds [114]. Finally, some studies have compared the effects of near-infrared light therapy with those of corticosteroids. These have observed that, compared to corticoids, light therapy increases collagen content, allows a better arrangement of the ECM, an increase in number of fibroblasts, and accelerated levels of epithelialization. Near-infrared light accelerates tissue repair even in the presence of dexamethasone [115-117]. Other physical therapy use on the treatment of wound healing is ultrasound. A study by Demir *et al.* compared the effects of laser, ultrasound, and combined laser and ultrasound treatments in experimental tendon healing. They concluded that both treatments increased tendon healing biochemical and biomechanical more than the control groups. No statistically significant difference was found between ultrasound and laser therapy and these therapies can be used successfully in the treatment of tendon healing [118].

Many diseases of the elderly, such as Alzheimer's disease, could benefit from NIR-LED therapy studies. The injury to the brain during the progression of Alzheimer's disease is also compounded by inflammation and studies should be completed to understand the effects of NIR-LED therapy on Alzheimer's inflammation [49].

Finally, aging and many pathologies related to aging, are closely associated to inflammatory processes and are the target of many therapeutic options, often with undesirable side effects. NIR-LED is emerging as an adjunctive treatment option without adverse effects, which makes it an interesting option in adult patient who frequently consume too many drugs which could help decrease, or not potentiate, adverse effects. NIR-LED can exert therapeutic effects at different stages of the inflammatory process and tissue repair. This makes it a therapeutic option of great interest for clinical application and research for its promising modulatory effects at the molecular level.

Conclusions

GaAs-based NIR-LEDs represent a novel, non-invasive, and effective coadjutant therapeutic intervention for the treatment of numerous diseases linked to inflammation and wound healing. The equipment is easy to obtain, economically more sound

than other methods of NIR radiation, can be used several times during the day, simple to use with little training, and versatile for use in many fields and locations.

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