Wound Healing and Hyperbaric Oxygen Treatment

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Abstract

Background: In developed countries wounds are one of the most common causes of morbidity. They reduce the quality of life and cover an important portion of the overall health payments. Wound healing requires the concordance and harmony of different cellular events. These cellular events are phagocytosis, chemotaxis, mitogenesis, synthesis of collagen and other matrix components. Wound healing progresses in several phases; namely, coagulation, inflammation, reepithelization, angiogenesis and reconfiguration.

Hyperbaric oxygen therapy has been used and is recommended in the last 40 years without sufficient scientific data or confirmation about its effects and reliability. Increasing study reports especially the ones on experimental and molecular platform showed that hyperbaric oxygen therapy can be an important alternative by different mechanisms. At the present time suspicions about the reliability of hyperbaric oxygen therapy are completely cleared and the therapy model achieved a scientific basis.

Dermal Wound Healing

There are four stages (phases) of dermal wound healing: inflammation, cellular events, contraction and reconfiguration [6, 7].

Inflammatory Phase

This phase of dermal wound healing begins with vasodilatation and an increase in the vascular permeability. Later on polymorphonuclear leukocyte, monocyte and lymphocyte migration occurs. In sutured wounds this phase is about 4-5 days long.
while in open wounds the duration might be as long as 7-10 days. The influence of chemotactic factors leads to the migration of polymorphonuclear leucocytes into the wound and prevents infections, also causes enzymatic digestion and phagocytosis leading to natural necrotic tissue debridement. Activated T lymphocytes release chemotactic factors for the fibroblasts.

In case of PMNL or lymphocyte deficiency, the course of normal wound healing will be incomplete. Some cytokines induce collagen synthesis and angiogenesis via providing monocytes and fibroblasts migration whereas some cytokines cause retardation in collagen synthesis. As a matter of course drugs affecting monocyte functions inherently affect wound healing. If the inflammatory phase will be retarded for any reason the risk of cicatricial tissue formation will be increased [6, 7].

**Cellular Phase**

Progression to cellular phase begins with reduced capillary permeability and exudation. The granulation tissue including monocytes, fibroblasts and capillary vessels will be formed after 7 to 10 days. First approximately at the fifth day some growth factors are produced by fibroblasts with stimulation of the cytokines. Fibrin and fibronectin stimulation causes migration of new fibroblasts and collagen synthesis begins. This procedure reaches the peak point in approximately the sixth or seventh days and continues two or four weeks.

Cicatricial tissue formation improves inherently with collagen synthesis because collagen compromises more than 50% of the whole protein in this tissue. With the formation of cross ligature of collagen the strength of tension in the healing wound increases. Thereafter the monocytes stimulate endothelial cell proliferation and with decreasing oxygen pressure increased lactate concentration stimulates vascular development [6, 7].

**The Phase of Contraction**

In this phase the decrease in the wound size begins on the seventh day and becomes visible on the fourteenth day. Myofibroblasts (transformed fibroblasts) play the main role in this stage. In sutured wounds myofibroblasts are scarce. Superficial wounds only extending to the papillary dermis show little contraction while contraction is prominent in wounds involving the reticular dermis. This may be explained by the localization of myofibroblasts in the reticular dermis.

The localization of the wound also affects the contraction and contraction occurs more slowly in regions like scalp and the anterior aspect of the tibia where the epidermis is thick. Also round-shaped wounds show a slower contraction compared to the angular ones. In the wounds laying on the joints grafting can be preferred to avoid unwanted contractures [6, 7].

**Remodeling**

In this phase capillary formation, erythema and edema decreases. The number of fibroblasts increase consequently the scar tissue becomes devoid of cells. But the remodeling of the collagen may last months. While the collagen dissolves, on the other hand the synthesis of the newly formed collagen decreases and following this the tensile strength of the skin slowly increases. In sutured wounds the rate of collagen synthesis is more than the rate of dissolving collagen and in 3-4 weeks a balance occurs. But in hypertrophic scars and keloids synthesis dominates the dissolving collagen.

The tensile strength of the skin becomes evident on the 6th day and rapidly increases until the 6th week. Though the increase in the tensile strength continues for about one year, it will never be fully normalized [6, 7].

**Epidermal Wound Healing**

Reepithelization of the wound is provided by the suprabasal cells and this procedure begins approximately 12 hours after the skin damage. On deep wounds these main repairing cells are located only at the margins of the wound while if the skin damage is superficial these cells exist in all parts of the wound and the skin appendages. Therefore reepithelization of superficial wounds is much more faster than the deep wounds. On sutured wounds reepithelization is almost fully accomplished after 24-48 hours
while in open wounds after 36-48 hours only an increase in the mitotic activity can be observed.

The most appropriate ground surface is accepted as a clean, live and humid medium. Crust formation, foreign residual materials, topically applied hemostatic or caustic agents, scar tissue occurring after electrosurgical or cryosurgical attempts are the factors which will delay epithelization [6].

Another classification concerning wound healing can be made according to the way of the wound formation. Wound healing after any surgical procedure is called primary healing while healing of open wounds occurring after skin and tissue damage is called secondary wound healing [6, 8].

**Primary Wound Healing**

On such wounds reepithelization is faster but in contrast strength of tension occurs rather slowly. Strength of tension is related to cross-binding of collagen fibers rather than collagen synthesis. Wound healing is accomplished at about 60% after 6 weeks, but strength of tension exceeds 80% of the normal rates [6].

**Secondary Wound Healing**

In secondarily healing wounds the rate of healing is parallel to reepithelization and the intensity of skin appendages in that region. On the face skin appendages are placed close to each other and as a result of this superficial wounds tend to heal faster in this region.

A lot of factors play role in healing of deep wounds. Wounds localized on the acral parts regenerate (repair themselves) much more slowly compared to the wounds localized on the central parts of the body. In terms of localization the most prompt wound healing occurs on the facial region. As it can easily be anticipated the larger the wound the later the epithelialization [6].

**Wound Healing and Oxygen**

Experimental and clinical trials suggest that oxygen has a critical role on wound healing. Oxygen facilitates extermination of bacteria via oxidative products and plays an important role in reepithelialization, angiogenesis and collagen synthesis [5, 9, 10].

**Oxygen and Cellular Activity**

The most important role of oxygen on cellular events is that of oxidative phosphorylation occurring in the mitochondria. Reactive oxygen species (ROS) such as hydrogen peroxide and superoxide radicals play an important role in exterminating the bacteria. Both hypoxia and hyperoxia cause an increase in reactive oxygen species. These reactive oxygen species affect the cellular transmission system including angiogenesis, cytokine formation and cellular activities; all playing a role in the course of wound healing. Especially hypoxia with the assistance of HIF-1 alpha (hypoxia induced transcription factor-1 alpha) coordinates glucose metabolism, erythropoiesis, iron transportation, vascular tonus and angiogenesis. However, hypoxia may cause a decrease in the level of interleukin 8 and 12 which both have roles in the activation of macrophages, T lymphocytes and neutrophils [5].

**Oxygen and the Inflammatory Stage**

**Coagulation**

At the onset of tissue damage, interruption of circulation and increase in oxygen consumption cause a hypoxic medium in the damaged region. While the arterial pO₂ is 100 mm Hg in the central part part of the wound partial pO₂ is between 0-10 mm Hg and at the periphery it is about 60 mm Hg [5, 8]. In the wounded region the amount of oxygen differs according to the blood perfusion and oxygenization and the partial oxygen pressure is directly related with the rate of diffusion from the blood to the tissue. The hypoxic medium in the wound activates reactive oxygen species. This hypoxia is essential for cytokine release from the platelets and monocytes at the onset of wound healing process [5, 10].

Cytokines (TGF-β, VEGF, TNF-α, endothelin -1) affect cell proliferation, chemotaxis, vascular permeability and all the other events concerning wound healing. In the beginning of the wound healing process, hypoxia
stimulates healing while in chronic hypoxia there is no such stimulation [5].

Prevention of Infection

Hypoxia is important for coagulation, but in the inflammatory stage of wound healing the presence of oxygen plays a critical role in the prevention of infection. Especially reactive oxygen species have an important role. After the onset of coagulation, neutrophils and monocytes increase in the wounded region and after this ROS production begins. This is the main standpoint of prevention of wound infection. Reactive oxygen species are produced with the NADPH-bound oxygenase enzyme which is produced by neutrophils and macrophages and the effectiveness of this enzyme requires the presence of oxygen in the medium.

Trials concerning this concept suggest that for average ROS production the required oxygen pressure is about 45-80 mmHg. These reactive oxygen species also play role in neutrophil chemotaxis [5]. Oxygen in advanced cases has been shown to reduce wound infection rates. In an experimental trial on animal models it has been observed that after *E. coli* inoculation into the wound highly oxygenated medium has reduced the rate of tissue necrosis [5, 11].

Besides this it has also been shown that high oxygen levels can prevent the infection of surgical wounds. In a prospective study on 500 colorectal resection patients it has been shown that high oxygen rates have a pronounced effect in reducing wound infection. The patients were divided into two groups and in one group peroperative and postoperatively 80% oxygen was administered while in the other group 30% oxygen was administered to the patients. In the patient group taking 80% oxygen infection rate has found to be half of the other group [5, 11, 12]. In an other study it has been observed that wound infection rates showed an inverse proportional relationship with subcutaneous oxygen pressure[5, 13].

Oxygen and Proliferative Stage

Reepithelialization

Previous studies have shown that oxygen activates reepithelialization and that hypoxia has critical importance for rapid reepithelialization [5, 10, 14]. It has been observed that hypoxia increases keratinocyte motility in several trials. Keratinocytes do this via increasing the expression of main proteins (ezrin, radixin and moesin) which are responsible of cell motility. In addition to this, hypoxia stimulates type 4 collagenase and decreases the expression of laminin 5 which reduces keratinocyte motility.

Certain investigators have shown that with lower ROS levels keratinocyte motility and proliferation are inhibited. Furthermore, growth factors affecting reepithelialization need ROS and other oxygen metabolites to be efficient. Age is also a factor in this way and it has been observed that the response of keratinocytes against hypoxia is lower in the elderly (people over 60 and people between 20-40 years are compared) [5, 15]. In another study low concentrations of hydrogen peroxide which is used for disinfection of open wounds have been observed to inhibit keratinocyte motility and proliferation [14].

Collagen Synthesis

Both the presence or absence of oxygen in the medium affect collagen synthesis. TGF-β1 procollagen is responsible for gene transcription. It has been shown that the activation of TGF-β1 causes an increase in the motility of newly cultured fibroblasts. In a study of Falanga and coworkers it has been reported that hypoxia increases TGF-β1 synthesis and secretion and also procollagen gene expression in vitro [16]. Siddiqui and coworkers showed that acute hypoxia achieves an increase in fibroblasts, collagen synthesis and TGF-β1 mRNA expression. But in hypoxic conditions this activity is decreased and therefore collagen synthesis is negatively affected [17].

Increased oxygen pressure prevents the growth of cutaneous fibroblasts. Instead oxygen pressure under 137 mm Hg improves the growth of fibroblasts [18]. Reactive oxygen species inhibit the proliferation of fibroblasts with hyperbaric oxygen therapy [19].

Oxygen is also effective in posttransitional proline and lysine hydroxylation, maturation and transverse binding of collagen during collagen synthesis. Proline and lysine...
Hydroxylase enzymes use oxygen as cofactor. Oxygen plays an important role in wound contraction which occurs with the transformation of fibroblasts to myofibroblasts [5].

**Angiogenesis**

Likewise the collagen synthesis hypoxia also initiates angiogenesis [5, 10, 20]. The most effective angiogenic growth factor secreted from damaged tissue is vascular epithelial growth factor (VEGF). But the mechanism of VEGF release from fibroblasts, keratinocytes and macrophages is not fully understood.

In an experimental study on animal models it has been observed that angiogenesis is improved considerably in hyperoxic medium compared to hypoxic conditions [20]. Experimentally it has been shown that VEGF can be expressed both in hyper and hypoxic medium [21]. This can be explained by destabilization of VEGF in normoxic medium [5, 15].

Endothelial progenitor cells play an important role in revascularization and hence wound healing. In diabetic wounds these cells are fewer both in the circulation and the damaged region and their mobilization is decreased. This is presumed to be a result of a defect in eNOS-NO cascade system in the bone marrow. Hyperbaric oxygen therapy increases the release and mobilization of endothelial progenitor cells from the bone marrow. Thus the number of endothelial progenitor cells increase both in the circulation and wounded area [22].

In patients who have had tracheal resection, it has been observed that hyperbaric oxygen therapy provides a more rapid angiogenesis and decreases the complications [23].

**Hyperbaric Oxygen Therapy**

Hyperbaric oxygen therapy has been used and is recommended in the last 40 years without sufficient scientific data or confirmation about its effects and reliability and therefore confronted an extreme suspicion for a long time. But during the last years experimental and clinical studies presented obvious scientific evidence and registered clinical results. Especially the worldwide increase in diabetes mellitus cases and complications, diving sports becoming more and more widespread every other day and the increase in carbon monoxide (CO) intoxication cases attributed a special importance to hyperbaric oxygen therapy and increased its usage.

Increasing study reports especially the ones on experimental and molecular platform showed that hyperbaric oxygen therapy can be an important alternative by different mechanisms. At the present time suspicions about the reliability of hyperbaric oxygen therapy are completely cleared and the therapy model achieved a scientific basis.

The simplest explanation of hyperbaric oxygen therapy can be made as a medical therapy model used on clinical patients by administration of 100% oxygen infusion in completely isolated pressure rooms under higher pressures than normal atmospheric pressure [24].

Hyperbaric oxygen therapy is usually performed once a day but there are also different therapy modalities. The advantages of hyperbaric oxygen therapy can be emphasized in four main categories, namely; mechanical, bacteriostatic, intoxication and hypoxia healing effects [10]. Hyperbaric oxygen has two main effects on the body:

- mechanical effect on body gases
- achieving an increase on partial oxygen pressure (pO2). The therapeutic efficacy of this therapy in most cases depends on these two main effects [24].

In the Figures 1a and 1b the treatment unit of hyperbaric oxygen therapy is seen.

**Effect on Oxygen Solubility**

Under normal conditions only a small amount of oxygen is present in the blood in soluble form (1.5-3%). But it is possible to obtain an amount of soluble oxygen in the plasma which will be sufficient for all the routine needs of the body under hyperbaric conditions. For example under 3 atmospheric pressure the volume of the soluble oxygen content in the blood will be elevated to 6.8%. If the soluble oxygen rate in the plasma is over 6% oxyhemoglobin can be transferred from the arterial system to the venous system without any change. This is because soluble oxygen in the plasma can
be much more easily used compared with the hemoglobin binded oxygen.

Thus the plasma itself will have the capacity to supply the oxygen demand of the tissues. The high oxygen pressure in the blood not only serves for an increase in the tissue oxygenation but also has numerous other effects: in cases of gaseous gangrene inhibition of alpha toxin production, increase in the killing capacity of the leucocytes, decreasing the adherence capacity of leucocytes on the vessel wall, vasoconstriction of normal vessels, growth of fibroblasts and increase in collagen synthesis, preserving ATP in the cell, suppression of the specific immune system, increase in osteoclastic activity, increase in capillary vessel proliferation, decreasing ocular lens elasticity, decrease in surfactant production in the lungs in CO intoxication though indirectly ending the lipid peroxidation and removing CO from hemoglobin rapidly are the most important ones.

When hyperbaric oxygen increases the oxygen saturation in the venous system to 100%, CO2 levels in the blood also increase and consequently consumption of hemoglobin to transport CO2 causes a decrease in pH. The increase in partial PO2 inhibits the reduction of oxyhemoglobin to hemoglobin and the rate of soluble CO2 transport increases in the plasma. Consequently CO2 retention occurs and causes a slight increase of hydrogen ion in the tissues.

In the blood 70% of excess CO2 is in bicarbonate form and the remaining is in soluble form and is transported as carbonic acid.

As a consequence when venous hemoglobin achieves 100% saturation with oxygen the partial CO2 pressure in the brain venous system shows an increase about 5-6 mmHg. In an otherwise normal individual if blood flow is stable CO2 does not further increase in the blood and the tissues [24]. If at 3 atmospheric pressure 100% oxygen is inhaled the difference between arteriovenous oxygen pressure can increase to 350 mm Hg. When tissue blood flow falls to the half of normal values arterial pO2 will be 288 and the venous pO2 will be 50 mm Hg (a difference of 238 mm Hg). Hence if the arterial pO2 rises in large amounts, sufficient cellular oxygenation can be obtained even in circumstances showing a manifest decrease in blood flow [24]. It can clearly be seen that with inhalation of 100% oxygen at 3 atmospheric pressure it is possible to increase tissue oxygenation 10-15 fold.9 This raised tissue oxygenation continues about 30 minutes to 4 hours after hyperbaric oxygen therapy [24].

The Pathophysiologic Effects of Hyperbaric Oxygen

In clinical use hyperbaric oxygen shows a therapeutic effect by several known or unknown mechanisms. Hyperbaric oxygen therapy is limited with a maximal 3 atmospheric partial pressure in clinical usage. Increasing this maximal pressure will not provide an extra benefit but in contrary can increase the toxic effects of oxygen [24].

The toxic effects of oxygen are more mani-
fest in the organ systems where the blood flow is rather intense compared with other organ systems, namely the brain (acute cerebral oxygen toxicity) and the lungs (chronic pulmonary oxygen toxicity). Another potential risk is barotrauma affecting either the ears, sinuses and the lungs \[9, 25\]. Besides these relatively serious risks some other unwanted effects can be seen mainly because a problem in pressure regulation like headache, pain in the ears, cranial sinuses and the teeth \[26\].

The Effects of Hyperbaric Oxygen on Tissue Blood Flow and Oxygenation

If oxygen is inhaled at 2 atmospheric pressure the result is vasoconstriction of the vessels and a 20% fall in tissue blood flow. Normally oxygen pressure in the tissues is about 30-40 mmHg but in such pathological states such as infections, trauma or edema, the resultant ischemia causes a decrease in \(pO_2\). If the oxygen pressure falls under 30 mmHg fibroblast and leukocyte functions will be markedly diminished.

As mentioned before with hyperbaric oxygen therapy the number of fibroblasts and the bactericidal effects of leucocytes increase hence collagen formation becomes easier. If hyperbaric oxygen is applied at 2 atmospheric pressure on normal skin tissue, tissue \(pO_2\) will rise to about 250-300 mm Hg. Thus the 20% decrease on the blood flow in hyperbaric oxygen applied tissue will be even exceedingly compensated by the increased \(pO_2\) pressure in the tissue \[24\].

The Effect of Hyperbaric Oxygen on Healing of Hypoxic Wounds

Hyperbaric oxygen therapy was first used in 1960s as an adjunctive to the standard treatment modalities for wound healing. Troublesome wound healing is in any case due to chronic hypoxia. Many clinical and experimental trials have revealed that under hypoxic conditions wound healing is delayed \[8, 9, 24, 25\].

In the inflammatory stage of wound healing NADPH oxidase consumes a lot of oxygen and causes the production of reactive oxygen species in high levels. The capacity of this enzyme is 50% when partial \(pO_2\) is between 40-80 mm Hg, but if partial \(pO_2\) can be risen to 400 mmHg the capacity of this enzyme will increase to 90%. Phagocytic capability and antibacterial efficacy of the leucocytes is diminished at 30 mm Hg and even more so under this pressure. Even though phagocytosis is possible at these low pressure levels, the so called oxidative outburst, that is NADPH oxidase dependent superoxide formation, will be inhibited.

Hyperbaric oxygen therapy increases oxygenation and hence assists neutrophils to kill the bacteria in the hypoxic wound region. The oxygen level in the wounded tissue is the main factor which is determinative for wound infection. Oxygen is not only an important energy supply but also acts as an antibacterial.

It is well understood in recent studies that not only the phagocytes but almost all the cells in the wounded region possess some specific enzymes that can transform oxygen to reactive oxygen species. These reactive oxygen species also assist intercellular correspondence and support wound healing in this way \[24\]. In a preliminary study carried out on 6 patients with chronic ulcers the NO levels after hyperbaric oxygen therapy were evaluated to be increased. According to this reference it was suggested that the increased NO levels after hyperbaric oxygen therapy is directly related with wound healing and complete epithelization \[27\].

When partial oxygen pressure in tissue rises from 10 mmHg to 40 mm Hg collagen synthesis increases sevenfold. If the \(pO_2\) around the wounded area is below 10 mm Hg fibroblast migration to the region can not be achieved effectively. Increased oxygen does not cause extreme healing this concept is rather related with the speed of the healing procedure. The extra oxygen obtained by blood flow accelerates angiogenesis in the ischemic wound and hence the healing time is shortened. As well as it has been shown that hyperbaric oxygen also increases capillary proliferation and can be used in the treatment of radiation induced bone and soft tissue damage.

Hyperbaric oxygen therapy can also be used for troublesome wounds like ulcers accompanying peripheral vascular insufficiency, venous stasis ulcerations, decubitus ulcers, infected wounds, tissues exposed to radiation damage, cold damage and toxic animal bites \[24\].
The Use of Hyperbaric Oxygen Therapy on Wound Healing

Hyperbaric oxygen therapy is generally applied once or twice a day for 45-120 minutes at an atmospheric pressure changing from 1.5 to 3 changing according to the character of the case. In wounds showing a chronic course the mean therapy duration is about 20-30 times. But if necessary therapy can be prolonged to 60 times [9].

At the present time there are several treatment protocols on the use of hyperbaric oxygen therapy for wound healing. But the worldwide accepted indications, contraindications, complications and side effects are listed below (Tables 1, 2, 3) [3].

In pyoderma gangrenosum hyperbaric oxygen therapy can be used as an adjuvant and it has been reported to reduce pain and facilitate wound healing, but these reports are limited in number [28, 29]. In another report concerning livedoid vasculitis it has been reported that 8 of 12 patients showed good response to hyperbaric oxygen therapy [30]. In another similar study it has been reported that 2 patients with livedoid vasculitis resistant to other treatment modalities have responded to hyperbaric oxygen therapy.

During and after photodynamic therapy the alterations of oxygen pressure on the skin have been suggested to be an important parameter. Thus in photodynamic therapy evaluation of subcutaneous oxygen usage can provide some hints about the efficacy. Multiple sclerosis, septic shock syndrome, fibromyalgia, migraine, hemorrhagic cystitis are the examples for this group of disorders [32].

Hyperbaric oxygen therapy is also recommended for cerebral palsy and autistic children but this still is a controversial concept. It has been proposed that hyperbaric oxygen therapy rises the oxygen levels in the region where sleeping (dormant) neurons are found and hence reactivate these neurons. But this is only a hypothesis and has not been proven in any way [24].

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The pictures of this manuscript is used by permission of Dr. Kemal Cenk Gülğin.

References

Table 1. Indications for Hyperbaric Oxygen Therapy [10, 24]

- Air and gas embolus
- Decompression
- CO intoxication and smoke inhalation
- Non-healing ulcers
- Troublesome wounds
- Skin flaps and grafts
- Crush wounds
- Compartment syndromes and acute traumatic ischémias
- Gas gangrene / clostridial infections
- Necrotizing soft tissue infections
- Acute blood loss
- Burns
- Intracranial abscesses
- Post anoxic encephalopathy
- Sudden hearing loss
- Ocular ischemic conditions
- Tissue damage due to radiation
- Persistent chronic osteomyelitis

Table 2. Contraindications of Hyperbaric Oxygen Therapy [7, 24]

**Absolute Contraindications**

- Some simultaneously applied treatments (doxorubicin, bleomycin, disulfiram, cisplatin, maphenide acetate)
- Untreated pneumothorax

**Relative Contraindications**

- Upper respiratory tract infections and chronic sinusitis
- Emphysema with CO₂ deposition
- High fever
- History of spontaneous pneumothorax
- History of thorax surgery
- History of surgery for osteosclerosis
- Viral infections
- Congenital spherocytosis
- History of optical neuritis
- Barotrauma of the ear
- Damage in the inner ear
- Sinusal pressure
- Visual refractive changes
- Numbness on the fingers
- Certain dental problems
- Clostrophobia
- Hypoglycemic attacks
- Pulmonary oxygen toxicity
- Laceration in the pulmonary vessel system
- Oxygen hypersensitivity

Table 3. Complications and Side Effects of Hyperbaric Oxygen Therapy [10, 24]

- Barotrauma of the ear
- Damage in the inner ear
- Sinusal pressure
- Visual refractive changes
- Numbness on the fingers
- Certain dental problems
- Clostraphobia
- Hypoglycemic attacks
- Pulmonary oxygen toxicity
- Laceration in the pulmonary vessel system
- Oxygen hypersensitivity

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