White Paper:

A Treatise on Pain and Using Virtual Reality as a Novel Way to Defeat It

"And life without Pain is a long endless chain
Of errors repeated again and again..."
--lyrics from Pose Ode, by the musical band, Pain.

Contents

Introduction

In order to understand how immersion into a virtual reality (VR) can relieve pain, it is first necessary to understand pain itself. Pain is essential for our survival as a species. As *Homo sapiens* has evolved, so too have the complicated processes of both warning us of danger and facilitating our escape to prevent further injury. Furthermore, there are different types of pain. Examples include acute, chronic, inflammation, soft tissue, musculoskeletal, visceral, neuropathic, referred, phantom, burns, headaches, and many others. This evokes an appreciation of how VR affects the types of pain differently; this may seem like a problem, but in fact it creates an advantage and multiple opportunities. One significant aspect of VR, unlike a molecule of medication or the setting on an ultrasound machine, is that it is flexible--authored content that can be customised for the type of pain addressed and as unique as the individual treated.

Scattered reports of those rare individuals who have genetic mutations[1] that eliminate the perception of pain are self-evident testimonies to the importance of pain in survival: these persons do not do well. They are subject to burns, self-mutilation,[2] trauma,[3] and ultimately infection that is life-threatening. This is a sobering aspect of our evolution because, in the days before antibiotics, surgery, and anti-inflammatories, individuals insensitive to pain would have perished long before being able to reproduce. So evolution goes, and this explains how such a devastating autonomic recessive mutation is so rare.

Pain insensitivity also can occur without mutation. One common problem and an excellent example of the importance of pain is a condition called diabetic neuropathy. Diabetics have degeneration to the nerves and blood supply to them, which lessons sensitivity to discomfort, especially in dependent areas like the soles of the feet or pressure points. Positions that put pressure on skin squeeze away the microvascular blood supply to tissue, causing ischemia (low oxygen delivery) and then necrosis (tissue death). Unawareness of this process continues the process, leading to infection of necrotic tissue (pressure ulcers), spread of infection into the blood supply (sepsis), and even death if not aggressively treated.

A simpler version of this happens in a limited way to everyone. When we sleep, we often assume positions that kink/obstruct the blood supply to nerves, e.g., waking up with "pins and needles," a phenomenon called *"paresthesia."* The fact that we notice it, even subconsciously without waking up, allows us to shift position. The key to preventing injury, therefore, is awareness, and this is where pain figures into our survival. Individuals with genetic mutations are rare, while a common condition of pain insensitivity—diabetic neuropathy—has a large economic impact globally[4] as well as individually due to its pathogenesis that leads to the most common cause of amputations.[5]

Whether discussing diabetic foot ulcer complications or normal paresthesias, there are two phenomena at work--peripheral change in the nerve signals to the brain and decreased perception in the brain itself. VR is designed to step in and change things in the brain via distraction, which lessens the signals from the periphery.

The steps of pain are complex:

1. Initiation of nociception.
2. Propagation of signal.
3. Processing at the spinal level.
4. Crossing over to the other side of the spine via an "interneuron."
5. Ascent to the brain via the spinothalamic tract.
6. Distribution of signal to disparate areas of the brain that stimulate discomfort, localisation, emotion, memory, and subsequent executive decisions (e.g., escape strategies).

The evolved human body, therefore, warns of damage or injury by the attention-getting signal of pain. That is not the end of the pain story, however, because of a problem arising from an evolutionary need to stop the pain: immobilisation due to pain does not portend well for survival. Equally important to pain is the re-establishment of function, after pain, so that escape from the danger is possible. The brain uses chemicals—biochemicals called neurotransmitters—to make this chain of events possible. When fight-or-flight sees the fight as lost, flight is made possible by a counter-volley of inhibitory neurotransmitters that act to dampen the pain centrally (brain), at the spinal level, and peripherally (at the site of injury). This means that pain is not undefeatable, which has immense clinical promise.

Besides this balance of pain excitation and inhibition, the emotional component also can mitigate pain by way of distraction, since the limbic system is in intimate communication with the somatic brain--a communication of two-way traffic.

> Distraction, per se, is the crucial point of this whitepaper: the anatomy, physiology, and relief of pain are presented as a backdrop for the innovative approach of using virtual reality (VR) as pain treatment. VR is an immersive pseudo-environment that can aid in distraction as well as tip the balance between pain excitation and inhibition toward overt suppression for the suffering patient. It also can enhance interaction with the emotional aspect as an additional distraction. Therefore the term, "distraction," is an oversimplification but is used here to describe how remaps the brain around the speedbumps that pain lays down in one's sensorium. Another sensorium is established—an alternate route around these speedbumps. This is based on the concept of *"neuroplasticity,"* which is a phenomenon explained by Donald Hebb's 1941 aphorism that *"neurons that fire together, wire together."*[6]

Every experience, perception, and learning experience causes neurons to wire together, which is the basis of memory. The more that the same neurons fire together, the more solidly they are wired together.

Thus, the repetition of immersive elements is more than distraction, but a new blueprint for relegating pain into a position of secondary importance in the mind.

PART I: ACUTE PAIN

Pain is All in the Head

At the site of injury from any trauma, temperature, burn, etc., pain receptors, *"nociceptors,"* initiate an electrical signal that travels from that site of injury to the brain where this signal is appreciated as pain, *"an unpleasant sensory and emotional experience that is associated with actual or potential tissue damage or described in such terms."*[7] Prior to the brain's interpretations, the signals from nociceptors are just data; it is at the brain where an individual perceives (feels/appreciates) pain. The brain is not merely a landing site for this data, however, but is designed to process it and reprocess it, activating parts of the brain that will make for not only learning and remembering it as a valuable lesson for the future, but for lessening it as well (i.e., restoring function). As will be described later, VR also is designed specifically to be "all in the head," immersively replacing one reality for another to kindle other tactics for addressing pain.

The Purpose of Acute Pain and Its Downside

Pain is a warning signal. Simply, it is the body's way of getting one's attention to stop doing things contrary to survival. This was more important in prehistoric Man who relied on just him-/herself to avoid the life-threatening traps the environment posed (i.e., animal dangers, harm from competitors, and even the laws of physics). Today, modern medicine offers remedies for otherwise ill-fated mishaps—a second chance to undo the harm. Unfortunately, ancient times saw unprotected individuals naked and vulnerable to the consequences of their poor choices, accidents, or bad luck.

Pain—to be effective—is often disabling, interfering with normal function. The caveman who gets swiped by a tiger should be made to understand that this is undesirable: pain; but then he must be able to run away before the second swipe: function.

A person experiencing pain may have time to reason that walking away is prudent. However, severe pain does not portend well for survival when the sufferer is immobilised, cringing impotently, to wit, a "sitting target" for more. Injury can be so precipitous that it does not allow the luxury of time for reason and an escape plan. Alternatively, it can be so overwhelming as to shock a person into a temporary catatonic state, inviting further harm. Counteracting these downsides are processes as firmly entrenched in human physiology as pain itself. Inhibitory processes,[8] spinal blocking,[9] and endogenous painkiller biochemicals are some of these internal remedies for pain that allow for follow-through function.

Because VR is immersive, it also is internal--as perceived. As such, VR introduces other mechanisms for counteracting pain, partnering with the internal mechanisms already in place.

The Internal Remedies for Acute Pain: The Hammer Falls

The cliché of hitting one's thumb with a hammer illustrates well the inhibition of pain for the purpose of re-establishing function. When hammer meets thumb, nociceptors take the fastest routes to the brain using the fastest (myelinated) nerves. The "victim" suddenly grasps the injured thumb firmly and a moment later it is not hurting as badly. *Why is this?* It certainly is not that this thumb is any *less* injured than it was a moment ago. This change is via the internal processes that immediately respond:

1. Descending Noradrenaline Inhibitory Pathway (DNIP).
2. Parafascicular (PF) inhibitory neurons.
3. Gate mechanisms at the spinal level (Gate Theory).
4. Endogenous opioids.
5. Anti-inflammatory counterbalance to inflammatory processes.

1. DNIP

The *Descending Noradrenaline Inhibitory Pathway (DNIP)* originates in the brainstem (part between the brain and spine) called the locus coeruleus (and select other brain regions), which is stimulated to act with the perception of pain whose signals ascend from the spine on their way to various other neural regions. (Pain signals from nociceptors land at a vertebral segment site, enter the spine, cross to the other side, then travel up a nerve tract—the *"spinothalamic tract"*—to deliver the pain signal up to the brain.) The DNIP uses the neurotransmitter *noradrenaline* (norepinephrine), which activates inhibitory neurotransmitters at the spinal region where the incoming pain is landing. *Serotonin*, another neurotransmitter, is also active in this inhibitory process.[10]

How this signal crosses over to the other side of the spinal cord is via an intermediary neuron called the *"interneuron."* When the interneuron reacts to the inhibitory signal from the DNIP, it becomes inhibitory itself, and the continued incoming pain signals diminish. The interneuron decreases the volume of the pain signal.

Result: *the thumb hurts less.*

2. PF

There is also an ascending alteration of pain which is turned on by incoming pain signals. The *parafascicular neurons* (PF)[11] of the thalamus, an ancient part of the brain, have opioid receptors that are turned on by incoming noxious stimuli. Besides endogenous opioids, the neurotransmitter dopamine seems to contribute to this RF stimulation that results in inhibition.

Result: *the thumb hurts less.*

Thus, there are dual ascending and descending inhibitory pathways that are governed by the amount of noxious stimuli signal entering the spine and then the brain. At the brain, because these processes are not fixed tracts but vacillating consortia of neuronal constellations changing from moment to moment, VR offers opportunities to temper those interactions.

3. Gate Theory

In 1965, Canadian psychologist Ronald Melzack and British neuroscientist Patrick Wall introduced their "Gate Theory" [9] for pain. This explained how pain is lessened by competing signals that can block pain signals. They postulated that non-painful stimulations landing at the spinal entrance where the painful stimulations are entering will close the nerve "gates" to the pain input, blocking them from travelling up to the brain. This is why dentists will shake your cheek while injecting anesthetic; why a child's scraped knee really will feel better when a doting mum kisses it; or why grabbing one's thumb after an unfortunate hammer strike helps.

Result: *the thumb hurts less.*

Thus, the Gate Theory describes how pain signals are blocked at the spine; meanwhile, the DNIP converts an interneuron into an inhibitory neuron, and parafascicular neurons send inhibitory influences upward to mitigate pain perception.

4. Endogenous Opioids

Pain signals land at opioid receptors stimulate their production of endogenous opioids (chemicals which bind to them that decrease pain centrally and peripherally). Three such chemicals (beta-endorphins, dynorphins, and enkephalins) act on three types of receptors (mu, delta, and kappa), respectively.[11]

In contrast to the immediate responses, less-than-immediate responses also step in to control pain.

5. Anti-inflammatory Processes

Inflammation is part of the innate immune system in which the response to injury or infection is designed to draw more blood and white blood cells into the area so that healing may begin. Therefore, inflammation is part of the healing process. Like most things in the body, there is a balance, and inflammation is policed by the body's anti-inflammatory processes.[12] Cytokines—proteins that either promote ("inflammatory cytokines") or reverse ("anti-inflammatory cytokines) inflammation, are the body's checks-and-balances system so that there is enough inflammation to begin the healing process, but not enough to damage the very areas trying to heal. [13]

VR, by redefining a person in space, time, and location, can alter all of these processes which begin with perceptions that are re-written according to a personalised immersion in a different space, time, and location.

PART II: CHRONIC PAIN

Chronic pain perverts the body's dealings with acute pain.

Acute pain is self-limited. Injuries, even bad injuries, will either heal or scar. The nociception discontinues. Acute pain, therefore, is meant to be self-limited—that is, warn, then go away. The natural, intuitive response to acute pain is to stop hitting one's thumb repeatedly with the hammer.

This begs the question:
what happens when the hammer keeps hitting the thumb?

Chronic pain is defined as, *"pain that persists 6 months after an injury and beyond the usual course of an acute disease or a reasonable time for a comparable injury to heal, that is associated with chronic pathologic processes that cause continuous or intermittent pain for months or years, that may continue in the presence or absence of demonstrable pathologies; may not be amenable to routine pain control methods; and healing may never occur."*[14] Chronic pain, as a syndrome (disease) itself, is *"defined as a complex condition with physical, psychological, emotional, and social components."*[15] While acute pain evokes anger (well associated with a thumb-vs-hammer scenario), chronic pain evokes depression.[16]

The most common cause of chronic pain is inadequate treatment of acute pain,[17] which is like the hammer continuing to see everything as a nail—including the thumb. Repeated nociceptive waves of pain landing at the interneuron in the spine overwhelm the gate, even against the strongest non-painful competitors. Another ill effect occurs that is the basis for chronic pain: continued nociception perverts the inhibitory interneuron to become an amplification neuron. So it is with continued pain that pain is no longer being inhibited; actually, it is being amplified as chronic pain.

While acute pain is a *warning*, chronic pain is a *disease.*

VR, as purposely deceptive as it is, can prove beneficial in such situations as wound management, burn treatments, trauma, and other causes of acute pain. Chronic pain, however, is a bigger challenge since it adds neuropathy to the mix; but even neuropathy is not immune to the brain's ability to reroute itself around these abnormalities. The chronicity of the pain barrage may have diminished the "volume" of the internal remedies for pain, and VR has been found to rise to the additional challenge.[18]

Chronic pain: it gets worse.

There are inhibitory cells in the nerve root of the spine that inhibit the pain signal as it enters. When these are overwhelmed, they die and do not come back;[19] the added amount of inhibition that they provided dies as well.

Chronic pain: it gets even worse.

Pain signals that land at the spine are not isolated to just that spinal segment. Their signal can radiate up and down another 3-4 spinal segments, mimicking pain originating from sites those segments represent. This explains how pain in one area can "spread" to involve adjacent areas of the body.[20]

The External Remedies for Chronic Pain, Their Limitations, and Their Pitfalls

1. Opiates: the double-edged sword.

Opiates have been recognised for their pain-killer properties since ancient times. They have helped people with pain consistently throughout history, even when they "helped them to death." Narcotic medication blocks pain by competing with neurotransmitters that turn on pain perception receptor sites on neurons. This is done centrally in the brain as well as in the spine. As governments began getting into promoting the public welfare, e.g., the controlled substance legislation and the CDC, both the successes and the tragedies due to opioids became less hidden to society. With social media, the outcry to opiates' downsides has become amplified and journalistically tainted anecdotally. While there was a significant enough problem to label these unfortunate events as legitimate tragedies, the balance in the public's mind between help and injury clouded—the tragedies garnering most of the attention. More legislation followed and law enforcement became an integral ingredient in the debacle. Additionally, opiates presented other problems besides abuse and toxicity, such as addiction, tolerance, and dependence, fuelling more knee-jerk societal reactions.

Clearly a new approach was direly needed.

2. Anti-inflammatories.

Beginning with aspirin, newer medications have offered the hope of adjunctive analgesia to narcotics or even—in a perfect world—an effective replacement. Cox-inhibitors, steroids, and the non-steroidal anti-inflammatories have all offered promise but come up short by either not being as effective as opiates or by having too many side effects. The body turns out to be very frugal with its physiology in that one hormone, protein, cytokine, etc., may have many functions. This makes using one substance, e.g., an anti-inflammatory to address inflammation, problematic in that it also may invoke many other effects. Some of these effects can be destructive, such as bone resorption, gastric erosions and ulceration, and diminished immunity to infection.

Clearly a new approach was direly needed.

3. Antidepressants.

Looking back at the DNIP, there are three main neurotransmitters at work in propagating this inhibitory signal:

1. Noradrenaline.
2. Serotonin.
3. GABA (gamma-aminobutyric acid).

The noradrenaline and serotonin are antidepressant in nature. Keeping them from degrading (from preventing their reuptake from synapses between neurons) is the main idea in many antidepressants, the SSRIs (selective serotonin reuptake inhibitors) and the NRIs (selective noradrenaline reuptake inhibitors). GABA is a pain-inhibitory neurotransmitter that is normally in balance with glutamate, the pain-excitatory neurotransmitter. Side effects of the SSRIs and NRIs often limit the usefulness of antidepressants to treat pain, e.g., decreased appetite, sexual dysfunction, mood alterations.

Clearly a new approach was direly needed.

4. Anti-seizure medications.

Some medications that were developed to slow nerve impulses in hopes of preventing seizures turned out to be ineffective, but showed a surprising property of dampening pain, possibly by the very nature of slowing these impulses. Gabapentin (not related to GABA) and its "pre-drug" formulation, pregabalin, are used as adjuncts with other pain regimens. (Pregabalin, a pre-drug, breaks down into gabapentin in the body after being metabolised.) Side effects, however, often limit their usefulness, e.g., fatigue, somnolence, swelling.

Clearly a new approach was direly needed.

5. Topical stimulation.

This external remedy actually makes use of an internal remedy: the Gate Theory. A TENS (topical electrical nerve stimulator) electrical device sends non-noxious nerve sensations to close the gate where the pain signals are landing at the spine. Unfortunately, coverage of a painful area is patchy at best, unless electrodes are threaded into the epidural space to directly send impulses to the affected spinal segments; however, such electrode leads are prone to moving and can stimulate actual pain.

Clearly a new approach was direly needed.

PART III: VIRTUAL REALITY

Remapping the Brain and Side-stepping Pain

Can one really be distracted from pain? If so, how powerful a distraction would be needed to be effective?

As stated above, while distraction is the operative in VR, the concept of diverting attention from pain is an oversimplification. The brain is not merely a sieve where some concepts are funneled into some parts and other concepts or experiences are funneled into others, yet the concept of distraction implies that consciousness is funneled into a portion of the brain where it is less aware of pain. This concept, which is *"pain-centric,"* is fraught with the misconception that pain can be seized, contained, and then moved around. The reality is that pain is *"mind-centric,"* part of a consortium of synapsing groups and regions that construct our reality, and it can no more be segregated away than separating half of salt, i.e., the deadly poisons sodium or chloride, and consider either merely half-salty and just as innocuous.

For all of us, our universe is contained within our minds as an interaction of all of the sensations we perceive, experience, and navigate, and these are all based on information passing through our consciousness.[20] It is *" an amalgam of affect, cognition, and sensation mediated through diverse brain regions...* [that is,] *a neuromatrix."*[21] Medical science attempts to address pain by targeting specific areas that mediate pain, such as nociceptors on neurons, neurotransmitters between synapses, amplification signals, inhibitory pathways, and even the innate immune system. These approaches all represent piecemeal attacks in hopes of a collapse of the entire pain process, as if pain were a Jenga tower or a house of cards.

What is needed, instead, is perhaps another neuromatrix, which is where virtual reality comes in. Consciousness becomes fully invested in virtual reality after only a few minutes, and the promise of using VR as a therapeutic strategy is based on the correct interpretation of the neuromatrix.

VR is the use of computer technology to render a substitute immersion in lieu of the universe normally perceived. There is no peripheral vision, and this encourages total focus and immersion into the substitute world. Patients aligning themselves with a different universe from their usual reference reality have an opportunity to have their pain reduced or even eliminated. Distraction as the oversimplification is a justifiable enough explanation for the moment-by-moment pain reduction while VR is in progress, but *can it "stick"? Can it last?* This is the part that supersedes the concept of mere distraction. Making it stick is where the remapping (rewiring of the brain) comes in. Pursuing such a result makes more sense than the one-shot standalone approaches of narcotics, anti-inflammatories, antidepressants, and anti-seizure medications, or worse, the clinical "rational polypharmacology" with its added risk of potentiating toxicity and increasing the risk of mortality that has become a political crisis pitting doctors against bureaucrats and law enforcement and academicians/scientists against media sensationalism.

The discovery among stroke patients that the brain can heal itself 6 by rerouting the neuromatrix has been bolstered by VR in a variety of acute and chronic pain conditions, specifically, fibromyalgia, phantom limb pain, and regional pain disorders.[22] There has been enough activity in the medical application of VR to garner meta-analyses documenting its effectiveness. The results indicate that *"virtual reality distraction* [that word again] *is a highly effective pain intervention."* [23, 24]

Virtual Reality Meets Clinical Reality

If all pain is perceived in the brain, then it makes sense to change what the brain perceives, that is, retrain the brain to think differently. Neuronal tracts can be altered and rerouted when a different reality, a painless reality, is constructed well enough to get the pained brain to suspend disbelief. This is no mere distraction, but true remapping—true neuroplasticity. The 3-dimensional portrayal rendered by VR is one such successful construction; eliminating *true* distractions of the real world (via immersion—stereoscopic goggles and dedicated sound) allows for the VR to do what it does for virtual gamers and virtual travelers, i.e., take the patient into a new world in which the pain of his or her clinical world is left behind.[25]

The Thumb Returns

Experiments with amputees who experience phantom pain, using mirrors to confuse the patient's mind that the missing limb is present, have accomplished what grabbing one's thumb does after the hammer attack. The DNIP becomes activated, and while there are no true competing non-painful signals to close the gate, other processes impact the gate. [26]

The clinical success of VR in mitigating pain will see a reduction in the use of controlled substances, in the overhead required to follow legislation and law enforcement protocols for them, and of their associated morbidity and mortality. VR, however, does much more than mitigate pain—it makes the mitigation of pain interesting for the patient (a secondary gain), and the milieu of each new universe is as varied as the human imagination. Even better, it can be authored as a bespoke program unique for unique pain presentations.

The Economy and Physiatry

Physiatry is the specialty of rehabilitation medicine. Rehabilitation is expensive, but original computer code becomes less expensive the more a code's VR portrayals are used. Computer storage is cheap and getting cheaper all of the time. Production of VR is via code and distribution is easy within existing infrastructures of today's healthcare. This means a minimum of investment for a maximum clinical and human impact.

In a capitalistic society based on supply and demand, demand begets advancements in technology to produce a competitive edge. As such, gaming—a major player in VR—will realise advancements that will be used to advantage in the clinical use of VR. In fact, the world is converting from analog to digital in all

aspects of information storage and handling. There will soon be virtual libraries, virtual filing cabinets, even virtual patients upon which surgeons will practice. The da Vinci® robotic surgery system has the surgeon sitting in a booth wearing stereoscopic 3-D goggles away from the patient within which he/she is manipulating operating instruments.[27] As computer-generated graphics (CGI) improves according to the same principles as Moore's Law[28] (rate of doubling of capacity of computers), there soon will be no difference between what a surgeon sees in goggles and anything else that can be portrayed on similar goggles for the sake of constructing a new reality that makes pain invisible.

VR has been proven to induce emotional responses,[29] which is unsurprising considering the effects that can occur from music, art, poetry, literature, and movies. There is a vast crossover of neurotransmitters between organic processes and psychological states. For example (among countless examples), serotonin and norepinephrine, as stated above, important in mood and depression, also orchestrate the DNIP; dopamine, the "reward" hormone, also is prominent in the PF system of pain inhibition. Other hormones, such as oxytocin and prolactin, also are players, sure to get involved in any new therapeutic constructed reality.

VR already has been proven effective in phobias, anxiety states, depression, and many other "mind" abnormalities other than pain in which extending "body space" can be a useful tool to remap the brain's perception of body.[30] While it can be valuable as an independent approach to pain and other mental conditions, it can also be integrated seamlessly into the conventional approaches underway in patients already receiving traditional care. That is, no ongoing therapy need be interrupted to include VR.

Summary and Conclusion

The human brain is where pain is perceived and it is prepared to regain functionality of the body via inhibitory mechanisms that naturally engage, as part of a cease and desist and escape strategy. External (artificial) inhibitory counter-methods are fraught with incomplete effectiveness, side effects, and/or illicit abuse. Virtual reality that is immersive excludes the reality upon which the brain relies and can replace it with a reality that can be tailored for specific untoward conditions such as pain[31] and psychological issues. Exchanging one reality for another does not reinvent the neurology of the brain, but remaps it while using the same vehicles consciousness has always used—the neurotransmitters. Distraction is probably the closest description to the modus operandi of immersive VR for treating pain, but it is more complicated than that because distraction implies inattention to something within the same reality, not a new reality being used, which is what VR is. [32]

VR is in its infancy, but already there has been great success in clinical practice. As Moore's Law increases the capabilities of the digital word exponentially, what becomes clear is that added to the benefits that VR can bestow is the equally advantageous aspect is that there is no disadvantage to it: there is no downside. Mental conditions and pain cost the USA over $193B per year in lost earnings[33]

and over £105.2B in the UK,[34] but these figures cannot include the intangible losses from overdose death, incarcerations, and broken families, nor the extra law enforcement/cost that enforcement and incarceration require. Pursuing a non-pharmacological strategy makes sense now more than ever, considering these financial and human costs.

Neuroplasticity is the final frontier in pain, because the brain is the foundation of all perception and it can be redesigned, remapped[35] and renovated via virtual reality.[36]

If Clearly a new approach is needed, VR is that new approach.

RESOURCES

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