



Review Article

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Depression, Anxiety, Posttraumatic Stress Disorder, Delirium and Succedent Social Isolation as Cause and Consequence of Long-Term Morbidity of ICU Patients

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Abstract

The four major mental disorders, related to ICU and HDU associated severe conditions are depression, anxiety, delirium and Post-Traumatic Stress Disorder (PTSD), all with the imperilment of culminating in suicide, are concisely analyzed in this communique, with special emphasis on the aspect of social defeat and social trauma. According to different statistics drawn from assorted environments, the overall incidence of these disorders is around 30-40% with versatile contributions. ICU care is heavily reliant on advanced technologies connected to patients via invasive and noninvasive means, with complex mathematical, physical, and biochemical support. In this environment, the emotional aspect of disease and care for patients and providers has to be constantly contemplated and accentuated. The majority of patients struggling with severe illness in ICU and beyond, live through lengthy recovery, in which strong family and broader social and physiotherapy treatment are the mainstay; their absence worsens the chances for good outcome. The reflection on ICU related mental stress is a call out to pinpoint the need for patronage and guardianship by social support groups. In addition to potent analgesics and sedatives, antipsychotics and antidepressants are abundantly utilized in ICU, hence clinicians are deemed to be equipped with fundamental knowledge and awareness of psychological and biochemical aspects and targeted treatments of mental disorders encountered in ICU.

Abbreviation: AI: Artificial Intelligence; ALI: Acute Lung Injury; ALS: Amyotrophic Lateral Sclerosis; BBB: Blood Brain Barrier; BDNF: Brain Derived Neurotrophic Factor; CDC: Centers for Disease Control and Prevention; CPTSD: Complex Posttraumatic Stress Disorder; FDA: Food and Drug Administration; ICD: International Classification Of Diseases; ICU: Intensive Care Unit; IDO: Indoleamine 2,3 Dioxygenase; IFN: Interferon; DTD: Developmental Traumatic Disorder; HDU: High Dependency Unit; LOS: Length Of Stay; MAOI: Monoamine Oxidase Inhibitors; MOR: Mu-Opioid Receptor; mTOR: Mechanistic Target of Rapamycin; NMDA: N-Methyl-D-Aspartate; PTSD: Posttraumatic Stress Disorder; SDI: Socioeconomic Index; SNRI: Serotonin And Noradrenalin Reuptake Inhibitor; SSRI: Selective Serotonin Reuptake Inhibitors; STD: Sexually Transmitted Disease; TCA: Tricyclic Antidepressants; VTA: Ventral Tegmental Area; WHO: World Health Organization

Introduction

We intensivists encounter patients from very diverse social backgrounds. The degree of comorbidities shows the greatest

correlation with the risk of mortality of ICU indicated acute illness, particularly that of sepsis [1], polytrauma and brain disorders. Acute and chronic mental disorders are major contributors to



mortality and morbidity, particularly when already present before hospitalization. According to a recent document, analyzing 268 studies, including 10 million people with depression and 2.8 billion controls, depression carries a 2-fold higher risk of mortality and 10-fold higher risk of suicide [2]. We acknowledge our obligation to support the patient and the family walking through the cumbersome and precarious path of healing.

Common Triggers to the Mental Stress

According to WHO, in 2008 depression was the third major contributor to global disease burden and pursuant to predictions, it will become the leading contributor by year 2030 [3]. Incidence rates are higher among women than men with peak between ages 60-64, disproportionately among young people the likelihood of suicide is 30 times higher than in non-depressed population, with raising incidence particularly in regions with low Socioeconomic Index (SDI). There is the more frequent major depressive disorder, characterized by low mood, lack of motivation, flare ups of variable intensity and dysthymia, a more persistent melancholic phenotype. According to worldwide statistics between 1990 and 2019, the major triggers for depression were intimate partner violence, bullying, victimization and childhood emotional and sexual abuse [4]. The true etiological and phenotypical landscape of depression is very diverse, and loss of partner and loss of significant relationship are unequivocally alarming triggers for mental decompensation. Treatment resistant depression was associated with suicidality, severity, recurrence, with younger age, female sex, cardiovascular disease, and pain [5]. In striking contrast to these objective statistics, public belief in 30% is that weak personality is the main cause of depression [6].

Divorce and Separation

Marriage traditionally is the backbone of society, originally built on mutual interest in economical and reproductive survival, a convention, which has been challenged by a desire to be united on a deeper level of emotional and intellectual congruence. The frustrations arising from the lack of mutual effort to create a true spiritual union, based on respect, freedom and reciprocal, collaborative support to grow as individuals with unchained opportunities of self - realization, embedded in a healthy level of compromise, led to increase in divorce rates, negatively affecting the society and children likewise. Post separation isolation and depression are neglected social traumas little addressed or aberrantly addressed by professionals and the society likewise. The disposable nature of our materialistic, pragmatic societies have their imprint on the way how the problem of social isolation and loneliness are addressed. The commercially and virtually oriented online dating and chat sites, according to victims and social studies, while seemingly opening wider horizons, due to ghosting, rejections, lack of reliability, responsible treatment of the parties, avoiding commitment and ethical rules, based on business-oriented attitude, supporting and insinuating the disposability and exchangeability of individual, creating false virtual images, they

substantially worsen depression and feelings of loneliness [7]. The particularly dangerous aspect of online dating apps is their virtual invisibility and disproportionally higher usage among younger adults and adolescents. Studies done among university students support the deviant attitude and set up of dating apps generally loosening ethical standards in increased frequency of depression, number of partners and STDs [8]. Reports on establishing successful lifelong relationships using dating apps are sparse, reflecting the problematic advocacy in partner liberty and distorted virtual reality, where irresponsible attitudes are tolerated without repercussions, enabling mentally challenged, socially deviant individuals to persist, by using business oriented, financially often extremely challenging, rather than non-profit approaches by online dating apps. These online forums are frequently intertwined, managed from the same headquarters, and their profiles are often fake, and manipulative. It is unfortunate that the persuasion of establishment of function and happy families and human relationships can be dishonored and disgraced in such an inferior way without legal repercussions. Money is drawn from people; exclusive interactions and virtual presents worth thousands of dollars are demanded by profiles that obviously are not capable of such investments themselves using alter egos and aliases, intruding privacy. Periodicals draw attention to the emerging fatigue using these sites, and upon deeper engagement, that is expected from more genuine and trustworthy users, severe mental disorders, particularly depression and posttraumatic stress disorders, financial difficulties are the outcome, but beyond publicizing these issues legal actions are seldom initiated [9]. Depression and adverse health outcomes, related to divorce, separation, and loneliness, disability and chronic illness, according to statistics, are on rise [10]. The strongest predictors of outcome are social status, level of divorce conflict, new partner status, age, number of previous divorces, in general the ratio of protective and risk factors during and after separation and stigmatization of process in certain societies. A large number of studies support a rise in anxiety, stress, rate of hospitalization and suicide. The risk of depression is higher among middle-aged, divorced women with low socioeconomic status than men of the same parameters [11].

Mental Disorders and Bullying [12]

Complex and developmental mental traumatic disorders emerge upon sequential bullying as part of dysfunctional interpersonal communications during social interactions on verbal and more treacherously on non-verbal levels, in real and virtual interactions, likewise. The symptoms may deepen gradually when the possibility of escape or distancing is difficult or serves as no viable alternative, with limited safety options for recovery. The presentations of bullying disorders are more complex than those of PTSD reflected in categorisation to CPTSD (complex posttraumatic stress disorder) and DTD (developmental traumatic disorder) conveying, that bullying affects the individual in complex means, by dysregulating and disrupting on affective, physiological, attentional, relational, complex emotional, cognitive and behavioral

levels. CPTSD diagnosis is already included as a new entity in the 11th revision of ICD - classification of diseases, the assessment is based on validated questionnaires and is particularly prevalent among children and adult immigrants living in conflict zones with heightened vulnerability and less chances of stopping this vicious circle [13]. Part of bullying is discrimination and subordination as tactics of aggressors, leading to increased stress, impaired self-esteem, and tribulation in denounced individuals. When university students were questioned in affected areas of the Middle East, the harm reported on them, friends or family members was over 90% psychological, in 67% lack of shelter, in 56% death. The further danger of CPTSD lies in creating a self-perpetuating pathological loop of traumatic events deeply embedded and imprinted in memories that upon new triggers culminate in amplified reactions of aggression, withdrawal or rejection. From a purely somatic standpoint they sensitise towards impaired immunity, poor muscle strength, eating disorders, obesity and cardiovascular disease, a multitude of somatic disorders. Prevention and treatment of CPTSD is based on trust and eliminating the threat by the courage of exposing [14]. The mainstay of treatment should be positive modeling and ultimately withdrawal from harmful environments, pre-eminently seeking peaceful solutions based on respect, tolerance, and compromise.

A significant aspect of mental stress is a social defeat. Emerging animal models on social defeat inflicted upon co-caging the individual with an aggressive animal mimic outcomes of social defeat in increased depression like symptoms, with hallmark features of withdrawal, social avoidance, anhedonia, lack of mobility and activity, often elevated levels of HPA axis, hence cortisone, changes in neuronal circuits particularly in ventral tegmental area, due to increased firing rates of dopamine neurons, which leads to hyperactive dopamine response in nuclei accumbens presenting with social avoidance and depression-like behaviour [15]. Part of social defeat is chronic stress and beyond depression-like behaviour the animals may demonstrate anxiety, PTSD, even schizophrenia. Some animals show greater resilience toward social defeat with special genotypes in ventral tegmental area and prefrontal cortex; these animals typically have lower IL-6 levels. Social avoidance is more paradigmatic for female behaviour, while male mice more often take a proactive, aggressive stand [16].

Attempted and Demonstrative Suicide and its Reverberation In ICU

An important group of ICU patients are suicide survivors with major mental issues, and the intensive care unit should serve as a launching point on the road to their recovery in appropriate psychological appellation and presenting the individual to multidisciplinary teams, enrolling into long term care. Psychiatrist involvement is crucial in acute crisis management, risk assessment, and planning of further care. The global crude suicide rates range from 3.6 to 12.4 per 100 000 on average. According to WHO reports with a male dominance in general, for example in the

USA four times higher among men than women, in 57% using firearms [17,18], according to the American Federation for Suicide Prevention. Reflecting from USA statistic among young people, ages 15 to 34, suicide is the second leading cause of death, in middle age is a female dominated pattern while in older age more men commit suicide [19]. We occasionally encounter demonstrative suicide attempts which are extreme signals for help, sadly the vast majority of suicidal patients have despair and fatalism embedded in their core so deeply, with such conviction, that a change in trajectory, looking at life with hope and faith, requires overflowing constant ongoing positive signals, that the society is barely prepared to offer. There is approximately one completed suicide for twenty attempts. Major triggers are mental health conditions, chronic pain or illness, poverty, isolation and significant stressors, while the strongest risk factor is previous suicide attempt [20]. In Europe and the United States among major contributors are severe academic or career pressure, issues with social relationships and identity. Excessive online social media and mobile usage have been linked to an increase in social isolation, suicide thoughts, self-harm, and suicides among young people [21]. The common contributors are cyberbullying, higher psychological distress, disrupted sleep, and the addictive nature of these platforms. They are designed to develop and nurture addictive behaviour, by creating dopamine loops in the brain using fake virtual positive reinforcement and rewards, for example using the like button is addictive and people tend to establish their self - worth based on approval metrics [22]. Engagement of the dopamine loop can lead to compulsive use, making it very difficult to disengage. A study in the UK found that nearly a quarter of young people who committed suicide had suicide-related online experiences [23]. These platforms often use AI recommender systems to personalize personal needs; they offer alternative reality and fictitious escape routes from unpleasant reality. Most regulations are restricted to disabling searching for harmful content and material, and positive reinforcement creating true addiction is seldom controlled for. A recent JAMA study has shown that adolescents with addictive use of social media have doubled the risk of suicidal behaviour and ideation [24]. Restricting access may be counterproductive, with unintended consequences of ban, shifting the responsibility to providers and the manipulative set up of their system would better address the root of the problem.

The Biochemistry of Depression

The classical theory relates depression to faulty serotonin metabolism, and serotonin uptake inhibitors are based upon this prerequisite. In a more comprehensive manner, the disbalance relates to monoaminergic and glutamatergic systems in general, one that is enhanced by inflammatory stimuli [25]. The latter has recently become more punctuated due to appreciation of glutamate metabolism disorder augmented by inflammation, leading to impaired neuronal plasticity, connectivity disruption and impaired neuroregeneration, to be considered particularly in classical treatment resistant phenotypes. With the bloom of inflammation

research, proinflammatory biomarkers have been associated with mental stress. An interesting study has found that early during the emergence of depression, among university students, regardless of the etiology, that is abuse history or economic difficulties, rather than upregulated inflammation, defective antioxidative mechanisms were present [26]. Serotonin metabolism is linked to tryptophan, an essential amino acid, in its vast majority metabolized through the kynurenine pathway; a smaller proportion is used to produce serotonin. Chronic or ongoing inflammation shifts tryptophan metabolism away from serotonin to neurotoxic kynurenine metabolites, such as quinolinic acid, that acts as a NMDA agonist. Another intersection is IDO (indoleamine 2,3 - dioxygenase), a rate limiting enzyme in the kynurenine pathway. The same enzyme participates in T cell regulation by suppressing T cell activation and proliferation broadly, while promoting regulatory T cell differentiation and function, shifting toward a regulatory phenotype, having a detrimental effect during the exhaustive phase of sepsis. Reducing inflammation shifts tryptophan metabolism away from kynurenine pathways [27].

In the line of monoamine theory, primarily SSRIs and SNRIs are used, acting mainly on 5HT1A and 5HT2A receptors indirectly, while MAO, TCA with more frequent side effects, are the third line of treatment [28,29]. Among newer alternatives aripiprazole, a partial dopamine D2 and 5-HT1A agonist and 5-HT2A antagonist are utilized. Aripiprazole uniquely combines antidepressant and antipsychotic effects. Among the novel antidepressants, ketamine, the prototypic dissociative anesthetic analgesic has gained recognition, due to its strong antidepressant effect arising early and lasting for several days [30]. Both R and S ketamine act via inhibition of NMDA receptors and possess agonistic opioid analgesic activity using MOR receptors. Ketamine induces neuronal synaptic plasticity and remodeling by activating mTOR signaling pathway, increases BDNF (brain-derived neurotrophic factor) release and monoamines (dopamine, noradrenaline, and serotonin). Ketamine induces a short surge in glutamate production improving plasticity and neuronal connections, while long term glutamate release, like during chronic inflammation has excitotoxicity via overstimulation of NMDA receptors and pathological calcium influx, leading to mitochondrial dysfunction or cell apoptosis in its most severe form. NMDA activation mimics the action of glutamate rather than increasing its production. Esketamine reduces T cell migration from gut to lung, suppressing ALI symptoms. Concurrent reports of adverse ketamine-related effects are available, and while its utility in ICU is appreciated, careful consideration and long-term follow-up of these patients should be subject to future studies. Esketamine is currently an FDA approved intranasal adjunct for the treatment of resistant depression, due to rapid induction of mTOR dependent synaptogenesis and clinical efficacy. Its action on amygdala, enhancing amygdala's communication with the prefrontal cortex, contributes to significant antidepressant action [31]. While low dose ketamine shows delirium sparing effect [32], continuous ketamine sedation may prolong ICU and hospital stay, likely due to longer half-life, while not decreasing mortality [33]. As ketamine is

unequivocally efficient in depression management, its role in PTSD is subject to ongoing research. Ketamine associated hallucination is dose and individual sensitivity pendent, in small antidepressant doses dissociative effects are transient, and may be alleviated using propofol, dexmedetomidine or benzodiazepines, which may blunt antidepressant effect in a dose proportional manner.

The global antidepressant market is steadily growing and in the year 2023 reached 13.8 billion dollars worldwide and according to prediction will grow to 30.5 billion dollars in ten years [34]. This steep incline is due to the growth in reactive mental disorders elicited by social stress, fundamental detrimental life changes such as divorce, separation, loss of family members, grief, loss of income, health related burden or drug abuse, living in conflict zones. The approach to managing reactive depression is heavily reliant on biochemical modification of brain processes by antidepressant medications. While bridging periods of altered life quality grants antidepressant utilization, seeking problem solution is nevertheless the priority goal. Antidepressants work in a large proportion of patients, may transiently decrease suicide ideation [35], some are refractory, and using them enables us to accept our frequently unsettling reality through pink glasses and function in a world of personal journeys where justice is not always attainable.

Depression, Sepsis and Immunity [36]

The incidence of reactive depression arising due to ICU-related severe illness, particularly sepsis, is high, 28% according to some studies. The stay in the ICU itself is a major stressor, due to extreme, unphysiological measures undertaken to save and preserve life. Sedative and analgesic usage is the mainstay of bridging the time while invasiveness of great extent, with occasional painful stimuli, lack of possibility of physical activity and disturbed day and night rhythm, is inevitable. The incidence of cognitive and physical impairment after sepsis survival is high and only one third of patients achieve full functionality after one year [37]. Post-sepsis depression seems to be associated with preexistent pre-sepsis depression and female sex. Likewise, post-sepsis cognitive and physical impairment is worse in previously depressed individuals [38]. Mental disorders may manifest years after discharge, when prolonged physical and social impairment upon surviving severe disease persists. During sepsis, the Blood Brain Barrier (BBB) is compromised, and IL-6 entering the brain has been shown to induce depression-like symptoms in mice. Depressive patients, according to meta-analyses, have higher levels of proinflammatory cytokines. Depression is often viewed as part of sickness behavior. During acute and chronic stress the body tunes to preserving energy resources and mobilizing acute response elements. Supporting this view, proinflammatory treatments elicit, while anti-inflammatory drugs suppress depression symptoms. During acute and chronic stress, through activation of the hypothalamic-pituitary-adrenal axis beyond fight or flight and cope mechanisms, the mental stress evolves. Hypercortisolemia and proinflammatory cytokine production depletes serotonin and stimulate neurotoxins, leading to astrocyte and microglial apoptosis [39]. The demonstrative

example is IFN alpha treatment duration leading to transient depression terminating upon IFN alpha withdrawal [40]. The idea of the brain behaving as an immunologically privileged organ is relative, and the tolerance is broken by pathological insults.

Proinflammatory cytokines lead to derailing tryptophan in its pathway from serotonin to kynurenine synthesis and also dopamine production is decreased, directly and indirectly via nitric oxide, that increases glutamate with the potential of apoptosis and neurodegeneration. Proinflammatory pathways decrease glucocorticoid receptor sensitivity. Beyond glucocorticoids, stress-related hormones adrenaline and noradrenaline lead to proinflammatory cytokine production via NF-kB activation [41], while the parasympathetic mediator acetylcholine inhibits NF-kB activation. Chronic inflammation and depression contribute to neurodegeneration and the apoptosis of astrocytes and supportive microglia. Depression carries a 40% higher risk of developing metabolic syndrome, that is abdominal obesity, insulin resistance, and dyslipidemia. Depression is associated with chronic inflammation, mitochondrial dysfunction and an energy sparing phenotype, characterized by fatigue, hypersomnia, Lead paralysis, that is the feeling of heaviness in limbs, mood reactivity, low motivation, anhedonia and increased sensitivity towards rejection. The mechanisms that link depression, defective immuno-metabolism, and metabolically unhealthy obesity are poorly studied. Perhaps immuno-hormones, such as leptin and insulin, trigger an energy accumulative, rather than expeditive phenotype in the brain [42]. Mental disorders may have in common a sick euthyroid phenotype, low levels of effector T3 and lack of feedback that is low or normal levels of TSH and T4. Chronic thyroid dysfunction is associated with depression and anxiety; the causative relationship is bidirectional [43].

Depression and Critical Care Illness

Mental stress is a common contributor to morbidity and disability after surviving a severe illness or trauma [44]. A large nationwide cohort study enrolling and analyzing antidepressant usage after ICU hospitalization using a population of over 125 000 ICU patients found at least 15% patients using antidepressants one year following ICU stay, with anticipated increase in their mortality, particularly among those on antidepressants, including suicide rates. Antidepressant usage was associated with hospital Length of Stay (LOS), disease severity, female sex, comorbid and preexisting mental conditions. This study with its own statistical results targeted a narrowed patient population by excluding prior to analysis over 45 000 patients who died within 3 months of ICU admission and over 35 000 patients who were on antidepressant medication at least 6 months prior to ICU admission [45].

Intensive Care Related PTSD [46]

Posttraumatic disorders are recognized among people surviving heavily stressful situations. Particularly combat soldiers are known to carry the burden, which is aggravated when traumatic brain injury is part of the damage, PTSD occurring with much higher

prevalence, complexity and severity, than in the general population needing ICU care [47]. Among their symptoms are experiencing the trauma through nightmares and flashbacks, intrusive memories, avoiding reminders of the events, negative directions in mood and thinking, increased reactivity, such as feeling constantly on edge. Chronic or recurrent stress leads to neuronal atrophy and altered neuroplasticity [48]. Delirium and delusional memories during critical illness are major predictors of PTSD [49]. While critical illness necessitating ICU or HDU stay lead to significant increase in mental stress, upon successfully overcoming the life-threatening danger and near death experience a posttraumatic growth happens. This positive outcome is assessed using self-reporting questionnaires, the Posttraumatic Growth Inventory, reflecting on areas like personal strength, spiritual change, appreciation of life, relation to others, and new possibilities, measured usually month to years after injurious event [50,51].

Intensive Care Related Delirium [52]

While components of the mental triad (depression, PTSD, anxiety) are insidious conundrums of stress and inflammation, arising slowly and persisting long delirium is a more immediate, transient acute mental disorder. It is an independent predictor of in-hospital mortality and prolonged hospital stay. Delirium arising upon ICU stay is perhaps the most comprehensively addressed mental disorder, particularly due to its frequency and immediate visibility during ICU stay. When triggering events are obliterated and appropriate, primarily non-pharmacological treatment is promptly implemented, delirium may become a rather transient event, while prolonged triggering and ineptness to successfully terminate delirium may lead to psychosis and dementia [53]. Among drug related triggers, anticholinergics, opioids, polypharmacy and benzodiazepines [54] stand out, even in lower doses, hence are administered cautiously. A major exception to this rule is alcohol abstinence syndrome, in which benzodiazepines are the first line in order to prevent delirium tremens. Lorazepam, while its metabolism in liver results in inactive products, has a terminal elimination half-life of 10 to 20 hours, while midazolam is metabolized into active intermediates, its half-life ranges between 1,5 to 2,5 hours depending on the liver function and both are eliminated renally. While delirium per se is not the objective of this article, when considering antipsychotic, antidepressant and anxiolytic medications, potential effects on delirium must be taken into account [55]. Traditional tricyclic antidepressants have strong anticholinergic effect, increasing risk of delirium, yet SSRIs and SRNIs are void of such negative effects.

Concluding Remarks

The psychological aspect of human suffering in society and during illness, during interpersonal and economic hardships, is awaiting appreciation and earnest consideration. The global and local statistics of incidence and prevalence are vastly underestimating the seriousness of the situation. Most people carry their pain in silence, out of fear from disproportionate

stigmatizations and debilitating consequences. Furthermore, a causative approach to solution is seldom offered by psycho-medicinal interventions. Our modern technocratic societies actively suppress emotional aspects of human existence. Emphasis is shifted towards economic and technological growth in a competitive manner that is in stark contrast with a more spiritual, emotional, considerate, caring and meditative, slow-motion lifestyle of societies that are becoming eliminated, pushed to the periphery and engulfed by the “we know it all better” technocratic world. Within this world, however, beneath the surface emotional suffering and frustration is brewing, reflected in the rising number of reactive mental disorders, despite economical wealth. Intensive care engulfs the extremes, the failed suicide attempts, the acute complications of drug abuse, life threatening acute psychiatric emergencies, and the frustrating lack of long-term comprehensive handling of severe illness and disability related mental disorders, defects in conscience and mobility by supportive groups from the society. Technocratic societies are based on competitive attitudes in every aspect of life, creating an immense burden of social defeat on those less fortunate, representing the vast majority. Social defeat is the most underestimated aspect to social stress culminating in mental disorders, while animal and human studies show its destructive force, fueling withdrawal, isolation, and aggression. Hence, the root of the problem and the preventive solution may be hidden in questions and answers, which are scarcely ever considered. Severe illness and disability are forms of social defeat. The road from intensive care and hospital release to renewed full economic activity is protracted. Our work is worthwhile, meaningful, and successful only if long-term qualitative survival can be achieved, with the help of the broader society and spiritual groups.

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Conflict of Interest

None.

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