Stress, depression, and vulnerability

Editorial
D. Moussaoui P1

Stress and depression
C. Nemeroff P2

Depressive vulnerability
E. Corruble P6
ife without trauma—and therefore without stress—does not exist. Delivery through the birth canal is the first traumatic event in the life of most human beings, as emphasized by Otto Rank. Most of the time, the consequence of trauma—stress—is integrated into the human psyche without any great damage, and may even strengthen the capacities of an individual by expanding his/her range of experiences. The above quotation by Nietzsche is a good illustration of this.

The relationship between stress and depression, the former being a possible trigger of the latter, is a common clinical observation. Yet "trigger event" does not mean "cause", since the causes of depression are varied and interact closely with one another. Resilience—the ability of a subject to resist the destructive effects of trauma and even to transform them into positive life experiences—varies from one person to another. There is probably a biological counterpart for resilience within the brain. In fact, it has been shown that the gene coding for the serotonin transporter protein is a biological marker for vulnerability, and possibly for resilience. Subjects who possess the long allele pair (l/l) of this gene on chromosome 17 can transport a higher number of serotonin molecules than those who have one short and one long allele (l/s), who in turn can transport more than those who possess two short alleles (s/s). The fact is that subjects with the s/s configuration are more vulnerable to adversity and tend to fall more easily and more severely into depression when faced with repeated negative life events. This is less true of subjects carrying the l/s gene, and markedly less true of those with the l/l gene. The latter, in fact, only tend to decompensate into depression after several severe traumas, and will not plummet further when faced with repeated life setbacks. We have observed a number of individuals who manage to keep their calm and maintain relative control of their life in the most horrifying situations: in the middle of a battle, a natural catastrophe, or in a concentration camp, for instance.

The remarkable thing is that this type of behavior has also been observed in rhesus monkeys. Those who carry the s/s allele show slower and calmer social behavior. When a stressful situation occurs in their environment—either a physical one, or one based on interaction with the other members of their group—their emotional reactions in comparison to those with the l/s or l/l genes tend to be excessive, thus creating havoc in their social relationships. However, genetic factors alone cannot determine all aspects of a subject’s life. Every individual who is hereditarily predisposed to hypertension or diabetes will not necessarily suffer from these conditions. Lifestyle is a key factor in whether such illnesses are triggered or not: eating too much salt or sugar, a sedentary lifestyle, and putting oneself in stressful social and/or family situations are all factors that can trigger hypertension and diabetes. Depression is also a multifactorial condition. It is clear that not all subjects with a genetic predisposition to an illness are fated to suffer from it. Some subjects with a tendency toward mood disorders are even able to harness this weakness in a positive manner—transforming it into artistic expression, for instance.

It is also obvious that societies throughout the world are becoming increasingly complex, requiring individuals to become increasingly capable of adapting to complexity. One doesn’t cross a small village street the same way one would cross an avenue in New York, London, or Buenos Aires; and one doesn’t take public transport in a small town in the same way one would take the subway in Paris or Tokyo. Complexity requires us to be able to function mentally in a simultaneous, "multi-task" mode. Subjects who, for one reason or another, are incapable of responding to the requirements of such growing urban complexity will find themselves in a weakened position and more subject to stress—and will tend toward depression, especially if they are genetically predisposed to it.

All this partially explains the fact that depression prevalence rates are constantly on the rise throughout the world. More than any other medical condition, depression is increasingly destined to become the predominant disease of the 21st century.

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Stress and Depression

Virtually no experienced practitioner would doubt the fact that stress and depression are inexorably linked. Stress can precipitate depression in genetically vulnerable individuals and depressed patients rendered euthymic by effective treatments often unexpectedly relapse when exposed to severe life stress events. In addition, there is now a burgeoning literature that suggests that stress early in life markedly increases the likelihood for the development of mood disorders in adulthood.

The current view of the etiology of depression is best summarized as virtually a prototype gene-environment interaction disease model as has been demonstrated for other complex diseases such as cancer, hypertension, and diabetes. Much of the neurobiological focus has been on the three major monoamine systems—serotonin (5HT), norepinephrine (NE), and dopamine (DA), and on a fourth neurotransmitter system—corticotropin-releasing factor (CRF). The emerging new tools of molecular neurobiology and functional brain imaging have provided additional support for the involvement of these systems, which are stress-responsive. In contrast to the previous focus on 5HT and NE, considerably more evidence now supports a preeminent role for CNS DA circuits. Many investigators suggest that the now well documented suboptimal therapeutic responses in many patients to selective serotonin reuptake inhibitors (SSRIs) and selective serotonin-norepinephrine reuptake inhibitors (SNRIs) may well be due, in part, to their relative lack of effect on brain DA circuits. As regards the CNS 5HT systems, even more evidence has accrued supporting a preeminent role for their involvement in depression. In addition to the very impressive evidence of reduced activity of serotonergic neurons in depression, as assessed in postmortem, cerebrospinal fluid (CSF), and neuroendocrine studies, new data from both postmortem and PET imaging studies demonstrate a reduction in the number of serotonin transporter (SERT) binding sites, the primary site of action of SSRIs, in the midbrain and amygdala of drug-free depressed patients, as well as a reduction in both presynaptic (in the midbrain) and postsynaptic (in the mesiotemporal cortex) 5HT1A receptor density. Taken together, these data suggest a net reduction in the number and/or function of the presynaptic SHT nerve terminals, and a reduction in postsynaptic serotonergic signal transduction, at least at one of the SHT receptor subtypes. Previous studies demonstrated an increase in SHT2 receptor density in depressed patients, perhaps secondary to a relative decrease in synaptic SHT availability.

Arguably, one of the most remarkable observations in all of biomedical research in the last decade is the observation that individuals with the s allele of the promoter region of the SERT gene are unusually vulnerable to the now very well documented depressogenic effects of early life stress, ie, child abuse or neglect, and, moreover, that this effect is dose-dependent, both in terms of the s allele (one copy or two) and in terms of the frequency and severity of the abuse. Thus, the most vulnerable to depression are individuals with the s/s genotype and the least vulnerable are those with the l/l genotype, with s/l individuals being of intermediate risk. This finding is all the more extraordinary because this polymorphism has been shown to function—s/s and s/l individuals exhibit reduced SERT binding sites in PET imaging studies compared with l/l individuals. Note that individuals with the l/l genotype are relatively immune to the depressogenic effects of early life trauma, representing a disease-resistant haplotype. This original observation by Caspi and colleagues has now been replicated in many, but not all subsequent studies, and these data have recently been reviewed.

Of the major catecholamine systems, norepinephrine-containing circuits have long been considered to be pathologically involved in the etiology of mood disorders. Similar to drugs that increase 5HT availability, NE reuptake inhibitors are effective antidepressants. Moreover, neurochemical and neuroendocrine studies in depressed patients and postmortem findings support a role for NE dysfunction in depression. Alterations in noradrenergic circuits may play a preeminent role in treatment-resistant patients. Whether antidepressants that are believed to act upon both SHT and NE neurons are more effective than those that act solely on SHT or NE neurons remains an area of great controversy.

In the last decade, partly because of the disappointingly low remission rates in large-scale clinical trials noted above with SSRIs and SNRIs, a potential role for one or another CNS DA circuit in depression has been postulated. This emergence of a DA hypothesis of depression is not surprising in view of the stress responsive nature of the mesolimbic and mesocortical DA circuits. Moreover, additional support for this hypothesis is provided by the fact that the inability to experience pleasure, anhedonia, is considered by many to be the most pathognomonic symptom of depression, and that pleasure, whether associated with eating, social or sexual behavior, is well documented to be primarily mediated by DA neurons. To briefly summarize the burgeoning evidence for a role for altered DAergic circuits in depression, both postmortem tissue and PET imaging studies have revealed reduced DA transporter (DAT) binding sites and increased postsynaptic DA D2/D3 receptor density, indicative of a reduction in the synaptic availability of DA in depression. These findings suggest that treatments that enhance DA neurotransmission, such as monoamine oxidase inhibitors (MAOIs), DA receptor agonists or triple (SHT, NE and DA) reuptake inhibitors (currently under development), may represent a novel approach to SSRI non-responders.

More than forty years ago, reports first appeared indicating that a significant num-
A variety of methods are now available to measure the activity of the HPA axis. The hierarchical organization of the HPA axis is illustrated in Figure 1.

One of the first tests of HPA axis function to be studied in psychiatric patients was the dexamethasone suppression test (DST), which was originally designed to aid in the diagnosis of Cushing’s syndrome. Small (1 mg) doses of the synthetic glucocorticoid, dexamethasone, are orally administered at 11:00 PM, and plasma cortisol concentrations are measured at 2 or 3 time points the following day. Dexamethasone primarily acts on the anterior pituitary corticotrophs to reduce the secretion of adrenocorticotropic hormone (ACTH), resulting in a decrease in the synthesis and release of cortisol from the adrenal cortex. Failure to suppress plasma cortisol concentrations after dexamethasone administration suggests impaired feedback regulation and hyperactivity of the HPA axis.

A sizeable percentage of drug-free patients with depression exhibit failure to suppress secretion of cortisol following administration of dexamethasone, commonly referred to as DST nonsuppression, and this was proposed as a biological diagnostic test for depression. However, multiple comprehensive analyses revealed that although many patients with depression did exhibit evidence of enhanced HPA axis hyperactivity, patients with other psychiatric diagnoses often did as well, including those with eating disorders, Alzheimer’s disease, bipolar disorder, and others. However, in depressed patients, DST nonsuppression has generally been found to be associated with depression severity and, when persistent, with a significant risk for relapse.

Undoubtedly, the greatest contribution of the DST was to serve as an impetus for subsequent studies exploring the pathophysiology of the HPA axis in depression.

In 1981, the long sought after hypothalamic-releasing hormone, corticotropin-releasing factor (CRF), a 41-amino-acid peptide, was discovered by Vale and his colleagues at the Salk Institute. This singular finding greatly accelerated research on the HPA axis, stress, and depression. Neurons of the paraventricular nuclei of the hypothalamus project to the median eminence where they secrete CRF into the hypothalamo-hypophyseal portal system. CRF is then transported in this specialized vascular system to the anterior pituitary where it acts on corticotrophs to increase ACTH secretion, thereby controlling HPA axis activity. Of paramount importance was the discovery that CRF is also widely distributed in extrahypothalamic brain areas where it functions, in concert with the hypothalamic CRF system, as a neurotransmitter coordinating the behavioral, autonomic, endocrine, and immune responses to stress (Figure 1).

The availability of synthetic CRF allowed the development and standardization of a CRF stimulation test. In this test, ovine or human CRF is administered intravenously and plasma ACTH and cortisol concentrations are measured at 30-minute intervals over a 2- to 3-hour period. Normal healthy volunteers respond to CRF infusion with increased secretion of ACTH, whereas depressed patients exhibit a blunted ACTH, but normal cortisol, response. Not surprisingly, the blunted ACTH response to CRF occurs in depressed DST nonsuppressors, but not in depressed patients with normal DST suppression.

Holsboer and colleagues at the Max Planck Institute in Munich developed arguably the most sensitive test of HPA axis activity, the so-called Dex-CRF test, which combines the DST and the CRF stimulation test. Thus, patients are pretreated with oral dexamethasone (1 mg) at 11 PM and given a 100 mg infusion of human CRF on the following day. In this paradigm, depressed patients exhibit enhanced secretion of ACTH and cortisol compared with normal volunteers, indicative of HPA axis hyperactivity. Interestingly, in this test, asymptomatic first-degree relatives of depressed patients exhibit increased HPA axis activity that is maintained over time, suggesting the presence of a heritable vulnerability to HPA axis dysregulation.

Most, if not all, of the HPA axis alterations in depressed patients may be a result of chronic CRF hypersecretion. Consistent with this hypothesis, depressed patients have repeatedly been found to exhibit elevated CSF-CRF concentrations. Further, postmortem studies of individuals depressed at the time of death or those who committed suicide have revealed a decreased density of CRF recep-
tors in the frontal cortex, decreased expression of CRF1 receptor mRNA and increased CRF concentrations in a variety of cerebrocortical brain areas and the locus coeruleus when compared with controls. Successful treatment of depression with either electroconvulsive therapy (ECT) or fluoxetine, an SSRI, has been shown to result in a reduction in the high pretreatment CSF CRF concentrations. Moreover, like continued DST non-suppression, persistently elevated CSF CRF in symptomatically improved depressed patients is associated with early relapse of depression. These data are even more impressive when considered together with the many laboratory animal studies that have shown that when administered directly into the CNS, CRF produces many of the signs and symptoms of depression, including decreased appetite and weight loss, decreased sexual behavior, disrupted sleep, and altered psychomotor activity. As noted earlier, approximately 30% to 40% of the risk of development of depression is believed to be heritable, with the remaining variability imparted by environmental factors. Exposure to stress, a process primarily regulated by CRF and the HPA axis, is known to precipitate depression in vulnerable individuals. Moreover, early life stress, such as child abuse, occurring during neurobiologically vulnerable periods of development, may be one means whereby the environment influences the development of depression. Our group has demonstrated that depressed women with a history of prepubertal sexual abuse exhibit persistently increased HPA axis activity as evidenced by a blunted ACTH response to CRF infusion, and both hypercortisolemia and increased ACTH secretion in response to a standardized laboratory stressor. Using the Dex-CRF test, we recently demonstrated increased HPA axis activity in adult men with major depression and a history of child abuse. Furthermore, in an inner city sample of highly traumatized patients recruited in the waiting room of a public hospital-based medical clinic, we identified individual single nucleotide polymorphisms (SNPs) and a common haplotype of the CRF1 receptor that modulates the depressogenic effects of child abuse and neglect. The CRF1 receptor antagonist R121919 showed promise in the treatment of depression, but was subsequently withdrawn from clinical trials due to hepatotoxicity. Other CRF receptor antagonists, which have repeatedly been shown to possess antidepressant and anxiolytic properties in laboratory animals, are novel antidepressant drug candidates currently being studied in randomized, controlled, double-blind clinical trials for efficacy in the treatment of depression and several anxiety disorders.

Although there is little doubt that various neurotransmitter systems are pathologically involved in the etiology of depression, no single neurotransmitter system appears to be solely responsible. This is not surprising when one considers the panoply of symptoms that comprise the depressive syndrome, including depressed mood, loss of interest in usual activities, inability to experience pleasure, impaired concentration, disturbed sleep, decreased appetite, and suicidality. A more recent conceptual approach to the biology of depression is to consider it a systems-level disorder involving several critical brain regions and pathways involving these regions. Advances in brain imaging have allowed for rapid advances in this area. Structural brain imaging studies using magnetic resonance imaging have generated a number of reports of altered volumes of several brain regions in patients with depression, most notably a reduction in the size of the hippocampus and caudate nucleus and an increase in pituitary volume. Because early life trauma occurs commonly in depression, it is now evident that certain of the previously described changes in certain brain structures may be more likely due to early life stress during a critical period in brain development than to depression per se.

Understanding the role of stress in the pathophysiology of depression, particularly the role of early life stress, will allow for the identification of a population of at-risk individuals, as well as for the rational development of biological strategies to develop a “vaccine” to prevent stress-induced precipitation or exacerbation of depressive episodes.

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"Stress, depression and vulnerability"

Lifetime changes in vulnerability to major depressive episodes

Introduction

Major depressive disorders are recurrent since more than 8 out of 10 patients with a first major depressive episode will have a recurrence in the following 15 years. The triggering of major depressive episodes by life events is a commonplace observation in daily clinical practice. Vulnerability to major depression has long been considered as a uniform and unchanging phenomenon influenced by personality traits and genetic or other factors. More recently, the complexity of depressive vulnerability has been emphasized, and studies have provided evidence of interactions between various factors, such as genetic and environmental.

In this paper, we will study vulnerability to major depressive episodes as a dynamic phenomenon in the life of a depressed patient. We will summarize the recent literature on this subject, consider the results of a large survey conducted in clinical practice, and discuss the clinical implications of these results.

Life events and the kindling hypothesis of depression

Kraepelin was probably the first author who suggested that psychosocial factors may have a greater impact in triggering first episodes of depression than subsequent episodes. Later on, electrophysiological results in the field of epilepsy illustrated the kindling phenomenon: the epileptogenic effect of electric stimuli progressively diminishes with subsequent stimulations. By analogy, the kindling hypothesis of recurrent depression was proposed. This assumes that the depressogenic effect of environmental stressors progressively diminishes with subsequent episodes, even minor life events being able to trigger new depressive episodes.

The impact of stressful life events in triggering major depressive episodes has been extensively studied for 30 years. The results, however, have been controversial, due to limitations in assessment tools and lack of power. Cross-sectional studies in clinical samples comparing first episodes to recurrent episodes or considering the number of previous episodes [review in Corruble et al 2006] yielded contradictory results and did not control for confounding factors, probably because of sample size. The only large prospective study available, conducted in 2395 twin females, showed a substantial decline in depressogenic life event exposure with increasing number of previous depressive episodes [Kendler et al 2000]. However, its results are not transposable to real-life clinical practice and cannot be generalized to other subgroups of patients, such as non-twins, males, or treatment-seeking patients.

The ACTUEL survey: a large survey in real-life clinical practice

The aim of the ACTUEL survey is to test in real clinical practice the relationship between the number of previous depressive episodes and exposure to life events, in a large sample of treated depressed patients.

In a cross-sectional survey approved by the French National Ethics Committee (CNIL) and conducted by 2408 physicians (general practitioners: 74.3%; psychiatrists: 25.7%), each physician was asked to include the first six consecutive patients fulfilling inclusion criteria in order to ensure representativity. In order to limit potential bias, raters were blinded to our hypothesis, and assessed life events first and depression afterwards.

The 13 377 subjects were aged 18 years or above, and were self-referred to their GP or psychiatrist for a DSM-IV unipolar major depressive episode. Patients with DSM-IV bipolar disorder, psychotic disorder, somatic disorder, or cognitive impairment were excluded.

DSM-IV diagnostic criteria for the current major depressive episode were checked by structured interview. The Montgomery-Asberg Depression Rating Scale (MADRS) [Montgomery and Asberg, 1979] was used to assess severity. The total number of previous depressive episodes was retrospectively recorded in five categories: 0, 1, 2, 3, 4, 5 or more.

Life events occurring in the 3 months preceding the current depressive episode were assessed retrospectively using the Life Events Inventory (LEI) check-list, which proposes a list of life events. Clinicians, blinded to the weighted scores, were asked to check life events on a yes/no basis. Each item has a weighted score (1–100) for the severity of stress that might typically be expected to result from the occurrence of the life event, not only in the general population but also in psychiatric patients. There are numerous ways to assess the total stress induced by life events. In order to avoid multiple testing, we limited the analysis to the sum of quantitative weighted scores of each life event during the 3 months before the major depressive episode, divided by the number of reported life events.

The 13 377 patients (66.4% women; 54.1% married) were of mean age 47.6±14.6 years. The average MADRS
score was 30 ± 6.9, and the mean life event exposure was 62.9 ± 15.2. Life event exposure was normally distributed, higher in women than in men (63.3 ± 15.1 vs 62.1 ± 15.4; t=4.27; P<0.001), and positively correlated with age (r=0.05; P<0.0001). Increasing number of previous depressive episodes was significantly associated with a linear increase in age, severity of depression, percentage of female gender, and a linear decline in life event exposure. Polytomic regression confirmed the independent linear decrease in life events exposure with subsequent episodes (Table 1), with no significant interaction between life event exposure and age (P=0.07), gender (P=0.35) and MADRS score (P=0.29).

This survey illustrates the key points of long-term outcome of recurrent major depression, confirming literature findings: severity of depression and the percentage of women increase linearly with subsequent episodes of major depression.

In this large sample of non-twin patients with unipolar depression treated either by their GP or by their psychiatrist, we found that with subsequent depressive episodes the average life events exposure was decreased, even when the confounding roles of age, gender, and severity of the episode were taken into account.

The main limitation of this study is that it is a retrospective survey, and so is liable to more rating bias. Nonetheless, its main value is its relevance in daily clinical practice, ie, in treated patients.

The most accurate conclusion of this survey could be that the increasing number of previous depressive episodes is associated with a significant linear decline in life event exposure, which is not completely explained by age, gender, and depression severity in a treated sample. This result therefore partly completes those of Kendler et al [2000] in a general population subgroup of female twins, and is consistent with gradual autonomy of the depressive disorder from environmental circumstances, as suggested by the kindling hypothesis.

**Perspectives**

Research over the last 10 years has revealed functional and structural brain alterations in depressed patients (summarized in Figure 1). Depressive episodes may induce a decrease in neuronal size and density, in particular in the hippocampus and prefrontal cortex. Sheline et al (1999) have shown that the decreased hippocampal size could be positively correlated with the lifetime number of major depressive episodes and with the lifetime duration of major depressive episodes. Moreover, preliminary data suggest that the decreased hippocampal size could be related to vulnerability to life events, independently of depressive episodes. Some interesting studies have also shown that the serotonin transporter (5-HTT) may be involved in hippocampal size and in sensitivity to life events. The long variant of 5-HTT polymorphism is related to reduced hippocampal volume in major depression. The 5-HTT gene may also be correlated with vulnerability to life events in depressed patients, since Caspi et al (2003) have shown that the influence of life stress on depression is moderated by polymorphism in the 5-HTT gene.

It could be assumed that vulnerability to life events and to depression is mediated by decreased hippocampal volume and the serotonin transporter. Brain-derived neurotrophic factor (BDNF) is a growth factor involved in neuronal survival and may also have a key role (Duman et al 1997) since stress induces a decrease in BDNF activity. The core role of the hypothalamic-pituitary-adrenal axis (HPA) stimulation secondary to stress should also be emphasized in this model. Its neurotoxic effects, especially in the hippocampus, occur in relation to glucose metabolism changes and glutamatergic activation.

Finally, the kindling model of depression may result from an interaction between genetic, biological, and environmental factors. The hippocampus may play a key role in this interaction, which could change over time during the life of a depressed patient. And neuroplasticity and its biological correlates may be relevant in our understanding of major depression and its etiology, and may open up new therapeutic perspectives.

From a treatment point of view, decreased neuronal size and density in major depression may be at least partly reversible. In

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*Table 1. Patient characteristics, MADRS, and life event exposure of 13 377 patients with major depressive disorder in clinical practice.*
Figure 1. Functional and structural brain alterations in depressed patients

animals, drugs such as lithium and antidepressants may increase hippocampal neurogenesis. Other treatments, such as electroshock therapy, may also induce neurogenesis and angiogenesis. Antidepressants may be able to reverse decreased neuronal size and density caused by major depressive episodes. This property may be mediated by HPA axis inhibition, stimulation of BDNF activity, and changes in the glutamatergic and monoaminergic systems.

Conclusion

The kindling hypothesis of depression may be relevant in everyday clinical practice: the increasing number of previous depressive episodes is associated with a significant linear decline in life events triggering these episodes. Interactions between life events, serotonin transporter, and brain alterations, especially in the hippocampus, have been shown in patients with recurrent major depressive disorder, and possibly explain the lifetime changes in vulnerability to major depression.

Implications for clinical practice

The objective of effective acute and long-term treatment of major depressive episodes should be full remission as well as prevention of relapses and recurrences, in order to reverse functional and structural changes in the hippocampus. It is also necessary to look for and prevent stress related to life events, even though these may decrease in impact with subsequent episodes of major depression.

Case study

Mrs X is a 62-year-old woman with a family history (mother) of unipolar depression. She had her first episode when she was 23, three months after her 6-month-old child died suddenly. She was treated both by her GP, who prescribed benzodiazepines, and by a psychotherapist. Her second episode occurred when she was 39, after her divorce. The third episode occurred when she was 56, one year after retirement. This episode, which was more severe, required antidepressants, which were prescribed by her GP. Unfortunately, response to treatment was incomplete and residual symptoms remained. Two years ago, she had her fourth episode, without a specific triggering life event. The GP had the patient admitted to a psychiatry department because of suicidal ideation and resistance to antidepressant treatment.

The medical history of this patient shows the increasing severity, frequency, and decreasing response to treatment of major depressive episodes, as well as the decreasing impact of life events in triggering these episodes.

FURTHER READING


REFERENCES

In 2008, for the fourth time, the World Psychiatric Association will be awarding the “Jean Delay” Prize. This prize is intended as a reward for contributions which forge links between clinical, biological, and social aspects of psychiatry, or between psychotherapy and pharmacotherapy.

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- 2002 Prof Hagop Akiskal, USA
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