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Persistence of pain in humans and other mammals

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Abstract

Evolutionary models of chronic pain are relatively undeveloped, but mainly concern dysregulation of an efficient acute defence, or false alarm. Here a third possibility, mismatch with the modern environment, is examined. In ancestral human and free-living animal environments, survival needs urge a return to activity during recovery, despite pain, but modern environments allow humans and domesticated animals prolonged inactivity after injury. This review uses the research literature to compare humans and other mammals, who share pain neurophysiology, on risk factors for pain persistence; behaviours associated with pain; and responses of conspecifics to behaviours. The mammal populations studied are mainly laboratory rodents in pain research, and farm and companion animals in veterinary research, with observations of captive and free-living primates. Beyond farm animals and rodent models, there is virtually no evidence of chronic pain in other mammals. Since evidence is sparse, it is hard to conclude that it does not occur, but its apparent absence is compatible with the mismatch hypothesis.

Keywords: behaviour; chronic pain; defence; evolution; exercise.
1 Evolutionary models of pain

Evolutionary models have been largely overlooked in the study of pain. The widespread view is that, while acute pain has clear survival value, chronic pain (outlasting healing) is an inevitable if rare malfunction of acute pain mechanisms, particularly peripheral and central sensitisation that ensure wound care and may heighten vigilance during healing. The neurophysiology of acute pain is extraordinarily conserved across animal phyla, vertebrate and invertebrate.

Pain in laboratory animals, mostly rodents, is usually studied over too short a short timespan to provide data on chronic pain, and chronic pain reported in farm, companion and zoo animals in veterinary medicine is often associated with ongoing pathology. But if chronic pain outlasting healing is an inevitable if occasional by-product of acute pain, more accounts would be expected in animals that survive acute injury. It could simply be that observations are lacking, and that chronic pain does occur in wild animals. It is also possible that pain-related behaviour habituates and is only provoked in rare circumstances. But, if it is actually very rare, and chronic pain in humans derives some unique contribution from the human brain or environment, then the ‘inevitability’ model of chronic pain needs re-examination.

Chronic pain is often described as without adaptive function, in humans (e.g. Woolf 2010) and in other animals (Molony 1997). Two of the main evolutionary bases for vulnerability to disease proposed by Nesse and Stearns (2008) apply to pain. Essential defence systems are subject to many false alarms (the smoke detector principle: Nesse & Stearns, 2008), given the balance of costs and benefits of action or inaction. An alternative explanation is mismatch of current conditions with evolved characteristics, since direction and intensity of natural selection can change with environmental shifts (Corbett et al. 2018). In wealthy societies, prolonged rest after onset of pain is possible, with no threat to survival; the same applies to domesticated and captive animals, provisioned and free from predation. This contrasts with ancestral conditions, and those for free-living animals, where survival may depend on activity despite pain.

This paper explores several questions: (1) do models of human chronic pain onset and persistence apply to other mammals; (2) are behaviours associated with chronic pain in humans observed in other mammals; (3) what is the function of pain-related behaviours, particularly in relation to social responses?

2 Pain mechanisms

Mechanisms of pain are highly conserved across mammalian species. Nociceptor input to the spinal cord is modulated at spinal cord level and subsequent synapses by descending controls, excitatory and inhibitory (Melzack & Wall 1965; Woolf 2010). Appraisal of threat in salience networks (Legrain
et al. 2009), contributions from memory, contextual and state considerations, and more, are represented in descending pathways. Pain drives peripheral and central sensitisation, changes in threshold and conductivity, changes in pre- and post-synaptic neurotransmitter release and uptake, and pruning and creation of connections in the brain. After injury, aversiveness of pain demands attention and action. After escape, heightened sensitivity and vigilance encourage wound care and avoidance of activities that could delay healing. So far, so adaptive: the function of pain is to promote escape, healing, recovery and learning, not to provide a quantitative representation of tissue damage.

Chronic pain, defined in humans as pain of more than three months, describes pain with and without identifiable cause: low back pain, joint pain from rheumatoid or osteoarthritis, neuropathic pains from traumatic injury or disease, and others; experience and impact are largely similar across types. Chronic pain has cognitive, mood, and behavioural components, such as avoidance of activity believed to be threatening, thereby maintaining fears (Vlaeyen & Linton 2000). Theories now emphasise goal priorities (Crombez et al. 2012; Vlaeyen et al. 2016), threat of pain, and vigilance to internal sensations (Linton et al. 2018). These models apply best to humans. The only model potentially applicable to other animals is that of classical conditioning, and little explored: it proposes that a defensive response becomes conditioned to cues associated with pain that elicit fear and anticipation of pain (Goubert et al. 2014).

3 Risk and protective factors

Given the common mechanisms for acute pain, it is useful to examine what predicts onset and persistence of chronic pain in humans, and whether the same risk factors are found in other mammals with chronic pain. The development of chronic pain is an active process (Kuner & Flor 2017). Plastic changes throughout the system and reorganisation in neural circuits subserving pain make for continued hypersensitivity to external stimuli and internal imbalances, for spontaneous pain discharges, and abnormal processing, increasingly in brain areas concerned with emotion rather than sensory input. Chronic pain may be driven by continued peripheral input, but can also be maintained by interactions with hormonal and immune system changes (Borsook et al. 2018).

3.1 Humans

Major risk factors for chronic pain in humans are characteristics such as female sex and greater age, the state of the individual in pain, and the type of pain. For instance, in a prospective study of mixed chronic pains (Landmark et al. 2018), the longer pain persisted, the less likely it was to remit: female sex and older age predicted both onset and persistence, and catastrophic thinking and sleep problems predicted more severe pain.
Chronic post-surgical pain follows traumatic injury of patients. Aside from peri-operative analgesia, one major predictor is the extent of nerve damage during surgery (Kehlet et al. 2006), driving abnormal nerve function. Pain before surgery is also a risk (Kehlet et al. 2006; Schug & Bruce 2017); female sex and greater age tend to increase risk; while negative affect (such as fear of pain) consistently predicts worse post-operative pain (Baert et al. 2016) and development into chronic pain (Katz & Seltzer 2009). Anxiety may also predict persistence of pain and disability after traumatic injury, including amputation (Schug & Bruce 2017; Bliss et al. 2016).

Chronic low back pain is more likely to develop in depressed individuals, with greater risk for more severe depression (Pinheiro et al. 2015; Tracey 2016), and fear and anxiety are robustly related to subsequent disability (Zale et al. 2013). Prospective fMRI study of the development of chronic pain confirms the importance of depressed affect before onset (Vachon-Presseau et al. 2016), the failure of descending inhibition, and dysregulation of normally well-integrated cognitive, emotional and behavioural processes (Elman & Borsook 2018). It may be that the reward value of pain relief is significantly disrupted (Navratilova & Porreca 2014; Borsook et al. 2016).

Early life stress, including pain (such as surgery or repeated blood sampling, common for preterm infants) affects the developing nervous system, producing changes in both pro- and anti-nociceptive mechanisms (Schwaller & Fitzgerald 2014), against which maternal care may partly protect. Serious psychological stresses such as maternal death and institutional care in early years are also associated with higher risks of pain in adulthood, with some evidence of cumulative risk from multiple adversities (Burke et al. 2017).

Chronic pain may be prevented by the combination of exercise and education, and possibly by exercise alone (Carey & Freburger 2016; Steffens et al. 2016). Physical activity reduced risk of chronic pain in two large-scale prospective studies: one of over-50s for whom vigorous, but not moderate, physical activity protected against onset over 10 years (Fancourt & Steptoe 2018); another of female twins where genetic factors dominated covariance in onset of pain over 12 years (Burri et al. 2018), but environmental factors, including underactivity, predicted persistence of pain. In a major review, Sluka et al. (2018) found fairly strong evidence for prevention of chronic pain by exercise, with some evidence for mitigation of existing pain (see also Geneen et al. 2017).

### 3.2 Other mammals

Are these predictors found in other mammals? Most veterinary and free-living mammal studies are uncontrolled, so factors such as sex and age have not been tested as risk factors for chronic pain, although likely (Viñuela-Fernández et al. 2007). Many rodent pain studies use young male rats (Rice
et al 2008), neglect affect, and are short-term. Parallels with the human literature are found for early life stress, emotional processing of chronic pain, and physical activity.

Rodent studies of early interrupted or impoverished maternal care show pups’ later vulnerability to pain and hypersensitivity to various stimuli (Burke et al. 2017; Schwaller & Fitzgerald 2014). In a single study, ewes who had been tail-docked without analgesia when a few days old showed more pain at parturition than did controls (Clark et al 2014). Rodents, like humans, increasingly process pain in emotion circuits as pain becomes chronic (Elman & Borsook 2018; Vachon-Pressau et al. 2016).

Several rodent studies have established the protective effects of exercise against neuropathic pain (Grace et al., 2016), and the pain-reducing effects of exercise in neuropathic and low back pain (De Azambuja et al. 2018; Sluka et al. 2018; Stagg et al. 2011). The effects are associated with structural and functional changes in the nervous system and brain (De Azambuja et al. 2018; Lee et al. 2015; Sabatier et al. 2009; Stagg et al. 2011), in neuroimmune signalling (Grace et al. 2016), and in pro- and anti-inflammatory cytokine production (Bushnell et al. 2013; Sluka et al. 2018). Activity levels, among other environmental factors, produce epigenetic changes and, ultimately, changes in brain connectivity (Polli et al. 2018).

Studies of prevention and mitigation of pain by physical activity have only involved rodents, but survival in the wild requires that the injured animal balances reduced activity for recovery with the need to eat and drink sufficiently and not to become isolated. Continuing, even if at a lower rate, to be physically active, may attenuate peripheral and central sensitisation processes. By contrast, companion, farm and other captive animals are protected from predation and other environmental hazards, and provided with food and drink; it is possible that by allowing inactivity, these conditions increase the likelihood of developing chronic pain.

4 Pain-related behaviour

Pain-related behaviours share features with sickness behaviours that conserve resources required for the immune response (Shattuck & Muehlenbein 2015), under the influence on the brain of pro-inflammatory cytokines (Dantzer et al. 2013), and may enable others to avoid contamination or infection (Shakhar & Shakhar 2015). Healing and recovery may be sensitive to social cues (Humphrey & Skoyles 2012): the presence of familiar conspecifics or of recognised ‘healers’ conveys safety, allowing suppression of defence in favour of recovery, hence the placebo effect. Injury is common in contemporary hunter-gatherers (Sugiyama 2004), as is support for those who are injured. Steinkopf (2015) describes symptoms both as defensive and as signals for help, which, when assured, renders symptoms redundant.
Particular attention is due to facial expression of pain, unique combinations of muscle actions that give a global impression of pain (Williams 2002). Although facial expression of emotion was initially conceptualised as a readout of internal state (Ekman 1993), it is better understood as a signal (Crivell & Fridlund 2018), making environmental and social context of critical importance.

Behaviour associated with pain on injury, across animals, was classified by Walters (1994) in relation to selection pressures. Immediate and rapid behaviour includes arousal, active or passive defence, and memory formation; in the model of Bolles and Fanselow (1980), this defensive stage is more associated with fear and inhibition of pain. By contrast, recuperation is associated with hyperalgesia, and in the Bolles and Fanselow model, with inhibition of fear. Although the Walters model describes recovery and healing with similar behaviours: protection by hiding, priming appropriate defences, keeping the wound clean, monitoring healing, and conserving energy, it also emphasis a high level of vigilance during recovery. The injured animal may have to choose between incompatible goals: of minimising or relieving pain by immobility, thereby becoming more vulnerable to predation, or satisfying needs for food and water, at the cost of pain. Such decisions are made in the limbic system of the brain (Vachon-Presseau et al. 2016; Bliss et al. 2016), but brain imaging (e.g. Seminowicz et al. 2009) is underused.

4.1 Humans

In humans, verbal report is assumed to be the most direct indicator, and used as a referent for interpreting other behaviour associated with pain (such as limping, guarding, taking analgesics, and seeking social support). These behaviours are described mainly as attempts to avoid pain (Vlaeyen & Linton, 2000). Behaviours may vary in function - protective versus communicative (Sullivan et al 2006) - or be related to fear rather than to pain (Olugbade et al. 2019). For comparison with other mammals, the focus here is on behaviours such as limping and guarding; changes in normal activities such as eating and social interaction; facial expression; and vocalisation.

4.2 Other mammals

Animal pain studies and observations present challenges of interpreting behaviour without verbal report, and in the context of cognitive, affective, and social capacities. A cross-species approach to pain including motivational and affective responses (Paul-Murphy et al. 2004) remains rare. A widely-used definition of pain (Molony 1997) resembles that for humans: “an aversive sensory and emotional experience” representing damage or threat, promoting recovery and preventing recurrence.

4.2.1 Rodents
Rodents are extensively used in studies of pain and analgesia (Burma et al. 2017), but few studies: use natural disease rather than inflicted injury (Mogil 2009); assess spontaneous rather than evoked pain; include affective, cognitive and social responses; or follow for months (Becker et al. 2018; Mogil & Crager 2004). Spontaneous behaviours, such as voluntary wheel-running or sleep changes, may sample an affective component of pain (Burma et al. 2017); standard non-pain rodent tests of anxiety and depression are widely used although they may be sensitive to analgesics (Roeska et al. 2009). Experimental paradigms that offer choice, such as conditioned place preference, or self-administered analgesia, provide proxies for self-report, and cumulative tracking of activity offers more ecologically-valid outcomes (Mogil & Crager 2004). Better recognition of the influence of environmental variables such as social conditions, handling, or housing is required (Lascelles & Flecknell 2010; Mogil 2009; Rice et al. 2008); notably, the analgesic benefits of an enriched environment are becoming evident (Tai et al. 2018).

4.2.2 Companion and farm animals

Larger mammals may offer better opportunities than do rodents for translation of pain models to humans: they vary more in genotype and phenotype; affective and social variables are often observed; and living conditions may be closer to those of humans (Jensen 2015; Lascelles & Flecknell 2010). Much pain from farming practices and incidental disease is overlooked or underestimated (McLennan 2018; Molony & Kent 1997; Viñuela-Fernández et al. 2007). Farm animals, young and adult, show specific behaviours that appear to be attempts to escape pain, such as changed posture and gait, and nonspecific behaviours such as restlessness, withdrawal, and facial expression, in acute (e.g. castration) and in some chronic pain situations (Gleerup et al. 2015; Molony & Kent 1997), and in persistent disorders, such as mastitis (Peters et al. 2015) and lameness (Whay et al. 1998) in cattle. Some postural and activity changes observed in pain may also indicate mood change (Whitaker & Howarth 2014), and social context can suppress pain-related behaviour, as in postoperative horses (Coles et al. 2018). For dogs, a scale estimating pain severity and interference is used across acute, chronic and cancer pain (e.g. Brown et al. 2007), although composite scales may obscure important differences in pain responses. Pain assessment in cats is less systematised, particularly in chronic pain; behaviour is very varied across gait, posture, rubbing, grooming, resting, appetite, and social interactions (Merola & Mills 2016; Robertson 2005).

4.2.3 Primates

Pain research using primates is relatively rare; welfare guidelines list behaviours such as reduced overall and social activity, appetite, and changed posture and gait (JWGR 2009), but, in an endometriosis model of chronic pain in the marmoset, extensive assessment, including cognitive
tests and social behaviours, no behavioural changes were detected other than a slight decrement in social grooming, reversed by treatment (Arnold & Espanier 2013). This contrasts with human endometriosis pain-associated reduced activity and depressed mood.

Observations of parturition in various species of captive and free-living primates suggest pain during contractions through particular postures and facial expression. Injury is common in free-living primates from conflict, falls, predator attacks, and environmental hazards such as snares. Post-injury, effective adaptation to feeding and locomotion seems to be the norm, with some reduced activity and avoidance of conflict (Dittus & Ratnayeke 1989; Goodall 1986), but few interpretations of behaviour in terms of pain. Such adaptation is not incompatible with pain; in species where rank determines access to food and mating, showing vulnerability could be seriously disadvantageous. Illness or disability is often associated with loss of rank, but the change may be small (Drews 1996), and a study of the social consequences of disability in macaques observed neither discrimination against nor care for disabled individuals (Turner et al. 2014).

4.2.4 Other free-living mammals

There are few studies of pain in free-living mammals. Healing of injury appears common (Forsman et al. 2006), even of long bone fractures or traumatic amputations, with survivors adapting effectively and with no unambiguous signs of chronic pain. For instance, a study of stags showed a lifetime rate of injury of 23%, 6% for permanent disabling injuries; both reduced reproductive success (Clutton-Brock et al. 1979). A study of roadkill deer found 11 of 24 had healed fractures, even of the pelvis, and one had lost her foreleg but carried a healthy foetus (Chapman & Chapman 1969).

4.3 Facial expression

Facial expression of emotion in mammals is highly conserved (Chambers & Mogil 2015; Vick et al. 2007), but may only be detectable in chronic pain when acutely exacerbated. Pain ‘grimace’ scales exist for many mammalian species (e.g. Chambers & Mogil 2015), despite the tenet that ‘prey animals’ suppress facial expression of pain (e.g. sheep: McLennan et al. 2016; horses: Dalla Costa et al. 2014). Studies in the mouse suggest that emotional experience of pain is encoded in facial expression, as in humans (Bushnell et al. 2013), with variation according to sex and context (Mogil 2012). The importance of facial expression of pain is that it is primarily communicative, which suggests a response of benefit to the signaller, so examination of social responses is warranted.

5 Social responses to conspecifics’ pain-related behaviour

Various pain-related behaviours may communicate pain; behaviour as a signal transmits information at some cost to the signaller (deterring faking), and the responses of signal receivers provide fitness
benefits (Schaedelin & Taborsky 2009). Receivers may also be enabled to avoid pain. Responses may constitute instrumental or emotional help, no response, or exploitation of the vulnerable individual in pain, and may occur between caregiver and infant or young, between young or adults, between kin, familiaris, competitors or rivals, and antagonists.

Signal and response might seem interdependent, but an experiment in artificial life showed that even when expression of pain/need disappeared, helping responses remained in the genotype (Williams et al. 2016). Agents either expressed or suppressed ‘pain’ when injured randomly and so unable to ‘forage’ for energy; they either helped (donated energy to), ignored or exploited (stole energy from) other agents expressing pain. Agents with most energy ‘bred’ and passed on their characteristics. Over multiple baselines and many iterations, expression of pain continued when it cost little energy, injuries were infrequent, and there was no exploitation. Although an oversimplified model, it offers ways to explore interactions.

5.1  *Humans*

Perception of another’s pain activates the salience network of the brain of the observer (Decety et al. 2015). Responses are often described in terms of empathy (De Waal & Preston 2017), but expression of pain does not necessarily elicit an empathic response (Williams 2002), even by adults to children in their care (Fearon et al. 1996); and clinicians tend to discount patients’ pain, believing their behaviour to be exaggerated (Tait et al. 2009; Kappesser this issue).

5.2  *Non-human mammals*

Responses to pain in a conspecific are rarely studied in non-human mammals, except rodents. The evolved capacity to tend to the needs of offspring could extend to other social attachments (Decety et al. 2015; De Waal & Preston 2017), and highly encephalised mammals with long-term social relationships are the most likely to show helping. Asian elephants comfort one another (Plotnik & De Waal 2014), but there are no accounts of pain. Ewes are attentive to lambs’ restlessness in pain from tail docking or castration (Hild et al. 2011), looking, sniffing and licking; it is unclear whether this mitigates a lamb’s pain, although the presence of its twin may do so (Guesgen et al. 2014). The only accounts of help to injured adults is in canines that routinely share food: among painted wolves (African wild dogs), wounded members are brought food and their wounds groomed (Dyer 2018).

Among adult primates, there is very little evidence of directed care, other than social grooming, with release of oxytocin and endorphins associated with reward and with analgesia (Dunbar 2010). Wounded individuals, in particular their wounds, may receive extra grooming that reduces risk of infection (Goodall 1986; Dittus & Ratnayeke 1989), and in captive and free-living populations adults sometimes comfort and protect dying individuals (e.g. Anderson et al. 2010; Campbell et al. 2016).
the contribution of pain recognition is unknown. Chimpanzees may wait for slow-moving disabled members but there is no evidence of sustained care for injured members, who tend to adapt remarkably effectively even to major injuries (O’Connell 1995). By contrast, infants with disabilities, unable to cling or ride, are carried long past the usual age of independent mobility, with significant energy cost to the mother or other carrier (Goodall 1986; Rhine et al. 1990).

Rodents have demonstrated surprising responsiveness to conspecifics’ needs (Mogil 2012). Mice orient to a littermate’s pain and synchronise pain behaviour (Langford et al. 2006), mediated by facial expression, and sensitive to rank and stress in males. Female mice provide social analgesia to another in pain, choosing to spend time close to a ‘jailed’ mouse in pain at one end of the apparatus rather than to another ‘jailed’ mouse without pain at the other end, with the effect of reducing pain behaviour in the former (Langford et al. 2010). In male mice, mild social threat produces hyperalgesia, but stronger threat analgesia (Langford et al. 2011). Rats show emotional contagion and will work to terminate another’s distress (Bartal et al. 2016), but these studies do not involve pain. These findings are intriguing, because they occur between adults, in rodent species with different social structures and behaviours, and imply social analgesia from the unaffected individual’s voluntarily staying close to the individual in pain. Social analgesia studies need replication in rats, but also in the companion and farm animals in which facial expression of pain has been identified.

6 Conclusions

Across mammals, pain neurophysiology is largely shared; risks and preventive factors are partly shared but much evidence is lacking; functions and trajectories of pain-related behaviours are poorly understood both in humans or other mammals. Pain-related behaviours in chronic pain may habituate or be suppressed, and tests such as self-administration of analgesia or avoidance of pain-related cues may be more sensitive than observation of spontaneous changes in movement, activity, and time budget. Where pain-related behaviours occur, they communicate pain, particularly to those close, and the possibility of social analgesia warrants investigation in other mammals. Pain needs to be studied in context, including broader lifestyle, to enable identification of conditions that might, as suggested by the mismatch hypothesis, contribute to chronic pain in humans and in domesticated animals.

6.1 Chronic pain in non-human animals

It remains unclear whether chronic pain is a dysfunction of the pain system, a sustained false alarm, or an artefact of modern life, or some combination. The paucity of reports of chronic pain in free-living animals could be due to lack of observations, lack of behavioural indicators, or rarity of survival
with chronic pain. It would be perverse to propose that injured non-human animals do not feel pain as do humans, given the common anatomy and neurophysiology and plentiful evidence of recovery and healing. Peripheral and central sensitisation are part of this phase, as rodent studies show. We know less of changes in the brain, or whether the contribution of anxiety, important in driving avoidance of activity and therefore increasing disability, is uniquely human.

In relation to the question of what causes acute pain to become chronic and to persist, some risks could be directly investigated in non-human mammals. Prediction of chronic pain by sex, age, and extent of nerve damage is easier to investigate in various animals than pain and mood, but there appear to be parallel findings across human and non-human mammals in early life stress and low levels of physical activity. Some living conditions would therefore be more conducive to development of chronic pain: a fixed home rather than nomadic lifestyle; sharing food rather than foraging individually. These would help evaluate the mismatch hypothesis of chronic pain.

6.2 Behaviours associated with pain

Common observations of pain-related behaviours in humans and other mammals arise largely from studies of acute pain, where behaviour may be directed towards escaping pain, whereas in chronic pain avoidance of exacerbation is predominant. Possible specific functions of behaviour are little discussed: stretching, writhing or rolling to try to relieve visceral pain; avoiding weightbearing for limb pain; scratching or biting at a superficial wound (Whitaker & Howarth 2014). These behaviours might extinguish if pain persists, so would not occur in chronic pain. Generic behaviours, such as resting, conserve energy, but may also be an expression of helplessness in unremitting pain. The ultimate aim of behaviours is to restore homeostasis (Elman & Borsook 2018), but motivation and learning may be dysregulated in chronic pain (Borsook et al. 2018). These distinctions need to be addressed in future studies.

6.3 Social context of pain-related behaviour

Young animals often seek and achieve contact with adults, often parents, although those adults’ instrumental responses are few except in primates, who carry disabled young. Except for female mice, it is unclear whether adults of various mammalian species seek proximity when in pain, but the prevalence of facial expression of pain suggests that the social analgesia seen in mice may be far more widespread. The mouse studies (Langford et al. 2010; Mogil, 2012) are replicable in other mammals. We do not know how a horse, rabbit, dog or sheep responds to another in pain; a familiar adult may be a safety signal (Humphrey & Skoyles 2012; Steinkopf 2015), reducing the threat value of pain, and generating descending inhibition of pain.
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