CLINICAL RESEARCH HISTOMARKERS FOR OBJECTIVELY ESTIMATING PREMORBID VAGAL TONE CHRONOLOGY IN GULF WAR VETERANS' ILLNESSES AND IN ACUTE STRESS REACTION

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Abstract: While laboratory techniques for estimating genetic susceptibility for adult psychopathology have received much recent attention, laboratory techniques for objectively estimating a person's early stress related autonomic nervous system perturbations have been under-researched. Biological psychiatric research on heart rate variability suggests that early life episodes of low vagal tone may predict poor stress resilience in adults. This chapter will detail a research technique for retrospectively estimating in adults the chronology of low vagal tone episodes experienced prior to age ten. This technique makes use of the developing enamel matrix, one of very few tissues that cannot recover after being stressed. This is likely to be clinically useful in understanding the etiology of several disorders, especially Posttraumatic Stress Disorder (PTSD) as well as post-deployment disorders of unclear etiology such as Gulf War Veterans' Illness (GWVI). Finally, our proposed technique may be useful in the research on Acute Stress Reaction, Acute Stress Disorder, and on stress resilience (hardiness) in populations expected to be exposed to high levels of cumulative stress (e.g., special forces and other active duty personnel during deployment).

1. Relevance to the department of defense and veterans affairs mission

Post-deployment disorders such as Gulf War Veterans' Illnesses (GWVI) has become a topic of considerable concern. Extensive research over the last twelve years strongly suggests that the most likely mechanism in the etiology of these disorders in most veterans is neurochemical brain changes resulting from stress sensitization. Additionally, there is extensive indirect evidence that pre-enlistment extreme stress is a predisposing factor for GWVI [8, 23, 29, 43, 55]. However, it has been very difficult for the scientific and federal community to convince GWVI patients and other stakeholders that the above neurobiological mechanism underlying GWVI makes it akin to Combat Related-Posttraumatic Stress Disorder (CR-PTSD) and thus probably amenable to evidence-based treatments currently established for PTSD.

We have reasoned that the current generation of patients and veterans is increasingly accustomed to expecting confirmation or refutation of medical decisions by laboratory tests. Laboratory tests are perceived as tangible physical evidence. Psychiatry has only recently embarked on including biomarkers to enhance clinical decision making. Therefore, an evidence-based biological laboratory estimate of pre-enlistment stress may be of interest for research in GWVI. Additionally, a biological laboratory estimate of pre-enlistment stress may be of interest for research on stress resilience and

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hardiness. Understanding resilience and hardiness is a new and growing area of emphasis at the DoD [44].

2. The parasympathetic nervous system in acute stress reaction

Extreme autonomic nervous system perturbations during early life can produce long-term deleterious effects. For reviews of recent important work see Porges et al. [34, 45], McEwen [18, 28, 52] and Sapolsky [47, 48].

Stress research has focused on the adverse effects of adreno-cortical activation. Following Porges' important theoretical contributions, there has been growing attention to low vagal tone as an important final common pathway leading to the adverse effects of the acute stress reaction [34, 45].

The vagus is a complex bi-directional system with a left and right myelinated branch. Each branch has two source nuclei with fibers originating either in the dorsal motor nucleus or the nucleus ambiguus. As Porges (1995) points out, while previous research has focused on the dorsal motor nucleus of the vagus, less attention has been given to the motor pathways originating from the vagal nucleus ambiguus.

The nucleus ambiguus is the more anterior and rostral (limbic) of the two vagal nuclei. Furthermore, a potentially important hemispheric lateralization exists in the ambiguus motor neurons. As articulated by Porges (1995, p. 228):

> "In the study of acute stress and emotional expression, vagal pathways originating in the right nucleus ambiguus are critical. The right nucleus ambiguus provides the primary vagal input to the sino-atrial node to regulate heart rate ...and to the larynx to regulate the vocal intonation. Acute stress, especially during painful procedures, is associated with high heart rate and high pitch vocalizations and cries (e.g., the high pitched cries of infants in severe pain). Both characteristics are determined by a withdrawal of vagal efferent outflow originating in the nucleus ambiguus. These vagal afferents can act instantaneously to change heart rate and the pitch of vocalizations. Unlike the involuntary and often prolonged, characteristic pattern of vagal outflow from the dorsal motor nucleus, the outflow from the nucleus ambiguus may exhibit rapid and transitory patterns associated with perceptive pain or unpleasantness. The central nucleus of the amygdala, implicated in emotional lability [and fear], directly communicates with the nucleus ambiguus. Thus, the branch of the vagus originating in the nucleus ambiguus is closely linked to the rapid expression and regulation of emotional state..."

3. Nucleus ambiguus control of enamel secretion by ameloblasts

The nucleus ambiguus has been implicated in several physiological markers of Combat Related-Posttraumatic Stress Disorder (CR-PTSD) such as heart-rate variability (respiratory sinus arrhythmia) [33, 46]. There has been little attention given to the fact that vagal cholinergic neurons originating in the nucleus ambiguus control the trophic parasympathetic regulation of blood flow to the enamel secreting ameloblasts. The nucleus ambiguus neurons ending in the ameloblast layer travel by a circuitous route through other cranial nerves [21, 32]. The dramatic slowing of enamel secretion by the

ameloblast is produced by an abrupt drop in ambiguus cholinergic activity (vagal tone) which also produces the change in vocal intonation, facial expression, and especially saliva secretion and thus the symptom of "dry mouth." All of these are well-documented physical signs of acute stress. These neurons affecting the rate of enamel secretion are of the same extended amygdala origin as the neurons that coordinate increased heart rate, breathing, and peri-laryngial constriction (high-pitch vocalizations and the feeling of a "lump in the throat") which are part of acute stress reactions [33].

As a rule, during acute stress reaction and acute stress disorder, the trophic parasympathetic functions slow or cease transiently [15]. Prior to age ten, the trophic "luxury" parasympathetic functions that typically slow or cease during stress include secretion of the still developing dental enamel matrix [19, 22, 51, 54].

4. "DDE-SH Rings": a proposed technique for estimating early vagal tone chronology

Our technique uses some of the histological markers known in the fields of anthropology and paleopathology as Developmental Defects of Enamel or DDE. In this review, we use the term DDE-Stress Histomarker Rings (DDE-SH Rings; pronounced "desh rings") primarily to differentiate them from other DDE which are mineralization defects but also to emphasize the recent understanding of the etiology of these histomarkers. DDE-SH Rings have been developed as a Histomarker based upon carefully conducted research by paleopathologists, forensic dental anthropologists, and bio-archeologists. For recent work see Dean, Leakey, and Reid, (*Nature* 2001).

DDE-SH Rings are dome-shaped malformations demarcating the layer of dental enamel secreted by ameloblast cells during periods associated with low vagal tone [2, 3, 9, 30, 41]. Both acute and more chronic stress can be estimated via DDE-SH Rings of various widths.

There are various grades of histological features which together we call DDE-SH Rings. These include microscopic histomarkers (Circadian Cross Striations, Circaseptan Striae of Retzius, Accentuated Striae of Retzius, and Wilson Bands) as well as clinically detectable histomarkers (Linear Enamel Hypoplasias and other Gross Enamel Hypoplasias) [16, 17, 20]. There is growing consensus in the paleopathology and dental anthropology literature that "Selyean stress" lasting one-week or longer will produce DDE-SH Rings [3, 22], and that the transient disruption of ameloblast activity during severely depressed vagal tone can be detected as long as the tooth remains largely intact [17, 26]. Studies by Wright [60] suggest that the DDE-SH Rings called Accentuated Striae of Retzius, may be especially useful and can be produced in as little as one or two days of extreme stress.

At present it may be too early to determine which histomarker will be the most useful in clinical stress research in humans. Nevertheless, based on the above literature and additional literature cited below, we have proposed that human enamel is an untapped resource for detecting periods of low vagal tone that occur during early brain development [5, 6, 7].

DDE-SH Rings are conceptually akin to tree rings that mark periods of environmental adversity during a tree's development. The developing enamel matrix is one of very few tissues that cannot recover after being stressed. [1, 11, 12, 13, 22, 36,

37, 38, 38, 39, 40, 51, 53, 59]. Thus, the developing enamel has promise as an accessible repository of information on vagal tone chronology prior to age ten when human 3rd molars (the last developing teeth) complete crown formation [19, 54].

As one of the very few premorbid physiological stress markers, DDE-SH Rings may be important for research on the etiology of anxiety and mood disorders. DDE-SH Rings may be useful in researching disorders such as Combat Related-Posttraumatic Stress Disorder (CR-PTSD), Chronic Fatigue Syndrome (CFS), and Fibromyalgia Syndrome (FS). Additionally, DDE-SH Rings may be useful in researching medically unexplained syndromes, such as GWVI, often seen in military veterans in which it is hard to determine whether pre-enlistment stress sensitization has an etiological role in the patient's current illness.

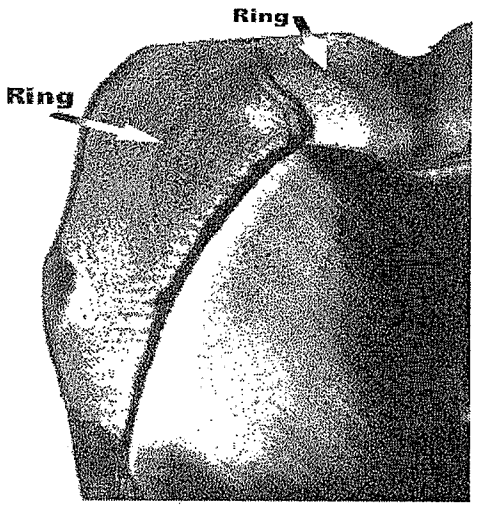

Figure 1: A single microscopic DDE-SH Ring in a combat veteran with a post-deployment disorder (Combat Related-PTSD). The stress Histomarker provides indelible evidence of stress sensitization occurring prior to enlistment, in this case at age 8. Incidentally, this particular tooth also demonstrates evidence of bruxism providing objective evidence of recent symptoms of anxiety.

5. Current clinical and forensic uses

Earlier DDE-SH Rings research in contemporary populations has focused almost entirely on deciduous dentition. DDE-SH Rings in deciduous teeth were found to be useful tools for ruling in, or ruling out, late prenatal, intranatal, and infancy distress in research participants [24, 25].

Several early studies of DDE-SH Rings conducted with deciduous teeth suggest that clinical DDE-SH Rings may be several times more common in patients with neurodevelopmental disorders than in controls. This finding is consistent with the role that low vagal tone during infancy, intranatal and prenatal period plays in the etiology of these disorders [10, 58]. Additionally, poorer clinical outcomes were shown to be associated with DDE-SH Rings [30]. Early stressors, as estimated by the location of

DDE-SH Rings, were associated with a more severe impairment [30]. These studies lend support to the potential utility of DDE-SH Rings.

In a forensic investigation, Skinner and Anderson [54] reported in detail the pattern and timing of a series of DDE-SH rings. They have demonstrated that the rings could be matched to a premortem record of physiological stress experienced. This chronological determination is possible since the rate of enamel elongation is well known. Prior studies observed that, although there is a certain amount of known non linearity in this rate, permanent enamel elongates in the cervical (root) direction at approximately 2.60 μm/day (about one millimeter/year). This information was obtained by measuring the mean inter-striae distance for a first permanent molar from a terminally ill child given timed injections of tetracycline which marked the enamel with orange striae [27].

6. Prevalence of DDE-SH rings in molars in non-clinical populations

Our current research specifically focuses on DDE-SH Rings in permanent molars. Permanent molars have been the least studied human teeth as far as vagal tone is concerned. The most severe form of DDE-SH Rings is Dental Enamel Hypoplasias which are relatively uncommon in permanent molars [31, 57]. Goodman and Rose [19], in their review of five large studies of contemporary populations (over 1,000 subjects), concluded that approximately 11% of first molars and 5% of second molars show enamel hypoplasias. In 3rd molars the prevalence is unknown. The one published study of 24 healthy subjects over age 16 [49], reported enamel hypoplasias in none of the 3rd molars.

The prevalence of less severe (subclinical) DDE-SH Rings is also unclear, although generally believed to be higher. Wright found that out of 43 permanent teeth with subclinical DDE-SH Rings, only 51% manifested clinical hypoplasias [60]. The first study of subclinical DDE-SH Rings specifically focusing on molars is currently being completed by our research team.

7. Evolutionary reasoning for research on DDE-SH rings

A research program investigating enamel markers of vagal tone perturbations is a step towards developing a clinical tool (biomarker) for researching the autonomic nervous system's response during Acute Stress Reaction. Evolutionary biological reasoning has led us to take this approach. Extensive research suggests that survival during extreme stress, throughout human evolution, depended primarily on blood supply to the brain and heart. Several other organs, such as skin, intestines, other mucousae, nails, hair, and bone were of lower priority and grow predominantly during spans of low stress such as sleep. We have reasoned that the anatomical structures of lowest survival priority may be a neglected indicator to the negative effects of stress. While little research has been done on the topic, amelogenesis of the still erupting teeth is one luxury trophic function likely to be among the lowest survival priorities during extreme stress.

8. Few bio-markers are indelible and unaffected by adulthood stress

One unique strength of our DDE-SH Rings technique for estimating premorbid vagal tone chronology is that enamel (the most durable human tissue and is the only human tissue that can withstand cremation) cannot naturally remodel or undergo repair after its initial formation in the way that other human tissues, including dentin, bone, and brain tissue can [19, 22, 42, 51, 54]. DDE-SH Rings therefore, cannot be affected by a stress reaction that occurs after the age at which enamel secretion ceases (shortly after age 10). Since enamel has the permanence of stone, DDE-SH Rings are indelible indicators of pre-adulthood experiences. In other words, DDE-SH Rings are a specific marker of infancy and childhood stress and are completely unaffected by post-pubertal and adult stress. Specifically, DDE-SH Rings cannot be produced by research confounding factors after age 10 such as current or recent exposure to alcohol, drug abuse, smoking, medical illness, medications, poor nutrition, or head injuries. Similarly, DDE-SH Rings are not affected by the research participants' quality of self-report as influenced by current mood, cooperativeness, current psychopathologies, or cultural factors.

9. Conclusions

The possible role of stress sensitization and kindling-like mechanisms in the etiology of anxiety and mood disorders suggests a wide range of disorders to which this technique may be applicable [4, 14, 35, 50, 56]. A histological marker that can retrospectively estimate vagal tone chronology during the first ten years of life would be valuable for clinical research on both PTSD and GWVI. Additionally, such a technique may be valuable for research on Acute Stress Reaction, Acute Stress Disorder, and for understanding stress resilience and hardiness. Finally, DDE-SH Rings may be useful in researching any post-deployment disorder in which it is difficult to convincingly determine whether or not pre-enlistment stress sensitization has an etiological role in the person's current illness.

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11. References:

1. Antoine D, Dean C, Hillson S. 1999. Dental Morphology 1998. In *Dental Morphology 1998*, ed. JT Mayhall, T Heikkinen, pp. 48-55. Finland: Oulu University Press
2. Ash MM. 1993. Dental Anatomy, Physiology and Occlusion Philadelphia: W.B. Saunders Company.
3. Aufderheide AC, Rodriguez-Martin C. 1998. The Cambridge Encyclopedia of Human Paleopathology Cambridge: Cambridge University Press.
4. Bell IR, Schwartz GE, Baldwin CM, Hardin EE. 1996. Neural sensitization and physiological markers in multiple chemical sensitivity. *Regulatory Toxicology and Pharmacology* 24:S39-S47
5. Bracha HS, Lopez HH, Flaxman NA, Lloyd-Jones JL, Bracha AS, Ralston T. 2002. Can Enamel Serve as a Useful Clinical Marker of Childhood Stress? *Hawaii Dental Journal* 9-10
6. Bracha HS, Ralston T, Yamashita J, Nelson G, Lopez HH, Cummings T. 2003. Stressful experiences in children and adolescents: Initial report from the PSEI-NCPV Honolulu study. *Hawaii Med. J.* 62:54-9
7. Bracha HS, Lloyd-Jones J, Flaxman N, Sprenger M, Reed H. 1999. A new laboratory estimate of cumulative autonomic perturbations during early brain development. *Clinical Autonomic Research* 9:231
8. Chalder T, Hotopf M, Unwin C, Hull L, Ismail K, David A, Wessely S. 2001. Prevalence of Gulf war veterans who believe they have Gulf war syndrome: questionnaire study. *BMJ* 323:473-6
9. Clark Spencer Larsen. 1999. Bioarchaeology: Interpreting behavior from the human skeleton Cambridge: Cambridge University Press.
10. Cohen HJ, Diner H. 1970. The significance of developmental dental enamel defects in neurological diagnosis. *Pediatrics* 46:737-47
11. Dean C. 1999. Hominoid tooth growth: using incremental lines in dentine as markers of growth in modern human and fossil primate teeth. In *Human growth in the past: studies from bones and teeth*, ed. RD Hoppa, CM Fitzgerald, pp. 111-127. Cambridge: Cambridge University Press
12. Dean MC. 2000. Progress in understanding hominoid dental development. *J. Anat.* 197:77-101
13. Dean MC, Leakey MG, Reid DJ, Friedeman S , Schwartz GT, Stringer C, Walker A. 2001. Growth processes in teeth distinguish modern humans from *Homo erectus* and earlier hominins. *Nature* 414:628-31
14. Essex M, Klein M, Cho E, Kalin N. 2002. Maternal stress beginning in infancy may sensitize children to later stress exposure: effects on cortisol and behavior. *Biol. Psychiatry* 52:776
15. Fagius J. 1997. Syndromes of autonomic overactivity. In *Clinical autonomic disorders evaluation and management*, ed. PA Low, pp. 777-790. Philadelphia: Lippincott-Raven
16. FitzGerald C.M. 1998. Do enamel microstructures have regular time dependency? Conclusions from the literature and a large-scale study. *J Hum Evol* 35:371-86

17. FitzGerald C.M., Rose JC. 2000. Reading Between the Lines: Dental Development and Subadult Age Assessment Using the Microstructural Growth Markers of Teeth. In *Biological Anthropology of the Human Skeleton*, ed. MA Katzenberg, SR Saunders, pp. 163-186. New York: Wiley-Liss, Inc.
18. Goldstein DS, McEwen B. 2002. Allostasis, homeostats, and the nature of stress. *Stress* 5:55-8
19. Goodman AH, Rose JC. 1990. Assessment of systemic physiological perturbations from dental enamel hypoplasias and associated histological structures. *Yearbook of Physical Anthropology* 33:59-110
20. Guatelli-Steinberg D. 2001. What can developmental defects of enamel reveal about physiological stress in nonhuman primates? *Evolutionary Anthropology* 10:138-51
21. Harati Y, Machkhas H. 1997. Spinal cord and peripheral nervous system. In *Clinical autonomic disorders evaluation and management*, ed. PA Low, pp. 25-46. Philadelphia: Lippincott-Raven
22. Hillson S. 1996. Dental anthropology Cambridge: Cambridge University Press.
23. Lee HA, Gabriel R, Bolton JP, Bale AJ, Jackson M. 2002. Health status and clinical diagnoses of 3000 UK Gulf War veterans. *J R Soc Med* 95:491-7
24. Levine RS, Turner EP, Dobbing J. 1979. Deciduous teeth contain histories of developmental disturbances. *Early Hum. Dev.* 3/2:211-20
25. Leviton A, Needleman HL, Bellinger D, Allred EN. 1994. Children with hypoplastic enamel defects of primary incisors are not at increased risk of learning-problem syndromes. *ASDC J Dent Child* 61:35-8
26. Liebgott B. 2001. The Anatomical Basis of Dentistry St. Louis: Mosby.
27. Massler M, Schour I, Poncher HG. 1941. Developmental pattern of the child as reflected in the calcification pattern of the teeth. *Am. J. Dis. Child.* 629:33-67
28. McEwen BS, Lasley EN. 2002. The End of Stress as We Know It Joseph Henry Press.
29. Morgan CA, III, Grillon C, Southwick SM, Davis M, Charney DS. 1997. Exaggerated acoustic startle reflex in Gulf War veterans with posttraumatic stress disorder. *Am. J. Psychiatry* 153:64-8
30. Murray GS, Johnsen DC, Weissman BW. 1987. Hearing and neurologic impairment: insult timing indicated by primary tooth enamel defects. *Ear Hear.* 8:68-73
31. Murray JJ, Shaw L. 1979. Classification and prevalence of enamel opacities in the human deciduous and permanent dentitions. *Arch. Oral Biol.* 24:7-13
32. Nieuwenhuys R, Voogd J, van Huijzen C. 1981. The Human Central Nervous System. A Synopsis and Atlas Berlin: Springer-Verlag. 1-253 pp.
33. Porges SW. 1995. Cardiac Vagal Tone: A Physiological Index of Stress. *Neurosci. Biobehav. Rev.* 19:2:225-33
34. Porges SW. 2001. The polyvagal theory: phylogenetic substrates of a social nervous system 3. *Int. J. Psychophysiol.* 42:123-46
35. Post RM, Weiss SRB, Smith MA. 1995. Sensitization and kindling: implications for the evolving neural substrates of post-traumatic stress disorder. In *Neurobiological and clinical consequences of stress*, pp. 203-224. Philadelphia: Lippincott - Raven

36. Reid DJ, Beynon AD, Ramirez Rozzi FV. 1998. Histological reconstruction of dental development in four individuals from a medieval site in Picardie, France. *Journal of Human Evolution* 35:463-77
37. Reid DJ, Dean MC. Brief communication: the timing of linear hypoplasias on human anterior teeth. American Journal of Physical Anthropology 113(1). 2000. Wiley-Liss, Inc. Ref Type: Generic
38. Reid DJ, Dean MC. 2000. The timing of linear hypoplasias on human anterior teeth. *Am. J. Phys. Anthropol.* 113:135-9
39. Risnes S. 1998. Growth tracks in dental enamel. *J Hum Evol* 35:331-50
40. Risnes S, Moinichen CB, Septier D, Goldberg M. 1996. Effects of accelerated eruption on the enamel of the rat lower incisor. *Adv. Dent. Res.* 10:261-9
41. Roberts C, Manchester K. 1997. The Archaeology of Disease Cornell University Press.
42. Rose JC, Armelagos GJ, Lallo JW. 1978. Histological enamel indicator of childhood stress in prehistoric skeletal samples . *Am. J. Phys. Anthropol.* 49:511-6
43. Roy M. 1994. *Fed. Prac.* In press
44. Rumsfeld DH. 2002. Transforming the Military. *Foreign Affairs* 81:20-32
45. Sahar T, Shalev AY, Porges SW. 2001. Vagal modulation of responses to mental challenge in posttraumatic stress disorder 4. *Biol. Psychiatry* 49 :637-43
46. Sahar T, Shalev AY, Porges SW. 2001. Vagal modulation of responses to mental challenge in posttraumatic stress disorder. *Biol. Psychiatry* 49:637-43
47. Sapolsky RM. 1997. McEwen-induced modulation of endocrine history: a partial review. *Stress* 2:1-12
48. Sapolsky RM. 2002. Chickens, eggs and hippocampal atrophy. *Nature Neuroscience* 5:1111-3
49. Sarnat BG, Schour I. 1941. Enamel hypoplasia (chronologic enamel aplasia) in relation to systemic disease: a chronologic, morphologic and etiologic classification. *J. Am. Dent. Assoc.* 28:1989-2000
50. Sax, Strakowski. 2001. Behavioral sensitization in humans. *J Addict Dis* 20:55-65
51. Scott GR, Turner CGI. 1997. The anthropology of modern human teeth: dental morphology and its variation in recent human populations Cambridge: Cambridge University Press.
52. Seeman TE, McEwen BS, Rowe JW, Singer BH . 2001. Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. *Proc. Natl. Acad. Sci.* 98:4770-5
53. Simpson SW. 1999. Reconstructing patterns of growth disruption from enamel microstructure. In *Human growth in the past: studies from bones and teeth*, ed. RD Hoppa, CM Fitzgerald, and pp. 241-263. Cambridge: Cambridge University Press
54. Skinner M, Anderson GS. 1991. Individualization and enamel histology: a case report in forensic anthropology. *J. Forens. Sci.* 36:939-48
55. Smith TC, Smith B, Ryan MA, Gray GC, Hooper TI, Heller JM, Dalager NA, Kang HK, Gackstetter GD. 2002. Ten years and 100,000 participants later: occupational and other factors influencing participation in US Gulf War health registries. *J Occup Environ Med* 44:758-68
56. Stam R, Bruijnzeel AW, Wiegant VM. 2000. Long-lasting stress sensitisation. *Eur. J. Pharmacol.* 405:217-24

57. Suckling GW, Pearce EIF, Cutress TW. 1976. Developmental enamel defects in New Zealand children. *New Zealand Dent. J.* 72:201-10
58. Via WF, Churchill JA. 1957. Relationships of cerebral disorder to faults in dental enamel. *Am. J. Dis. Child.* 94:137-42
59. White TD. 1991. Dentition. In *Human Osteology*, ed. AC White, pp. 101-110. San Diego: ACADEMIC PRESS
60. Wright LE. 1990. Stresses of conquest: a study of Wilson bands and enamel hypoplasias in the Maya of Lamanai, Belize. *Am. J. Hum. Biol.* 2:25-35

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