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Opiates Possibly Boosted Human Civilization

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Abstract

Testosterone is a fundamental biological drive for human survival. Evidence documents an association between the evolutionary suppression of testosterone and the civilization processes, especially their socialization and family colonization abilities, among early humans. Interestingly, opiates suppress testosterone as a side effect. However, in clinical practice, clients undergoing opioid substitution therapy have subnormal, normal, or even above-normal testosterone. This paper discusses a possibility indicating that opiates promoted civilization processes among early humans. We further suggest that modern humans might have inherited the positive impact of opiates on early humans as a biological propensity for using opioids. Some users may use opioids for self-medication to decrease their extraordinarily high testosterone levels.

Keywords: Aggression, Civilization, Evolution, Opiates, Testosterone

1. Introduction

1.1. Civilization and Testosterone

According to Lamarck's theory of evolution (1), animals respond to their emerging needs by exhibiting adaptive reactions. This endeavor changed their habits and functions and was further conveyed to animals' offspring and ensuing generations (2). Later, Darwin presented the natural selection theory (3). Darwin's theory, in contrast, addressed the influence of factors other than natural selection such as inheritance, gene mutation, and the environment (4). In both models, however, reproduction is a key element to preserve life (5). Evolution, therefore, is considered as a process of change in living organisms with the ultimate goal of preserving life and survival by adapting to the environment (6).

Reproduction is an adaptive process to generate new genetic variations and fresh and isolated organisms (7). However, reproduction requires liaison and integrated synergism of biological (internal) and non-biological (external) agents such as cells, hormones, paracrine factors, genes, epigenetic regulators, nutritional conditions, photoperiod, pheromones, and stress (8). The interactions among thousands of genes, the epigenetic control of gene expression, and environmental and lifestyle factors affecting genetic and epigenetic variants determines the resulting reproduction (9). Seasons, as an external factor, create distinct patterns for numerous natural processes and evolutionary adaptations, including mating rhythms (10). The climax of mating and reproduction behavior in many animals is confined to specific season(s) or years when their steroid cycle activity and sperm production are maximal (11).

Testosterone, a product of Leydig cells, is a key hormone in reproduction, and an appropriate level of which is required in the bloodstream for effective reproduction (12). A higher level of testosterone, however, is not necessarily beneficial and can even impede survival. For example, high-level testosterone in the youth increases the suicide risk (13). Testosterone has also been suspected as a risk factor in developing mental disorders such as schizophrenia (14). Suicidal thoughts in patients with positive symptom schizophrenia are also higher (15), which may reflected the augmented effect of testosterone. Accordingly, an optimal window effect of testosterone is likely for survival, and this effect is reversed in higher and lower levels. In other words, an agent (i.e., biology) may shield survival and evolution at one level and endanger survival at another level (i.e., social level).

Convincing evidence indicate the higher levels of testosterone in early humans (16). The gradual diminution in androgenic hair is the phenotypical evidence of lowered testosterone levels in humans (17). The decline of testosterone, however, appears to precede the evolution of civi-

lized humans (16). It also makes human males be less aggressive, less isolated, and less competitive; hence, they become more sociable, interactive, and stable in their relationships (18). Those changes seem to be prerequisites to civilization (19). In other words, the lower levels of testosterone and human civilization appear to be an intertwined evolutionary process. Although researchers have documented that human testosterone decline is still in progress (20), to the best of our knowledge, there is no clear explanation on how this decline is happening. Following the suppression of testosterone, however, early humans became self-domesticated and prosocial, began living in families, and became creative (21).

1.2. Opium Poppy and Testosterone

Previous studies have suggested that the opium plant acquired its poisonous property (22) to be avoided as an alimentary source for herbivores and, therefore, to secure its survival under hostile environmental conditions (22). However, some animals, including humans, evolved to benefit the useful properties (e.g., painkilling effects) of opium poppy and other alkaloid producing plants without being beaten by their fatal attributes (23). The painkilling and anti-inflammatory effects of opium (24) helped ancient humans tolerate trauma-related pain, thereby securing their survival (25). With their somniferous properties and the induction of pleasant feelings, opiates have been consumed by mankind throughout history (26).

According to Hamilton's rule, for a specific behavior to continue in a particular group or species, the advantage of practicing that behavior should outweigh its disadvantages (27). Opiate consumption may be associated with a wide range of side effects, including constipation (28), sleep disorders (29), respiratory depression (30), cardiovascular system effects (31), increased risk of bone fracture due to drug-induced falls (32), immune system suppression (33), and decreased testosterone level (34). In this regard, from an evolutionary perspective, the continued consumption of opium (35), despite their adverse effects, arouses the assumption indicating that the benefits of opium to humans outweigh such side-effects. In line with this assumption, the ceremonial rituals of opium use (36) further documents its superior benefits for humans. Opium has been used not only for medication but also for ceremonies as such the Sumerians called it the plant of Joy (37). Accordingly, one can postulate that male humans primarily used opiates for their painkilling and other positive effects; however, they were subsequently influenced by their testosterone-reducing effect.

Moreover, the evolutionary process of testosterone decline in humans seems to be mediated by narcotics, where a potentially counter-revolutionary selection- the adverse effects of opiates in this case- resulted in unprecedented survival privileges (38). With their capability of decreasing testosterone levels (39), narcotics may have regulated and modified testosterone levels to flourish and maintain humans' survival by addressing the other aspects of survival other than reproduction.

However, one might question the assumption indicating that testosterone decline in early male humans was a direct consequence of opiate consumption. In this regard, we suggest a two-level model explaining the role of opiates in expediting human civilization. Disregarding the civilization-promoting mechanism of opiates, this model assumes that some male humans happened to evolve during the unknown process(es) such as climate change at the end of the last ice age (40) or living under harsh environmental conditions (41). This was also accompanied by a declining testosterone level, making them be domesticated, sociable (42), and environment-conscious (43). This group of male humans could form families, have better access to females within familial colonies, and promote their genetic inheritance. One the other hand, those males who had not benefitted from that evolutionary modification and continued to have high testosterone remained marginalized with much less access to females and the higher risk of extinction. Considering different alimentary, physical, and mental effects of opium poppy, there is a good reason to believe that the marginalized males might have used opiates to benefit from its pleasant properties. Incidentally, opiates resulted in lower testosterone and helped the marginalized group of male humans to neutralize within domesticated human colonies. To sum up, opiate use augmented the civilization of humans by adding different numbers of domesticated males to human colonies. According to Hamilton's rule (27), humans enjoyed the effect of opiates on testosterone reduction and subsequent neutralization in colonies. Moreover, opiate using behavior should have resulted in epigenetic modifications reinforcing opiate use.

2. Arguments

2.1. Dilemma of Testosterone Level

In animal studies, opioids generally suppress testosterone (44). Studies on testosterone levels in human opiate users, however, are neither rich nor conclusive. Interestingly, some studies have reported a decrease in testosterone level in about half of the cases (45), while others noticed normal or even maximum high testosterone levels (46). Human studies show that factors other than opioids, including age (47), number of comorbidities (47), cognitive decline (48), and body mass index (49), play a role

in opioid-related testosterone reduction in both men (49) and women (50). Nonetheless, the influence of opiates on the endocrine system (51) and particularly on lowering testosterone (52) remains an area of debate. A possible explanation for inconsistencies between animal and human studies is that unlike animal studies that begin with healthy animals and the researcher creates a pathology in the animal (53), human studies have generally been on patients or long-term substance-using individuals; thus, the influence of coexisting pathologies on testosterone in humans might not be the same as that in lab animals (54). Furthermore, in animal studies, the researcher can measure the base level of the biological agent (i.e., testosterone) prior to interventions, while, at least for testosterone level, this has not been the case in many human studies. Moreover, an underlying complication is the significant variability in total and free testosterone serum levels due to intraindividual variation (55). The serum testosterone level even appears to be dependent on social status and fluctuates accordingly (56).

Higher testosterone levels influence social behaviors and reduce fear and anxiety (57) as well as violence (58). This mechanism has a surviving effect during wartime, where increased testosterone has been evidenced following troops' deployment in combat zones (59). Interestingly, however, as the Vietnam war extended, a heroin epidemic ensued among the servicemen (60). Moreover, heavy exercises and athletic activities are typical reasons explaining why human beings take exogenous testosterone and other anabolic steroids (61). Evidently, opioid use is more prevalent among athletes and bodybuilders taking exogenous testosterone (62). One may, hence, conclude that we are preprogrammed to reduce high testosterone levels by using opioids, and that the propensity for using opioids in response to high testosterone levels is rooted in the same evolutionary mechanism, making early humans domesticate and be civilized. In other words, instead of a side effect, the effect of the opioid on suppressing testosterone may be the nature's solution to the higher than expected level of testosterone. Referring to the fact that civilized humans have lower testosterone levels, one may further argue that opiates have played a critical role in this respect. Humans might have started using opiates for their pain-relieving effect. However, in the interim, opiates promoted civilization in the human species by suppressing testosterone.

Given that the evidence on serum testosterone level in subjects who use opioids for non-medical purposes is inconclusive, according to the fifth edition of the diagnostic and statistical manual of mental disorders (63), at least some individuals who may receive a label of an opioid use disorder, may have started using opioids under the influence of the evolutionary propensity for modifying high testosterone level by using opioids simply in response to their high testosterone level. Interestingly, the contradictory evidence on the effect of opioids on testosterone level (46) may also support this hypothesis since the measured testosterone level in individuals who use opioids has been below normal, normal, or even above normal. This model might even explain why some individuals benefit from methadone maintenance more than others regarding their baseline testosterone level (45). According to the above hypothesis, the normal and above normal testosterone levels in the presence of opioid use would still be predictable. In those cases, either the opioid dose has not been as high enough to suppress testosterone, or the baseline testosterone level has been too high to be subdued by opioids.

3. Conclusions

3.1. Future Considerations

The literature on opioids' effect on human testosterone level is inconclusive; hence, further studies are recommended to address this issue. Our observation (63) shows that testosterone levels in clients undergoing opioid substitution therapy might be subnormal, normal, or above-normal. In this regard, a focus on opioid dosage in association with testosterone level seems to be of greater significance. Stimulants, such as tobacco (nicotine), seem to play a similar role as opiates in reducing testosterone (64, 65), albeit with much less efficacy. An investigation of similarities between nicotine and opioids in modulating testosterone levels might open new frontiers in understanding underlying factors for the compulsive use of those substances in at least a group of individuals who become dependent on those substances. Differentiation has been made between proactive aggression and reactive violence and the causal effects of modernization and population in the development of aggressive behaviors (66). Studies on testosterone changes during wartime and its association with opioid use would also contribute to providing better biological descriptions and explanations on the roots of the tendency for war in human beings and peace-boosting methods.

We hypothesize that opium has played a role in the civilization of early humans by augmenting the suppression of male human testosterone levels. We further argue that the propensity for using opioids in some contemporary humans might result from the genetic and epigenetic footprints of opiates' effects on early humans.

Footnotes

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References

1. Burkhardt RJ. Lamarck, evolution, and the inheritance of acquired characters. *Genetics*. 2013;**194**(4):793–805. doi: 10.1534/genetics.113.151852. [PubMed: 23908372]. [PubMed Central: PMC3730912].
2. Por FD. The actuality of Lamarck: towards the bicentenary of his Philosophic Zoologique. *Integr Zool*. 2006;**1**(1):48–52. doi: 10.1111/j.1749-4877.2006.00012.x. [PubMed: 21395991].
3. Simpson GG. The world into which Darwin led us. *Science*. 1960;**131**(3405):966–74. doi: 10.1126/science.131.3405.966. [PubMed: 14447010].
4. Liu Y. Natural selection and pangenesis: The Darwinian synthesis of evolution and genetics. *Adv Genet*. 2018;**102**:121–42. doi: 10.1016/bs.adgen.2018.05.010. [PubMed: 30122233].
5. Fitch WM, Ayala FJ. *Tempo and mode in evolution: Genetics and paleontology 50 years after Simpson*. Washington (DC): National Academies Press (US); 1995.
6. Maryanski A, Machalek R, Turner JH. *Handbook on evolution and society: Toward an evolutionary social science*. Routledge; 2015.
7. Bernstein H, Hopf FA, Michod RE. The molecular basis of the evolution of sex. *Adv Genet*. 1987;**24**:323–70. doi: 10.1016/s0065-2660(08)60012-7. [PubMed: 3324702].
8. Scott CJ, Rose JL, Gunn AJ, McGrath BM. Kisspeptin and the regulation of the reproductive axis in domestic animals. *J Endocrinol*. 2018;**240**(1):R1–R16. doi: 10.1530/JOE-18-0485. [PubMed: 30400056].
9. Gunes S, Esteves SC. Role of genetics and epigenetics in male infertility. *Andrologia*. 2021;**53**(1). e13586. doi: 10.1111/and.13586. [PubMed: 32314821].
10. Varpe O. Life history adaptations to seasonality. *Integr Comp Biol*. 2017;**57**(5):943–60. doi: 10.1093/icb/icx123. [PubMed: 29045732].
11. Kivela SM, Valimaki P, Gotthard K. Evolution of alternative insect life histories in stochastic seasonal environments. *Ecol Evol*. 2016;**6**(16):5596–613. doi: 10.1002/ece3.2310. [PubMed: 27547340]. [PubMed Central: PMC4983577].
12. Miller WL, Auchus RJ. The molecular biology, biochemistry, and physiology of human steroidogenesis and its disorders. *Endocr Rev*. 2011;**32**(1):81–151. doi: 10.1210/er.2010-0013. [PubMed: 21051590]. [PubMed Central: PMC3365799].
13. Sher L. Low testosterone levels may be associated with suicidal behavior in older men while high testosterone levels may be related to suicidal behavior in adolescents and young adults: a hypothesis. *Int J Adolesc Med Health*. 2013;**25**(3):263–8. doi: 10.1515/ijamh-2013-0060. [PubMed: 23893672].
14. Duko B, Ayano G. Suicidal ideation and attempts among people with severe mental disorder, Addis Ababa, Ethiopia, comparative cross-sectional study. *Annals of General Psychiatry*. 2018;**17**(1):1–5.
15. Comparelli A, Corigliano V, Lamis DA, De Carolis A, Stampatore L, De Pisa E, et al. Positive symptoms and social cognition impairment affect severity of suicidal ideation in schizophrenia. *Schizophr Res*. 2018;**193**:470–1. doi: 10.1016/j.schres.2017.07.027. [PubMed: 28712966].
16. Cieri RL, Churchill SE, Franciscus RG, Tan J, Hare B. Craniofacial feminization, social tolerance, and the origins of behavioral modernity. *Curr Anthropol*. 2014;**55**(4):419–43. doi: 10.1086/677209.
17. Goncharov NP, Katsiia GV, Dzhokua AA, Barkaia VS, Kulava ZV, Mikvabia Z. [The influence of dehydroepiandrosterone (DHEA) on the behavior in old non-human primates]. *Fiziol Cheloveka*. 2014;**40**(2):41–8. Russian. [PubMed: 25272705].
18. Trumble BC, Jaeggi AV, Gurven M. Evolving the neuroendocrine physiology of human and primate cooperation and collective action. *Philos Trans R Soc Lond B Biol Sci*. 2015;**370**(1683):20150014. doi: 10.1098/rstb.2015.0014. [PubMed: 26503687]. [PubMed Central: PMC4633850].
19. Kováč L. *Closing human evolution: Life in the ultimate age*. Springer; 2015.
20. Travison TG, Araujo AB, O'Donnell AB, Kupelian V, McKinlay JB. A population-level decline in serum testosterone levels in American men. *J Clin Endocrinol Metab*. 2007;**92**(1):196–202. doi: 10.1210/jc.2006-1375. [PubMed: 17062768].
21. Wrangham RW. Hypotheses for the evolution of reduced reactive aggression in the context of human self-domestication. *Front Psychol*. 2019;**10**:1914. doi: 10.3389/fpsyg.2019.01914. [PubMed: 31481917]. [PubMed Central: PMC6710405].
22. Guo L, Winzer T, Yang X, Li Y, Ning Z, He Z, et al. The opium poppy genome and morphinan production. *Science*. 2018;**362**(6412):343–7. doi: 10.1126/science.aat4096. [PubMed: 30166436].
23. Sullivan RJ, Hagen EH, Hammerstein P. Revealing the paradox of drug reward in human evolution. *Proc Biol Sci*. 2008;**275**(1640):1231–41. doi: 10.1098/rspb.2007.1673. [PubMed: 18353749]. [PubMed Central: PMC2367444].
24. Harrison AP, Hansen SH, Bartels EM. Transdermal opioid patches for pain treatment in ancient Greece. *Pain Pract*. 2012;**12**(8):620–5. doi: 10.1111/j.1533-2500.2012.00546.x. [PubMed: 22448887].
25. Clarke JL, Skoufalos A, Scranton R. The American opioid epidemic: population health Implications and potential solutions. report from the national stakeholder panel. *Popul Health Manag*. 2016;**19 Suppl 1**:S1–10. doi: 10.1089/pop.2015.0144. [PubMed: 26908092].
26. Mavrogenis AF, Saranteas T, Markatos K, Kotsiou A, Tesseromatis C. Pharmacies for pain and trauma in ancient Greece. *Int Orthop*. 2019;**43**(6):1529–36. doi: 10.1007/s00264-018-4219-x. [PubMed: 30413852].
27. Hamilton WD. The genetical evolution of social behaviour. II. *Journal of theoretical biology*. 1964;**7**(1):17–52.
28. Bell TJ, Panchal SJ, Miaskowski C, Bolge SC, Milanova T, Williamson R. The prevalence, severity, and impact of opioid-induced bowel dysfunction: results of a US and European Patient Survey (PROBE 1). *Pain Med*. 2009;**10**(1):35–42. doi: 10.1111/j.1526-4637.2008.00495.x. [PubMed: 18721170].
29. Yue HJ, Guilleminault C. Opioid medication and sleep-disordered breathing. *Med Clin North Am*. 2010;**94**(3):435–46. doi: 10.1016/j.mcna.2010.02.007. [PubMed: 20451025].
30. van der Schier R, Roozekrans M, van Velzen M, Dahan A, Niesters M. Opioid-induced respiratory depression: reversal by non-opioid drugs. *F1000Prime Rep*. 2014;**6**:79. doi: 10.12703/P6-79. [PubMed: 25343036]. [PubMed Central: PMC4173639].
31. Carman WJ, Su S, Cook SF, Wurzelmann JI, McAfee A. Coronary heart disease outcomes among chronic opioid and cyclooxygenase-2 users compared with a general population cohort. *Pharmacoepidemiol Drug Saf*. 2011;**20**(7):754–62. doi: 10.1002/pds.2131. [PubMed: 21567652].
32. Miller M, Sturmer T, Azrael D, Levin R, Solomon DH. Opioid analgesics and the risk of fractures in older adults with arthritis. *J Am Geriatr Soc*. 2011;**59**(3):430–8. doi: 10.1111/j.1532-5415.2011.03318.x. [PubMed: 21391934]. [PubMed Central: PMC3371661].
33. Sacerdote P. Opioid-induced immunosuppression. *Curr Opin Support Palliat Care*. 2008;**2**(1):14–8. doi: 10.1097/SPC.0b013e3282f5272e. [PubMed: 18685388].

34. Baillargeon J, Raji MA, Urban RJ, Lopez DS, Williams SB, Westra JR, et al. Opioid-induced hypogonadism in the United States. *Mayo Clin Proc Innov Qual Outcomes*. 2019;**3**(3):276–84. doi: 10.1016/j.mayocpiqo.2019.06.007. [PubMed: 31485565]. [PubMed Central: PMC6713891].
35. Lawler A. Cannabis, opium use part of ancient Near Eastern cultures. *American Association for the Advancement of Science*. 2018;**360**(6386):249–50.
36. Brownstein MJ. A brief history of opiates, opioid peptides, and opioid receptors. *Proc Natl Acad Sci U S A*. 1993;**90**(12):5391–3. doi: 10.1073/pnas.90.12.5391. [PubMed: 8390660]. [PubMed Central: PMC46725].
37. Cohen MM. The history of opium and the opiates. *Tex Med*. 1969;**65**(1):76–85. [PubMed: 4915472].
38. Chodasewicz K. Evolution, reproduction and definition of life. *Theory Biosci*. 2014;**133**(1):39–45. doi: 10.1007/s12064-013-0184-5. [PubMed: 23674095]. [PubMed Central: PMC3937540].
39. Brennan MJ. The effect of opioid therapy on endocrine function. *Am J Med*. 2013;**126**(3 Suppl 1):S12–8. doi: 10.1016/j.amjmed.2012.12.001. [PubMed: 23414717].
40. Ziegler M, Simon MH, Hall IR, Barker S, Stringer C, Zahn R. Development of middle stone age innovation linked to rapid climate change. *Nat Commun*. 2013;**4**:1905. doi: 10.1038/ncomms2897. [PubMed: 23695699]. [PubMed Central: PMC4354264].
41. Magid K, Chatterton RT, Ahamed FU, Bentley GR. Childhood ecology influences salivary testosterone, pubertal age and stature of Bangladeshi UK migrant men. *Nat Ecol Evol*. 2018;**2**(7):1146–54. doi: 10.1038/s41559-018-0567-6. [PubMed: 29942016].
42. Gettler LT, McDade TW, Feranil AB, Kuzawa CW. Longitudinal evidence that fatherhood decreases testosterone in human males. *Proc Natl Acad Sci U S A*. 2011;**108**(39):16194–9. doi: 10.1073/pnas.1105403108. [PubMed: 21911391]. [PubMed Central: PMC3182719].
43. Landry N, Desrochers JE, Hodges-Simeon C, Arnocky S. Testosterone, facial and vocal masculinization and low environmentalism in men. *Journal of Environmental Psychology*. 2019;**64**:107–12. doi: 10.1016/j.jenvp.2019.05.007.
44. Chrastil J, Sampson C, Jones KB, Higgins TF. Evaluating the affect and reversibility of opioid-induced androgen deficiency in an orthopaedic animal fracture model. *Clin Orthop Relat Res*. 2014;**472**(6):1964–71. doi: 10.1007/s11999-014-3517-x. [PubMed: 24549775]. [PubMed Central: PMC4016456].
45. Bawor M, Dennis BB, Samaan MC, Plater C, Worster A, Varenbut M, et al. Methadone induces testosterone suppression in patients with opioid addiction. *Sci Rep*. 2014;**4**:6189. doi: 10.1038/srep06189. [PubMed: 25155550]. [PubMed Central: PMC4143768].
46. Nazmara Z, Najafi M, Rezaei-Mojaz S, Movahedin M, Zandiyeh Z, Shirinbayan P, et al. The effect of heroin addiction on human sperm parameters, histone-to-protamine transition, and serum sexual hormones levels. *Urol J*. 2019;**16**(3):289–94. doi: 10.22037/uj.v0i0.4321. [PubMed: 30206922].
47. Cepeda MS, Zhu V, Vorsanger G, Eichenbaum G. Effect of opioids on testosterone levels: Cross-sectional study using NHANES. *Pain Med*. 2015;**16**(12):2235–42. doi: 10.1111/pme.12843. [PubMed: 26177122].
48. Yeap BB, Almeida OP, Hyde Z, Chubb SA, Hankey GJ, Jamrozik K, et al. Higher serum free testosterone is associated with better cognitive function in older men, while total testosterone is not. The Health In Men Study. *Clin Endocrinol (Oxf)*. 2008;**68**(3):404–12. doi: 10.1111/j.1365-2265.2007.03055.x. [PubMed: 17888021].
49. Vermeulen A, Goemaere S, Kaufman JM. Testosterone, body composition and aging. *J Endocrinol Invest*. 1999;**22**(5 Suppl):110–6. [PubMed: 10442580].
50. Martinez-Guisasola J, Guerrero M, Alonso F, Diaz F, Cordero J, Ferrer J. Plasma beta-endorphin levels in obese and non-obese patients with polycystic ovary disease. *Gynecol Endocrinol*. 2001;**15**(1):14–22. [PubMed: 11293919].
51. Khademi H, Kamangar F, Brennan P, Malekzadeh R. Opioid therapy and its side effects: A review. *Arch Iran Med*. 2016;**19**(12):870–6. [PubMed: 27998163].
52. Daniell HW. Opioid endocrinopathy in women consuming prescribed sustained-action opioids for control of nonmalignant pain. *J Pain*. 2008;**9**(1):28–36. doi: 10.1016/j.jpain.2007.08.005. [PubMed: 17936076].
53. Garner JP. The significance of meaning: Why do over 90% of behavioral neuroscience results fail to translate to humans, and what can we do to fix it? *ILAR J*. 2014;**55**(3):438–56. doi: 10.1093/ilar/ilu047. [PubMed: 25541546]. [PubMed Central: PMC4342719].
54. Sjoberg EA. Logical fallacies in animal model research. *Behav Brain Funct*. 2017;**13**(1):3. doi: 10.1186/s12993-017-0121-8. [PubMed: 28202023]. [PubMed Central: PMC5312558].
55. Herati AS, Cengiz C, Lamb DJ. Assays of serum testosterone. *Urol Clin North Am*. 2016;**43**(2):177–84. doi: 10.1016/j.ucl.2016.01.003. [PubMed: 27132574].
56. Geniole SN, Bird BM, Ruddick EL, Carre JM. Effects of competition outcome on testosterone concentrations in humans: An updated meta-analysis. *Horm Behav*. 2017;**92**:37–50. doi: 10.1016/j.yhbeh.2016.10.002. [PubMed: 27720891].
57. Eisenegger C, Haushofer J, Fehr E. The role of testosterone in social interaction. *Trends Cogn Sci*. 2011;**15**(6):263–71. doi: 10.1016/j.tics.2011.04.008. [PubMed: 21616702].
58. Carre JM, Archer J. Testosterone and human behavior: The role of individual and contextual variables. *Curr Opin Psychol*. 2018;**19**:149–53. doi: 10.1016/j.copsyc.2017.03.021. [PubMed: 29279215].
59. Reijnen A, Geuze E, Vermetten E. The effect of deployment to a combat zone on testosterone levels and the association with the development of posttraumatic stress symptoms: A longitudinal prospective Dutch military cohort study. *Psychoneuroendocrinology*. 2015;**51**:525–33. doi: 10.1016/j.psyneuen.2014.07.017. [PubMed: 25128222].
60. Stanton MD. Drugs, Vietnam, and the Vietnam veteran: an overview. *Am J Drug Alcohol Abuse*. 1976;**3**(4):557–70. doi: 10.3109/00952997609014295. [PubMed: 1032764].
61. Morgentaler A, Traish A. The history of testosterone and the evolution of its therapeutic potential. *Sex Med Rev*. 2020;**8**(2):286–96. doi: 10.1016/j.sxmr.2018.03.002. [PubMed: 29661690].
62. Kanayama G, Hudson JI, Pope HJ. Illicit anabolic-androgenic steroid use. *Horm Behav*. 2010;**58**(1):111–21. doi: 10.1016/j.yhbeh.2009.09.006. [PubMed: 19769977]. [PubMed Central: PMC2883629].
63. Segal DL. Diagnostic and statistical manual of mental disorders (DSM-IV-TR). *The Corsini Encyclopedia of Psychology*. John Wiley & Sons; 2010.
64. Wang W, Yang X, Liang J, Liao M, Zhang H, Qin X, et al. Cigarette smoking has a positive and independent effect on testosterone levels. *Hormones (Athens)*. 2013;**12**(4):567–77. doi: 10.14310/horm.2002.1445. [PubMed: 24457405].
65. Tushingham S, Snyder CM, Brownstein KJ, Damitio WJ, Gang DR. Biomolecular archaeology reveals ancient origins of indigenous tobacco smoking in North American Plateau. *Proc Natl Acad Sci U S A*. 2018;**115**(46):11742–7. doi: 10.1073/pnas.1813796115. [PubMed: 30373836]. [PubMed Central: PMC6243282].
66. Wrangham RW. Two types of aggression in human evolution. *Proc Natl Acad Sci U S A*. 2018;**115**(2):245–53. doi: 10.1073/pnas.1713611115. [PubMed: 29279379]. [PubMed Central: PMC5777045].