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Testosterone rules: it takes more than just a hormone to make a fellow's trigger finger itch

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Face it, we all do it -- we all believe in stereotypes about minorities. These stereotypes are typically pejorative and false, but every now and then they have a core of truth. I know, because I belong to a minority that lives up to its reputation. I have a generic abnormality generally considered to be associated with high rates of certain socially abhorrent behaviors: I am male. Thanks to an array of genes that produce some hormone-synthesizing enzymes, my testes churn out a corrosive chemical and dump the stuff into my bloodstream, and this probably has behavioral consequences. We males account for less than 50 percent of the population, yet we generate a huge proportion of the violence. Whether it is something as primal as having an ax fight in a rain forest clearing or as detached as using, computer-guided aircraft to strafe a village, something as condemned as assaulting a cripple or as glorified as killing someone wearing the wrong uniform, if it is violent, we males excel at it.

Why should this be? We all think we know the answer: something to do with those genes being expressed down in the testes. A dozen millennia ago or so, an adventurous soul managed to lop off a surly bulls testicles, thus inventing behavioral endocrinology. It is unclear from the historical records whether the experiment resulted in grants and tenure, but it certainly generated an influential finding: that the testes do something or other to make males aggressive pains in the ass.

That something or other is synthesizing the infamous corrosive chemical, testosterone (or rather, a family of related androgen hormones that I'll call testosterone for the sake of simplicity, hoping the androgen specialists won't take it the wrong way . Testosterone bulks up muscle cells -- including those in the larynx, giving rise to operatic basses. It makes hair sprout here and there, undermines the health of blood vessels, alters biochemical events in the liver too dizzying to contemplate, and has a profound impact, no doubt, on the workings of cells in big toes. And it seeps into die brain, where it influences behavior in a way highly relevant to understanding aggression.

Genes are the hand behind the scene, directing testosterone's actions. They specify whether steroida, building blocks are turned into testosterone or estrogen, how much of each, and how quickly. They regulate how, fast the liver breaks down circulating testosterone, thereby determining how long an androgenic signal remains in the blood-stream. They direct the synthesis of testosterone receptors-specialized proteins that catch hold of testosterone and allow it to have its characteristic effects on target cells. And genes specify how many, such receptors the body has, and how sensitive they are. Insofar as testosterone alters brain function and produces aggression, and genes regulate how much testosterone is made and how effectively it works, this should be the archetypal case for studying how genes can

control our behavior. Instead, however, its the archetypal case for learning how little genes actually do so.

Some pretty obvious evidence links testosterone with aggression. Males tend to have higher testosterone levels in their circulation than do females, and to be more aggressive. Times of life when males are swimming in testosterone -- for example, after reaching puberty -- correspond to when aggression peaks. Among many species, testes are mothballed most of the year, kicking into action and pouring out testosterone only during a very circumscribed mating season-precisely the time when male-male aggression soars.

Impressive though they seem, these data are only correlative -- testosterone found on die scene repeatedly with no alibi when some aggression has occurred. The proof comes with the knife, the performance of what is euphemistically known as a subtraction experiment. Remove the source of testosterone in species after species, and levels of aggression typically plummet. Reinstate normal testosterone levels afterward wilt injections of synthetic testosterone, and aggression returns.

The subtraction and replacement paradigm represents pretty damning proof that this hormone, with its synthesis and efficacy under genetic control, is involved in aggression. "Normal testosterone levels appear to be a prerequisite for normative levels of aggressive behavior" is the sort of catchy, humble phrase the textbooks would use. That probably explains why you shouldn't mess with a bull moose during rutting season. But its not why a lot of people want to understand this sliver of science. Does the action of testosterone tell us anything about individual differences in levels of aggression, anything about why some males -- some human males -- are exceptional violent? Among an array of males, are the highest testosterone levels found in the most aggressive Individuals?

Generate some extreme differences and that is precisely what you see. Castrate some of the well-paid study subjects, inject others with enough testosterone to quadruple the normal human levels, and the high-restosterone males are overwhelmingly likely to be the more aggressive ones. Obviously, extreme conditions don't tell us much about the real world, but studies of the nonnative variability in testosterone -- in other words seeing what everyone natural levels are like without manipulating anything -- also suggest that high levels of testosterone and high levels of aggression tend to go together. This would seem to seal the case that lnterindividual differences in levels of aggression among normal Individuals are probably driven by differences in levels of testosterone. But that conclusion turns out to be wrong.

Here's why. Suppose you note a correlation between levels of aggression and levels of testosterone among normal males. It could be because a) testosterone elevates aggression; b) aggression elevates testosterone secretion; or c) neither causes the other. There's a huge bias to assume option a, while b is the answer. Study after study has shown that if you examine testosterone levels when males are first placed together in the social group, testosterone levels predict nothing about who is going to be aggressive. The subsequent behavioral differences drive the hormonal changes, rather than the other way around.

Because of a strong bias among certain scientists, it has taken forever to convince them of this point. Suppose you're studying what behavior and hormones have to do with each other. How do you study the behavioral part? You get yourself a notebook, a stopwatch, a pair of

binoculars. How do you measure the hormones and analyze the genes that regulate them? You need some gazillion-dollar machines; you muck around with radiation and chemicals, wear a lab coat, maybe even goggles -- the whole nine yards. Which toys would you rather get for Christmas? Which facet of science are you going to believe in more? The higher the technology, goes the formula, the more scientific the discipline. Hormones seem to many to be more substantive than behavior, so when a correlation occurs, it must be because hormones regulate behavior, not the other way around.

This is a classic case of what is often called physics envy, a disease that causes behavioral biologists to fear their discipline lacks the rigor of physiology, physiologists to wish for the techniques of biochemists, biochemists to covet the clarity of the answers revealed by molecular geneticists, all the way down until you get to the physicists who confer only with God. Recently, a zoologist friend had obtained blood samples from the carnivores he studies and wanted some hormones in the samples tested in my lab. Although inexperienced with the technique, he offered to help in any way possible. I felt hesitant asking him to do anything tedious, but since he had offered, I tentatively said, Well, if you don't mind some unspeakable drudgery, you could number about a thousand assay vials." And this scientist, whose superb work has graced the most prestigious science journals in the world, cheerfully answered, That's okay. How often do I get to do real science, working with test tubes?"

Difficult though scientists with physics envy find it to believe, interindividual differences in testosterone levels don't predict subsequent differences In aggressive behavior among individuals. Similarly, fluctuations in testosterone levels within one individual over time don't predict subsequent changes in the levels of aggression in that one individual -- get a hiccup in testosterone secretion one afternoon and that's not when the guy goes postal.

Look at our confusing state: normal levels of testosterone are a prerequisite for normal levels of aggression. Yet if one male's genetic makeup predisposes him to higher levels of testosterone than the next guy, he isn't necessarily going to be more aggressive. Like clockwork, that statement makes the students suddenly start coming to office hours in a panic, asking whether they missed something, in their lecture notes.

Yes, its going to be on the final, and it's one of the more subtle points in endocrinology -- what's referred to as a hormone having a permissive effect." Remove someones testes and, as noted, the frequency of aggressive behavior is likely to plummet. Reinstate pre-castration levels of testosterone by injecting the hormone, and pre-castration levels of aggression typically return. Fair enough. Now, this time, castrate an individual and restore testosterone levels to only 20 percent of normal. Amazingly, normal pre-castration levels of aggression come back. Castrate and now introduce twice the testosterone levels from before castration, and the same level of aggressive behavior returns. You need some testosterone around for normal aggressive behavior. Zero levels after castration, and down it usually goes@ quadruple levels (the sort of range generated in weight filters abusing anabolic steroids), and aggression typically increases. But anywhere from roughly 20 percent of normal to twice normal and its all the same. The brain can't distinguish among this wide range of basically normal values.

If you knew a great deal about the genetic makeup of a bunch of males, enough to understand how much testosterone they secreted into their bloodstream, you still couldn't predict levels of aggression among those individuals. Nevertheless, the subtraction and

reinstatement data seem to indicate that, in a broad sort of way, testosterone causes aggressive behavior. But that turns out not to be true either, and the implications of this are lost on most people the first 30 times they hear about it. Those implications are important, however -- so important that its worth saying 31 times.

Round up some male monkeys. Put them in a group together and give them plenty of time to sort out where they stand with each other -- grudges, affiliative friendships. Give them enough time to form a dominance hierarchy, the sort of linear ranking in which number 3, for example, can pass his day throwing around his weight with numbers 4 and 5, ripping off their monkey chow, forcing them to relinquish die best spots to sit in, but numbers 1 and 2 still expect and receive from him the most obsequious brownnosing.

Hierarchy in place, its time to do your experiment. Take that third-ranking monkey and give him some testosterone. None of this within-the-normal-range stuff. Inject a ton of it, way higher than what you normally see in rhesus monkeys, give him enough testosterone to grow antlers and a beard on every neuron in his brain. And, no surprise, when you check the behavioral data, he will probably be participating in more aggressive interactions than before.

So even though small fluctuations in the levels of the hormone don't seem to matter much, testosterone still causes aggression, right? Wrong. Check out number 3 more closely. Is he raining aggressive terror on everyone in the group, frothing with indiscriminate violence? Not at all. He's still judiciously kowtowing to numbers I and 2 but has become a total bastard to numbers,1 and 5. Testosterone isn't causing aggression, its exagerating the aggression that's already there.

Another example, just to show we're serious. There's a part of your brain that probably has lots to do with aggression, a region called the amygdala. Sitting near It is the Grand Central Station of emotion-related activity in your brain, die hypothalamus. The amygdala communicates with the hypothalamus by way of a cable of neuronal connections called the stria terminals. (No more argon, promise.) The amygdala influences aggression via that pathway, sending bursts of electrical excitation that ripple down the stria terminalis to the hypothalamus and put it in a pissy mood.

Once again, do your hormonal intervention: flood die area with testosterone. You can inject the hormone into the bloodstream, where it eventually makes its way to the amygdala. You can surgically microinject the stuff directly into the area. In a few years, you may even be able to construct animals with extra copies of the genes that direct testosterone synthesis, producing extra hormone that way. Six of one, half a dozen of the other. The key thing is what doesn't happen next. Does testosterone make waves of electrical excitation surge down the stria terminalis? Does it turn on that pathway? Not at all. If and only if the amygdala is already sending an excited volley down the stria terminalis, testosterone Increases the rate of such activity by shortening the resting time between bouts. It's not turning on the pathway, its increasing the volume of signaling if it is already turned on. Its not causing aggression, its exaggerating the pre-existing pattern of it, exaggerating the response to environmental triggers of aggression.

In every generation, it is the duty of behavioral biologists to try to teach this critical point, one that seems a maddening cliche once you get it. You take that hoary old dichotomy

between nature and nurture, between intrinsic factors and extrinsic ones, between genes and environment, and regardless of which behavior and underliving biology you're studying, the dichotomy is a sham. No genes. No environment. just the interaction between the two.

Do you want to know how important environment and experience are in understanding testosterone and aggression? Look back at how the effects of castration are discussed earlier. There were statements like Remove the source of testosterone in species after species and levels of aggression typically plummet." Not remove the source... and aggression always goes to zero." On the average it declines, but rarely to zero, and not at all in some individuals. And the more social experience an individual had being aggressive prior to castration, the more likely that behavior persists sans cojones. In the right context, social conditioning can more than make up for the complete absence of the hormone.

A case in point. the spotted hyena. These animals are fast becoming the darlings of endocrinologists, sociobiologists, gynecologists, and tabloid writers because of their wild sex reversal system. Females are more muscular and more aggressive than males, and are socially dominant to them, rare traits in the mammalian world. And get this@ females secrete more of certain testosterone-related hormones than the males do, producing muscles, aggression, and masculinized private parts that make it supremely difficult to tell the sex of a hyena. So high androgen levels would seem, again, to cause aggression and social dominance. But that's not the whole answer.

High in the hills above the University of California at Berkeley is the worlds largest colony of spotted hyenas, massive bone-crunching beasts who fight each other for the chance to have their ears scratched by Laurence Frank, the zoologist who brought them over as infants from Kenya. Various scientists are studying their sex reversal system. The female hyenas are bigger and more muscular than the males and have the same weirdo genitals and elevated androgen levels as their female cousins back in the savanna. Everything is just as it is m the Wild -- except the social system. As those hyenas grew up, there was a very significant delay in the time it took for the females to begin socially dominating the males, even though the females were stoked on androgens. They had to grow up without the established social system to learn from.

When people first realize that genes have a great deal to do with behavior -- even subtle, complex, human behavior they are often struck With an initial evangelical enthusiasm, placing a converts faith in the genetic components of the story. This enthusiasm is typically reductivity because of physics envy, because reductionism is so impressive, because it would be so nice if there were a single gene (or hormone or neurotransmitter or part of the brain) responsible for everything. But even if you completely understood how genes regulate all the important physical factors involved in aggression-testosterone synthesis and secretion, the brains testosterone receptors, the amygdala neurons and their levels of transmitters, the favorite color of the hypothalamus -- you still wouldn't be able to predict levels of aggression accurately in a group of normal individuals.

This is no mere academic subject. We are a fine species with some potential, yet we are racked by sickening amounts of violence. Unless we are hermits, we feel the threat of it, often every day, and should our leaders push the button, we will all be lost in a final global violence. But as we try to understand this feature of our sociality, it is critical to remember the limits of the biology. Knowing the genome, die complete DNA sequence, of some

suburban teenager is never going to tell us why that kid, in his after-school chess club, has developed a particularly aggressive style with his bishops. And it certainly isn't going to tell us much about the teenager in some inner city hellhole who has taken to mugging people. "Testosterone equals aggression" is inadequate for those who would offer a simple biological solution to die violent male. And "testosterone equals aggression" is certainly inadequate for those who would offer the simple excuse that boys will be boys. Violence is more complex than a single hormone, and it is supremely rare that any of our behaviors can be reduced to genetic destiny. This is science for the bleeding-heart liberal: the genetics of behavior is usually meaningless outside the context of the social factors and environment in which it occurs.