A RECIPE FOR VIOLENCE

Potent mix of brain chemistry, brain damage, genetics, and environment leads to aggression

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HOOLIGANS Soccer fans' violence stems from a multitude of factors.

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It's not just pop psychology: along with the targets of their actions, violent and aggressive people are victims, too.

Although people are ultimately responsible for their own actions, their predilection for violence is shaped by the complex interplay between their genetic inheritance and the physical and psychological environment of their formative years and beyond. In addition to genetic defects, risk factors include child abuse, exposure to lead, alcohol abuse, and accidental brain damage. These negative influences can be ameliorated by protective genes, good parenting, and pharmacological intervention.

Chemists, medical professionals, sociologists, and others are teasing apart the threads that make up this messy tapestry of cause and effect in order to improve treatment of offenders and reduce the incidence of violence.

The need is great. Despite a downward trend in the past few years, 1.4 million violent crimes were committed in the U.S. in 2000, according to the
Bureau of Justice Statistics. The National Center for Health Statistics reports that homicides totaled 16,765 that year and 29,350 people committed suicide.

Of course, these statistics exclude a wide range of actions that don't meet the definition of a violent crime or that go unreported. Examples include socially sanctioned violence, such as a hockey brawl, and illness-related aggression toward a caretaker, such as that caused by Alzheimer's disease.

There are, in fact, multiple kinds of aggression or violence that can be categorized in numerous ways. One common division separates premeditated aggression—such as the 1999 Columbine High School massacre—from impulsive, unplanned aggression, which usually occurs in response to a frustrating or irritating stressor.

Researchers realized two decades ago that violent behavior was associated with flaws in the serotonin neurotransmitter system—but only in impulsive aggressive people, explains Emil F. Coccaro, director of the Clinical Neuroscience & Psychopharmacology Research Unit at the University of Chicago. Most of the early research into the biochemistry of violence thus centered on impulsive aggression, and that allocation of resources continues to this day. But just because serotonin does not appear to be involved in planned violence, Coccaro is quick to note, "that does not mean there isn't a biology to premeditated aggression."

Serotonin, also called 5-HT, is primarily an inhibitory neurotransmitter that acts as a kind of brake on impulsiveness. Individuals with normal or higher levels of serotonin show more restraint and think things out, says J. Dee Higley, a research psychologist at the National Institute on Alcohol Abuse & Alcoholism (NIAAA). Those with low serotonin levels, on the other hand, "act first and think later, and that gets them in trouble."

BUT IMPULSIVE BEHAVIOR isn't all bad. "Under certain settings, impulsiveness probably pays a benefit," Higley says. In war, for instance, it may require an impulsive person to succeed at a daring charge to take the top of a hill. Likewise, explorers and settlers may also be impulsive characters who are willing to take risks.

"The problem is if you're impulsive and you have a short fuse, and you get into a setting that's likely to elicit violence, you are going to be more prone to exhibit aggressive behavior," Higley says.

Consider a man who goes into a bar and sees his girlfriend chatting with another man. If the boyfriend suffers from impaired serotonin function, he may "impulsively jump right in, ending up in an altercation and perhaps some sort of fracas," Higley says. But if the boyfriend's serotonin system functions well, he may eye the stranger and say, "Hey, he's got a beer bottle in his hand. He's bigger than me. Maybe I'll wait and talk about this later on..."
with my girlfriend."

Although serotonin appears to be the major neuro-transmitter involved in aggression, it's not the only game in town.

Higley has devoted more than 25 years to the study of violence, working for the past 15 years with a colony of about 5,000 free-ranging rhesus monkeys that live on a South Carolina island. He gauges serotonin system function by periodically taking a little cerebrospinal fluid (CSF) from the monkeys and measuring levels of 5-hydroxyindoleacetic acid (5-HIAA), a serotonin metabolite.

Levels of 5-HIAA, which remain consistent over the years in individual monkeys, confer a "personality style" on each animal, Higley says. Those with low 5-HIAA—and presumably with impaired brain serotonin systems, he says—sport more scars and wounds. Although other monkeys in the colony are just as likely to initiate aggression, the low-5-HIAA monkeys tend to escalate an incident out of control. What "starts off as a play bout or a mild tussle over a piece of chow escalates to where the monkeys are jumping through the trees or rolling around biting each other—both of which are pretty high-risk kinds of violent behavior," he says.

Even when the low-5-HIAA monkeys aren't having tantrums, they are daredevils. Typical monkeys move throughout the island by way of the treetops, which are 10 to 20 meters high, by carefully pulling a branch over to cross to the next tree or by retreating if they can't find a reasonable route. The low 5-HIAA monkeys are not deterred by a gap between trees; they just spontaneously leap from
one to the next. The performance is "stunning to watch, but very dangerous
to the impulsive monkey," Higley says.

**THESE SEROTONIN-impaired monkeys also show marked behavioral
differences during a test in which the animals can access food but end up in a
trap from which they cannot escape. After going through this experience,
many monkeys avoid the setup for a year or two. However, the low-5-HIAA
monkeys repeatedly return for food despite the trap, sometimes on
successive days.

Results with the monkeys are borne out by human behavior. Higley's
NIAAA colleague, the late Markku Linnoila, studied arsonists and found that
those who committed the crime impulsively had low serotonin. On the other
hand, those who did it for pay had normal levels of 5-HIAA. Linnoila also
studied prisoners who had committed impulsive, violent crimes. He found
that "the more violent they were, the more times they had acted aggressively
throughout their lives, the lower the 5-HIAA that they had," Higley says.

Coccaro has also been studying the human serotonin system for years. In his
early work, he looked at patient response to a drug, fenfluramine, that
increased serotonin activity in the brain.

Patients who were more aggressive showed a lower response than the less
aggressive patients, presumably because the more aggressive patients' 
serotonin systems were less active. And people with a history of suicidal
behavior also showed a lower response, "because the serotonin system
relates both to aggression directed outwardly and aggression directed
inwardly," he says. Coccaro notes that brain serotonin levels are lower in
those who commit suicide as compared to those who die violently by other
means.

In a subsequent study, Coccaro attempted to boost patients' serotonin levels
by decreasing the neurotransmitter's reabsorption by neurons. In this work,
he compared the selective serotonin reuptake
inhibitor Prozac (fluoxetine) and a placebo in patients
with impulsive aggressive personality disorder—
"people who are hotheads."

Coccaro found that some of the Prozac recipients
improved. And when he recently reanalyzed the
results of that study, he discovered that "the
improvement was entirely in people who were moderately aggressive." Unlike those patients, Coccaro reasoned, their more aggressive fellows had
such damaged or poorly functioning serotonin systems that a drug such as
Prozac couldn't help.

Anticonvulsants that can also be used as mood stabilizers are an alternative
treatment. Coccaro plans to compare Prozac and the mood stabilizer
Depakote (divalproex sodium) in the treatment of moderately aggressive
patients. These drugs may work by a different enough mechanism that they
could even be used to treat the more violent patients, he says.

Although the mechanism isn't fully understood, Depakote is known to increase brain levels of \(\gamma\)-aminobutyric acid, an inhibitory neurotransmitter. It also may increase serotonin activity through a different mechanism than Prozac does, Coccaro says.

Dilantin (phenytoin), an anticonvulsant used to treat epilepsy, cut the number and intensity of aggressive acts committed by impulsive convicts, according to a study by Ernest S. Barratt, a professor in the psychiatry and behavioral sciences department at the University of Texas Medical Branch in Galveston. But the drug had little effect on those who committed premeditated aggression.

The anticonvulsant carbamazepine and the mood stabilizer lithium may also prove helpful in reducing violent behavior. Carbamazepine's activity isn't clearly understood. But lithium is believed to boost serotonin levels.

Although serotonin appears to be the major neurotransmitter involved in aggression, it's not the only game in town. Coccaro found a positive correlation between a life history of aggression and elevated levels of the neurotransmitter vasopressin in the subject's CSF. There is also evidence that high levels of norepinephrine and dopamine are positively related to aggression, he says.

HORMONES MAY also be a factor, although their impact is unclear. Coccaro, for instance, has not found a link between levels of the steroid hormone testosterone and aggression.

In his own studies, Higley says monkeys with high testosterone levels "were more likely to act competitively, but they were no more likely to act in a violent manner" than monkeys with lower testosterone levels. But low levels of 5-HIAA mixed with high levels of testosterone created "the worst characters in the whole study. These are the guys who were chronically in trouble and tended to act aggressively in a wide variety of settings and in unrestrained fashion," Higley says. These results suggest "that testosterone is the push to act in an aggressive manner, but the brakes that control the setting, to whom, and the level that you're going to express it at are based in the serotonin system."

Armed with new understanding of the role of neurotransmitters and hormones in aggression, the medical profession can apply treatments that compensate for flaws in these biochemical systems. Eventually, it may even be possible to fix underlying genetic faults. But that's a long-term goal. For now, "we know very little about the identity and function of specific genes that contribute to the risk for violent behavior," says
Evan S. Deneris, associate professor of neuroscience at Case Western Reserve University School of Medicine, Cleveland. "So it's pretty foggy."

Deneris and his colleagues are trying to pierce that fog by identifying which genes are important in the development of the brain's serotonin neurons. They discovered a gene, designated Pet-1, that proves to be critical for the development and proper function of serotonin neurons. In mice that are genetically engineered to lack this gene, brain serotonin levels are only 10-15% of the normal level [Neuron, 37, 233 (2003)]. As expected, Deneris says, the knockout mice exhibit heightened aggression and anxiety.

Mouse aggression can be gauged by how staunchly males defend their territory. A "resident mouse" in its home cage will become perturbed if another male mouse—the "intruder"—is introduced into the cage, Deneris says. A wild-type resident mouse "will go up to the intruder, sniff it, groom it, and eventually may even attack the intruder by biting it, chasing it around the cage, and trying to get it out. So typically, there's a period of nonaggressive curiosity that can be followed by physical attack," Deneris says. The resident mouse "is being cautious about what it's doing. It's not being impulsive."

Deneris measured the time it took for wild-type resident mice to attack intruder mice. Then he measured this "attack latency" for his Pet-1 knockout resident mice. "Our knockout mice spend a lot less time in nonviolent, exploratory behavior," he says. "They're very impulsive, and oftentimes they don't spend any time exploring. They don't spend any time thinking about what they're doing. They just go straight for the intruder and start to attack it." In addition, the knockout mice carry out more attacks and more severe attacks than the wild-type mice.

"Our findings identify the first gene that impacts aggressive behavior in the adult through control of fetal serotonin neuron development," Deneris says. "The goal now is to determine the mechanisms through which the Pet-1-dependent genetic program regulates serotonergic modulation of aggression." He also plans to study "what has happened to the rest of the brain in the face of this low level of serotonin. Have the postsynaptic targets of serotonin neurons modulated themselves by either increasing or decreasing receptor expression?" That's not a simple question, given that the brain has more than a dozen types of serotonin receptors.

The human and mouse serotonin systems share many features, and the same Pet-1 gene is present in the human genome. Thus, Deneris also wants to find out whether the human version of Pet-1 performs a similar function and whether naturally occurring genetic variants of the Pet-1 program exist and contribute to the risk for aggressive behaviors.

Researchers are studying the role of
other genes as well. For instance, knockout mice lacking the gene for neuronal nitric oxide synthase, an enzyme involved in neurotransmission and production of nitric oxide, are extremely aggressive. In studying these mice, Randy J. Nelson, a social and behavioral sciences professor at Ohio State University, and colleagues concluded that "neuronal-derived NO is essential to the normal function of the central 5-HT system."

For instance, "parents appear to play a critical role in the development of the serotonin system," which occurs during childhood, Higley says. In monkeys, association with nurturing parents can lastingly curb arousal and anxiety in their offspring. The impact becomes apparent when comparing monkeys raised by their mothers to "peer-reared" monkeys raised in the absence of adults. Serotonin system development of the monkeys in the two groups begins to diverge as early as two weeks of age—with the peer-reared monkeys showing diminished levels of 5-HIAA—and the differences persist well into adulthood.

THOSE RESULTS show the impact of the loss of good parenting on young monkeys with normal genes. Higley and his NIAAA colleague Allyson J. Bennett performed another study that revealed the impact of good parenting on young monkeys with defects in the genes that determine the characteristics of the serotonin reuptake system [Mol. Psychiat., 7, 118 (2002)].

A short allele produces an impaired transporter for the serotonin reuptake system that can lower the amount of available serotonin. Higley and Bennett found that rearing by a mother compensates for the serotonin system deficit caused by this genetic defect. Regardless of whether they had the short or long version of the allele, mother-reared monkeys produced about the same amount of 5-HIAA. The buffering effect is lost when monkeys' parents are missing and they are raised by peers. Peer-reared monkeys with the defective allele produced much lower levels of 5-HIAA than those with the regular allele. Higley is trying to find out how rearing by a mother overcomes the transporter defect.

Apparently, environment can compensate for poor genes. In some cases, the
reverse is true: Genetics can confer protection from a hostile environment. Avshalom Caspi, a University of Wisconsin psychology professor, published a paper last summer about the interaction between genes and the environment [Science, 297, 851 (2002)]. Caspi and his colleagues reported that they "studied a large sample of male children from birth to adulthood to determine why some children who are maltreated grow up to develop antisocial behavior, whereas others do not.

The lead-exposed monkeys proved to be so aggressive that the test was halted early because an animal was injured.

Specifically, the researchers looked at genotypes that affect production of monoamine oxidase A (MAOA). This enzyme breaks down dopamine and norepinephrine—two neurotransmitters that may promote aggression—as well as serotonin. Depressed levels of MAOA enzyme are associated with aggressive behavior. The team found that "maltreated children with a genotype conferring high levels of MAOA expression were less likely to develop antisocial problems" than those with low MAOA expression.

Generally speaking, however, kids who are severely punished or who witness aggression or parental dysfunction are more likely to exhibit aggressive behavior later in life, Coccaro says.

One hypothesis suggests that people with this kind of history develop abnormalities in their social information processing skills. For instance, if a participant in a karate match hurts an opponent in the process of winning the match, the loser could interpret the situation in any number of ways. "The average person who doesn't have these sorts of deficits in social information processing and hostile attributional bias—which is what you tend to get when you have been abused as a child—would say, 'It was an accident,' or, 'That's what he thought he needed to do to win the match,' " Coccaro explains. "All things being equal, if you think somebody did something to you by accident, you're not going to retaliate."

On the other hand, "Someone who's been abused as a child and who's experienced a lot of aggression will say, 'That guy wanted to hurt me. He wanted me to look bad.' " In turn, Coccaro says, "that's going to be a trigger for him to do something back. What's underneath that neurobiologically, we're not certain of. But there are brain circuits involved in emotional regulation processing, and they're probably affected."
In fact, positron emission tomography (PET) and magnetic resonance imaging scans indicate that the prefrontal cortex is smaller or less active in impulsive murderers and those who have antisocial personality disorder (ASPD) than in control subjects and "cold-blooded" killers who plan their crimes, according to University of Southern California psychology professor Adrian Raine. The prefrontal cortex, the outer part of the brain located just behind the eyes, controls impulses and is involved in emotion, arousal, attention, the interpretation of sensory stimuli, and conscience. Raine has also determined that both types of murderers have higher activity in the right-hemisphere subcortex than control subjects. The subcortex includes the amygdala, hippocampus, midbrain areas, and thalamus. It is believed to be involved in generation of aggressive feelings and behavior, Raine notes.

In addition to parenting quality, other environmental influences include television and other media that can deliver violent content to minors. Results from research into the behavioral impact of such viewing have for the most part been contradictory, according to Coccaro. But he is impressed by data recently published by L. Rowell Huesmann, who tracked the TV viewing habits of kids as they grew up and correlated it with the development of aggressive behavior [Dev. Psych., 39, 201 (2003)]. Huesmann, who heads the University of Michigan's Aggression Research Program, is a professor of communication studies and psychology.

Huesmann found that viewing violence on TV had a more negative impact if it started when kids were younger, with ages from six to nine being especially vulnerable, Coccaro says. The type
of violence they watched and identified with also made a difference. For instance, "Dirty Harry does really violent things to really bad people. He wins the day and the glory from it," Coccaro says. "If kids identify with that, that's more problematic than watching a horrible criminal do a horrible thing, because that's not reinforced. He ultimately doesn't get rewarded for it. He gets his comeuppance at the end."

More tangible environmental hazards include lead. While working at the University of Wisconsin's Harlow Center for Biological Psychology, senior scientist Nellie K. Laughlin studied a group of adult female monkeys that had been exposed to lead for research into the metal's impact on babies. Laughlin observed the social behavior of small groups of the adults, including activities such as grooming.

"I was naive," she recalls. "I thought, 'They're females; there won't be any aggression.'" But Laughlin was wrong. The lead-exposed monkeys proved to be so aggressive that the test was halted early because an animal was injured.

In a recent paper, Herbert L. Needleman, a professor of child psychiatry and pediatrics at the University of Pittsburgh School of Medicine, and his colleagues confirmed the link between delinquency and elevated body burdens of the metal [Neurotoxicol. Teratol., 24, 711 (2002)]. Lead interferes with synapse formation, lowers serotonin levels, and increases dopamine sensitivity, among other central nervous system effects, he wrote. And it may indirectly increase the likelihood of misbehavior by impairing cognitive function and school performance. However, "the specific biological mechanisms underlying lead's effect on aggression and impulsiveness are not known," according to Needleman.

Other factors that have been blamed for inciting aggression include poor nutrition. Deficits in consumption of vitamins, minerals, and essential fatty acids may interfere with the production of neurotransmitters. Oxford physiologist C. Bernard Gesch found that administering nutritional supplements to young adult prisoners significantly reduced their antisocial behavior, including violence, as measured by disciplinary offenses [Br. J. Psychiat., 181, 22 (2002)].

Some researchers believe that low levels of cholesterol may be linked to an increased likelihood of violent behavior and violent death, possibly resulting from reduced serotonin activity. Backers of this controversial theory include Beatrice A. Golomb, a physician at the Veterans Affairs Medical Center in...
One risk factor about which there is no controversy is alcohol, considered to be "one of the largest contributors to violence," Higley says. "About half of the episodes that occur—whether they are murders, rapes, or whatever—tend to be under the influence of alcohol."

**ALCOHOL MAY** "lead a person to misjudge social cues, thereby overreacting to a perceived threat," according to a statement from NIAAA. Furthermore, alcohol may "lead to an inaccurate assessment of the future risks of acting on an immediate violent impulse." From a physiological point of view, alcohol may exacerbate aggressive tendencies by metabolizing serotonin. In addition, ASPD, which is characterized by a "disregard for the rights of others, often manifested as a violent or criminal lifestyle," may share a genetic basis with early-onset alcoholism, according to NIAAA.

Higley's low 5-HIAA monkeys drink more alcohol and have a harder time stopping when they start. Once they're drunk, they are more likely to be aggressive than monkeys whose serotonin systems function normally. Higley adds: "Alcohol appears to lower the threshold that it takes to elicit aggression, making individuals that are already aggressive especially dangerous. In fact, the only time that I've ever been chased by any of these monkeys—which are about a sixth of my size—is when they are intoxicated. And the ones that do it are the animals with low serotonin."

Illicit drugs, including cocaine and phencyclidine (known as PCP or angel dust), are also associated with increased violence. Cocaine damps down serotonin synthesis and release and boosts release of excitatory neurotransmitters such as adrenalin. It also interferes with the reabsorption of dopamine. PCP, too, affects multiple neurotransmitter systems.

Researchers are clearly making headway in their studies of violence and aggression. But their work yields complicated legal and ethical conundrums. For instance, it seems logical to punish a violent criminal. But given what scientists have learned about the serotonin system, can a person who commits a violent act as a result of flawed brain chemistry be held responsible for the deed?

"People who have risk factors for being more likely to commit an aggressive act should get treated for those factors if possible," Coccaro says. "But it doesn't free them of criminal responsibility. They can still step back from these behaviors." The mitigating factors of biology and life history are more relevant to sentencing, he believes.

Another equally thorny issue concerns prophylactic intervention. "In our society, we would not espouse treating individuals simply because they have some sort of characteristic that makes them more prone to developing aggressive or violent behavior," Higley says.
Nevertheless, he is analyzing whether early behaviors can serve as warning signs that a child may develop into a violent or aggressive person. In monkeys, one revealing type of encounter is rough play, which young animals use to learn to express aggression at an intensity that's appropriate to the setting.

"It appears that early play behavior predicts which individuals are going to become aggressive later on, with monkeys that practice rough play a lot early in life learning to inhibit aggression and express it appropriately," Higley concludes from his studies. "Monkeys that seldom play early in life, on the other hand, do not learn such skills, and they act aggressively when they become teenagers."

Even if a particular warning sign is present, however, it may not prove a definitive signal. "It's pretty clear that biology is not destiny," Higley notes. "It's a risk, but it's not a guarantee."

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