

Violence—a noxious cocktail of genes and the environment

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In 1991, Stephen Mobley shot and murdered a pizza store manager during an armed robbery in Georgia, USA.¹ During his trial, the US lawyers requested that their client be tested for a specific genetic mutation found in the monoamine oxidase A gene which if present would explain his violent behaviour and thus exonerate him. Two courts rejected this request because of the lack of scientific evidence for such causation. However, if research were to yield good evidence of genetic influences on violence, future cases might be decided differently.

Until recently, violence has been regarded as normal or at least non-pathological behaviour. It has been a feature of all civilizations, and in primitive societies violent behaviour was a necessity, to fend off adversaries, hunt for food and secure the desired mate. Through 'natural selection', those with more aggressive traits have succeeded in passing down their genes. Clearly, some capacity for violence is needed for species survival. But can violence-related genes excuse some of our misdeeds?

The World Health Organization (WHO) defines violence as: 'The intentional use of physical force or power, threatened or actual, against oneself, another person, or against a group or community, that either results in or has a high likelihood of resulting in injury, death, psychological harm, maldevelopment or deprivation'.² In the year 2000, some 1.6 million people worldwide died from violence, half from suicide, one-third from homicide and one-fifth from the effects of war.³ Much research has been conducted into environmental influences on violent behaviour such as childhood maltreatment and substance abuse, and these can be valuable in risk assessment. However, less attention has been given to the genetic contribution to this 'noxious cocktail'. In this review I concentrate on the role of genetics in the programming of individuals who exhibit violent behaviour towards others. I do not include deliberate self-harm, suicide or war-related violence. The terms 'aggressive' and 'violent' are used interchangeably.

THE GENES

All of us have the capacity to be violent, but most people can control this force. Thus, if violent tendencies are

distributed on a bell-shaped curve, a few individuals at the extreme can be found to readily lose control. Another perspective is to see violence as a disease, by analogy with, say, non-insulin-dependent diabetes mellitus. In type 2 diabetes there are both genetic and environmental contributions, and the genetic component has been related to the 'thrifty gene hypothesis'.⁴ According to this hypothesis, genes that evolved to cope with periods of starvation and hunger are disadvantageous when an affluent lifestyle presents us with large amounts of carbohydrate. In the same way, a mutation or polymorphism that evolved for protective reasons might today, in combination with certain environmental stimuli, predispose to antisocial behaviour.

The first suggested evidence of a human genetic mutation associated with aggressive behaviour came from a study by Brunner *et al.* in 1993.⁵ Genetic and metabolic studies were conducted on a large Dutch family in which several of the males had a syndrome of borderline mental retardation and abnormal behaviour. The undesirable behaviour included impulsive aggression, arson, attempted rape and exhibitionism. In each of the affected males, the genetic defect was located to the X chromosome in the region of p11–12; a point mutation was identified in the eighth exon of the monoamine oxidase A (MAOA) structural gene which changes glutamine to a termination codon.

The enzyme monoamine oxidase A catalyses metabolism of several kinds of neurotransmitter in the brain including serotonin, dopamine and noradrenaline. The metabolites are excreted in urine and 24-hour urine analyses performed by Brunner *et al.* pointed to disturbed monoamine metabolism with low concentrations of 5-hydroxyindole-3-acetic acid (5-HIAA) and other MAOA-breakdown products. Cerebrospinal fluid was not examined but the urinary findings were assumed to reflect central neurotransmitter metabolism. The interpretation was that high concentrations of non-metabolized neurotransmitters, due to low MAOA activity in the brain, might cause impulsive bouts of aggression.

This point mutation is extremely rare, and there has so far been no replication of the findings reported by Brunner *et al.* However, experiments on mice have yielded supportive evidence. In 1995, Cases *et al.* developed a line of transgenic mice that were lacking in MAOA.⁶ In adults, the brains had abnormally high noradrenaline concentrations

and showed cytoarchitectural changes in the somatosensory cortex. These mice displayed a distinct behavioural syndrome which included enhanced aggression in males. Cases *et al.* concluded that aggressive behaviour was a direct consequence of the MAOA deficiency and its effects on neurotransmitters. Further animal models have shown behavioural abnormalities due to single gene mutations. Neuronal nitric oxide (NO) is a neurotransmitter found in high densities in emotion-regulating brain regions, neuronal nitric oxide synthase (nNOS) being the enzyme that aids its synthesis. In mice, Nelson *et al.* found that disruption of the nNOS gene resulted in a large increase in inappropriate aggressive and sexual behaviour.⁷ This abnormal behaviour was attributed to the consequent low levels of NO in the brain. Another suggestion was that NO neurons communicate with serotonin cells, in which case the defect might also involve the serotonin pathway and tie the findings in with the results of Cases *et al.* The murine models used by Cases and Nelson pointed to a simple relationship between a single disease gene and abnormal behaviour. But in man violent behaviour is almost certainly a complex trait/disease. To gain understanding and knowledge, mutations associated with the disorder must be identified first and then 'reconstruction of the crime' begins—a method termed 'reverse genetics'.⁴ Difficulties arise from the multiplicity of genes associated with the complex trait and in accounting for the environmental factors. Genetic analysis is also complicated by incomplete penetrance, polygenicity and phenocopies, all of which reduce the correlation between phenotype and genotype, and the possibility that the relevant genes might differ between ethnic groups.

This year, 2003, the complete human genome will be available for all behavioural geneticists to analyse. With new technologies such as DNA microarrays, thousands of genes can be compared simultaneously.⁸ It may be possible to gather samples of DNA from groups of violent criminals and individuals who display other sorts of antisocial behaviour, and test their genomes for mutations or polymorphisms that differentiate them from the general population.

THE COCKTAIL

What of the non-genetic contributions? A universal risk factor for the development of antisocial behaviour in adulthood is childhood maltreatment. Young boys who are abused or have coercive and castigatory parents are generally more likely to develop an antisocial personality or become a violent offender.⁹ An investigation by Maxfield and Widom highlighted the intergenerational transmission of aggressive and violent behaviour from parents to children.¹⁰ In a retrospective study of over 900 abused children in Indianapolis, USA, they found that children who

were physically abused up to the age of 11 years were at excess risk of becoming violent offenders in the subsequent 15 years. The researchers suggested that, having learned by example, these individuals saw aggression as a legitimate way to deal with challenges.

The earlier a child experiences maltreatment, the greater the risk of subsequent antisocial behaviour; nonetheless, most maltreated children do not become criminals or delinquents. Maltreatment is believed to increase the risk of adult criminality by about 50%.¹¹ The explanation for the considerable differences between children in response to maltreatment could be genetic susceptibility. Caspi *et al.*⁹ investigated the role of a particular genotype—a specific function variable number tandem repeat (VNTR) polymorphism in the promoter region of the MAOA—in determining susceptibility to maltreatment and in modifying the influence of maltreatment on development of antisocial behaviour. They began by enrolling 442 individuals from the New Zealand Dunedin Multidisciplinary Health and Development Study, a cohort of over a thousand followed since birth. To reduce ethnicity-related genetic variation, children with four Caucasian grandparents were selected and categorized as severely maltreated, moderately maltreated or controls (no evidence of maltreatment). The genotype of MAOA activity was recorded for each individual, high or low, according to the VNTR polymorphism. When the participants had reached 26 years of age, it was noted whether they had developed a conduct disorder, had been convicted for a violent offence, had developed a disposition towards violence, or were exhibiting an antisocial personality disorder. The results showed clear differences. Among males with the low MAOA activity genotype, antisocial scores were higher in those maltreated in childhood than in those not maltreated. By contrast, among males with high MAOA activity, there was no excess of antisocial behaviour in relation to child abuse. Furthermore, the males who experienced moderate to severe maltreatment as children and had the low MAOA activity genotype, although constituting only 12% of the study group, committed 44% of the total crimes.¹² In the words of one of the researchers (T Moffitt), 'they're doing four times their share of rape, robbery, and assault'.⁹ Seemingly, the low MAOA activity genotype is a vulnerability factor which, together with an environmental factor, predisposes to violent behaviour; or, alternatively, the high MAOA activity genotype protects against environmental insults.

The findings of this study seem to present an important advance in behavioural and psychiatric genetics. However, replication is essential because of the colossal medical, social, legal and ethical implications of this type of research. The results could form the basis of pharmacological interventions (for example, drugs that counter the effect

of low MAOA activity in the brain) or even gene therapy. It has been suggested that social workers and therapists would benefit from knowing which abused children are most at risk of developing behavioural abnormalities in adult life.¹² Legal connotations include the attitude of courts to violent offenders who express the genetic defect and have a proven history of childhood abuse. On a larger community scale, the ability to predict criminally violent behaviour could give rise to strategies implementing crime prevention—for example, electronic tagging of predisposed individuals, or even detention before the crimes are committed.

ETHICS

The bioethics of violent behaviour is a controversial area. At a genetic level there will be difficulties in measuring the effects of behavioural genes on any one individual, especially in view of varied environmental influences. Moreover, with a continuous variable it will be hard to decide who has the disorder and who has not. The parallel with type 2 diabetes continues: definitions based on glucose tolerance have changed several times since its first classification. To medicalize violence would be a complex process, especially when such behaviour has previously been accepted as non-pathological. Usually we work from the principle that people are morally responsible for actions performed by choice. But, since genetic make-up is predetermined, some might seek to make genes an excuse for misbehaviour. The identification of strong genetic influences on violent behaviour and other personality traits would carry risks of unscrupulous exploitation, public misinterpretation and discrimination against individuals or groups.¹³ The case of Stephen Mobley, reported in the opening paragraph of this review, is a case in point.

The testing of individuals for presence or absence of undesirable genotypes would have potential for both good and harm. On the plus side, early identification of a hazardous trait might allow prevention by genetic, medical or environmental interventions.¹³ However, consider the case of an individual who, though not yet having committed any violent crimes, is detained in a psychiatric institution as 'socially undesirable'. In December 2000, the Department of Health and the UK Home Office published a White Paper for a new Mental Health Act, 'Managing Dangerous People With Severe Personality Disorder'.¹⁴ The document outlined two proposals for compulsorily detaining those with 'dangerous' severe personality disorder (DSPD), who are thought to pose a threat to the safety of others. Three categories of people are encompassed under DSPD—those leaving secure hospitals, those leaving prison and those in the community.¹⁴ According to Professor Anthony Maden (personal communication) DSPD represents 'a risk of 50%

or more of an individual committing a serious offence, associated with a severe personality disorder'.

The first proposal of the White Paper was to change the present framework of criminal and mental health law in order to prevent people with severe personality disorders being released from prison or hospital if they presented a risk to the public. The second proposal suggested a new legal framework that would provide new powers for the indefinite detention of people with DSPD in criminal and civil proceedings. In simple terms the British Government wishes to incarcerate people according to the opinions of others as to their propensity to behave dangerously at some point in the future. Pilot assessment centres for DSPD candidates have already been set up to examine the feasibility of confining individuals with this disorder.¹⁵

These legislative plans have fuelled a great debate on the morality of preventively detaining 'innocent' individuals, who have been labelled with a disorder that has yet to be clearly defined and for which no treatment can be offered. As a result of the dispute, Buchanan *et al.* in 2001 began an investigation to examine and analyse twenty-three published studies on the accuracy of 'dangerousness' assessments.¹⁴ The sensitivity and specificity of the procedures were evaluated, and on this basis they estimated that six people with DSPD would need to be detained for one year to prevent one violent act within that year. Buchanan *et al.* remarked that, in practice, the number of people that would have to be detained would be in excess of that figure. Commenting on these findings, Farnham and James observed, 'The forecasting of dangerousness remains like that of the weather—accurate over a few days, but impotent to state longer-term outcome with any certainty'.¹⁵ For the five needlessly detained individuals, not only has the medical profession let them down, but the law has ignored the basic notion of 'innocent until proved guilty'.

RISK FACTORS

There are several circumstances in which clinicians legitimately assess the probability that a patient will behave in ways damaging to others.¹ Existing criteria regarding predisposition to act in a violent or fear-inducing manner are based on a plethora of well-researched behavioural, social and environmental influences. A notable risk factor is social isolation; another is an intensely dependent but discordant relationship with a single person. However, certain gregarious individuals demand attention—for example, adolescents with strong friendship networks who disengage from parental supervision and allow peer pressure to dictate their actions. In the words of Tarter *et al.*, 'Adolescents who are delinquent and aggressive affiliate with peers who are similarly aggressive and delinquent'.¹⁶

This could be a case of learned behaviour, or merely conformity to subcultural tribal customs such as football hooliganism.

Substance abuse is probably the largest independent environmental precipitator of violence in adults and adolescents. In the American Epidemiologic Catchment Area Study, published in 1990, self-reported violence in the past year was measured among a representative community sample of 10 059 individuals.¹⁷ The prevalence of violence was 2% in people with no psychiatric disease, 24% in alcohol misusers and 34% in those with drug misuse or dependence disorders. The prevalence in patients with schizophrenia was just 8%.

These are just a few of the factors to be considered by a psychiatrist trying to manage imminent risk or devise a long-term strategy to minimize harm. Thus, remedial action might include reduction of social and interpersonal stressors, treatment of mental disorder, control of substance abuse, and an attempt at avoiding provocations. The approach is not coercive: the model is fluid, subject to constant shifts depending on the interaction between the current state of mind with situational triggers.¹ So far, the role of genetic inheritance in offending behaviour has not been included. As research moves on, this may change.

CONCLUSION

From the information assembled here, it is clear that violent behaviour is a complex multifactorial trait. Evidence for a genetic contribution is growing in strength, and can usefully be examined in relation to currently accepted environmental factors. Optimism that discovery of a genetic basis for mental disorders would 'enhance diagnostic accuracy, improve treatment and radically alter clinical practice'¹⁸ has been fortified by the completion of the Human Genome Project. The question of whether violence is a disease or just a conscious deviance from the norm seems to be reaching a natural resolution through the evolution of psychiatric research.

In the past, violence was regarded as an obvious infringement of basic human law and self-control, but now there are strong pressures to medicalize this undesirable conduct, exemplified by the UK Government's plans to incarcerate potential offenders under medical orders. Whatever their motives, there is mounting evidence that violent behaviour has a pathological basis and that interventions could be preventive. Risk factors such as the availability of firearms, socioeconomic inequalities, political instability and exposure to violence in mass media can all be targeted by governments without special legislation. The WHO recommends primary prevention responses such as preschool and social development programmes for children

and adolescents, parental training, and support programmes.²

Alongside work on the aetiology of violence, the ethical issues must be kept in view. Much of the science remains insecure. Currently, the strongest known genetic marker for violence is the Y chromosome.¹¹ Incarceration of all males of the species would hugely reduce the rates of violence. This simple but preposterous example illustrates the complexity of the issues, and the need for scientific and ethical rigour.

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