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EDITORIAL

Chemistry: Shaping Bodies, Moulding Minds

We are in the midst of a year that celebrates the richness and utility of chemistry. Chemicals are ubiquitous; there is no escape from them. Biology's foundations are deeply rooted in chemistry. The DNA double helix, whose formulation heralded the birth of molecular biology, established the chemical basis of heredity. Natural selection, so fundamental to thinking about biology, operates at the level of molecules and their functions, determining the biochemistry of living organisms. The burgeoning field of materials science has chemistry at its core. Nanoscience, with its promise of spawning technologies that will transform our lives, seems suspiciously dependent on traditional chemistry. Even physicists and engineers, who seem to move with facility into the greener pastures of biology, are compelled to acknowledge that molecules and their chemistry are hard to ignore. Chemicals are often perceived as harmful, pollutants and poisons among them. The popular press is full of stories about endosulfan, an insecticide that has gained notoriety in India, and the dioxins which are slowly leached from the ubiquitous 'plastic' bottle. Chemistry's public image is not helped by the fact that chemists communicate in a language of structural formulae, which is largely indecipherable for the uninitiated. Chemicals are, however, central to life and a broad public understanding of chemistry may be useful even in shaping policy. In a commentary appearing in this issue, one of India's most prominent researchers in the area of nutrition asks, 'Can a malnourished nation become a sporting nation?' (Bamji, M. S., *Curr. Sci*., 2011, **101**, 602). Despite the widespread discussion on the spread of diabetes and obesity, problems of excess rather than scarcity, there is little doubt that undernourishment may be the fate of a majority of Indian children. Mahtab Bamji notes that nutritional deficits are alarming: 'There is rampant deficiency of micronutrients (vitamins and minerals), iron deficiency anaemia (50–70%), iodine deficiency and vitamin A deficiency being of particular concern. Deficiencies which are knocking at the door to be recognized on the basis of recent evidence are: vitamin D deficiency (despite the tropical sun), B-vitamins (folic acid, B_{12} and B_2) and zinc.' The constant and often unedifying discussions on India's sporting performances fail, in Bamji's view, to address an important issue: 'Vast segments of people in India, particularly those residing in the villages where the talent lies are malnourished and in poor health.' She emphasises the connection between nourishment and 'physical build' and quotes a report that advances the urge to rapidly build physical strength in talented but poorly nourished athletes as a reason behind the current doping scandals that have swept through the community of athletes. The reference to 'doping', the use of banned substances that enhance physical performance, caught my eye. Chemistry seemed to intrude again.

The news reports on Indian athletes highlight the fact that many appeared unaware of the nature of the drugs ingested; most believe that they were nutritional supplements. The finger of suspicion pointed to coaches, many of whom emerged from countries that were once part of the erstwhile Soviet bloc. The cries of outrage and demands for swift and exemplary punishment seemed hypocritical, especially when they emanated from those who manage sporting bodies. The fact that 'doping' is widespread in international sports only suggests that exposure of Indian athletes to performance enhancing drugs has happened at a relatively late stage, as compared to the more advanced countries. It is in the area of 'doping' that science and sport meet in full measure. While science and scientific methods can enhance sporting performance, most attention is directed at the use of substances that promote physical performance. On the eve of the 2008 Beijing Olympics, *Science* (2008, **321**, 624) asked: 'Neuroimaging, high-tech materials, new asthma meds, detection-eluding drugs, thermoregulation—will all these make athletes stronger and faster at the 2008 Summer Games in Beijing?' Undoubtedly, the question will be repeated next year when the London Olympics begin. In discussing doping, the *Science* article noted that 'by the tough standards of modern medicine there is little hard evidence for the efficacy of dozens of compounds on the list of the World Anti-Doping Agency (WADA)'. Carefully conducted trials including placebo controls are rare, with a few notable exceptions, amphetamines and the anabolic steroids among them. The former promote performance 'in short explosive activities, such as sprinting', while the latter 'increase muscle mass and enhance performance among male athletes in sports that require strength, such as weightlifting and shot-putting; in women they appear to work for endurance sports as well'. Many drugs on WADA's banned list are useless for the purpose of enhancing performance and 'are listed simply because athletes used them or were rumored to use them'. While clinical trials must precede approval of therapeutics, no real trials can be easily done to evaluate the efficacy of many chemicals in improving athletic performance. The most notorious of the many drugs that

have plagued sport is testosterone, an androgenic, anabolic steroid. A highly readable review that appeared before the Beijing games traces the use of testosterone to the 1954 World Weightlifting Championship in Vienna. The effects of androgens in improving sports performance were widely known in what is described as the 'underground press', including a source intriguingly called the 'Underground Steroid Handbook'. This is an area where the 'scientific literature was years behind' (Fitch, K. D., *Asian J. Andrology*, 2008, **10**, 384).

Analytical chemistry using cutting edge technologies is the major weapon in the battle against drug abuse in sports. The classical radio-immunoassay used in the mid-1970s, has now been replaced by gas/liquid chromatography, coupled to increasingly sophisticated mass spectrometers. However, the problems of establishing an acceptable level for an endogeneous substance can sometimes be difficult. Fitch describes in his review the tale of testosterone (T). He recounts work in the 1980s which established a criterion for the ratio of two chemicals, T and an isomer, epitestosterone (E). The T/E ratio was accepted as an indicator of ingested T. Doping with steroids was practically state policy in the German Democratic Republic (GDR, East Germany), during the period 1965–1989. From evidence which came to light after German reunification, it became clear that the most detailed understanding of the T/E ratio was possessed by the head of the GDR Doping Laboratory. When the T/E ratio became the gold standard for detection of androgen abuse, the GDR handlers administered E just before international competitions. Fitch notes that the head of the GDR program 'was a member of the IOC Medical Committee from 1981 to 1989'. The infirmities of sporting bodies appear to have a long history. As in any arms race, the advances in analytical methodology to detect the presence of banned substances have been countered by ingenious strategies to evade detection. 'Designer drugs' which can pass unnoticed are a product of innovative 'underground chemistry'. Sadly, the efficacy of many substances used by athletes is questionable, even as their detrimental effects on long term health are well established. WADA, the international watchdog has introduced a 'biological passport' for athletes. Regular monitoring of as many as eight hematological parameters is recommended to identify physiological effects even when the drug is no longer detectable. An editorial in a scientific journal calls for a 'rapid expansion of this panel to include measurements of endocrine function' and, in anticipating future developments suggests that 'the potential for gene doping must also be explored' (Heath, V., *Nature Reviews Endocrinology*, 2010, **6**, 413). In any general discussion on substance abuse one viewpoint suggests legalization of drugs as a potential solution. Should performance enhancing drugs be permitted in sports under medical supervision? A carefully presented analysis suggests that this is undesirable and concludes that any suggestions in this direction 'should not be entertained' (Wiesing, U., *Sports Medicine*, 2011, **41**, 167).

When athletes fail a doping test the resultant effect on their careers can be devastating. Is the 'science of doping' robust enough to avoid errors, which can destroy careers of innocent athletes? In the run up to the last Olympics *Nature* pronounced judgement: '…drug testing should not be exempt from scientific principles and standards that apply to other biomedical sciences, such as disease diagnostics. The alternative could see the innocent being punished while the guilty escape on the grounds of reasonable doubt' (*Nature*, 2008, **454**, 667). This editorial view was prompted by the appearance of a provocative commentary on 'The Science of Doping', which argued that 'the processes used to charge athletes with cheating are often based on flawed statistics and flawed logic' (Berry, D. A., *Nature*, 2008, **454**, 692). In testing for chemicals, both sensitivity (the ability to detect substances at very low concentrations) and specificity (the ability to detect only a very specific component in a complex mixture of substances, some of which may appear quite similar) are critical. These are key issues in medical diagnostics where the need to avoid both 'false positives' and 'false negatives' is well recognized. Berry argues that in sports drug testing validation leaves much to be desired and statistical analysis is clouded by faulty reasoning, which is termed as 'prosecutor's fallacy'. Berry uses the case of the cyclist Floyd Landis, accused of taking synthetic testosterone, to illustrate the fact that 'false positives' may not be as rare as one might expect. The reactions to the charge of flawed reasoning were quick, with critics noting that 'anti-doping is a forensic science not a medical one'; a statement that implies different standards for validating the results of chemical analysis (Sottas, P.-E. *et al.*, *Nature*, 2008, **455**, 166). Both guilt and innocence seem difficult to establish in the arena of sports drug testing.

Chemicals influence both the body and the mind. A recent essay by a prominent chemist describes how his research on molecules that act on the brain has been used to produce designer drugs that can be marketed as substances producing 'legal highs' (Nichols, D., *Nature*, 2011, **469**, 7). Indeed, work published by Nichols, on 4-methylthioamphetamine (MTA) in the 1990s, was used by 'underground chemists' to produce MTA, which when ingested caused some deaths. Laboratory chemistry never has as its objective the task of testing the safety of molecules that are synthesized. None of the hundreds of thousands of compounds produced in academic laboratories are intended for human consumption. Nevertheless, the spectre of an 'entrepreneur' finding a profitable, but dangerous, use for some classes of substances is an ever present danger that Nichols highlights. There is a dark side to chemistry.

Nutrition, sports doping and designer drugs, three diverse topics that I have touched upon in this column are tied together by the unifying thread of chemistry. We are indeed prisoners of the molecules that shape our bodies and mould our minds.

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