

EDITORIAL

Autism, vaccines and editors

Autism is a term used to describe a group of developmental disorders that lead to severe behavioural abnormalities. Autistic children may be severely limited in their social interactions, display unusual behaviour patterns and often appear withdrawn and uncommunicative, despite possessing 'average or superior cognitive skills' in specific areas. Autism can be devastating for affected families; there can be no more wrenching experience than to watch a severely disabled child struggle with life in a world with which they can hardly communicate. The description of autistic syndromes can be traced to the work of Leo Kanner and Hans Asperger in the 1940s. Since then the 'autistic spectrum' has widened and there is a much greater awareness of the range of clinical symptoms that may signal autism. As awareness has increased, so have the number of reported cases of autism, worldwide, particularly in the developed countries. Some estimates place the incidence of autism at a figure of 1 in 500 people; in India this would suggest a figure of about 2 million affected individuals (www.autism-india.org). There is a limited awareness about autism amongst medical professionals in India, with childhood symptoms often dismissed by impatient and insensitive doctors. 'Mental retardation' is such an all-encompassing term to rationalize developmental disorders, that autistic children may have to wait for several years before their special status is recognized. In this period, they may be subjected to an educational system that can be harsh, impersonal and rigid. The established fact that some autistic children display exceptional abilities and have extraordinary I.Q's makes the management of autism an extremely challenging task. At present, the causative factors that precipitate autism remain unknown; treatment with drugs has proved elusive. Management of autism by educating parents and other care-givers appears to be the only pragmatic approach towards alleviating the enormous burden that autism imposes on its sufferers.

Even as reported cases of autism have increased, attempts to establish a connection between environmental factors and autism have intensified. In 1998, Andrew Wakefield of the Royal Free Hospital, London and a large number of colleagues published a paper in *Lancet* enti-

tled, 'Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children' (1998, **351**, 637–640). Despite its forbidding title, the paper had a message which was clearly understood by the general public in Britain, aided by the inevitably sensational reporting in the press; the authors suggested a direct connection between the administration of the measles, mumps and rubella (MMR) vaccine and the onset of the behavioural disorders characteristic of autism. This paper was to touch off a furious debate on the connections between the MMR vaccine, inflammatory bowel disease and autism in children. The Wakefield paper was an obviously limited study, that was followed by a spate of reports, many of them in *Lancet*, which appeared to cast doubt on the Wakefield conclusions. The *British Medical Journal* entitled an editorial: 'MMR vaccination and autism 1998. *Deja vu* – pertussis and brain damage 1974?' The reference was to a 1970s scare which resulted in a fall in pertussis vaccination levels, leading to many deaths in Britain and elsewhere. The authors noted: 'Since each year over 600,000 British children received MMR in their second year, an age when autism can typically manifest itself, chance alone dictates that some cases will appear shortly after vaccination. Cases will be selectively referred to a group known for its interest in MMR, inflammatory bowel disease, and autism, so the hypothesis rests on clinical anecdote rather than on an epidemiologically sound base'. The authors concluded on a cautious note: 'While (no) vaccine can be guaranteed to be without any risk, this has to be weighed against the huge advantages of protection against disease. Seeds of concern have been sown among parents and no doubt will continue to be spread. Those advising families must make sure parents can base their decisions on hard science and evidence'. (A. Nicoll, D. Elliman and E. Ross, *BMJ*, 1998, **316**, 715–716). Despite the vigorous criticism of the Wakefield paper, public doubts about the MMR vaccine resulted in a significant drop in the rate of administration of the vaccine to children in Britain, falling from a coverage of about '90% in 1998 to its current level of less than 80%' (J. Giles, *Nature*, 2004, **427**, 765). The MMR controversy reached its highest level of visibility when the British

Prime Minister, Tony Blair, was questioned in Parliament on whether his youngest child had been vaccinated.

The Wakefield study has now returned to centre stage. In February, a review of the available scientific evidence categorically stated that 'MMR does not cause autism or any particular subtypes of autistic spectrum disorder' (F. Destefano and W. W. Thompson, *Expert Review of Vaccines*, 2004, **3**, 19–22). The British press also found that Andrew Wakefield did not declare a potential conflict of interest in which he conducted a paid study for the Legal Aid Board on 'whether parents whose children had allegedly been harmed could sue manufacturers of the MMR vaccine' (*Nature*, 2004, **427**, 765). In a further development, 10 of the paper's 13 original authors, Wakefield was not one of them, published a curiously worded retraction in March 2004: 'We wish to make it clear that . . . no causal link was established between MMR vaccine and autism as the data were insufficient. However, the possibility of such a link was raised and consequent events have had major implications for public health. In view of this, we consider now is the appropriate time that we should together formally retract the interpretation placed upon these findings in the paper, according to precedent'. In an extraordinary move to preempt the inevitable media blitz following the unearthing of the Wakefield 'conflict of interest' story, the *Lancet* editorially declared the paper 'flawed' and stated that the paper would not have been published if the authors had declared the apparent 'conflict of interest'. Interestingly, such declarations appear routinely in the biomedical literature. Why did it take *Lancet* six years to uncover scientific flaws and did the 'conflict of interest' have any bearing on the interpretation? Do declared 'conflicts of interest' legitimize scientific findings? Editors of scientific journals and editors of high profile biomedical journals in particular confront difficult situations in such cases.

An organization called the Committee on Publication Ethics (COPE), based in London, was established in 1997 to help editors discuss ethical issues. Their most recent document, The Cope Report 2003 is an engaging production with an explicit section on 'editorial accountability' (www.publication-ethics.org.uk). In his introduction to the section Richard Smith, Editor of the *British Medical Journal* says: ' . . . We don't really know what misconduct is in an editorial context. We have vague ideas, but we don't really have a clear idea'. He adds, for good measure: 'And editors are peculiarly unaccountable – perhaps some of the most unaccountable people in the world because of their traditions of editorial freedom'. The report details many specific cases where editors and journals have been found wanting, providing a spectrum of examples which should strike a chord in many editors. The all time classic in editorial misconduct is cited by Smith, in which Cyril Burt founded the *British Journal of Statistical Psychology*. Burt ran riot, publishing his own flawed, unrepeatable work extensively. Interestingly, he altered

'the work of others without permission, sometimes adding favourable references to his own work'. With biomedical publishing becoming a frenetically competitive activity, both authors and editors confront situations where corners are cut. Considerations of ethics and accountability may fade into the background, resulting in frequent public controversies when questionable practices are brought to light.

The public discussion of the link between MMR and autism however raises important issues of vaccine safety. The eradication of smallpox, the drive against polio and the protection against the common infections of childhood, diphtheria, pertussis, tetanus and measles have contributed enormously to improved standards of public health, worldwide. Universal immunization programs seek to eliminate human reservoirs of pathogens, with the ultimate goal of decisively eliminating specific diseases. Thus far, smallpox is the most dramatic global success story. But as the disease burden diminishes, concerns about vaccine safety begin to surface. Side effects in rare cases are always possible; sometimes coincidence can confuse interpretation. In the case of a very low occurrence of side effects, policy makers must wrestle with the difficult choice of deciding public acceptability of a vaccine. As seen in the MMR controversy, compliance will be determined by public perception; in most countries coercion may not be a viable strategy. But, as biomedical research advances, the portfolio of vaccines that compete to enter universal immunization programs will increase. Given the size of the potential market, commercial pressures will build. Champions will be found in the scientific community and in governments to advance the claims of specific vaccines. In many cases, acceptably low toxicity may be easier to demonstrate than efficacy. The uncertainties in the design of many epidemiological studies contribute to the difficulties in this area. In India, a hepatitis B vaccine is already being pushed by government directive. Pressures will mount for its inclusion in the universal immunization program. Those of us who took the 'typhoid and cholera vaccines' in the 1960s and 1970s will wonder: 'Were these shots effective and whatever happened to them'.

The MMR controversy has now turned its focus to Wakefield's conflict of interest and the *Lancet* editor's response to the growing criticism of the original paper. The public debate, raucous at times, indicates that a fragile thread connects scientific research outcomes and vaccine acceptability. It is a sobering thought that 'conflicts of interest' may drive both proponents and opponents of vaccines. But, in the heat and dust of this controversy we must not forget that the causative factors of autism remain unknown and that effective treatment of this disorder must be an important goal of biomedical science.

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