

principal mechanisms—first, by causing damage to DNA and, second, by inducing immunological unresponsiveness. In mice tumour necrosis factor- α polymorphism determines the ability of acute low-dose ultraviolet B radiation to affect cutaneous immunity adversely.¹³ The ability to predict an individual patient's genetic and environmental susceptibility to cancer and acute rejection will enable clinical management to be tailored to optimise graft survival and minimise patient morbidity.

In the shorter term prophylactic therapy with synthetic retinoids is likely to be used more liberally than now. There is good evidence that these agents can prevent skin cancer in kidney recipients, albeit with side-effects such as dry mouth and hair loss.¹⁴

For now, high-risk patients need to be persuaded to treat sunshine as radiation. The level of awareness of risk is disappointing. Despite verbal advice and written information at time of hospital discharge for all newly transplanted patients at St James's Hospital, Leeds, only half of them subsequently recall receiving advice, and compliance with sun protection measures is poor.¹⁵

Finally, in weighing up risk and benefit for the patient, it is important to remember that many studies have shown that renal-transplant patients have a better quality of life and live longer than do patients maintained on dialysis.¹⁶ Also the patient's view of the balance of risks has to be taken into account; it may differ from that of the medical adviser.¹⁷

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Vaccine adverse events: causal or coincidental?

See pages 637, 646

Although immunisations rank among the most important public-health measures, no vaccine is perfectly safe.^{1,2} Because vaccines are given to millions of healthy people, usually infants, extremely high standards for vaccine safety are demanded.³ It is therefore important to examine, critically and with an open mind, the report by Andrew Wakefield and colleagues of several children whose chronic bowel and behavioural abnormalities were linked by their parents and physicians to measles, mumps, and rubella (MMR) vaccination.

An adverse event can be said to be caused by a vaccine (ie, a true reaction) if it is associated with a specific laboratory finding⁴ and a specific clinical syndrome⁵ or both. Alternatively, a clinical or epidemiological study is needed to find out whether the rate of a given syndrome in vaccinated individuals exceeds that expected among unvaccinated controls. Such studies require acquisition of data in an unbiased way.³ Because of the inherent methodological limitations of epidemiological studies, biological plausibility, consistency, strength, and specificity of association must also be considered in inferring causation.^{1,2} How well then do the features of the association reported by Wakefield and colleagues fit with causality?

First, hundreds of millions of people worldwide (including those in Scandinavia and North America, where there are excellent clinical facilities) have received measles-containing vaccine without developing either chronic bowel or behavioural problems since the mid-1960s. This finding provides important negative evidence as well as an appropriate framework for the assessment of the cases described by Wakefield and colleagues—namely,

Maximum and current reported cases of vaccine-preventable diseases and adverse events, USA

Disease	Prevaccine era* (year)	1997†	% change
Diphtheria	206 939 (1921)	5	-99.99
Measles	894 134 (1941)	135	-99.98
Mumps	152 209 (1968)	612	-99.60
Pertussis	265 269 (1934)	5519	-97.92
Polio (wild)	21 269 (1952)	0	-100.00
Rubella	57 686 (1969)	161	-99.72
Congenital rubella syndrome	20 000 (1964-5)‡	4	-99.98
Tetanus	1560 (1948)‡	43	-97.24
Invasive Hib disease	20 000 (1984)‡	165	-99.18
Total	1639 066‡	6644	-99.59
Vaccine adverse events	0	11 365	+++

*Maximum cases reported in prevaccine era and year.

†Provisional. ‡Estimated because no national reporting existed in the prevaccine era.

Hib = *Haemophilus influenzae* b

that if MMR vaccine does cause this syndrome, it does so extremely rarely.

Is the syndrome reported today clinically unique? Ileal lymphoid hyperplasia is non-specific. Autism was known well before MMR vaccine became available. Are there unique laboratory features, including detection of vaccine viruses in clinical specimens where they would not be expected? Although Wakefield has reported the detection of these viruses in patients with inflammatory bowel disease (IBD), other investigators, using more sensitive and specific assays, have not been able to reproduce these findings.^{6,7} Another negative report, by M A Azfal and colleagues, is published in today's *Lancet*. There is no report of detection of vaccine viruses in the bowel, brain, or any other tissue of the patients in Wakefield's series.

This leaves epidemiology as the other means of evaluating causation. Is there selection bias? The Wakefield report is based on cases referred to a group known to be specially interested in studying the relation of MMR vaccine with IBD, rather than a population-based study. A first dose of MMR vaccine is given to about 600 000 children every year in the UK, most during the second year of life, the time when autism first becomes manifest. Not surprisingly, therefore, some cases will follow MMR vaccination. Biased case-ascertainment, as in this study, will exaggerate the association.

Was there recall bias? It is usually difficult to date precisely the onset of a syndrome such as autism. Parents and others may attempt to relate its onset to an unusual event such as coincidental postvaccinal reaction. The clearest example of such an association was the link between infantile spasms and pertussis vaccines; the vaccine tends to unmask rather than cause the syndrome.¹

There are other reasons for doubt about the association reported by Wakefield and colleagues. They suggest that MMR immunisation may lead to IBD, which results in malabsorption, consequent neurological damage, and "autism". However, behavioural changes preceded bowel symptoms in almost all their reported cases. No clear case-definition was presented, a necessary requirement of a true new clinical syndrome and an essential step in any further research. Recent evidence also suggests that measles (or MMR) does not contribute to the development of IBD,⁸ the antecedent necessary for autism according to Wakefield and colleagues. Moreover, they have not completed the critical virological studies in these children needed to support their hypothesis that persistent measles (vaccine) viral infection plays a part in the causation of the illness.

Vaccine-safety concerns gain prominence whenever the incidence of vaccine-preventable diseases falls to negligible levels and when the number of vaccine adverse events, whether true reactions or those coincidental to the vaccination but falsely attributed to it (table), rises as a consequence of high vaccine coverage.⁹ False attribution usually occurs because many developmental abnormalities first manifest in the early years of life, which is also when several vaccines—which can cause crying, fever, and, occasionally, febrile seizures—are given.

Effective and credible systems are needed for the detection of vaccine-associated adverse events through pharmacovigilance, for distinguishing causal reactions from coincidental reactions by pharmacoepidemiological or other studies, and for risk communication.^{1-3,9} Without such a system, vaccine-safety concerns such as that reported by Wakefield and colleagues may snowball into

societal tragedies when the media and the public confuse association with causality and shun immunisation. This painful history was shared by the UK (among others) over pertussis in the 1970s¹⁰ after another similar case-series was widely publicised,¹¹ and it is likely to be repeated all too easily over MMR.¹² This would be tragic because passion would then conquer reason and the facts again in the UK.

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How the colon begets gallstones

Bile is secreted by the liver, and gallstones are generally formed in the gallbladder. How then can the intestine influence the biliary system? Interest in this question has recently revived, especially with reference to the formation of cholesterol gallstones.

In normal human bile the three bile salts that predominate are the conjugates of cholate, of chenodeoxycholate, and of deoxycholate. Cholate and chenodeoxycholate, the primary bile salts, are synthesised by the liver from cholesterol. Deoxycholate is entirely the product of colonic bacterial metabolism of any cholate that has escaped reabsorption by the active bile-salt transport system in the ileum (figure). Some of the newly formed deoxycholate is reabsorbed through the colon and returned to the liver via the portal system. After hepatic conjugation, deoxycholate joins the major enterohepatic circulation of bile salts, being subsequently recirculated mainly by ileal absorption. Deoxycholate constitutes 10-30% of the bile-salt pool. What effect does the extent of enterohepatic circulation of this bacterial metabolite have on bile lithogenicity?

Cholesterol gallstones form in bile that contains more cholesterol than can be maintained in micellar or vesicular solution by its solubilisers, bile salt and phospholipid. Oral administration of chenodeoxycholate has long