

CORRESPONDENCE

Autism, inflammatory bowel disease, and MMR vaccine

Sir—We are concerned about the potential loss of confidence in the mumps, measles, and rubella (MMR) vaccine after publication of Andrew Wakefield and colleagues' report (Feb 28, p 637),¹ in which these workers postulate adverse effects of measles-containing vaccines. As a result, we fear there may be a reduction in vaccine uptake in the UK and elsewhere. The main thrust of the report is to add to the record 12 possible cases of bowel disease associated with developmental regression (including autism), which is a useful contribution to research. However, an association was also alluded to between these two factors and environmental triggers such as receipt of MMR vaccine.

Wakefield and co-workers state "We did not prove an association between measles, mumps, and rubella vaccines and the syndrome described". However, there are enough references in the text to lead the reader to the assumption that there is sufficient evidence provided by the study, and by other scientific publications, to suggest that there is a likely (although as yet unproven) link.

The study suggests a temporal relation between the so-called autism-bowel syndrome and administration of MMR in eight of the 12 cases. However, the interval between receipt of vaccine and onset of symptoms is provided in only five cases (1–14 days), and the age at which the vaccine was given was provided in only three (15 months, 16 months, and 4.5 years). Parents identified MMR to be the immediate precursor of developmental delay in eight of the 12 children, but developmental delay is likely to be detected by a gradual awareness over a period of time, not on a particular day. Although autism is rarely diagnosed before 18 months, the insidious onset of symptoms often predates the diagnosis by many months. As described by Wakefield, parents had trouble making a temporal link between the onset of autism and the

onset of gastrointestinal symptoms for similar reasons. We therefore question the conclusion that there was a temporal association of the autism-bowel syndrome and MMR.

To prove a causal relation is much harder—it requires a selection of patients and matched controls, and a sample size that is capable of detecting a statistically significant difference between the two groups. The investigators may need to be blinded for such aspects as clinical assessments and laboratory tests. How does Wakefield's study match up? There was no patient selection other than 12 patients referred to him. There were no controls. There was no blinding of investigators. The accompanying commentary by Robert Chen and Frank DeStefano² elegantly explains the difference between temporal and causal association. We concur with them that Wakefield's study fails at every level to make a causal association.

Is it possible that we are confronted by a genuine causal association which has shown up by chance in these eight cases? Is it possible that these cases have brought to light a previously unnoticed association? Wakefield claims that the association between autism and MMR has been documented in the past—an important point to clarify. However, the two references they cite from Fundenburg and Gupta (refs 16 and 17 in their report) need further scrutiny. The first deals mainly with the association of autism and transfer factor (DLyE) and also mentions "live rubella immunization at 15 months has precipitated fever convulsions followed by autistic symptoms; so has live hepatitis B vaccine in 2 infants at 2 years". These anecdotal associations do not advance the argument for causality. We could not obtain the Gupta reference through usual library channels.

Wakefield and colleagues' findings confront us with a new hypothesis—that measles-containing vaccine may trigger developmental regression. It is

known that such speculation may seriously damage important public health programmes, causing a decline in vaccine uptake and a rise in the target disease.³ We can now expect such damage to occur in many countries. We question the merit of publishing this particular study.

Publication of this study is especially tragic because WHO and all consulted national public health authorities agree that it does not alter in any way the continued recommendation to use measles-containing vaccines throughout the world. Current measles containing vaccines are highly safe and effective.

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- 1 Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998; **351**: 637–41.
- 2 Chen RT, DeStefano F. Vaccine adverse events; causal or coincidental? *Lancet* 1998; **351**: 611–12.
- 3 Gangarosa EJ, Galazka AM, Wolfe CR, et al. Impact of anti-vaccine movements on pertussis control: the untold story. *Lancet* 1998; **351**: 356–61.

Sir—Andrew Wakefield and colleagues' report a case series of 12 patients and use this to generate a hypothesis that gastrointestinal disease and an associated developmental disorder may be related to MMR. This research was widely reported in the mass media and has generated considerable public concern, despite the weight of evidence supporting the efficacy and safety of MMR vaccination discussed by Robert Chen and Frank DeStefano.² Previous experience suggests that adverse publicity about vaccination, even though subsequently shown to be exaggerated or unfounded, results in reduced vaccine coverage with serious public health consequences.³ The

widespread reporting of this case series is likely to have a similar impact.

The publicity generated by this paper is out of proportion to the strength of evidence presented. Description of the strength of research evidence is straightforward. There are standard scoring systems in common use that enable consumers of research to quickly understand the weight that should be given to the evidence presented.⁴ In this example a reasonable score might be IV—"evidence inadequate owing to problems of methodology, eg, sample size, length or comprehensiveness of follow up, or conflict of evidence".⁵ This paper was marked Early Report and accompanied by a critical commentary,² although the report itself did not contain a strength of evidence score.

Research is essential to the advancement of knowledge and will always be newsworthy. However, we believe that it is now time for research publications to carry health warnings so that the public and health professionals are adequately appraised about the strength and quality of evidence presented. A critical commentary published along side is helpful, but not sufficient.

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- 1 Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998; **351**: 637-41.
- 2 Chen RT, DeStefano F. Vaccine adverse events: causal or coincidental? *Lancet* 1998; **351**: 611-12.
- 3 CDSC. MMR vaccine coverage falls after adverse publicity. *Commun Dis Rep CDR Wkly* 1998; **8**: 41, 44.
- 4 Stevens A, Raftery J, eds. Health care needs assessment: the epidemiologically based needs assessment reviews. Oxford: Radcliffe, 1997.
- 5 Williams MH, Frankel SJ, Nanchahal K, et al. Total hip replacements. In: Health care needs assessment: the epidemiologically based needs assessment reviews, vol 1. Oxford: Radcliffe Medical Press, 1994.

Sir—By publishing Andrew Wakefield and colleagues¹ work purporting to show a link between MMR vaccination and inflammatory bowel disease and autism and related problems you give increased credence to their report. *The Lancet* is a prestigious, peer reviewed journal with high public profile. The profession, journalists, the public, and especially distressed parents of ill children suppose that a publication in your journal will be true. In this example you print a commentary,

which if it had been a peer reviewer's report, should have led to the rejection of the paper.

The result of publication and the subsequent general publicity is predictable, from previous experience well documented by E J Gangerosa et al (Jan 31, p 356)³ for whooping cough vaccine. Such publicity has led to parents refusing vaccination for their children and a resurgence of the disease (and deaths), and more anguish for the parents who expected recompense from the courts which usually failed for lack of evidence of causality. Also it frightened many manufacturers from continuing development and production of vaccines.

If my predictions are correct, then I think you will bear a heavy responsibility for acting against the public health interest which you usually aim to promote. Moreover, you will only increase the anguish of the parents of the sick children with whom all doctors will sympathise.

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- 1 Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998; **351**: 637-41.
- 2 Chen RT, DeStefano F. Vaccine adverse events: causal or coincidental? *Lancet* 1998; **351**: 611-12.
- 3 Gangarosa EJ, Galazka AM, Wolfe CR, et al. Impact of anti-vaccine movements on pertussis control: the untold story. *Lancet* 1998; **351**: 356-61.

Sir—Renewed speculation surrounding the safety of MMR vaccine has followed the publication of Andrew Wakefield and colleagues¹ report of parents or physicians linking MMR vaccine with the development of autism. The Inflammatory Bowel Disease Study Group (IBDSG) has previously suggested links between exposure to wild measles virus and/or vaccine-related strains and an increased risk of developing Crohn's disease and ulcerative colitis. Evidence published in peer-reviewed journals has, however, failed to confirm a relation between measles vaccination and subsequent development of inflammatory bowel disease.² The epidemiological flaws in this latest paper concerning autism have also been well rehearsed.³

There is already evidence that current speculation has undermined confidence in the vaccine since coverage of MMR vaccine fell by 1% between the second and third quarters of 1997 across the UK. MMR coverage in Scotland has fallen to 93.7%. An

increasing number of parents, according to the latest Health Education Authority tracking programme, now apparently believe that MMR vaccine poses a greater risk than wild measles virus infection.⁴ The extent to which this misplaced anxiety is reinforced by professional uncertainty, indecision, and reluctance to promote vaccination has yet to be established, although we have good evidence that this was an important factor in the low uptake of measles vaccination in the 1980s.⁵

There is a temptation to blame the media for the drop in vaccine coverage. There is, after all, a substantial amount of evidence that contradicts the findings of the IBDSG but which tends not to achieve the same prominence in the popular press. No wonder parents are worried—they tend to hear only one side of the argument. But is it fair to blame the press? Should not the researchers shoulder the burden of responsibility? It is, after all, an awesome responsibility.

It should not be forgotten that measles vaccination has substantially improved the health of children worldwide, protecting against the considerable burden of mortality and morbidity caused when the transmission of wild measles virus went unchecked. In denting parental, and possibly professional, confidence in MMR vaccination, we must not forget the consequences of wild measles virus infection, should we see its resurgence. One in 15 children would develop complications ranging from ear problems and bronchitis to pneumonia and fits. One in 5000 children would develop encephalitis and 15% of them would die. Furthermore, if the IBDSG's earlier theories have any foundation, a resurgence of wild measles virus would itself be a risk factor for the development of inflammatory bowel disease and autism.

The debacle following concerns over the safety and efficacy of pertussis vaccine, based on evidence that was not later substantiated, impeded the control of whooping cough considerably in many European countries. Should we see the same situation with MMR vaccination, it would be another public health disaster.

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- 1 Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-

- specific colitis, and pervasive developmental disorder in children. *Lancet* 1998; **351**: 637-41.
- 2 Metcalf J. Is measles infection associated with Crohn's disease? The current evidence does not prove a causal link. *BMJ* 1998; **316**: 166.
 - 3 Chen RT, DeStefano F. Vaccine adverse events: causal or coincidental? *Lancet* 1998; **351**: 611-12.
 - 4 Begg N, Ramsey M, White J, Bozoky Z. Media dents confidence in MMR vaccine. *BMJ* 1998; **316**: 561.
 - 5 Carter H, Jones IG. Measles immunisation: results of a local programme to increase vaccine uptake. *BMJ* 1985; **290**: 1717-19.

Sir—Any future investigation of causation will need to address the two main weaknesses of Andrew Wakefield and colleagues¹ case series—that the cases were highly selected and the underlying population is not clear. We conducted a population-based study in the summer of 1997 in Swansea which was designed to avoid selection bias and could be replicated across the UK. The study was undertaken in response to concerns being expressed in the local media about the postulated link between MMR and autism; in particular parents had raised the question of whether there could have been a local problem with a batch of faulty MMR vaccine. This aspect of the investigation (particular batches) was unremarkable and not reported here.

The district-wide child health computer system has a vaccination record for all children in Iechyd Morgannwg (formerly West Glamorgan), and it also has information about important medical problems for any children referred to Community Child Health Services. A search was done for all children born since 1990 with an ICD 9 or ICD 10 code for autism.

The computer vaccination history was examined to establish whether the child had received a first-dose MMR vaccination. The proportion of children with autism who had received MMR vaccination was calculated and compared with that for all children in the district.

18 children with a diagnosis of autism, born between 1990 and 1994 were identified, 16 of whom had received MMR vaccination, giving a first-dose MMR vaccination rate for children with autism of 88.9%. The vaccination rate for all children was 95.3%. The difference in vaccination rates is not statistically significant.

The method, based on the rapid interrogation of child-health computer systems could be replicated on a larger scale as a formal, UK-wide, case-control or retrospective cohort study. A case-control study with four controls

for every case and an 80% power to detect a two-fold increase in the risk of autism after MMR vaccination would require 691 cases—an assumption of a population MMR coverage of 95%. If the morbidity recording were similar to that of West Glamorgan (population 370 000) this would require combining results from a general population of 14.3 million people. We suggest that this is a practical way of rapidly investigating this speculative association.

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- 1 Wakefield AJ, Murch S, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998; **351**: 637-41.

Sir—We were surprised and concerned that the *Lancet* published the paper by Andrew Wakefield and colleagues¹ in which they alluded to an association between MMR vaccine and a non-specific syndrome, yet provided no sound scientific evidence. The commentary by Robert Chen and Frank DeStefano² points out the serious flaws in the paper.

We acknowledge that anecdotal reports may sometimes contribute to the generation of hypotheses, but risk factors for rare conditions, such as those described, can only be identified by well designed epidemiological studies.

This publication provided a platform for the expression of views about MMR vaccination that have no proven scientific foundation: this could have damaging effects on public and professional confidence in vaccines in general. The MMR vaccination programme has been successful in this country, and we are now at a point when the elimination of measles is a real possibility. If, as a result of this paper, parents reject MMR vaccine, this could lead to a re-emergence of measles infection with associated deaths and permanent neurological damage among young children, and a resurgence of rubella infection leading to a rise in congenital rubella births and terminations of pregnancy. Has nothing been learned from the experiences with pertussis vaccine in the 1970s?³

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- 1 Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998; **351**: 637-41.
- 2 Chen RT, DeStefano F. Vaccine adverse events: causal or coincidental? *Lancet* 1998; **351**: 611-12.
- 3 Gangarosa EJ, Galazka AM, Wolfe CR, et al. Impact of anti-vaccine movements on pertussis control: the untold story. *Lancet* 1998; **351**: 356-61.

Sir—The account given by Andrew Wakefield and colleagues¹ is interesting, yet the structure of the study with biased case ascertainment and no suitable controls makes the findings no more than anecdotal. Perhaps the only saving grade for *The Lancet* is the accompanying well balanced commentary.²

Chronic non-specific colitis, as described by Wakefield, is a common form of non-infective colonic inflammation in the age group studied. Furthermore, of 329 consecutive colonoscopies done at Great Ormond Street Hospital (children aged 1 month to 16 years with chronic diarrhoea), 40 children were noted to have macroscopic ileal/ileocolonic lymphoid nodular hyperplasia, giving a prevalence in this selected population of 12%. 85% of these children had minor immunodeficiencies, as reported by Wakefield, but none had neuropsychiatric disorder.

The investigators concede that they have not proven an association between MMR immunisation and the syndrome described, and have in reality presented no hard data on this matter. The report has led, intentionally or otherwise, to the erroneous assumption by the media and parents of a cause and effect relation between MMR immunisation, inflammatory bowel disease, and developmental disorder, resulting in parental confusion about the safety of immunisation. This country's childhood immunisation programme has dramatically reduced wild-type measles infection with its associated significant morbidity and mortality. Wakefield's account risks setting back child health 30 years through disruption of this programme. If these researchers are able to prove cause and effect between immunisation and the described syndrome they should do so straight away. If they are unable to do so they should publicly set the matter straight lest the health of our nation's children suffers.

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- 1 Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998; **351**: 637–41.
- 2 Chen RT, DeStephano F. Vaccine adverse events; causal or coincidental? *Lancet* 1998; **351**: 611–12.

Author's reply

Sir—Our publication in *The Lancet* and the ensuing reaction throws into sharp relief the rift that can exist between clinical medicine and public health. Clinicians' duties are to their patients, and the clinical researcher's obligation is to test hypotheses of disease pathogenesis on the basis of the story as it is presented to him by the patient or the patient's parent. Clearly, this is not the remit of public-health medicine. The approach of the clinical scientists should reflect the first and most important lesson learnt as a medical student—to listen to the patient or the patient's parent, and they will tell you the answer. Accordingly, we have now investigated 48 children with developmental disorder in whom the parents said "my child has a problem with his/her bowels which I believe is related to their autism". Hitherto, this claim had been rejected by health professionals with little or no attempt to investigate the problem. The parents were right. They have helped us to identify a new inflammatory bowel disease that seems to be associated with their child's developmental disorder. This is a lesson in humility that, as doctors, we ignore at our peril. In many cases, the parents associated onset of behavioural symptoms in their child with MMR vaccine. Were we to ignore this because it challenged the public-health dogma on MMR vaccine safety? As they expound the virtues of MMR vaccine, public-health officials would do well to reflect upon the fact that published pre-licensure studies of MMR vaccine safety have been restricted to 3 weeks. For three live viruses given in combination at a different dose, route, strain, and age, compared with the normal pattern of exposure of these viruses, 3 weeks seems woefully inadequate.

In citing pertussis as an example of how scare stories can damage health strategies, it is important to bear in mind that pertussis vaccine can be associated with neurological sequelae, albeit that the risks of the disease far outweigh those of vaccine. Recognition of this led to the passing of the Vaccine Damage Payments Act in 1979. Until now, about 900 children have been awarded vaccine-damage payments, qualifying as 80% disabled. Had clinicians, in the conduct of their duty,

not raised the issue of adverse neurological events with pertussis vaccine, shamefully, these children would have been put to one side, and there would have been no imperative for the production of a safer, acellular vaccine. Assumptions of vaccine safety, based upon inadequate safety trials and dogma contribute largely to confusion and public loss of confidence in vaccination. Public-health officials would do well to get their own house in order before attacking the position of either clinical researchers or *The Lancet* for what we perceive as our respective duties.

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Authors' reply

Sir—We welcome the response from Keith Lindley and Peter Milla, as we too had been concerned that the main thrust of the report—the detection of a consistent pattern of mucosal abnormality in children within the autistic spectrum—had been rather lost in the emotionally charged debate about a potential role for MMR vaccine in its pathogenesis. Their points about the absence of hard data supporting the link with MMR were made both within the paper, and forcefully by ourselves at the press conference accompanying publication. We emphatically endorsed current vaccination policy until further data are available. We would refer them to reports in *The Guardian* and *Independent* about the sober nature of this conference. We have not seen a single newspaper report inferring causality, as Lindley and Milla suggest. The media response has in fact been notably balanced, with almost all reports endorsing current immunisation schedules, until further evidence is forthcoming.

Should we have published? We believe that it was correct to do so, for two major reasons. First, this mucosal abnormality has been apparent in 47/50 children within the autistic spectrum, whether or not there is any perceived link with immunisation. Thus the lymphoid hyperplasia/ microscopic colitis changes were found in over 90% of the autistic children studied. Even if there is no immunodeficiency, the lymphoid hyperplasia in many cases is remarkable, with germinal centres showing higher numbers of proliferating (Ki67 positive) cells than we have detected in any immunodeficient controls with lymphoid hyperplasia. We are very familiar with the detection of lymphoid hyperplasia in children with minor immunodeficiency, as are

Lindley and Milla, and have published several reports on this topic. We were thus ideally placed to detect the exaggerated lesion found in many of these children. The colitis itself is variable, but may feature crypt abscesses, increased macrophage infiltration and unregulated class II major histocompatibility complex expression.

Second, we have noted important behavioural responses in several of the children when their intestinal pathology is treated. Plain radiography confirms severe constipation with acquired megarectum in almost all affected children, despite many receiving treatment for constipation. Most parents note a honeymoon period of behavioural improvement after the bowel preparation for colonoscopy and this is maintained if recurrent constipation can be prevented. Further cognitive improvement has occurred in response to aminosaliclates, provided that constipation is prevented.

Thus, we believe the report to be aimed at those involved in the care of autistic children, as a further indication that the intestine is involved; this is not apparent unless hunted for specifically by investigation, as simple as plain abdominal radiography or as invasive as colonoscopy. We re-emphasise the fact that there is a consistent pattern of gut inflammation in a high proportion of children within the broad autistic spectrum. Understanding the link between the bowel and the brain in autism may allow new insights into this devastating illness. We suggest that the accompanying commentary was not the only saving grace for *The Lancet*

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Editor's reply

The Lancet has been quick to criticise scientific and journalistic exuberance about the release of data that might unduly aggravate public concern.¹ By contrast with these past episodes and with the implied criticism in the letters we publish this week, the paper by Andrew Wakefield and colleagues² is an example of how researchers, editors, and those concerned with the public's health can work together to present new evidence in a scientifically balanced and careful way. Wakefield et al informed the UK Department of Health of their findings in 1997 and supplied them with a final copy of their *Lancet* paper in advance of publication (Wakefield AJ, personal communication). There are at least four parts to this story.

First, the decision to publish. There was no question in my mind that, subject to external peer review and editorial debate, we should publish this work. The description of what seems to be a new syndrome and its relation to possible environmental triggers was original and would certainly interest our readers. Peer review confirmed that the paper merited publication, with suitable revisions and editing, as an early report—there were no scientific grounds to do otherwise. One could, and our correspondents do, question our editorial judgment. But consider the alternative: rejection because these data might, on balance, do more harm (stop parents seeking MMR vaccination for their children) than good (describe a new syndrome and raise an empirically reasonable hypothesis that deserves testing). Recent history, the tale of new variant Creutzfeldt-Jacob disease, for example, tells us that full disclosure of new data is preferable to well-meaning censorship.

Second, how to publish. As with any provocative report, we always consider the value of running a commissioned commentary in the same issue. In this instance, it was a necessity. Most observers seem to agree that Robert Chen and Frank DeStefano³ wrote an important and helpful critique of Wakefield and colleagues' work.

Third, how to report these data to the media. We chose not to include this study in our weekly press release. We let the paper and commentary speak for themselves. However, we did assist those who organised a press briefing at the Royal Free Hospital on Thursday, Feb 26, by providing copies of the journal (with the commentary that Wakefield et al did not have) to journalists. Reported adverse comments about the safety of MMR vaccination were made at this press conference. By contrast, the views expressed in the paper are unambiguously clear: "we did not prove an association between measles, mumps, and rubella vaccine and the syndrome described".²

Finally, what has been the outcome? In particular, has harm been done? There are three endpoints. (1) The press reaction. In every UK report that I have read, journalists urged readers to interpret the study cautiously. *The Times* included a panel explaining the benefits of measles vaccination; *The Independent* led its front page story by reporting the government's advice to parents "to continue to take their children for immunisation"; and *The Guardian* summed up the genuine dilemma in its headline, "damned if they publish, damned if they didn't".

(2) The number of children harmed by not receiving measles vaccine. We have no idea what this figure is, but it should be easy to discover with time. This question needs to be asked because its answer will help us all to do better in our reporting next time. One anxiety is why it took the Department of Health 2 weeks to send out a reassurance cascade message to general practitioners. And (3), are Wakefield and colleagues' observations reproducible? Again, we do not know. But rather than dismiss what they have reported, other investigators must urgently seek to confirm or refute their findings.

Richard Horton

- 1 Horton R. ICRF: From mayhem to meltdown. *Lancet* 1997; **350**: 1043-44.
- 2 Wakefield AJ, Murch SH, Anthony A, et al. Ileal lymphoid-nodular hyperplasia, non-specific colitis, and pervasive-development disorder in children. *Lancet* 1998; **351**: 637-41.
- 3 Chen RT, DeStefano F. Vaccine adverse events: causal or coincidental? *Lancet* 1998; **351**: 611-12.

Twinning, cancer, and genetics

Sir—A J Swerdlow and colleagues (Dec 13, p 1723)¹ conclude that breast and testicular cancer have a prenatal aetiology compatible with raised maternal unbound free oestrogen concentration in twin pregnancies. This conclusion is based on the recorded higher risk of breast and testicular cancer for dizygotic twins than in monozygotic twins.

Swerdlow and colleagues do not take into account that monozygotic and dizygotic twinning per se is a familial trait inherited both paternally and maternally.² Moreover, the genetic components for monozygotic and dizygotic twinning seems to be independent.³

With these facts in mind their findings of a higher risk of breast and testicular cancer in dizygotic than in monozygotic twins could be interpreted as resulting from the co-segregation of the genetic component for twinning (monozygotic and dizygotic) and that for breast or testicular cancer. Whether raised unbound free maternal oestrogen concentration advocated by Swerdlow and co-workers is linked to these genetic components remains to be established, but it is likely to be the result of a gemellar pregnancy and not the cause.

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- 1 Swerdlow AJ, De Stavola BL, Swanwick MA, Maconochie NES. Risks of breast and testicular cancer in young adult twins in England and Wales: evidence on prenatal and genetic aetiology. *Lancet* 1997; **350**: 1723-28.
- 2 Paris P, Gatti M, Prinzi G, Caperna G. Familial incidence of twinning. *Nature* 1983; **304**: 626-28.
- 3 Lichtenstein P, Olanson PO, Kallen AJ. Twin births to mothers who are twins: a registry based study. *BMJ* 1996; **312**: 879-81.

Sir—A J Swerdlow and colleagues¹ report a non-significant increase in risk of breast cancer in female dizygotic compared with female monozygotic twins and a significantly higher risk of testicular cancer in male dizygotic than in male monozygotic twins. They argue that these findings are compatible with prenatal exposure to raised maternal oestrogen concentrations. For this hypothesis they rely heavily on reports of gonadotropin and sex-hormone concentrations in mothers of dizygotic and monozygotic twins.^{2,3} However, none of the data in these reports are in accord with the aetiological mechanism suggested by Swerdlow and co-workers. In fact one report deals with raised secretion of gonadotropins and sex-hormones in non-pregnant mothers of dizygotic twins.² The only report of differences in hormone secretion in pregnant mothers of dizygotic versus monozygotic twins describes lower concentrations of human placental lactogen in mothers of monozygotic twins and no differences in oestrogens.³

We therefore suggest an alternative mechanism for the observation that testicular cancer risk is higher in male dizygotic than in male monozygotic twins. Dizygotic twins inherit a tendency of hyperstimulation by endogenously raised concentrations of follicle stimulating hormone (FSH) that causes multiple follicle growth, high oestrogens, and multiple ovulations in females.² In males, the increase in carcinoma of the testis could result from over-exposure to FSH. No data are available on the secretion of gonadotropins in familial male dizygotic twins. However, hypersecretion of FSH in these males is likely, because the hereditary trait of having dizygotic twins (and high FSH) is inherited in an autosomal manner. The observation of an increase in testicular carcinoma in dizygotic twins would circumstantially support this male type of natural FSH hypersecretion since testicular carcinoma (and ovarian neoplasia) are associated with increased FSH action.⁴

In view of the reported substantial increase in risk of testicular cancer it seems time for endocrine evaluation of familial dizygotic male twins. In

addition, the high concentrations of FSH in familial dizygotic twinning might also reveal a risk of ovarian carcinoma, which would justify epidemiological studies in this area. We cannot say to what extent our hypothesis of familial increased FSH and testicular cancer also applies to an increase in breast-cancer risk. Swerdlow et al report no differences in occurrence of breast cancer between dizygotic and monozygotic twins. Their finding is consistent with results from a large Swedish study that showed no differences in occurrence of breast cancer between mothers of dizygotic and monozygotic twins.⁵

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- 1 Swerdlow AJ, De Stavola BL, Swanwick MA, Maconochie NES. Risks of breast cancer and testicular cancers in young adult twins in England and Wales: evidence on prenatal and genetic aetiology. *Lancet* 1997; **350**: 1723–28.
- 2 Martin NG, El Beaini JL, Olsen ME, Bhatnagar AS, Macourt D. Gonadotropin levels in mothers who have had two sets of DZ twins. *Acta Genet Med Gemellol* 1984; **33**: 131–39.
- 3 Kappel B, Hansen K, Moller J, Faaborg-Andersen J. Human placental lactogen and dU-estrogen levels in normal twin pregnancies. *Acta Genet Med Gemellol* 1981; **34**: 59–65.
- 4 Sicinsky P, Donaher JL, Geng Y, et al. Cyclin D2 is an FSH responsive gene involved in gonadal cell proliferation and oncogenesis. *Nature* 1996; **384**: 470–74.
- 5 Murphy MFG, Broeders MJM, Carpenter LM, Gunnarskog J, Leon DA. Breast cancer risk in mothers of twins. *Br J Cancer* 1997; **75**: 1066–68.

Authors' reply

Sir—We agree with Rafaël Levy that if there were co-segregation of genes for propensity to dizygotic twinning and genes for breast cancer, this could explain the raised risk of breast cancer in women born as such twins, and hence would give an alternative potential explanation of our findings. We know of no evidence, however, that there is such co-segregation; indeed mothers of twins, who ought to have twinning genes more often than the twins themselves, have been found to have a decreased risk of breast cancer,¹ which would be evidence against the co-segregation proposed.

C B Lambalk and D I Boomsma raise an interesting alternative explanation for the excess of testicular cancer in dizygotic twins, which we

agree is worth pursuing. On the basis of published work, however, it seems speculative rather than well founded that high FSH concentrations would be inherited along with a tendency to dizygotic twinning; we have not seen the paper by Lambalk and colleagues, currently in press, which may hold substantial evidence for such an association in mothers. It would still, however, be a hypothesis that needs testing whether FSH concentrations are increased in boys born as dizygotic twins.

We agree that the existing evidence for raised gonadotropin and sex hormone concentrations in mothers of dizygotic twins is neither consistent nor conclusive, but taking together the three studies cited in the discussion section of our report plus the other evidence cited within these publications, we think that our comment in that section that “some evidence suggests” raised concentrations remains true. Further evidence on these concentrations in mothers of twins is needed to clarify this issue.

With respect to breast cancer, Lambalk and Boomsma take the Swedish finding regarding breast cancer in mothers of twins¹ as the most appropriate comparison with our results on the twins themselves, but the most comparable data, as noted in our paper, are in another Swedish paper in breast cancer in women who were themselves twins.² This study found a significantly raised risk of breast cancer under age 30 for women born as dizygotic twins, a result similar to ours.

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- 1 Murphy MFG, Broeders MJM, Carpenter LM, Gunnarskog J, Leon DA. Breast cancer risk in mothers of twins. *Br J Cancer* 1997; **75**: 1066–68.
- 2 Braun MM, Ahlbom A, Floderus B, Brinton LA, Hoover RN. Effect of twinning on incidence of cancer of the testis, breast, and other sites (Sweden). *Cancer Causes Control* 1995; **6**: 519–24.

Sir—A J Swerdlow and colleagues' report¹ of increased testicular cancer risk among dizygotic (DZ) twins, as compared with monozygotic (MZ) twins, led us to examine data from the NAS-NRC Twin Registry, a US registry containing 15 924 male/male twin pairs born in 1917–27, both members of which served in the military.² We reported³ a greater death rate due to testicular cancer among dizygotic than in monozygotic twins

and a greater rate of testicular cancer in dizygotic than in monozygotic twins who participated in a recent telephone survey.⁴ However, neither difference was statistically significant.

We now report additional testicular cancers ascertained through 1985 from military records, including entrance processing records; hospital records from several sources; sick calls; and veterans records, including hospital, disability, and death records that are quite complete probably because of previous veteran death benefits. There were a total of 39 twins with a diagnosis of testicular cancer. The rate for dizygotic twins was 0.18% (27/15 108) and for monozygotic twins 0.08% (10/11 866), with an odds ratio of 2.12 ($p=0.038$). Among twins of undetermined zygosity the rate of testicular cancer was 0.04% (two of 4874).

None of the 39 cases carried a diagnosis of cryptorchidism from military or veteran records, although cryptorchidism was noted for 160 twins in the registry. Six of the 39 cases had testicular cancer on their death certificates³ and another 16 of the 39 cases survived to be identified by the recent telephone survey as testicular cancer survivors.⁴

In accordance with Swerdlow and colleagues' and other investigators' findings we found statistically higher odds of developing testicular cancer in dizygotic than in monozygotic twins. Although clarification of the mechanism of increased testicular cancer in dizygotic twins awaits further work, the evidence is consistent with the notion that prenatal factors, such as hormones, are associated with the development of cancer in adults. In an analogous line of research, Swerdlow and other investigators, and our group, have also reported rises in early onset breast cancer among dizygotic twins. We should consider the possibility that prenatal hormones, perhaps affected by differences in maternal diet, play a part in the wide international variation in incidence and the migration effects seen for breast cancer.

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- 1 Swerdlow AJ, De Stavola BL, Swanwick MA, Maconochie NES. Risks of breast and testicular cancers in young adult twins in England and Wales: evidence on prenatal and genetic aetiology. *Lancet* 1997; **350**: 1723–28.
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Atkinson GF. The NAS-NRC Twin Panel: methods of construction of the panel, zygosity diagnosis, and proposed use. *Am J Hum Genet* 1967; **19**: 133-61.

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- 4 Braun MM, Caporaso NE, Page WF, Hoover RN. Prevalence of a history of testicular cancer in a cohort of elderly twins. *Acta Genet Med Gemellol* 1995; **44**: 189-92.
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Somatostatin for acute oesophageal variceal bleeding

Sir—The trial reported by A Avgerinos and co-workers (Nov 22, p 1495)¹ raises a few questions. These workers refer consistently to SDs throughout their article, but this notion seems wrong—eg, mean age 58.7 (1.2) or mean number of blood products transfused 2.64 (0.35) cannot be SDs and must be standard errors.

The identity of the treatments was kept in sealed envelopes, but were the envelopes opaque so that the identity could not be revealed before a patient was allocated? Avgerinos and colleagues did not record number of blood products transfused after stopping the trial drug. What was the total amount of blood given during the whole follow-up period of 6 weeks, since they say that the amount they report for the placebo group is an underestimate? Since baseline haemoglobin was the same in the two groups, there seems to be no need to adjust the number of blood products by use of haemoglobin as a covariate. They define one unit of fresh frozen plasma as equivalent to 0.5 units of blood products. How was this decision reached? It would be more informative if the unadjusted numbers of blood products were provided for each type of blood product separately and for the whole 6 weeks period, which would also make it easier to combine the data from this trial with other such trials.²

Use of balloon tamponade was regarded as a treatment failure. How many patients in each group received this treatment? Five interim analyses were done but the stopping rules are not entirely clear—eg, p values for the interim analyses are not shown. It could also be discussed that Avgerinos and colleagues do not adjust the p values for the secondary endpoints, especially since the secondary endpoints are correlated to the primary one that determined when the trial was stopped.

These workers say that there were differences in the overall failure rate between centres but that there was a consistent benefit of somatostatin in all centres. This finding is highly surprising, since the difference in treatment failures between the two treatment groups was only 22 patients. Thus, to arrive at a consistent benefit in all nine centres in the study, each centre would need to have about two treatment failures more on placebo than on somatostatin. One would have expected the variation to be considerably larger than this—for example, that some centres would have had more failures on somatostatin than on placebo or perhaps five or more failures on placebo than on somatostatin.

Six similar trials have been published but Avgerinos et al refer to only four. The trials they fail to mention are the two most negative.^{3,4} A meta-analysis of these six trials has been published and an update, including the present trial, will soon appear.² Taken together, the seven trials of somatostatin or octreotide versus placebo show no effect on mortality (91 vs 85 deaths, odds ratio 1.04, 95% CI 0.74-1.46) whereas, on average, active treatment saves one blood transfusion per patient, precisely as reported in the present trial (95% CI 0.8-1.6).

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- 1 Avgerinos A, Nevens F, Raptis S, Fevery J, and the ABOVE Study Group. Early administration of somatostatin and efficacy of sclerotherapy in acute oesophageal variceal bleeds: the European Acute Bleeding Oesophageal Variceal Episodes (ABOVE) randomised trial. *Lancet* 1997; **350**: 1495-99.
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Authors' reply

Sir—There was indeed a typographic error, and SDs should have been shown as standard errors. We clearly stated

that the study was double-blinded and therefore we used non-transparent envelopes. We also made clear that blood products received after stopping treatment were not recorded because of differences between patients; some died and some went on to other treatments. Even though the baseline haemoglobin was the same in the two groups, precision in the amount of blood given was improved by use of the residual variation in regression analysis. Blood products were defined according to our protocol as: one unit of packed cells; one unit of plasma expanders was equivalent to one unit of packed cells; one unit of fresh frozen plasma was equivalent to half a unit of packed cells. Similar definitions have been used by others.¹

The total amount of each type of blood products (mean, SE) used during infusion were:

| | SST (n=101) | PLC (n=104) | All patients (n=205) |
|---------------------------------|----------------|----------------|-------------------------|
| Packed cell (units) | 2.0 (0.3) | 2.6 (0.3) | 2.3 (0.2) |
| Plasma expanders (units) | 0.4 (0.1) | 0.7 (0.1) | 0.5 (0.1) |
| Fresh frozen plasma (units)* | 0.8 (0.2) | 0.7 (0.2) | 0.7 (0.1) |
| Total (units)† | 2.8 (0.4) | 3.7 (0.4) | 3.2 (0.3) |

SST=somatostatin, PLC=placebo. *Fresh frozen plasma is given as measured (raw data), †total units are packed cells (units)+plasma expanders (units)+half fresh frozen plasma.

An average of 2.8 units was transfused in the somatostatin group and 3.7 units in the placebo group. The corresponding means adjusted for baseline haemoglobin were 2.6 units and 3.6 units, respectively. For the intent-to-treat analysis, the p value to test for a treatment effect by analysis of covariance adjusting for baseline haemoglobin was 0.052, indicating a statistical trend in favour of somatostatin. Among the 92 patients (35 on somatostatin and 57 placebo) who were regarded as failures ten received balloon tamponade (three and seven, respectively).

Stopping boundaries constitutes one of the basic features of sequential designs. They are constructed from the qualitative and quantitative objectives of the trials, and we tested our hypothesis thus.²

With respect to the overall failure rate, two centres provided more than 70% of the patients. In these centres there was a consistent benefit of somatostatin over placebo. The remaining 30% of patients came from six centres. One centre withdrew after one patient (on somatostatin) had been evaluated. This patient was excluded from final analyses. In only two of these centres were there more failures in the somatostatin than in the

placebo group (three *vs* two and four *vs* two, respectively):

| Centre | Failures (no of patients) | |
|--------------------------|---------------------------|---------|
| | SST | Placebo |
| A (n=100) | 10 | 20 |
| B (n=44) | 11 | 17 |
| Remaining centres (n=61) | 14 | 20 |

We were restricted in the number of references, so we had to be selective. However, we included two meta-analyses in which all the data on somatostatin has been cited.

It is true that octreotide contains part of the aminoacid sequence of somatostatin. However, during the past few years there is accumulating evidence that somatostatin and octreotide display different effects and hence therapeutic profiles, and in terms of effectiveness in stopping variceal bleeding, whether they are comparable in efficacy is unclear.^{3,4}

The definitions of end-points used to evaluate treatment efficacy after combined endoscopic and pharmacological treatment are so disparate as to make a meaningful meta-analysis impossible.⁵

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Autism

Sir—As the father of an autistic child and a physician, I was disappointed to note the omission of useful scientific information about therapeutic options for autism in Lorna Wing's (Dec 13, p 1761)¹ otherwise excellent article.

She states (1764) that “Many therapies have been promulgated on

anecdotal grounds but scientific evidence for their efficacy is lacking”. I feel sure that she must be aware of the pioneering work of Ivor Lovaas and others in the USA in the application of behavioural analysis in autism, published in peer-reviewed and reputable journals and replicated in Australia. Lovaas and others have shown^{2–4} in both short-term and long-term follow-up of treated children, much better outcomes than in their non-treated controls, and this method of therapy has been applied widely in the USA and latterly Australia with substantial improvement in quality of life for both the affected children and their families.

It is important that scientifically and statistically demonstrated advances in the treatment of this difficult condition receive adequate attention so that the best possible outcomes can be achieved.

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Magnetic-resonance pelvimetry in breech presentation

Sir—Aren van Loon and colleagues (Dec 20/27, p 1799)¹ report a randomised controlled trial (RCT) of magnetic-resonance (MR) pelvimetry in breech presentation at term. The trial showed that MR pelvimetry did not lead to a lower rate of caesarean section, though the MR group had a higher elective caesarian-section rate than did the control groups' greater rate for emergency sections in labour. These workers report this finding as allowing “better selection of the delivery route, with a significantly lower emergency caesarian-section rate”. They suggest that with the MR pelvimetry evidence of pelvic capacity the clinicians concerned had greater confidence to press on for vaginal delivery. Conversely, in the control arm, without such reassurance, clinicians lacked confidence to push

ahead with vaginal delivery.

The acceptable pelvic measurements for vaginal delivery are not based on any clear evidence. van Loon and colleagues have effectively arrived (arbitrarily) at these values not on the basis of findings from RCTs but by adoption of conservative values used to indicate eligibility into some RCTs, or merely from non-blind observational studies. These measurements may therefore be rather more restrictive than are appropriate. It would be a shame if this excellent study gave misplaced credibility to the values used.

The number of values used (8) is well in excess of the information, which many of us currently obtain from MR pelvimetry. Of the 20 controls classified as one or more abnormal pelvic measurements, 14 were primiparous (from table 2). Of these 14, six were delivered by caesarian section anyway (without benefit of MR pelvimetry, clinicians predicted problems); the remaining eight were delivered by emergency section in labour (presumably clinicians recognised problems in labour). The six multiparous women with abnormal pelvic measurements all delivered vaginally with no adverse outcome. There were only 41 multiparas enrolled in the study, being largely excluded by the entry criteria.

With van Loon and colleagues' data (figure 2), I calculate that 6.2 MR pelvimetry scans would be needed to convert one emergency caesarian section to an elective procedure. At the same time 14% of multiparous women who would have been judged as needing pelvimetry would have elective caesarian section rather than an uncomplicated vaginal breech delivery. The high rate of general anaesthesia for emergency caesarian section differs strikingly from current UK practice.

The message that I take from this study is that there are no established values of pelvic measurements for safe vaginal breech delivery; there is no place for MR pelvimetry in multiparous women; and that if obstetricians feel confident about vaginal delivery, safe vaginal delivery is more likely to happen.

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- van Loon AJ, Mantingh A, Serlier EK, Kroon G, Mooyaart EL, Huisjes HJ. Randomised controlled trial of magnetic-resonance pelvimetry in breech presentation at term. *Lancet* 1997; **350**: 1799–804.

Sir—We have two comments on Aren van Loon and colleagues¹ interesting report on the use of MR pelvimetry in breech presentation at term. The control subgroups (with MR results on either side of a cutoff point, table 2) had virtually identical emergency caesarean section rates: 40% versus 44%. This finding suggests actual pelvic measurements had in the end little influence on the route of delivery, which could be related to the use of old radiological data to define their cutoff value. Separation based on MR-pelvimetry derived, receiver-operator-characteristics curve would have been more appropriate.

Our second comment concerns the possible explanation for the significantly lower emergency section rate reported in the patient group. Table 3 shows different numbers of prolonged first stages: ten in the patient group versus 31 in the control group. Could the obstetrician be more inclined to allow the first stage to continue when assured by MR that the pelvis is adequate? To refute this assumption, one needs to know the data on the actual progress of the first stage of labour in all cases.

The search for the nugget of knowledge that predicts the risk and outcome of each and every breech delivery is like the quest for the Holy Grail. Van Loon et al, have—in our opinion—not solved this highly dynamic multifactorial riddle by applying just one, albeit expensive test. Their study will have some impact, however, because it will boost our patience in all first stages of labour.

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- 1 van Loon AJ, Mantingh A, Serlier EK, Kroon G, Mooyaart EL, Huisjes HJ. Randomised controlled trial of magnetic-resonance pelvimetry in breech presentation at term. *Lancet* 1997; **350**: 1799–804.

Authors' reply

Sir—A randomised controlled trial is probably the best method to evaluate a diagnostic test such as MR pelvimetry in breech presentation at term.¹ The diagnostic test is linked to a strict management protocol in the group of participants whose results are used, which means in our case that minimum acceptable pelvimetry data should be (and were) defined beforehand. In this way, the management policy adopted by the obstetrician in relation to MR

pelvimetry forms the central issue and not the influence of the actual measurements on the route of delivery.

In part we agree with Malcolm Griffiths' first point that our cutoff values are arbitrary, but they are not conservative. We previously compared radiographic data with MR data.² In the discussion section of our report we stated that it would be an oversimplification to think that the limits we used are absolute and that more than pelvimetry data alone should be taken into account.

Griffiths' interpretation of our table 2 is not correct, and therefore his conclusion is false: there were 18 (not 14) primiparous women and only two (not six) multiparous women with one or more pelvic abnormalities in the control group. Of the primiparous women, only six delivered vaginally, four had an elective caesarian section, and eight had an emergency section. Both the multiparous women had an elective caesarian section.

Subgroup analysis, as suggested by J A M Van der Post and J B Maathuis, is interesting, but cannot be viewed as conclusive. Of course there is little difference between the emergency caesarian section rates of the women with normal and abnormal pelvimetry within the control group: the pelvimetry results were not disclosed until 8 weeks post partum, and to a large extent the decisions of the obstetrician rather than the actual pelvic measurements determine the outcome. Analysis of the results with different cutoff points and creating a MR-pelvimetry derived, receiver-operator-characteristic (ROC) curve is interesting, but not appropriate within the design of this trial.

As we stated in the discussion section of our report, we fully agree with Van der Post and Maathuis' second point that the obstetricians may have been reassured about proceeding with the vaginal delivery in the study group. The mean first stage of the vaginal-delivery category in the study and control groups was 456 and 429 minutes, respectively ($p=0.49$). The mean first stage (from the start of labour to the second stage or caesarian section) of the emergency section category was 706 and 528 minutes, respectively ($p=0.02$).

We concluded in our report that our results do not solve the breech dilemma, and we certainly do not claim to have found the Holy Grail. If one considers that the vaginal delivery of any breech is unacceptable, then the question of whether pelvimetry is worthwhile is irrelevant. We agree

with Walkinshaw's commentary on our report: the hope is that the answer to this question will come from the multinational Term Breech Trial.³ However, as long as the question of whether planned vaginal delivery in selected cases or elective caesarian section in all cases is better remains unresolved, we suggest MR pelvimetry should be part of the selection procedure for a planned vaginal delivery. However, before starting to use MR pelvimetry radiologists and obstetricians should fully acquaint themselves with the technique and measure their intraobserver and interobserver limits of agreement.⁴

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- 1 Sackett DL, Rosenberg WMC, Gray JAM, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ* 1996; **312**: 71–72.
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- 3 Walkinshaw SA. Pelvimetry and breech delivery at term. *Lancet* 1997; **350**: 1791–92.
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Understanding human parturition

Sir—In her Dec 20/27 commentary¹ on contemporary theories of human parturition, Lisa Barrie Schwartz postulates that a key event at term is oestradiol stimulation of placental 11 β -hydroxysteroid dehydrogenase (11 β -HSD)

According to the hypothesis, induction of 11 β -HSD type 2, which catalyses the rapid inactivation of cortisol to inert cortisone, attenuates fetal exposure to maternal cortisol, which, by inference, is purported to contribute much to fetal cortisol concentrations until that stage. She suggests that the fall in transplacental passage of cortisol at term activates the fetal hypothalamic-pituitary-adrenal axis, stimulating secretion of fetal adrenal androgen which fuels further placental oestrogen synthesis, inducing labour.

Good evidence exists in animals, including the baboon, for such a change in the pattern of fetal exposure to maternal glucocorticoids as

pregnancy advances.² We confirmed by direct perfusion of the term human placenta immediately after delivery³ that placental 11 β -HSD type 2 at term converts most (up to 95%) maternal cortisol to inert cortisone during transplacental passage. However, despite these findings, this hypothesis is unlikely in human beings because it contradicts data that suggest a lack of transplacental passage of cortisol from early gestation, with an up to ten-fold materno-fetal gradient of cortisol from early gestation.

Contrary to the suggestion reviewed by Schwartz, the fetal adrenals are active from 16 weeks of gestation or earlier⁴ and, although fetal and maternal cortisol concentrations rise during pregnancy, most circulating fetal cortisol throughout gestation is of fetal adrenal origin.³ Additionally, 11 β -HSD type 2 is expressed in human placenta and fetus from early gestation and probably excludes maternal cortisol from the fetus in early and mid-gestation, a view supported by in-vivo human studies.⁵ Thus, cortisol does not easily cross the human placenta at any stage, and is therefore unlikely to have an important role in the initiation of human labour. Unlike human placenta, both 11 β -HSD type 2 and type 1 are expressed in baboon placenta. The latter, a reductase, catalyses the reverse reaction, regenerating active cortisol from inert cortisone in intact cells,² complicating extrapolation from this species. Finally, in people who harbour rare deleterious mutations in the 11 β -HSD type 2 gene, transplacental passage of cortisol is thought to be unrestricted, and consistent with this, such pregnancies are associated with substantial retardation of fetal growth, but not apparently preterm labour.

It is still possible that 11 β -HSD and cortisol are involved in the initiation of human labour, but the hypothesis presented by Schwartz is surely inadequate. A more plausible hypothesis would be cortisol-related ontogenetic changes in the expression of glucocorticoid receptors and perhaps of 11 β -HSD in fetal tissues involved in feedback regulation of the fetal hypothalamic-pituitary-adrenal axis, as documented in the rodent hippocampus.

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1 Schwartz LB. Understanding human

parturition. *Lancet* 1997; **350**: 1792–93.

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Kangaroo mother care

Sir—In his Dec 13 commentary¹ on Kangaroo mother care, Lex Doyle synthesises the major aspects of our RCT on Kangaroo mother care. We agree with most of his comments, but wish to clarify some of the points raised by Doyle. We would like to refer to each one of the restrictions to applicability identified by him.

First, although 8% of all livebirths in the study hospital (which is a national referral hospital for social security) were babies with birthweights under 2000 g, almost two-thirds of them were preterm infants adequate for gestational age (26–36 weeks gestation). For them, the same restrictions for eligibility (ability to suck and swallow properly) applied, as would be the case in developed countries. Median postconceptional age at eligibility of these infants was 34 weeks. For example, a baby born at 26 weeks of gestation was likely to be eligible when reaching a postconceptional age around 30–32 weeks (mature enough to suck and swallow), after spending 6–8 weeks in the neonatal-care unit, which could be similar to the situation in many neonatal units.

Second, in our experience in developed countries, it is the exception rather than the norm that a preterm infant is discharged before reaching a weight of 1800 g. Our experience differs from Doyle's perception of the current practice in neonatal nurseries in developed countries. Therefore, each reader should decide of applicability, based upon prevalent local practices.

Third, the comment on limitations of sample size for detecting differences in mortality is correct. Because of

space constraints, the paper does not expand on all the considerations made when computing sample size. For an α error level of 5%, our sample size had an 80% power to detect a difference in frequency of severe infection of 20% (from 8% to 10%); a 95% power to detect a 10% difference in proportion of breastfeeding (from 90% to 99%), and an 80% power to detect a 1-day mean difference in length of hospital stay, among others. Given that there is evidence that Kangaroo care does not jeopardise survival, we focused not only on mortality reduction, but also on improvement in the quality of life of survivors (morbidity, breastfeeding, mother-to-child bonding, &c), which accords with the spirit of Doyle's commentary.

Fourth, there is a misunderstanding with regard to intensity of efforts invested in the ambulatory care while in kangaroo position. Doyle understood that daily follow-up visits were conducted at home. Follow-up visits were conducted at the Kangaroo mother-care clinic, a fact that again, due to space limitations, was not explicitly stated in the methods section of our paper. Home visits were reserved for non-compliers only. We completely agree on the need to conduct a full-scale economic evaluation, as highlighted by Doyle in his comment. We are concerned not only with the costs of providing Kangaroo care as opposed to costs in minimal-care neonatal units, but also with quantification of utilities, not only in terms of survival and morbidity but also for satisfaction and quality of family-to-infant bonding and relationship.

With regard to Doyle's concern about completeness of follow-up, we have currently finished the data-gathering process up to 1 year of corrected age, with complete follow-up in 85% of recruited participants, and with accurate information on survival for 93% of the study population. Follow-up of this group continues to date, and, depending on availability of funds, we plan to evaluate them at age 4–5 and 7–8 years.

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1 Doyle LW. Kangaroo mother care. *Lancet* 1997; **350**: 1721–22.

Rembrandt's self-portrait

Sir—In his discussion of Rembrandt's self-portrait (Dec 20/27, p 1835),¹ Carlos Espinel looks at the picture as if Rembrandt were sitting before him as a patient. I have compared the self-portrait from 1659, which Espinel describes, and one from 1660 which is in the Metropolitan Museum of Art in New York to see whether Espinel's diagnosis is valid.

The only point on which I agree with Espinel is that Rembrandt's skin showed signs of senile degeneration. In his later self-portrait I do not find any signs of teleangiectasis, rosacea, or rhinophyma. I think that the rosy cheeks with reddish dots do not indicate a disease that disappeared a year later, but are probably a stylistic device.

In the 1660 portrait, Rembrandt's eyes are normal, although the left eye is slightly narrower than the right eye. I did not notice any palpebral ptosis or a pterygium. The bright line that Espinel diagnoses as possibly an arcus senilis is just a normal reflection of light from the cornea, which can be seen in many of Rembrandt's paintings, for example, in the eyes of Saskia's portrait in Amsterdam's Rijksmuseum. There are no signs of xanthelasma in the 1660 self-portrait.

It is unlikely that Rembrandt had temporal arteritis, since one can hardly notice his temporal artery, even in the 1659 portrait. Indeed, I doubt whether he could have seen enough to paint his later self-portraits if he had really had temporal arteritis. Thus, although the analysis of Rembrandt's diseases based on the 1659 self-portrait is an excellent intellectual exercise, and is most interesting, I doubt whether Rembrandt really had the diseases mentioned by Espinel.

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1 Espinel CH. A medical evaluation of Rembrandt. His self-portrait: ageing, disease, and the language of the skin. *Lancet* 1997; **350**: 1835–37.

Sir—Like Carlos Espinel,¹ I have also examined many of Rembrandt's self-portraits and question whether his "wrinkled, haggard face", and "possible xanthelasma and arcus senilis" at the age of 53 years reflect the distress of financial and personal losses. I agree with Espinel that such features could be signs of premature ageing or another disease. I had come

to the conclusion that the consistently dull and expressional facies, periorbital puffiness, dry and sparse hair and eyebrows (outer third), pale skin, and slight obesity could be signs of hypothyroidism, and that perhaps the xanthelasma and arcus senilis were due to secondary hypercholesterolaemia.

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1 Espinel CH. A medical evaluation of Rembrandt. His self-portrait: ageing, disease, and the language of the skin. *Lancet* 1997; **350**: 1835–37.

Sir—Carlos Espinel's clinical study¹ of Rembrandt's face, seems to reveal no serious illnesses, only premature ageing and rosacea; the evidence for temporal arteritis is insufficient. Unfortunately, we have no diaries or letters of Rembrandt in which he comments on his own health, so we have no history (almost always the most valuable part of the clinical examination in leading to a diagnosis) and are left with only inspection—percussion, and palpation being out of the question.

Fortunately for us there is much to be inspected: Rembrandt's many self-portraits from his early years right up to the year of his death in 1669, leave a sort of pictorial autobiography.² In a later self-portrait (c 1661) in Kenwood, London, Rembrandt looks healthy and robust and has put on weight. Perhaps he had some transient illness. The possibility of such an illness has been raised by Kenneth Clark³ who wrote, "In the next year the philosopher-king has vanished, and the image of anxiety has returned. We find it in the picture in the Mellon Collection at Washington, which has some of the Ellesmere portrait but with, I feel, an added suggestion of disease . . . But we may assume that in middle age he had his fair share of illness, and the self-portraits suggest that this took place in 1659. He seems to have been well enough in 1658 . . . It is the picture of a sick man . . . Then, as he recovers his balance, comes the portrait in the Louvre dated 1660. We see that his illness has left him battered and changed". However, with regard to the known facts of Rembrandt's life, Clark cautiously states that it is dangerous to relate Rembrandt's self-portraits to any of these.³

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- 1 Espinel CH. A medical evaluation of Rembrandt. His self-portrait: ageing, disease, and the language of the skin. *Lancet* 1997; **350**: 1835–37.
- 2 Veth J. Rembrandts leven en kunst, 2nd edn. Amsterdam: H J W Becht, 1941: 246.
- 3 Clark K. An introduction to Rembrandt. Newton Abbott: Readers Union, 1978: 11–38.

The yield of meta-analysis

Sir—The point of view of Janice Pogue and Salim Yusuf (Jan 3, p 47)¹ on the basic requirements for meta-analysis to produce an optimum information size (OIS) and be a worthwhile component of scientific literature "at least as rigorous as well-designed and adequately powered" randomised controlled trials (RCT) is a clear criterion to be agreed and followed.

There is, however, an intrinsic ambiguity of both RCT and meta-analysis.²⁻⁴ The latter has been generated mainly out of the need to compensate for the inadequacy of RCT. Non-adequate trials represent a rule in most areas of medicine (eg, most of those included in the meta-analytic efforts of the Cochrane Collaboration: from those in primary care, to psychiatry, to peripheral arterial disease). The adherence to formal rules of meta-analysis will never be able to overcome the substantial biases of heterogeneity and publication which characterise non-independent, product-oriented or technique-oriented investigations.

On the other side of the rare areas where problem-oriented large-scale trials are available (eg, breast, fibrinolytic, and antiplatelet), the compliance with the OIS criteria is easier, and meta-analysis has a different role: to explore and qualify the generalisability of main results to important and clinically plausible subgroups.

Meta-analysis, as well as its basic component, the RCT, cannot be seen as an unambiguous scientific tool to produce reliable knowledge.⁴ The rules of a competitive market are likely to be a powerful confounder. As in every market, the rights and the duties of consumers and producers depend on the precarious interaction between the declared compositions of the products and the intelligence of the users. The OIS could be welcome against its well set-out predeclared goal to generate hypotheses for widespread diseases with moderate-size expected/observed benefits.

At variance with hypothesis-generating meta-analysis, decision-making oriented overviews should

strictly follow methodological sound guidelines. Meta-analysis, however, is useful also to rapidly summarise the amount of scientific information that is available in a definite point of time and has a unique value for rare diseases that have few adequately sized RCT. The OIS criteria are at risk of excluding these already orphan areas from the visibility (and motivation) of literature. By looking for more promising scientific hypotheses, hypothesis-generating meta-analyses could be useful for researchers to evaluate the opportunity of starting ad-hoc research work. Readers, on the other hand, could have access to critical reviews of scientific literature.

The key point in these cases is that the exploratory nature of the analysis should be clearly underlined to avoid false expectations of efficacy. As a scientific tool, meta-analysis should follow strict methodological rules. To select papers, referees should evaluate whether strict methodological rules have been correctly followed by the investigators, and above all, a clear definition of the use the investigators propose for the available data should be clearly stated. Meta-analyses that are inclusive are less likely to be accepted and published, but, a more liberal approach could help researchers as well as readers to have a clearer picture of the state-of-art, especially in fields not directly covered by their expertise.

This work was supported by the Italian National Research Council.

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- 1 Pogue J, Yusuf S. Overcoming the limitations of current meta-analysis of randomised controlled trials. *Lancet* 1998; **351**: 47–52.
- 2 Le Lorier J, Gregoire G, Benhaddad A, Lapierre J, Derderian F. Discrepancies between meta-analyses and subsequent large, randomized, controlled trials. *N Engl J Med* 1997; **337**: 536–42.
- 3 Editorial. Meta-analysis under scrutiny. *Lancet* 1997; **350**: 675.
- 4 Linde K, Clausius N, Ramirez G, et al. Are the clinical effects of homeopathy placebo effects? A meta-analysis of placebo-controlled trials. *Lancet* 1997; **350**: 834–43.

Genetic associations

Sir—Associations between gene polymorphisms and diseases are a growing part of published medical work. The statistics of association are often difficult for the general reader to evaluate. Highly publicised associations are not confirmed subsequently, leading to confusion in

the published research

There are two simple points of interpretation of genetic associations that may be helpful. The first involves the added value of a new genetic association to one that is firmly established. This paradigm frequently involves finding an increased odds ratio for the two associations when used together, compared with that of the established association, but the size of the study is rarely large enough to establish any individual effect for the new putative association. Subsequent studies may not find the same effect and eventually, after a flurry of papers, the association is buried.

A second and more basic error is when a single nucleotide polymorphism is used to rule out the association of a gene with a particular disease. These negative analyses are usually published when a particularly promising candidate gene is evaluated. Frequently, however, the analysis of a single polymorphism within or near a candidate gene causes researchers to conclude that the gene is not associated with the disease. This is incorrect.

For example, there are two major polymorphisms that occur within the sequence of apolipoprotein E, one responsible for the transition from APOE4 to APOE3, and another from APOE3 to APOE2. Both are single nucleotide polymorphisms, yet only the first is associated with increased risk and lower age of onset of Alzheimer's disease. The second would never be identified by testing patients with Alzheimer disease versus controls, particularly because APOE2 is associated with decreased risk and older age of onset distributions. Thus, two polymorphisms in the same small gene (299 aminoacids) provide quite different results in an association study. Of course, in a broader sense, physicians have known this to be the case for more than half a century. Of the tens of polymorphisms of β -globulin, only the single sickle-cell polymorphism is associated with sickle-cell disease.

Genomic companies and screeners who are counting on the construction of screening tools with representation of one polymorphism for each gene for research on disease association need to reconsider that strategy. Associations, even those within a region of genetic linkage, must be validated by assessment of the biological relevance of all of the variants to the disease.

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The pleasures of pipe smoking

Sir—I am an 87-year-old retired physiologist who has just enjoyed his first pipe after a period of abstinence when in hospital, not for a respiratory disease. Like many of my contemporaries I enjoy smoking in moderation. It helps me to relax and come to terms with the restrictions imposed by advancing years. In the past I thought (this may be a delusion) that it helped me to concentrate when writing for *The Lancet*.

I was encouraged to smoke by the example of my father, a general practitioner. I encouraged my three sons to smoke; one is now an inveterate pipe smoker but the other two have no use for tobacco. We differ in our reactions to drugs. About a third of the population can probably use tobacco sensibly and enjoy it.

I support strongly *The Lancet* and the Royal Colleges in their efforts to act to get the advertising of cigarettes banned and would go further to press for a ban on cigarette manufacture. The tobacco industry would be forced to turn to pipe tobacco; few of the brands that I enjoyed as a young man are now available. Also, there are now in Edinburgh only two shops with a good selection of pipes and most of these of heavy he-man ones, unsuitable for an edentulous old man or a young lady.

I am now rereading Walter Scott's novels which I had enjoyed as a student. They record how in the eighteenth century many women in Scotland enjoyed their pipes. I advise those ladies today, who enjoy smoking, to follow their example. As Sir Richard Doll and his colleagues showed many years ago the risk to health from pipes is trivial when compared with that from cigarettes.

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DEPARTMENT OF ERROR

Left-ventricular volume reduction or mitral valve reconstruction—This correspondence letter by Kazuo Komamura and Kunio Miyatake (Nov 1, p 1327), was omitted from the inside contents page.