Letters

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Investigating allegations of research misconduct

Worst outcome of Griffiths report would be that research becomes increasingly difficult

EDITOR—The Griffiths report contained a critique of two specific research projects and proposals on the regulation of research generally.

Hey and Chalmers express no view on these proposals.[1] However, the accompanying editorial by Smith agrees with the report's main recommendations on the need for better research governance in the NHS without citing supporting evidence.

The Griffiths report made three main recommendations which could inhibit clinical research.

Firstly, concern about consent for research at times of stress. Most intensive care research requires consent at times of stress and if the researchers waited this research would be impossible. The financial cost of the suggested consent from a third party would inhibit research.

Secondly, the inquiry stated that brain damage could not be reliably assessed at a short period of follow up and was critical that follow up was determined by the amount of funding available. To place a requirement that all research in children involves long term follow up studies would abolish much research. The resources required are not addressed.

Thirdly, trusts should ensure that arrangements are in place for active monitoring of the progress of research. There is no indication that new funding will be available for this. Furthermore, "research involving vulnerable groups should be subject to an even greater degree of independent supervision than clinical research in general."

Not for the first time will there be the paradox of well-meaning discrimination against children. This has been the case for trials of new drugs, in which the perceived obstacles deter research in children.[2] The Department of Health's draft research governance "to protect participants, improve quality and stop research fraud" gives no evidence of the magnitude of these problems and does not discuss the resource implications of implementation.[3] "There are already powerful incentives to adhere to many of the principles" in the framework, including the law, duty of care, and high professional standards of researchers. No evidence is quoted to assess how often these safeguards fail. Unreferenced "recent enquiries into adverse incidents relating to research" are inadequate justification.

Patients must be protected from inappropriate research, and informed consent must be obtained. However, extrapolating from the Griffiths report to clinical research throughout the United Kingdom must be thought through. Currently, 40% of drugs prescribed for children are not licensed,[4] partly because of the existing deterrents to research in children. More hurdles are likely to inhibit research further,[5] and ultimately it is children particularly who will suffer.

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1 Hey E, Chalmers I. Investigating allegations of research misconduct: the vital need for due process (with commentary by R Griffiths, TE Stacey, J Struthers). *BMJ* 2000;321:752-6. (23 September.)
2 Aynsley-Green A, Barker M, Burr S, Macfarlane A, Morgan J, Sibert J, et al. Who is speaking for children and adolescents and for their health at the policy level? *BMJ* 2000;321:229-32. (22 July.)
3 Department of Health. Research and development. Research governance framework for health and social care (draft) consultation paper. www.doh.gov.uk/research/announcements/researchgovernanceconsult.htm; accessed 15 November 2000.
4 Conroy S, McIntyre J, Choonara I, Stephenson TJ. Drug trials in children: problems and the way forward. *Br J Clin Pharmacol* 2000;49:93-7.
5 Anonymous. UK paediatric clinical research under threat. *Arch Dis Child* 1997;76:1-3.

CNEP trial was greatly flawed

EDITOR—Hey and Chalmers are quick to discredit the Griffiths inquiry for not pursuing issues beyond its remit, but they themselves have conducted a biased review.[1]

The scoring system has been proved to allow bias in favour of continuous negative extrathoracic pressure (CNEP) ventilation over intermittent positive pressure ventilation. A baby who died receiving CNEP could score higher than its surviving matched pair receiving conventional treatment. If this scoring system and the statistical approach were supposed to enable termination of the trial if the subjects suffered harm why did the study continue after the 10th infant was strangled to death by the neck seal?

The trial did not run as it was designed to. Protocols were ignored and criteria overlooked, rendering the results invalid. The pilot study on the neck seal and whether it affected cerebral blood flow was not done until half way through the main study and used children who were already part of the main study.[2 3] This suggests that the study was carried out without the researchers knowing the safety and efficacy of CNEP, rendering any consent form invalid.

Peer review was conducted by the National Perinatal Epidemiology Unit, Medical Research Council, and National Heart and Chest Hospital in 1990. How is this peer review when the trial began in 1989?[2]

The "bonding questionnaire" asks parents how they bonded with their children while in neonatal intensive care. It implies that CNEP was standard practice and does not mention the consent process.

We were constantly discouraged from handling our children because of the loss of negative pressure through the portholes. No research has been conducted on the effect of opening a porthole on an infant's cerebral circulation, despite the researchers' concerns.[4] However, nurses mentioned that transferring a sick infant into CNEP compromised the rules on minimal handling.[2 4] It could take up to one hour and at

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least two nurses to establish CNEP. One baby died during transfer.

Hey and Chalmers disagree with the Griffiths inquiry that "it is not possible to be sure who completed some of the consent forms." Perhaps the inquiry could not believe that any parent would misspell their name or produce a perfect signature when unconscious.

The worst implication in this article is that CNEP could be beneficial neurologically. Some of the children who scored maximum points for normal cranial ultrasound findings had severe brain damage. In one such case an independent autopsy ascertained the cause of death as cerebral haemorrhage.

The retrospective audit being set up will definitively find the true number of children neurologically compromised by the use of CNEP; Hey and Chalmers should not pre-empt this.

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1 Hey E, Chalmers I. Investigating allegations of research misconduct: the vital need for due process (with commentary by R Griffiths, TE Stacey, J Struthers). *BMJ* 2000;321:752-6. (23 September.)
2 Samuels MP, Raine J, Wright T, Alexander JA, Lockyer K, Spencer SA, et al. Continuous negative extrathoracic pressure in neonatal respiratory failure. *Pediatrics* 1996;98:1154-60.
3 Palmer KS, Spencer SA, Wickramasinghe YA, Wright T, Southall DP, Rolfe P. Effects of positive and negative pressure ventilation on cerebral blood volume of newborn infants. *Acta Paediatr* 1995;84:132-9.
4 Raine J. Continuous negative extrathoracic pressure in the neonatal respiratory distress syndrome [MD thesis]. Manchester: John Rowlands University, 1993.

British Association of Perinatal Medicine welcomes analysis of Griffiths report

Editor—Incompetent would not be too harsh an adjective to describe the Griffiths report,[1] particularly considering that the authors use equally strong language following their cursory indictment of the randomised controlled trial of continuous negative airway pressure (CNEP) in North Staffordshire in general and of Professor David Southall in particular. Many professionals and parents have suspected that the conclusions of the report were wrong. Now, the analysis by Hey and Chalmers shows that the inquiry team's report was indeed deeply flawed.[2]

Hey and Chalmers considered in detail documents that the inquiry team could have consulted but did not. Their assessment reveals an alarming degree of incompetence by the inquiry panel, which seems to have been content to rely on allegations made in oral evidence offered years after the events in question.

In the same issue Smith acknowledges that his previous editorial was based on a false assumption that the inquiry had been well conducted.[3 4] Hey and Chalmers have done patients, clinicians, and researchers a great service in showing that what has been suspected by many of them is true. After external scientific and ethical review the CNEP trial in Stoke was carried out to well established standards. Indeed in many ways it was ahead of its time, a fact reflected in its publication in the world's leading paediatric journal.[5]

Neonatal research in the United Kingdom has always set high standards and has an excellent record of collaborative trials to evaluate and establish more effective and safer treatments. As in all fields of medicine, good research is essential to serve patients well and the understanding and willing involvement of parents will always be required.

The Griffiths panel failed to appreciate this, possibly because the distance of the panel members from the clinical arena clouded their interpretation of the facts. The response of the Griffiths panel members to the Hey and Chalmers paper ends with a statement that they consider their "job done" and will not take part in further debate. It is disingenuous of them not to defend their report, considering the extent of the damage it has done, not just to the doctors and nurses in Stoke on Trent but to all those caring for newborn babies and their parents.

We trust that Hey and Chalmers's painstaking analysis of this affair will set the record straight about the quality of the research and care in Stoke on Trent in the early1990s and re-establish confidence in the governance of British neonatal research after the damage done by the Griffiths inquiry.

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1 NHS Executive West Midlands Regional Office. Report of a review of the research framework in North Staffordshire Hospital NHS Trust (Griffiths report). Leeds: NHS Executive, 2000. (www.doh.gov.uk/wmro/northstaffs.htm, updated 8 May 2000.)
2 Hey E, Chalmers I. Investigating allegations of research misconduct: the vital need for due process (with commentary by R Griffiths, TE Stacey, J Struthers). *BMJ* 2000;321:752-6. (23 September.)
3 Smith R. Inquiring into inquiries. *BMJ* 2000;321:715-6. (23 September.)
4 Smith R. Babies and consent: yet another NHS scandal. *BMJ* 2000;320:1285-6.
5 Samuels MP, Raine J, Wright T, Alexander JA, Lockyer K, Spencer SA, et al. Continuous negative extrathoracic pressure in neonatal respiratory failure. *Pediatrics* 1996;98:1154-60.

Nurses undertaking the CNEP trial give their support and describe their experiences

Editor—The Griffiths panel wrote the following:

"9.3.5 The Review Panel is in no doubt that the nursing sister assigned to the project worked many more hours than she was contracted for, but she did not appear to have been provided with a protocol or system of documentation which made sure that everything was complete for all patients.

"Nursing staff and the sister in particular had not been trained or had adequate research experience for the job that they were being asked to do.

"Supervision from the researchers was inadequate, and the staff were poorly supported by trust nursing management."[1]

As the clinical nurse specialist employed for the project, one of us (TW) took on a support nursing sister (KL) shortly after the trial had started. KL covered periods of leave and helped in the running of the trial while also working as a sister on the neonatal unit. She then took on the role of clinical nurse specialist on a full time basis to supervise the last six months of the trial. Thus we were the two senior nurses running the project in Stoke.

We strongly refute the suggestion that there was an inadequate protocol or means of documenting all of the material relating to each of the patients in the trial. We kept each patient's data in a dedicated folder, and we understand that all of this material is available at the trust for relevant staff, the quality of our work being there to see.

The panel did not ask to see either of our curricula vitae, which would have shown the previous research experience of TW, including involvement in West Midland's perinatal audit, a small part in a research study comparing two preterm formula milks, and the development and organisation of a small randomised controlled trial of continuous negative extrathoracic pressure (CNEP) in chronic lung disease of prematurity.

It is also a matter of record that the panel interviewed only one of us (TW).

It was intimated in the Griffiths report that we did not receive support from Professor Southall during the period of the trial. Although Professor Southall was based in London for a large part of this time, we always found him to be available to talk to and extremely approachable if we had any queries or concerns, however minor, about the trial. He provided us with continuous support, advice, and reassurance, being available seven days a week day and night on a rotational basis with Dr Martin Samuels, who was also extremely supportive.

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It is time to learn the lessons from Stoke

Editor—The careful and scholarly analysis of the Griffiths report by Hey and Chalmers is most welcome.[1] The multiple inquiries into the research and the child protection work of Professor Southall and his colleagues at the North Staffordshire Hospital have unavoidably been very damaging—not only to the doctors and other professionals caught up in this but to the clinical investigation and management of child abuse,[2] the readiness of academics to embark on innovative and therefore high risk research,

and the reputation of the NHS for impartial handling and investigation of complaints.

It is easy with the wisdom of hindsight to be critical of government, the management of the trust concerned, and the panels of investigators, but the serious allegations which had been made could not be ignored, and doubtless everyone involved acted in good faith. Unfortunately, those ordering and carrying out the investigations lacked adequate guidelines to inform the proceedings, and this must now be rectified urgently. Unless inquires are conducted with the same rigour as the research that they purport to investigate, their findings will always be subject to criticism, but to do this adequately will need substantial funding. Furthermore, such inquiries will be subject to the same variability of opinion as the refereeing of research papers, so panels must be chosen with great care. No research team is perfect, and any clinical or academic unit subjected to the scrutiny which Professor Southall has undergone[3] would surely reveal imperfections, errors, and omissions. But I doubt whether many of us would come out of it as well as he has, especially some 10 years after the events that were the subject of the original complaint.

The original charges against Professor Southall were to do with his work in the child protection field. One disturbing result of the whole saga is an increasing reluctance on the part of paediatricians to take part in child protection work. This has always been a difficult area of practice because clinical decisions can easily be challenged, uncertainty is the rule rather than the exception, and giving evidence in court is often intimidating. As a result of the attacks on Professor Southall's work on how parents fabricate illness, this reluctance has escalated. The complaints procedure must now be revisited and restructured in cases of child abuse.

If the lessons are learnt and acted on swiftly, this unhappy series of events may yet have some benefits for research, clinical practice, and children.

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1 Hey E, Chalmers I. Investigating allegations of research misconduct: the vital need for due process (with commentary by R Griffiths, TE Stacey, J Struthers). *BMJ* 2000;321:752-6. (23 September.)
2 Marcovitch H. Diagnose and be damned. *BMJ* 1999;319:1376. (20 November.)
3 Royal College of Paediatrics and Child Health. www.rcpch.ac.uk; accessed 15 November 2000.

Nothing but the truth must emerge from these investigations

Editor—Perhaps Professor Southall would like to explain how he had copies of the consent forms he sent to Hey and Chalmers[1] and whether he had parental consent to release part of a child's medical records to a third party.

Professor Southall states on a public website (www.baspcan.org.uk) that an investigation into his child protection work at North Staffordshire Hospital was undertaken because of two ridiculous statements attributed to me. In fact, I went to North Staffordshire with a parent and presented documentation to support allegations; the parent accompanying me laid several of her own complaints about the way in which her case had been handled (she has now been fully vindicated and cleared). A preliminary NHS inquiry found the concerns so serious that two independent expert panels were convened to take a further and more in-depth look at Professor Southall's work.

The Griffiths inquiry was set up to look at the research undertaken at North Staffordshire. Covert video surveillance was research; it has been published as research and therefore did fall within the remit of the inquiry. Ms Nash and Dr Harrison visited my home just as the inquiry was being set up. I presented them with a police statement written by Professor Southall in 1992 in relation to such a case. The content of this police statement showed a total disregard for the health and safety of a child by the doctors viewing the events. It was also pointed out that while this had happened, there had been absolutely no approval from either Staffordshire police or social services because of their concerns for the welfare of the child.

Professor Southall's suggestion that those campaigning about the continuous negative extrathoracic pressure (CNEP) trial are trying to sabotage his child protection work is outrageous and shows a distinct lack of compassion for the parents who have lost their children during a clinical trial. I am appalled that anyone would stoop this low, let alone somebody who claims his life's work is for children.

I stand by every word that I have ever had published about Professor Southall. There has never been a concerted effort to stop the protection of children. The exact opposite is true: it is for the sake of children that I have campaigned so hard for nothing but the truth to emerge.

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Some questions still need answers

Editor—Hey and Chalmers's clarification of their position on the continuous negative extrathoracic pressure (CNEP) trial in their rapid response to their article is welcome.[1 2] They say: "We have not concluded that there were no irregularities in the way the CNEP study was undertaken."[1]

However, there was another clarification which Chalmers could have offered, indeed might have thought helpful to declare as a conflict of interest, even have drawn to the attention of the Medical Defence Union when reviewing this sad business, which is that international collaborators with the Cochrane Centre in Oxford, of which he is director, will very likely review the CNEP study as part of its ongoing work—unless they decide to exclude the study altogether.

For example, a recent Cochrane Library review of continuous distending pressure for respiratory distress syndrome in preterm infants omitted the Queen Charlotte's-North Staffordshire CNEP study, despite a report having been available since 1996, saying that this study was "awaiting assessment."[3] Hey and Chalmers's lively criticism of the Griffiths inquiry will I am sure not influence the neonatal editorial group responsible for this aspect of Cochrane reviews. I hope it doesn't prejudice them against CNEP.

I am, however, confused by another electronic response in which Rowlands says: "I became interested in the human rights and welfare of the NHS aspects of this issue purely as a reader of the *Independent* whose coverage has been particularly deplorable—purely sensational and not at all concerned with the damage it has wrought."[4]

Hey and Chalmers, however, rely on unattributed hearsay evidence from the health editor of the same newspaper: "Jeremy Laurance's article in the 22 September issue of the *Independent* states that 'Health department officials are known to have had strong reservations about the quality of the (Griffiths) report.'"[1] Is the *Independent* "deplorable," "sensational," "not at all concerned with the damage it has wrought," or is it instead a reliable source of information?

And if I might add, the 18 000 word rebuttal to the Griffiths report, written by Professor Southall, was withdrawn by BASPCAN (the British Association for the Study of Child Abuse and Neglect) from its website (www.baspcan.org.uk) for a time after representations. Another (3500 word) dossier, written by Professor Southall and formerly lodged with the BMA,[5] was also removed, not yet to be restored. The rebuttal has been reinstated, but given a statement from BASPCAN that such postings are time limited and that the Charity Commission is looking into an alleged misuse of the BASPCAN site, there is at least the possiblity that the rebuttal may yet again be removed.

Should, or would, the removal of these documents also lead to the withdrawal of articles which rely on them as sources?[2 5]

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Mr Morgan as a freelance journalist may earn income from writing or broadcasting about these events.

1 Hey E, Chalmers I. The Griffiths inquiry into research in Stoke on Trent failed to use due process. Electronic response to: Investigating allegations of research misconduct. bmj.com 2000;321 (www.bmj.com/cgi/eletters/321/7263/752#EL58; accessed 15 November 2000).
2 Hey E, Chalmers I. Investigating allegations of research misconduct: the vital need for due process (with commentary by R Griffiths, TE Stacey, J Struthers). *BMJ* 2000;321:752-6. (23 September.)
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4 Rowlands I. Competence of the Griffiths review. Electronic response to: Investigating allegations of research misconduct. bmj.com 2000;321 (www.bmj.com/cgi/eletters/321/7263/752#EL38; accessed 15 November 2000).
5 Marcovitch H. Diagnose and be damned. *BMJ* 1999;319:1376. (20 November.)

Response to concerns raised by Mr and Mrs Henshall

EDITOR—Mr and Mrs Henshall voice important concerns in their rapid response and the letter above.[1] Professor Southall is genuinely distressed that NHS managers did not let him discuss these directly with the family when they were first raised and equally frustrated that legal advice restrains him from responding personally to this correspondence even now. Because the family deserve some answers I will address as many of these concerns as my knowledge of the documents allows.

They say that the 10th baby recruited to the study was "strangled to death," but this is to misunderstand the autopsy information. There was trauma to the skin round the neck, which triggered increased nursing vigilance and further (very effective) improvements in the design of the neck seal, but no evidence that this contributed to the baby's death. Rather the reverse. Skin blood flow was so poor, because the baby was already dying, that a pressure sore developed.

Clear rules for monitoring the progress of this study were in place and in the hands of an independent statistical adviser, who would have stopped the study at once had any evidence of excess harm come to light. Such rules have increasingly become a component of all good trials in the past few years, but the continuous negative extrathoracic pressure (CNEP) trial was ahead of its time in having these in place in 1989.

The scoring system designed to make this possible has been widely misunderstood. It was only possible for a baby who died to be awarded a better (higher) score than one who survived intact by treating those who survived with severe lung damage (the main problem the trial was trying to address) as "intact" survivors. Scores were not the only way progress was monitored. Nor were they used to evaluate the final outcome. An audit of all deaths, and all survivors with cerebral untrasound abnormality, was also maintained. Perhaps a belief that everyone would assume this was undertaken explains its omission from the final trial report.

The Henshalls rightly question the statement in the parents' information sheet about the technique having been "shown to be safe and effective" and wonder why, if that were true, further studies were undertaken in parallel with the CNEP trial to look at what such treatment did to cerebral blood flow. All ethics committees require evidence of safety, but, in the nature of things, such statements have to be more provisional than is generally acknowledged. As the recent spotlight on what the last chief medical officer had to say about British beef reminds us, all that can ever be said is that there is, as yet, no evidence that something is unsafe.

Early work using CNEP had been promising,[2] and no evidence had emerged to suggest such treatment was unsafe. The CNEP trial was undertaken specifically to confirm that it was indeed safe when offered to very small babies and to determine whether the benefits outweighed any possible hazard. The advent of infra red technology while the trial was in progress made it perfectly proper to do further studies to confirm that cerebral blood flow was unaffected. Indeed, it would have been unethical not to do this.

The Henshalls say that they have evidence that the CNEP trial did not run as it was designed to and that protocols were ignored. The Stoke clinicians deny this, and Dr Chalmers and I uncovered no significant protocol violations during our examination of the records. We would accept, however, that the trust never gave us access to any of the clinical case notes. Since these concerns were first raised four years ago, it is clearly time that they were addressed publically. The families concerned deserve this, and so do the clinicians in Stoke. The editor of this journal clearly concurs.[3]

The family question the timing of peer review. The study was peer reviewed by experts in the National Heart and Chest Hospitals before it opened in London in October 1989. In the context of my review of the Griffiths inquiry I merely referred to the additional review it underwent before it opened in Stoke in April 1990.

The family are right to emphasise that the nurses were concerned from the outset that handling and frequent opening of the chamber portholes could be detrimental. The trial was designed to try to test this but was only able to look at outcome to discharge and not long term outcome for funding reasons. The Henshalls rightly emphasise that there is only a limited correlation between the appearance of the brain on early ultrasonography and long term ($\geq$2 years) prognosis and that all major neonatal trials should address long term prognosis. Even the published trials funded by the Medical Research Council in the United Kingdom have not, as yet, done this. It is time public pressure made all funding bodies do this because some treatments of short term value may, in the long term, do more harm than good.[4] It remains scandalously difficult to get money to research this.

Finally, although the Henshalls's own child is tragically disabled, it remains to be shown that this is a consequence of her CNEP care rather than her preterm birth. While they can name individuals in this regard, they also know that the General Medical Council bars any doctor from making clinical information public by way of rebuttal without their consent.

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1 Henshall C, Henshall D. Investigating allegations of research misconduct. Electronic response to: Investigating allegations of research misconduct. bmj.com 2000;321 (www.bmj.com/cgi/eletters/321/7263/752#EL1; accessed 15 November).
2 Samuels MP, Southall DP. Negative extrathoracic pressure in treatment of respiratory failure in infants and young children. *BMJ* 1989;299:1253-7.
3 Smith R. Inquiring into inquiries. *BMJ* 2000;321:715-6. (23 September.)
4 Tarnow-Mordi W, Mitra A. Postnatal dexamethasone in preterm infants. *BMJ* 1999;319:1385-6.

Authors' reply

EDITOR—Our article presented the results of our investigation into the report of the Griffiths inquiry and showed that it had not been well conducted. Had it been, the inquiry report would not contain so many factual errors. Others, apparently including civil servants, share our concerns: on 22 September the *Independent* reported, "Health department officials were known to have strong reservations about the quality of the report."[1]

It is disingenuous of the panel members[2] and ministers[3] to ignore our criticisms of the conduct of the inquiry by trying to divert attention instead to the series of recommendations made about research governance. These were not a focus of our article, although we could perhaps have emphasised more strongly that national recommendations should not be based on an incompetent inquiry into just two studies conducted nearly 10 years ago in one NHS hospital.

One of us (EH) has responded separately to the issues raised about the continuous negative extrathoracic pressure (CNEP) study by Mr and Mrs Henshall (above). Although it was not the purpose of our investigation to judge the quality of this study, we stand by our suggestion that its general conduct was "exemplary." However, without knowing what specific criticisms some families raised with the panel or examining relevant papers to which we have not had access, we could not possibly conclude that there were no irregularities. We have seen some documents that others have not seen; others have seen documents we have not seen. What remains unacceptable is that the Griffiths panel apparently never sought or examined many key documents. To insinuate now that these were "owned" by Professor Southall (rather than by the whole study team) and state that "he did not provide" these documents to them[2] is a further distortion: the panel's own records make clear that they knew that NHS managers had told Professor Southall not to hand over the crucially important study log book.

Like us, the clinicians in Stoke still do not know, except in the most general terms, what concerns parents have raised about the conduct of the CNEP study. People cannot be expected to defend themselves, or provide relevant documentation, until they know what they have been accused of. Many of the factual errors in the Griffiths report could have been avoided had the panel been more specific about the allegations, examined relevant documentation, and invited those they criticised to comment on a draft of the report.

It is easy to understand the frustration of families who still feel they have not been told what went on in the CNEP study, four years after some of them raised concerns about its conduct. Many of your correspondents on bmj.com (www.bmj.com/cgi/content/full/321/7263/752) have chided the medical profession for arrogance and secrecy in these matters. However, we have seen correspondence showing that, years ago, Stoke clinicians wanted to meet the parents who first raised these concerns but were prevented from doing so by NHS managers. Perhaps it is managers who need to heed the words of the under secretary of state for

health, who, in his first public comment on our article, is reported to have said "The NHS belongs to the public, who have a right to know what goes on in it."[4]

Until there are proper ground rules for the conduct of inquiries of this sort in the NHS nobody is going to receive much justice. Some parents clearly feel that justice has still not been done to them or their children. Equally, many of the doctors and nurses in Stoke who tried to provide care for these children and to find ways of improving the care of all vulnerable preterm babies feel that their efforts have been criticised unjustly. Others, not as directly involved, are confused by partial information and continued lack of transparency. It is a serious indictment of the way the NHS is currently managed that the president of the Royal College of Paediatrics and Child Health needs to ask for such inquiries to be "conducted with the same rigour as the research they purport to investigate."

Consensus has been sought and reached on the elements needed for the conduct and reporting of some other forms of research.[5] The obvious inadequacies of the Griffiths inquiry and report make it abundantly clear that consensus is urgently required on how official inquiries in the NHS should be conducted and reported. Until that happens, they are unlikely to serve the interests of those using the NHS, let alone those working in the service. Many will be alarmed to learn that ministers still "do not believe that the [Griffiths] review was out of order or kilter with others which have taken place, or are taking place, within the NHS."[3]

Finally, we confirm that Mr Morgan is right to conclude that the content of the Cochrane review he mentions is the sole responsibility of its authors and the editors of the Cochrane Neonatal Group in North America.

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1 Laurance J. Top doctors hit back at "witch hunt" inquiries. *Independent* 2000 Sept 22:10.
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The ISOLDE trial

Side effects with inhaled steroids should not be forgotten

Editor—Burge et al in the ISOLDE study have shown a small but significant improvement in clinical outcomes with high dose inhaled fluticasone in patients with chronic obstructive pulmonary disease, without influencing the decline in lung function.[1] Their recommendation for using high dose inhaled steroids needs to be tempered on the basis of their potential for producing systemic adverse effects, especially in susceptible elderly patients.

In the ISOLDE study there was a significant but small degree of adrenal suppression, as shown by 11% and 14% falls in serum concentrations of cortisol measured at 8-10 am after six and 24 months of fluticasone compared with no change in the placebo group. Spot measurement of cortisol concentrations at 8-10 am is extremely insensitive at detecting adrenal suppression,[2] which makes the finding of any significant fall even more relevant as a surrogate marker for potential systemic bioactivity in these patients. This is supported by the fact that there are more patients with bruising after taking fluticasone than placebo: 7% compared with 4% of patients. As bruising is a visible marker of altered collagen turnover in skin, similar collagen adverse effects might conceivably have also occurred in bone tissue. A recent study of asthmatic patients found a significant inverse relation between cumulative inhaled steroid dose and lumbar bone density.[3]

Consequently, the modest efficacy gains with high dose fluticasone should be balanced against the long term potential for systemic adverse effects. Without long term data on bone mineral density it is difficult to make rational recommendations for the use of high dose fluticasone in elderly patients with chronic obstructive pulmonary disease who may be at risk of developing steroid induced osteoporosis.

This may particularly be the case for fluticasone, which, because of its high lipophilicity, has a large volume of distribution and consequently a large reservoir of drug at steady state residing in systemic fat tissues, which equilibrates with the blood.[4] An analogy is to consider a wet sponge with the constant drip representing the low plasma levels of fluticasone and the total body exposure as the amount which comes out when the sponge is squeezed. This is supported by meta-analysis of 21 studies where fluticasone exhibited significantly greater dose related adrenal suppression than other inhaled steroids—for example, 4.3-fold ($P < 0.001$) greater than budesonide.[5]

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Competing interests: Professor Lipworth's wife and his mother have shares in GlaxoWellcome. The department has received financial support from GlaxoWellcome for attending scientific meetings and has received second hand computer equipment. The department has also received financial support from AstraZeneca, Aventis, Schering Plough, and 3M for clinical trials, giving talks, and meetings.

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Side effects are source of concern

Editor—Since the topic of the paper by Burge et al is important in primary care, and its methods, results, and conclusions are clearly presented,[1] I thought that it might make an interesting subject for a tutorial on critical reading with my general practice registrar. A more than normally careful scrutiny made me realise how much I must miss in my usual scanning of the *BMJ*. I would like to raise three points.

(1) The diagnostic criteria chosen differ from those currently recommended by the British Thoracic Society, which do not refer to forced expiratory volume in one second after bronchodilatation, and mild chronic obstructive pulmonary disease is defined as 60-79% predicted, compared with 85% in the article.[2] What is the rationale behind these criteria?

(2) Table 2, under forced expiratory volume in one second after bronchodilator, refers to predicted forced expiratory volume in one second at three months and three years: should this read "mean forced expiratory volume in one second?"

(3) The finding that an oral steroid trial does not predict response to an inhaled steroid not only runs counter to the current guidelines, which recommend such a trial, but surely demands more discussion than it is accorded.

I share other commentators' concerns at the side effects, such as hoarseness and bruising, and the doubtful cost benefit, given the high cost of inhaled fluticasone and the comparatively minor reduction in exacerbations on treatment.

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Pharmaceutical companies should admit high cost of treatment

Editor—I refer to the paper by Burge et al on the use of fluticasone in patients with mild chronic obstructive pulmonary disease.[1] Since inhaled corticosteroids are of great value in chronic asthma one can understand the clinical logic of assessing this form of treatment in chronic obstructive pulmonary disease and also the commercial incentives behind this form of research. The AstraZeneca attempt to cash in on this enormous market failed to convince astute clinicians that inhaled steroids were of benefit to patients with comparatively mild chronic

obstructive pulmonary disease.[2] Now we have to contemplate whether inhaled fluticasone propionate in a dose of 500 µg twice daily has any convincing cost efficiency benefits, when given for three years, to patients with more advanced chronic obstructive pulmonary disease.[1]

Burge et al conclude that these improvements in clinical outcomes support the use of this treatment in patients with moderate to severe chronic obstructive pulmonary disease. The improvements refer, however, to a minimal reduction of inadequately defined exacerbations and an improvement of an assessment of health status. The fact that there was no change in the primary end point of decline in forced expiratory volume in one second between the active and placebo groups has apparently not dampened the enthusiasm of Burge et al with regard to the value of fluticasone in chronic obstructive pulmonary disease.

I do not believe in any cost benefits of treatment with inhaled corticosteroids in patients with chronic obstructive pulmonary disease of any severity. This study should have been performed using a dry powder inhaler rather than a pressurised metered dose inhaler since the surfactants in the pressurised inhaler could have had a deleterious effect in the placebo group, as has been reported to occur in asthmatic subjects.[3 4] The effect of twice daily inhalation of a placebo by pressurised metered dose inhaler for three years in patients with chronic obstructive pulmonary disease is unknown but could be responsible for the slightly greater number of exacerbations in this group. Any adverse effects of the surfactants or lubricants in these inhalers might have been negated by fluticasone in the active group.

Gratitude is due to AstraZenica and GlaxoWellcome for sponsoring these huge expensive trials. I believe, however, that both companies should now admit that the value of inhaled corticosteroids in the treatment of chronic obstructive pulmonary disease of any severity has not yet been established. This form of treatment is not inexpensive, and on the present evidence the NHS should not be expected to fund the long term use of inhaled corticosteroids in patients with chronic obstructive pulmonary disease.

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Devaluing clinical skills

Disparity of clinical skills is obvious

Editor—I congratulate Wilmshurst for his brave and accurate description of the crisis of clinical skills in our universities and the *BMJ* for publishing it[1]; it is a shame it was not given the same prominence as the apparent crisis in academic careers.[2]

Anyone who has trained in general and teaching hospitals cannot help but notice the disparity of clinical skills. Without doubt trainees are being trained and taught by people with inadequate skills. I, like most of my peers, learnt clinical medicine in the district general hospital parts of rotations, learning from skilled clinicians providing direct patient care. My recent teaching hospital training included being told the reason for doing a certain investigation was "because this is a teaching hospital and we can do it."

I too am aware of doctors being accredited and appointed to senior academic appointments without having seen a patient for six or more years; such people cannot provide their trainees with suitable tuition and guidance.

The issue has wider implications for those who practise clinical medicine away from "the centre." Our specialist society is proposing revalidation by peer review. This includes visits from and being observed by outside validators. Are good clinicians going to be judged by those prominent individuals from university hospitals who have inferior training and skills? I hope not but fear it will be so. Those with and using the clinical skills should do the appraising, but it may be too much to hope for consultants at district general hospitals appraising senior academics.

Wilmshurst's article deserves wider discussion; the lack of response from senior academics arguing their clinical cause is interesting. Are they feeling guilty? Are they worried they have been found out? Most worrying of all, they probably believe that they genuinely have the same (or probably better) clinical skills as their general hospital peers. I am looking forward to revalidation of clinical practice by log book, clinical portfolio, and examination so long as the exam tests what we really do: general medicine and a specialty rather than super-subspecialty and basic laboratory research.

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1 Wilmshurst P. Devaluing clinical skills. *BMJ* 2000;320:1739. (24 June.)
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Clinical skills are valued by clinical academics

Editor—Wilmshurst claims that "many" recently appointed senior clinical academics are inadequately trained in their clinical specialties and therefore lack clinical competence, to the detriment of patient care, undergraduate teaching, and postgraduate training.[1] He does, however, not say how many. He presents no hard evidence to support such an extreme view. His comments seem to be based on a single poorly substantiated case. Would you allow a contributor of a personal view to extrapolate, unchallenged, from the Shipman case to imply that "many" general practitioners are murderers?

Wilmshurst ignores those clinical academics who undertook substantive posts as registrars and senior registrars in the NHS, which led to conventional specialist accreditation, before being awarded honorary consultant contracts, as I did. Wilmshurst also overlooks colleagues who undertook approved higher training in clinical lectureships. Most worrying of all, he shows that his understanding of specialist training is years out of date. Since implementation of the Calman reforms the only way of becoming a consultant, honorary or otherwise, is by being eligible for entry on the specialist register. For clinical academics this can only be achieved by obtaining a certificate of completion of specialist training by exactly the same mechanism as NHS colleagues or, in a tiny minority of cases, through the academic and research route, which requires national excellence in a circumscribed area of clinical practice. Recent proposals for training in clinical academic medicine have re-emphasised the view that an excellent clinical training leading to a broad based conventional certificate is essential.[2 3]

A major interest in research that makes a long term contribution to patient care in the NHS is not incompatible with the acquisition and maintenance of clinical competence. Instead of bickering, I would like to see both clinical academics and NHS colleagues understand and accept this principle and work together so that standards of care, teaching, and training improve rather than decline.

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1 Wilmshurst P. Devaluing clinical skills. *BMJ* 2000;320:1739. (24 June.)
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Clinicians with academically prepared minds are needed

Editor—I hope that I am not alone in detecting the parallel between recent "doctor bashing" in the media and Wilmshurst's academic bashing article,[1] which promotes an old prejudice: bumbling, arrogant, ivory tower, academic versus hard working, "front line" clinicians who have their feet firmly on the ground. Although some popular narratives resonate precisely because they have some truth to them, others simply appeal to

baser instincts, such as envy and resentment. In most, it is a mixture. In the case of doctor bashing in the media, we have all seen smatterings of half fact whipped up into gross stereotypes and served as pious concern. In his article, Wilmshurst generalises well beyond his legitimate concerns.

Much of the criticism of medical academics stems from a failure to appreciate that there are important differences between the NHS and the universities. Many of the aims overlap, but the priorities, the responsibilities, and the performance indicators are not the same. In the medical school where I work, the teaching of clinical skills and the production of clinically competent graduates are valued highly. But the institution does more than teach medical undergraduates. It researches, innovates, and relies on a large number of extremely talented scientists, who in turn rely on scientifically sophisticated academic clinicians in the partnership necessary to translate contemporary science into care. Much of this hard work is invisible to many NHS staff.

Academic medicine has become increasingly specialised, in much the same way as any other element of medical practice. We need to recognise the limitations that specialisation brings, work together constructively, and develop mutual respect. There are tensions, but on the whole academics enjoy outstanding support from the local primary care NHS trust. My own discipline, psychiatry, desperately needs recruits with a grounding in hard academic science (and molecular biology) if it is to serve its patients to its full potential—perhaps nowhere else in medicine is folklore more likely to retard the development of innovative, good quality clinical care. We particularly need those clinicians with the kind of academically prepared mind that experience will favour.

Of course, clinically incompetent academics are bad news: that is the way with any kind of incompetence. If Wilmshurst has specific concerns about the safe practice of individuals, academic or otherwise, then he is duty bound to blow the whistle and submit evidence, not gossip, for publication.

More importantly, to imply that academic status today necessarily confers some sort of institutionalised clinical incompetence is simply to perpetuate an empty stereotype. It is perfectly proper, and timely, to debate the strengths and weaknesses of academic medicine, but the debate has to rise above the level of unpleasantness set by Wilmshurst in his concluding paragraphs.

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Author's reply

Editor—Some basic scientists have trained in a clinical specialty and justifiably hold an honorary clinical consultant appointment. This should not reduce concerns about those who hold honorary clinical appointments without adequate clinical training. The letters from Savill and Reid were the only two published on bmj.com up to 17 October that disputed the opinions expressed in my article. Three people (only one a doctor) wrote letters which neither supported nor opposed my view. The remaining 10 contributors were doctors, including Beales, who supported my concerns.[1] One is a senior lecturer and consultant in Reid's hospital. I have received universal agreement from many other doctors, including professors and an officer of a medical royal college, who have contacted me personally.

My article was subject to open peer review, so I know the identities of the referees. One is a professor of medicine like Savill. The other is a professor of psychiatry like Reid. Both favoured publication. The professor of psychiatry wrote that the article was "largely correct in its analysis of the problem." The professor of medicine thought that some of the issues I raised were "timely and real problems of the present."

Savill incorrectly presumed that my concerns are based on the single case which I used as an example. Reid need not advise me of my responsibilities. I wrote in December 1999 to the General Medical Council (with copies to the health minister and the chief medical officer) expressing concerns. A reply acknowledges that "pre 'Calmanisation' [in 1996] individual academics may have got on to the specialist register grade without having completed what would now be regarded as required training." It should not be assumed that those who received honorary consultant appointments before Calmanisation have been adequately trained in the four years since then because a consultant post is not recognised for training. Other academics were given honorary consultant appointments in the "transition period" after Calmanisation despite being as much as four years short of necessary experience in specialist registrar or equivalent clinical training. In one teaching hospital several academics with honorary consultant contracts responsible for acute medical takes have not completed what their regional director of public health regards as current required training. However, the regional director made it clear that he is not interested in the potential for poor clinical performance that would result from lack of adequate training but in proof that training had been inadequate as demonstrated "with respect to particular incidents or care of particular patients." If enough patients suffer at the hands of an academic with clinical responsibilities the academic will be considered to be inadequately trained. Will patients be reassured by this method of assessing adequacy of training?

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1 Electronic responses. Devaluing clinical skills. bmj.com 200;320 (www.bmj.com/cgi/content/full/320/7251/1739; accessed 17 October).

Confidence intervals should be used in reporting trials

Editor—The dispute between Barber and Thompson,[1] who are advocating a *t* test, and Williams, Cohen, and Russell, who are advocating a Mann-Whitney U test,[2] has its roots in the use of P values rather than confidence intervals. If Williams et al had reported their results as a confidence interval for the difference in mean cost, as recommended for the results of clinical trials published in the *BMJ*, the question would not have arisen. The sample size is surely large enough for the large sample Normal comparison, which does not require data to follow a normal approximation and to which the *t* method approximates, to be valid, even with such highly skewed data. This gives a confidence interval for the difference in cost of secondary treatment (routine minus open access) equal to –£180 to + £238, the point estimate being £29, and the same P value as the *t* test.

Barber and Thompson are correct in that the Mann-Whitney U test makes an overall comparison of distributions in the two groups, in terms of both shape and location, and does not specifically test for a difference in means. Although it is often described as a test of the difference between medians, this is only the case if we can assume that the two distributions being compared have exactly the same shape. Under these circumstances, it would be a test for the difference between two means also. This is not the case here, as the standard deviations are different. Thus Barber and Thompson are correct in arguing that a significant Mann-Whitney U test implies only a difference in distribution, not mean. Cost data typically have very uneven distributions, with many observations having the same low value and a few observations being very high. Distributions can differ considerably and yet have the same or similar means. I agree with Barber and Thompson that Williams et al have misinterpreted the Mann-Whitney result.

Williams et al say that the Mann-Whitney U test was only an interim analysis, but I could find no mention of this in their original paper. The actual observed difference is only 5% of the mean for the standard treatment, so the statement by Williams et al that analysis to be published elsewhere confirms that open access greatly reduces secondary care costs is very surprising. I look forward to seeing it.

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Evidence based policy for promoting cycle use in Britain

Editor—We warmly welcome the Chancellor of the Exchequer's pre-budget announcement that value added tax (VAT) is to be

removed from cycle helmet sales.[1] The decision, taken to "encourage road safety," is supported by growing evidence of the protection offered by helmets against serious head injury.[2 3] This is a small step, but a step that is certainly in the right direction.

But much more could and should be done. Evidence that regular cycling benefits health is beyond doubt, substantially improving fitness and lowering the risk of heart disease.[4] The exemption of bicycle helmets from VAT aims "to encourage cycle use," yet it sits alongside a raft of proposals that will do little to curb the use of cars. Improvements in air quality from cleaner fuels will clearly benefit cyclists but will not reduce the volume of traffic. Measures that would genuinely encourage cycle use are a reduction in traffic volume, more dedicated cycle lanes, greater traffic calming—and what about removing VAT from bicycles? For a substantive evidence based policy bicycles need to be taken seriously; cycling must come back into the mainstream, and cyclists must not be pushed literally and metaphorically into the kerb.

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Pitfalls of pharmacoepidemiology

EDITOR—Skegg[1] is concerned about the differences between our study[2] and that of Jick et al.[3] We share his concerns but are disappointed that he did not discuss the crucial differences between the studies and how these might affect the findings.

The general practice research database comprises data from general practitioners that are collated, quality controlled, and distributed by the Medicines Control Agency. We normally use all available data or exceptionally use well-defined subsets. Our recent study focused on practices that contributed data continuously between 1993 and 1998.[2] Jick et al used an undefined subset.[3] They asserted that "over the past 12 years we have removed over half of the original practices because of inadequate data quality" without defining the criteria used. We estimate that they have used at most 55% of the database. Studies by Jick et al are difficult to interpret because they use different subsets in different studies. Their paper on venous thromboembolism and combined oral contraceptives reported on two studies.[4] The first used a population of 303 470 women and the second 238 470 women, and the reasons for this have never been disclosed. Their 1998 paper reporting on the changes in rates of pregnancies after the 1995 warning "reviewed the experience of all women."[5] Unlike national statistics, they found little change in the frequencies of pregnancies associated with the pill scare. They also reported "little change in the proportion of women who stopped using the pill," which is inconsistent with sales figures of combined oral contraceptives.

Skegg is right to call for the Medicines Control Agency to conduct a thorough investigation. Some confusion could be resolved immediately. Either the database is quality controlled and all the data, or relevant well-defined subsets, should be used for all studies or the database is flawed and the substandard practices should be specified by the agency.

Jick et al misrepresent our identification of potential cases and the methods used to exclude those with an identifiable proximal cause.[2] We searched the database for women with a record of a deep vein thrombosis or pulmonary embolism and for women who died while using combined oral contraceptives. All records of potential cases were reviewed individually—the same method used by Jick et al. Cases were excluded using the same criteria as Jick et al. All our cases had records of treatment with oral anticoagulants. We did not require cases to have a coded record admission as a criterion because we have shown that a significant proportion of the verified cases that had been admitted had no coded record of admission.[6] Jick et al's claim that the coding of admission is 90% complete is not supported by the references they cite. Moreover, admission for deep vein thrombosis is not inevitable in the United Kingdom. It is possible that the very low incidence rates of venous thromboembolism that Jick et al report resulted from using admission as a primary search criterion and that some of the discrepancy between the studies is due to their underidentification of cases.[7] We wrote "the methods and case identification are described elsewhere." The "elsewhere" was referenced.[8] We have never said that the cases were identified using an automated computer search and are astounded that Jick et al should misrepresent our methods.

The studies have other differences. Jick et al restricted their investigation to women aged 15 to 39 years, whereas 11% of our cases were aged 40 to 49 years. They restricted their study to women exposed to levonorgestrel, gestodene, or desogestrel combined oral contraceptives; 10% of our cases before the pill scare and 28.9% of those after were exposed to other combined oral contraceptives. Had we used the same constraints as they did, we would have discarded 27.3% of all the cases of venous thromboembolism. The Committee on Safety of Medicine's warning was neither limited to age nor "third generation" and levonorgestrel combined oral contraceptives.[9]

In the hypothetical calculation of the expected numbers of cases we assumed that third generation combined oral contraceptivess had twice the risk of the second generation ones. The absolute incidence rates were derived from period 1 and then applied to period 2 given the age and product specific utilisation during that period. We used 5 year age bands, not year of age and happily point out this correction.

We are criticised for inadequate control for confounding. In their cohort investigation Jick et al used similar methods to us; in both studies rates were adjusted by year of age. Had adjustment for factors such as body mass index and smoking reduced the post pill scare rates to a significant extent this would have meant that combined oral contraceptives were preferentially prescribed to higher risk women after the scare. The adjustment for factors other than age that Jick et al reported was from a case-control study. We did not publish the results of a case-control study.

We have confidence in our results; the rate of venous thromboembolism among users of combined oral contraceptives was unaffected by the dramatic change in patterns of use after the pill scare. Our findings are consistent with those of Goldacre et al with the Oxford morbidity and mortality database.[10]

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Competing interests: The department is supported by grants from several pharmaceutical companies including NV Organon, Schering AG, and Wyeth. The companies have no control over the conduct of any research or over publications. RF has been reimbursed expenses for attending conferences by pharmaceutical companies; he has also been paid fees for speaking and consultancy.

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