

PostScript

LETTERS TO THE EDITOR

Ultrastructural examination of bronchial specimens from children with moderate asthma

We have read the paper by Çokuğraş and colleagues on bronchial biopsies in asthmatic children with great concern.¹ These authors performed a study in asthmatic children in which prophylactic medication was discontinued for 1 month before a bronchoscopic examination which was performed solely as a research procedure.

The Royal College of Paediatricians and Child Health states that "High risk procedures such as lung or liver biopsy, arterial puncture, and cardiac catheterization are not justified for research purposes alone. They should be carried out only when research is combined with diagnosis or treatment intended to benefit the child concerned".² Other authorities state that "Non-therapeutic research is particularly difficult to defend in moral terms when undertaken on children".³

The risks of rigid bronchoscopy are surely no less than an arterial puncture, and discontinuing presumably necessary medication could only increase those risks. How can such a study possibly be justified by the authors or their ethics committee, and how can the Editors of a reputable journal possibly justify the publication of such a study? That the science is valuable is unquestionable, even though the use of more sophisticated pathological techniques would have enhanced it; but the scientific value by no means justifies the disregard of ethical principles. A journal such as *Thorax* should know better, particularly in the light of the scholarly and ethical review in the same issue.³

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References

- 1 Çokuğraş H, Akcakaya N, Seçkin İ, et al. Ultrastructural examination of bronchial biopsy specimens from children with moderate asthma. *Thorax* 2001;56:25-9.
- 2 Royal College of Paediatricians and Child Health Ethics Advisory Committee. Guidelines for the ethical conduct of medical research involving children. *Arch Dis Child* 2002;82:177-82.
- 3 Branthwaite MA. Ethical problems in respiratory care: the role of the law. *Thorax* 2001;56:78-81.

Author's reply

In our study all the parents were informed and gave their consent. At the time of the

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The editors will decide as before whether to also publish it in a future paper issue.

examination all children were clinically stable. We stopped inhaled steroid and sodium cromoglycate treatment 4 weeks before bronchoscopy and followed each patient very closely. The parents were informed about the probable complications of stopping treatment and we agreed to give bronchodilators such as salbutamol in cases of exacerbation; however, no exacerbations occurred. If it occurred we could exclude the patient before bronchoscopy; the life and the comfort of all our patients is very precious to us.

I believe this study is very important for childhood asthma as it shows that bronchial inflammation of children with moderate asthma is very similar to that observed in adults, which is important for diagnosis and for treatment.

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An Associate Editor's view

The article published by Çokuğraş *et al*¹ reported the results of bronchial biopsies performed in 10 children with moderate asthma. The study showed thickening and "hyalinisation" of the basement membrane in nine of the patients as well as the presence of "overactive fibroblasts, degranulating mast cells, and lymphocyte infiltration in the submucosa". The authors concluded that these changes were similar to the bronchial inflammation seen in adults with asthma. Importantly, however, eosinophils were seen in only one biopsy specimen. Data such as these are not commonly available from children with asthma, partly because of the practice of performing bronchoscopies in children under general anaesthesia.

This article has prompted Dr Bush and colleagues to write berating *Thorax* for daring to publish such data which they contend were collected without regard for proper ethical standards. They quote from the guidelines for the ethical conduct of medical research involving children published by the Royal College of Paediatrics and Child Health (UK), stating that high risk procedures are not justified for research purposes alone. The authors have responded, saying that they believe they had taken appropriate precautions, informed the parents fully, and obtained appropriate

consent. They went to some lengths to point out in their original paper the precautions they undertook to ensure the safety of the children.

That research, like all human behaviour, must follow appropriate ethical guidelines is a fundamental principle under which we all work. However, the development of modern codes of ethics is a relatively recent phenomenon, accelerated by the unethical research practices carried out during the Second World War. The Belmont Report,² published in 1978, established three basic ethical principles. The first was *respect for persons*—that is, that individuals should be treated as autonomous agents and that persons with diminished autonomy (such as children) are entitled to protection. The second, *beneficence*, describes the obligation to maximise possible benefits and minimise possible harms; and the third, *justice*, expounds the principle that the burden of research should be spread widely to ensure that the benefits are also widespread. This principle is likely to be behind the current push by regulatory and granting agencies to ensure that all groups in society are represented equally in research studies unless valid scientific reasons dictate otherwise. In addition to these three principles, the integrity of researchers is of extreme importance. This integrity includes the commitment to research questions that are designed to advance knowledge; the fundamental commitment to the pursuit, protection and propagation of truth; and a commitment to use appropriate methods to conduct scientifically valid research.

While the basic principles recognised by the authors of the Belmont report reflect the high value that the dominant Western tradition places on individual autonomy, it is important to realise, as stated in the National Statement on Ethical Conduct in Research Involving Humans published by the National Health and Medical Research Council of Australia,³ that this is not the only way in which human interaction and responsibilities are conceptualised. In various non-Western societies, and in some communities within Western societies, individual rights are viewed differently or constrained by community values. Thus, it is not always a straightforward exercise to impose the ethical standards of one community onto another. Even within a relatively homogenous community such as Australia, a single ethics committee is not considered to be acceptable. Each local community has its own standards to which it expects its researchers to conform.

As mentioned above, research involving children imposes additional responsibilities on the community. Children are not legally able to consent to their own participation in research and this consent is given on their behalf by parents or legal guardians. In the Australian National Research Ethics Guidelines³ specific conditions are imposed on research involving children and young people. These guidelines state that such research should only be conducted where:

- (a) the research question posed is important to the health and well being of children or young people;
- (b) the participation of children or young people is indispensable because information

available from research on other individuals cannot answer the question posed in relation to children or young people;

(c) the study method is appropriate for children and young people; and

(d) the circumstances in which the research is conducted provide for the physical, emotional and psychological safety of the child or young person.

Let us now examine the study by Çokuğraş *et al*¹ in the light of the above discussion. They received appropriate permission to conduct the study and adequately informed the parents about the risks involved. There is no doubt that the question that the authors were addressing was one of fundamental importance to the health and well being of children with asthma in general and, arguably, to the individual participants in their study. Most knowledge of the pathogenesis of chronic asthma, especially the current focus on chronic airway inflammation and remodelling, has come from studies in adults with asthma.⁴ Studies such as these have been partly responsible for the current practice of treating adult asthma with corticosteroids in order to prevent and/or reverse airway fibrosis and remodelling. This practice has been translated to children with inhaled corticosteroids considered to be first line treatment in many parts of the world. This treatment approach may be reasonable if the pathogenesis of asthma in children is essentially the same as that in adults. However, considerable doubt exists as to whether all asthma in children does have a similar basis to chronic asthma in adults. For a start, different wheezing syndromes are recognisable in children and many children with asthma lose their symptoms later in childhood.⁵ In addition, recent reports from the Childhood Asthma Management Program (CAMP) study⁶ do not support the contention that all children with asthma require treatment with inhaled corticosteroids.

Furthermore, many parents would prefer not to treat their children with corticosteroids, especially if they are not warranted. Steroid therapy is not without risk. While the

risks are small if inhaled steroids are used according to current guidelines, even small risks are unacceptable if the treatment is not warranted. Thus, the question of the need to treat asthmatic children with corticosteroids is important to the health and well being of children and can only be answered in asthmatic children. Furthermore, Çokuğraş *et al*¹ made sure that the methods used were appropriate for children and the physical safety of the children was safeguarded.

So are Bush and colleagues wrong to complain about *Thorax* publishing the original paper by Çokuğraş *et al*? I believe that they were well within their rights, both as well respected members of the paediatric respiratory community and as advocates for the rights and well being of children. The ethics of research, as well as of medical practice, are not straightforward and should be the subject of continued and vigorous debate. Asthma management is also fluid. Studies such as the one by Çokuğraş *et al*¹ are required to place the use of corticosteroids in children with asthma on a firm scientific basis.

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- 3 National Health & Medical Research Council (NHMRC). *National statement on ethical conduct in research involving humans*. Canberra: NHMRC, 1999.
- 4 Jeffery PK, Laitinen A, Venge P. Biopsy markers of airway inflammation and remodelling. *Respir Med* 2000; **94**(Suppl F):S9–15.

5 Martinez FD, Wright AL, Taussig LM. Asthma and wheezing in the first six years of life. The Group Health Medical Associates (see comments). *N Engl J Med* 1995;**332**:133–8.

6 Anon. Long term effects of budesonide or nedocromil in children. The Childhood Asthma Management Program Research Group (see comments). *N Engl J Med* 2000;**343**:1054–63.

NOTICE

Mayneord-Phillips Summer School 2003

A 5-day residential course on “The lungs: function, diagnosis and treatment” will be held at St Edmund Hall, Oxford University, on 6–11 July 2003. The course will be given at a postgraduate level by internationally acclaimed speakers/world experts in their fields and will be of benefit to scientists, clinical staff, postgraduate students and others wishing to have a better understanding of the function of the lungs.

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CORRECTION

In the paper entitled “A meta-analysis of the effect of Bacille Calmette Guérin vaccination on tuberculin skin test measurements” by L Wang *et al* which appeared in *Thorax* 2002;**57**:804–9, an error occurred in the Results section of the abstract. The second sentence should have read “Patients who had received BCG vaccination were more likely to have a positive skin test (5 TU PPD: relative risk (RR) 2.12 (95% confidence interval (CI) 1.50 to 3.00); 2 TU RT23: **2.65** (95% CI 1.83 to 3.85))”.