LETTERS TO THE EDITOR

Paracetamol and asthma

The study by Shaheen *et al*[1] rightly pointed out that some patients with asthma deliberately avoid aspirin and are more likely to use paracetamol, hence a "consumer selection bias". However, they failed to mention the "professional's selection bias". Any standard textbooks or prescribing references state that aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) could potentially worsen asthma.[2] Health professionals will therefore certainly choose paracetamol for patients with asthma to avoid potential adverse reactions to NSAIDs and litigation problems.[3]

It is unlikely that this bias could be resolved by a pharmacoepidemiological study. Recent reports in the general press and television about the study could convey the wrong impression to patients with asthma which could direct them to self-select aspirin or ibuprofen. Fatal or near fatal cases associated with aspirin and NSAIDs have been reported.[4 5] Finally, I agree with Shaheen *et al* that further studies are required.

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We were interested to read of the association between paracetamol use and asthma in adults reported by Shaheen *et al*.[1] We recognise that the link is not causal and that further randomised trials are needed to clarify this link.

In their paper they comment that they have controlled for potentially confounding factors. We were concerned that one of their definitions for "asthmatic" was the positive answer to the question "Have you been woken by an attack of shortness of breath over the last 12 months?". The association they have shown was with people who use paracetamol weekly or daily. We do not believe that there has been an attempt to control for confounding factors, particularly anxiety leading to headaches and symptoms of breathlessness and hyperventilation. We would encourage researchers taking this matter further to consider this in their study designs.

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Shaheen *et al* have stated that there is a positive association between paracetamol use and asthma.[1] However, they have not really provided compelling evidence for an association, let alone causality, as the odds ratios for the associations between varying levels of paracetamol and asthma were all less than 3.

Case definition, paracetamol consumption, and respiratory symptoms were all based on postal questionnaires and were therefore highly subjective. The reliability of the information from such questionnaires is questionable. No objective measures were used to verify the diagnosis or severity of asthma in this study. Furthermore, the questionnaire response rate was only 50% and Shaheen *et al* dismiss the other 50% of non-responders in their discussion. The authors argue that it is "unlikely" that paracetamol use was strongly negatively associated with asthma in the non-responders.

Shaheen *et al* have not excluded concurrent illnesses such as influenza or respiratory tract infections, or non-steroidal anti-inflammatory drug use which may have increased asthma symptoms. This could give a false impression that increased paracetamol use led to more asthma symptoms.

The authors point to animal studies of glutathione depletion in the lung to help explain the association of paracetamol and asthma. In one of the studies paracetamol was administered to rats in doses of 3 g/kg[2]. In an average 70 kg human this would be equivalent to a dose of 210 g or 420 × 500 mg tablets. Other studies in mice have shown pulmonary toxicity with doses of more than 800 mg/kg[3]. This indicates that, in order to support the glutathione depletion hypothesis, the patients would have had to exceed the LD_{50} of paracetamol; the glutathione hypothesis is therefore biologically implausible.

Other studies have shown that paracetamol antagonises ATP, bradykinin and arachidonic acid induced bronchoconstriction in guinea pigs.[4 5]

We would agree with Shaheen and coworkers when they say that their findings "should be interpreted with caution". The data presented do not support an association between paracetamol use and asthma. They certainly do not fulfil Bradford Hill's criteria for causality and our view is that asthmatic patients should not be advised to avoid paracetamol on the basis of this paper.

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Shaheen *et al*[1] have observed an important association between asthma and paracetamol intake in adults. They have drawn attention to the reduction in glutathione (GSH) caused by paracetamol and propose that this may be the underlying mechanism of the observed association. I wish to propose an alternative mechanism to explain the association between paracetamol and asthma.

Shann[2] has pointed out the marked immune modulating effect of paracetamol leading to less fever, less immune activation and, in turn, to increased viral load and prolonged viral shedding. If we accept that viruses can provoke asthma then there is a prima facie connection.

I therefore propose that paracetamol leads to an increased viral load which, in turn, increases the provocation of asthma, hence explaining the observed association. Another way of putting it is that "asthma is an immune disease, paracetamol affects the immune system, therefore paracetamol may affect asthma" (or, indeed, any other immune disease).

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I read with interest the report by Shaheen *et al*[1] of an association between paracetamol (acetaminophen) use and symptoms of asthma which, according to the authors, corresponds with bronchial hyperresponsiveness (BHR). They speculate that, by depleting glutathione in the airway, paracetamol enhances Th2 like inflammation and thus increases BHR.

As the extent of airway inflammation does not necessarily correlate with BHR, I would propose another hypothesis to explain their findings. The mechanism of action of paracetamol is unknown, but it is known to affect serotonin (5-HT, 5-hydroxytryptamine) metabolism and can falsely increase levels of 5-HT metabolites in the urine during evaluation of patients for carcinoid syndrome.[2] It also appears that the anti-nociceptive effect of paracetamol involves the central serotonin system by increasing 5-HT and its effect on the 5-HT_2 receptor.[3] In a mouse model of allergic asthma, ketanserin, a 5-HT_2 receptor antagonist, has been found to prevent BHR and airway eosinophilia after allergen challenge.[4] This same agent increases forced

expiratory volume in one second (FEV_1) in subjects with asthma[5] and reduces methacholine hyperresponsiveness.[6] Increased levels of serotonin in plasma have also been demonstrated in patients with symptomatic asthma.[7] Thus, frequent use of paracetamol may affect BHR more than actual airway inflammation; this would account for the lack of correlation of paracetamol use with rhinitis in subjects with asthma in Shaheen's paper. It is also of interest that a recent case control study[8] found that irritable bowel syndrome, a disorder also associated with smooth muscle hyperreactivity,[9] is associated with frequent paracetamol use.

Shaheen *et al* found some evidence that aspirin use was protective, although the data were inconsistent. The authors also dismiss my hypothesis[10] regarding the protective effect of aspirin in preventing childhood asthma as asthma was not more common before the introduction of aspirin. I would suggest, however, that all allergic diseases are new to this century. According to the widely quoted National Health Interview Survey on chronic diseases in the United States, the prevalence of hay fever among children has remained steady over the last 17 years while asthma has increased by 80%. As atopy is the best known risk factor for asthma in children, and viral infection is the most common trigger of asthma exacerbations in children, I would propose that the immune response to viral infection has been altered in atopic children due to the removal of COX-2 inhibition[11] and/or an adverse effect of paracetamol. Data to support this hypothesis are provided by a recent report by Lesko and Mitchell in a double blind, controlled study on the safety of ibuprofen in 1879 children with asthma and fever.[12] Compared with paracetamol, ibuprofen was associated with a significant reduction in surgery visits for asthma in the 30 days following treatment. A dose response effect was observed with ibuprofen (5 mg/kg versus 10 mg/kg) on this beneficial effect, suggesting a protective effect of COX-2 inhibition.

In our laboratory we are currently investigating the effect of paracetamol on non-specific BHR. We are also treating children with ibuprofen and adults with specific COX-2 inhibitors at the onset of viral upper respiratory symptoms with anecdotal success in preventing viral induced asthma exacerbations.

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The prevalence of sensitivity to aspirin and other non-steroidal anti-inflammatory agents (NSAIDs) is quite low. In a postal survey of a population based sample of 4300 adults in Southern Finland, Hedman and colleagues[1] found the prevalence of symptomatic aspirin intolerance was 1.2%. This was higher (8.8%) in doctor diagnosed patients and those with allergic rhinitis (2.6%). Recent media attention to the paper by Shaheen *et al* highlights the public concern regarding the use of analgesic drugs in patients with asthma.[2] In a population based case control study of patients with asthma registered with 40 general practices in Greenwich, the authors found the odds ratio for asthma was 1.06 in infrequent users, 1.22 in monthly users, and 2.38 in daily users of paracetamol. The strength of the association increased with the severity of the disease. In a review of 92 patients with severe asthma requiring ventilation Picado *et al* found that, in seven patients (8%), the attack was precipitated by an NSAID.[3] Of these, one patient died as a result of anoxic encephalopathy. She had asthma for three years requiring continuous bronchodilator and beclomethasone treatment and had taken a capsule of herbal medicine which contained 500 mg aspirin. Five of these patients had a history of asthma precipitated by NSAIDs. The other two were first presentations.

Aspirin, paracetamol, and other NSAIDs are extremely valuable drugs in the treatment of arthritis and other inflammatory diseases. Public perception of the safety of these drugs may result in treatment being withheld inappropriately. Unpredicted severe reactions with no previous history are rare and so they should be tried and withdrawn if there is deterioration in asthma control. While it is important to uphold the principle of "primum non nocere", we submit that such treatment should not be automatically withheld from all patients with asthma.

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With regard to the study by Shaheen *et al*[1] of the use of paracetamol in adults with asthma, there are several issues we would like to raise concerning the findings of this study and the authors' conclusions.

Firstly, we question whether the association between paracetamol use and asthma could be explained by the influence of the 1993 BTS asthma management guidelines which specifically mentioned avoidance of aspirin.[2] The guidelines were widely disseminated before the initial 1996 Greenwich asthma study,[3] from which this current study is based, and were used by nurse specialists to educate patients in that study. If patients with asthma were advised to use paracetamol in preference to aspirin, then this may result in an apparent association between paracetamol and asthma, but one that is iatrogenic.

Secondly, the response rates in the original Greenwich study were low at only approximately 50% (12 238 respondents of 24 400 surveyed). The response rates in this study were also only approximately 50%, potentially resulting in a highly selected subset of the initial Greenwich population, raising the possibility of selection bias. Also, the diagnosis of asthma based on questionnaires may overestimate the true prevalence of asthma.[4]

Thirdly, we wonder about the postulated mechanism of paracetamol causing worsening of asthma due to reduction in lung glutathione (GSH). Although the authors quote evidence from animal studies, we are not sure of the applicability to humans. If decreased GSH due to paracetamol ingestion worsens asthma, why is this not a problem in, for example, paracetamol overdose? We have not found this mentioned in the literature, nor has it been seen locally by clinicians treating these patients.

In conclusion, we are concerned that the reported association between paracetamol and asthma may well be contaminated by the recommendations of the BTS guidelines, affected by selection bias, and of uncertain biological plausibility.

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AUTHORS' REPLY Dr Wong raises the possibility that avoidance of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) by asthmatic individuals might explain our findings. While we did not have information on use of NSAIDs, we did address the issue of aspirin avoidance in our discussion and concluded that this could, at best, only partly explain our findings since the association between frequent paracetamol use and asthma was not restricted to individuals taking paracetamol only, but was also seen in those who reported using aspirin too.[1]

Drs MacDonald and Furness were concerned that the symptom of "waking at night

with shortness of breath" might represent anxiety induced hyperventilation rather than asthma. However, this symptom has been validated as a strong predictor of bronchial hyperresponsiveness in adults.[2] Furthermore, in our study the majority of cases of asthma were not defined on the basis of this symptom alone (most were defined by reported asthma (treatment or attacks) with or without this symptom). Nevertheless, we agree that anxiety and depression should be considered as potential confounders in future studies as these conditions may be associated with increased use of analgesics and with asthma symptoms.

While questionnaires have their limitations, as pointed out in our paper, these are not likely to have been responsible for the results reported and we do not agree with Shin *et al* that they should be dismissed as a source of valid information. We would reiterate that the questionnaire on respiratory symptoms has been extensively tested and used,[3] and that the unbiased error implied by Shin *et al* would have reduced, rather than increased, the estimate of any association. Questionnaire data on analgesic use without blood levels may be inadequate in clinical toxicology, but they have proved highly informative in previous epidemiological studies.[4]

Shin *et al* are wrong to say that our data do not support an association between paracetamol use and asthma. An association is clearly present and the issue is rather one of interpretation. We were careful to emphasise that a causal link between paracetamol and asthma was only one of the possible explanations for our findings, but the clear dose-response relation would support such an interpretation. We would also disagree that the glutathione (GSH) hypothesis is biologically implausible. Whilst we acknowledge that previous animal experiments may have used toxic doses to deplete the lung of GSH, recent in vitro studies have suggested that depletion of GSH in pneumocytes and alveolar macrophages can occur with clinically relevant doses of paracetamol.[5] Balzer suggests a different mechanism to explain our findings, although Shann's review of the literature suggested that possible effects on the immune system and viral load were not specific to paracetamol, but were also seen with aspirin.[6] Varner's speculations are interesting and also provide an alternative possible mechanism for the effect.

We agree with Shin *et al* and with Raghuram and Archer that asthmatic patients should not be advised to avoid paracetamol, and that effective analgesia should not be "automatically withheld". Like Wong, our biggest concern prior to publication was that press coverage might result in widespread switching from paracetamol to aspirin or NSAIDs. Whilst sensitivity reactions are uncommon, they are potentially life threatening, as illustrated by Picado's study.[7] Hence, we would stand by the advice to adult asthmatic patients that we emphasised in our paper and in our communications with the media, namely:

(1) If patients have taken aspirin or NSAIDs and know that these drugs do not adversely affect their asthma, they should continue to take them.

(2) If they do not know whether aspirin or NSAIDs affect their asthma, they should avoid them (or be formally tested for sensitivity in a clinical setting).

(3) While we have not established a causal link between frequent paracetamol use and asthma, it would nevertheless seem sensible for daily users to see whether they are able to reduce their usage. Apart from a possible improvement in their asthma, this might be beneficial in other ways—for example, the predominant indication for frequent paracetamol use in our study was headache, and it is well recognised that excessive analgesic use can make headache worse.[8]

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Hyperventilation syndrome

In his comprehensive review of the hyperventilation syndrome[1] Gardner points out the difficulties in terminology and definition that have dogged this complicated and confused area. As he states, it is physiologically inappropriate to use the term "hyperventilation" in the absence of demonstrated hypocapnia. The term "hyperventilation syndrome" has, however, gained wide currency both in research studies and in clinical practice, often without precise diagnostic criteria being specified or hypocapnia rigorously demonstrated. This situation may have arisen from the perception of many clinicians that there is a real but poorly defined clinical entity causing morbidity in real world practice resulting from breathing abnormalities. Abnormal breathing patterns may, indeed, result in hyperventilation and hypocapnia, but rapid, irregular and shallow breathing may not necessarily result in increased ventilation yet may still cause significant symptoms. Isocapnic hyperventilation studies have shown that many of these symptoms are independent of hypocapnia,[2] and other mechanisms have been suggested.[3] Other descriptive labels have been applied to patients with characteristic symptoms associated with breathing abnormalities, with or without hypocapnia, such as "disproportionate breathlessness", "air hunger", and "behavioural breathlessness", but these terms have not gained widespread acceptance. Van Dixhoorn has used the term "dysfunctional breathing" to describe the production of symptoms directly as a result of abnormal breathing patterns.[4] We are used to considering functional problems in other physiological systems but have not applied this concept to breathing until recently. The diagnosis of dysfunctional breathing may be suggested by characteristic symptom patterns and clinical pictures but, as Gardner points out, these symptoms are all non-specific. Ultimately the verification of the label must lie in the response to breathing retraining interventions in these patients. This umbrella term allows inclusion of patients with and without hyperventilation, and moves the focus of attention from physiological hypocapnia to pragmatic clinical responses.

Gardner points out that the "hyperventilation syndrome" has been associated with other conditions, including psychiatric syndromes and asthma. The association of dysfunctional breathing with asthma may explain the anecdotal success of interventions which rely on breathing retraining, such as the Buteko method, to improve patients' well being. Studies are needed to clarify the presence of abnormal breathing in common and important clinical situations and to objectify anecdotal reports of responses to breathing retraining interventions.

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