mucosal dose inhalers and tachycardia and prolonged Q-T interval have been reported
generally with nebivolol or oral β agonists.7 The advised daily dose of oral bamil-
olot (20 mg) is 200 times that of inhaled salmeterol (100 µg).8

Secondly, Dr Lindmark reiterates our point that the results must be interpreted with care
because the study was observational, and hence definitive evidence would come from a
powerful randomised trial. Nevertheless, hypotheses about drug safety concerns are
often generated from observational studies.9 Such studies further research because they
provide a "prius" hypothesis and allow the development of a clinically relevant
point. Until results from prospective trials become available, observational re-
search using cohort or case-control technique

in the UK, and there are many difficulties associated
with reporting schemes.10 The study of a review by Astra
Draco has found no evidence from pre-
marketing or post-marketing studies of an
association between bamilolot and cardiac
failure. In general, pre-marketing studies have their own limitations,11 as evidenced by the
recent withdrawal on safety grounds of two
newly launched drugs.12 Similarly, differ-
ent types of post-marketing surveillance
studies including PEM, have different ad-
vantages and disadvantages and, in general, one system cannot be relied upon to provide
all the evidence needed.13 This point also
applies in response to the fourth comment.
In particular, it should be noted that there is
cross-under-reporting of suspected adverse
drug reactions to the Committee on Safety of Medicines14 as other regulatory auth-
ori, and there are many difficulties associated
with interpreting data from spontaneous
reporting schemes.15

Finally, as is stated clearly in our paper, it is possible that the association may be
explained by factors such as confounding by
the concomitant disease and disease severity.
Interestingly, the rate of cardiac failure associated with bamilolot in the first
month of treatment was higher than that for 11 cardiovascular drugs previously studied by
PEM (table 1). Only two cardiovascular drugs including the inotropic sympathomimetic
xameterol (licensed for use in mild heart
failure) had higher rates of cardiac failure. Since it is highly unlikely that the rate
of cardiovascular disease in the bamilolot
cohort was higher than that for patients
taking cardiac drugs, and the bamilolot
cohort was the youngest, these data provide
further evidence that an association cannot
be discounted. Our findings require confir-
mation, but we remain concerned about the
size and biological plausibility of the associa-
tion.

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5 Walter PC, Coulson RA, Wood SM. Regulatory pharmacovigilance in the United Kingdom:
current principles and practice. Pharmacova-
6 Li Wan Po A, Zhang WY. What is evidence can be learnt from the real world of
8 Marlin RM, Kapoor KV, et al. Underreporting of adverse drug reactions to newly marketed,
black triangle drugs in general practice in England: observational study. BMJ 1998;317:
119-20.

Dr Richard Bellamy alludes to the important
fact, frequently ignored by immunologists, geneticists and epidemiologists, that tuber-
culosis has several different clinical forms.16 Physi-
cians have emphasised the difference between
primary tuberculosis, which is com-
parable to Lurie's susceptible rabbits with
dissemminated disease, and post primary
tuberculosis, best characterised by smear
positive pulmonary tuberculosis and Lurie's
"resistant rabbits". Confirmations of associa-
tions with tuberculosis have indeed been inconsistent when all forms of tuberculosis are included.
However, the HLA association with DR2,
and particularly with its subtype DR15
in linkage disequilibrium with DQS,
was found only in patients with smear
positive pulmonary tuberculosis.17 These
observations have been refined using DNA
based HLA typing and have confirmed a link
with the genes DRB1*1501 and
DQB1*0502.18 Antibody levels to epitopes of
the 38kDa antigen of Mycobacterium tuber-
culosi restricted antigens were higher, suggest-
ing an enhanced immune responsiveness in
those with HLA-DR15. The relative
importance of the genes involved in suscept-
ibility can be assessed by the gene frequency,
but also by the attributable risk—that is, how
much of the disease can be attributed to the
presence or absence of a particular gene
(34% with 95% confidence intervals of 16 to
43% were suggested for DR15 in one popula-
tion).19

The Lurie experiment suggests that a com-
parison between patients with different forms
of tuberculosis, matched by ethnic origin,
may be valuable in identifying candidate
genes for susceptibility to tuberculosis. Since
there is no evidence that tuberculosis is
responsible for transmission of the disease, an
understanding of its pathogenesis will be
especially important in finding new ways to
control tuberculosis.

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1 Bellamy R. Genetic susceptibility to tuberculosis in human populations. Thorax
2 Brahmapuroy J, Pritchapn RM, Kakkanaiah VN, et al. Association of pulmonary tubercu-
losis and Mycobacterium tuberculosis in South India. Tubercle 1991;72:
123-32.
3 Bothamley GH, Schroeder GMT. Human leukocyte antigen, tuberculosis and Mycobac-
4 Meyer CG, May J, Stark K. Human leukocyte antigen in tuberculosis and leprosy. Trends

Chlamydia pneumoniae and asthma

The paper by Cook et al examines the possi-
ble association between Chlamydia pneu-
moniae infection and asthma. The authors
conclude that their data do not support this
association. However, we feel that the sero-
logical tests performed give important infor-
mation on the prevalence of infection, but are
not sufficiently complete to make definitive
conclusions on the incidence of acute C
pneumoniae infection in these populations
under study. The major pitfall in the study, as
pointed out by the authors, is the small propor-
tion of patients from whom a convales-
cent serum sample was drawn. Moreover, the
arbitrary exclusion of IgM positive patients
for the diagnosis of acute C pneumoniae infec-
tion may have been misleading since the
possibility of cross reactivity with rheumatoid
factor could have been effectively ruled out
by using IgG absorption prior to IgM micro-
immunofluorescence determinations.
Notwithstanding these facts, the authors con-
clude that the study does not support "an
association between C pneumoniae antibody
titres and the incidence of acute asthma attacks."

An analysis of table 1 indicates that the acute
asthma and control populations appear to be
significantly different in terms of age and sex
distribution, the control population being
significantly older and showing a male
predominance. Both these factors are associ-
ated with increased C pneumoniae incidence
and prevalence. The authors report using a
logistic regression modelling method in
which the age value is implemented as "+10
years", which is roughly equivalent to the dif-
ference in mean age between the acute
asthma and control populations.

This study is certainly noteworthy in that it
underlines an association between C pneumo-
moniae infection and severe chronic asthma,
particularly "brittle" asthma, which will
require further investigation in the future.

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1 Cook DJ, Davies P, Tunnicliffe W, et al. Chlamy-
dia pneumoniae and asthma. Thorax
2 Verkhoyen MP, Hazenberg MA, Van Haaren
GH, et al. Age-related interference with Chlamy-
dia pneumoniae microimmunofluorescence
serology due to circulating rheumatoid factor. J

I read with interest the recent report by Cook
et al in which they report that, compared
with hospital controls, outpatients with
chronic severe asthma had significantly more
C pneumoniae antibody titres (IgG > 256 and/or
IgA > 8) indicating previous infection,
whereas unselected patients admitted to hos-
pital for acute asthma attacks had titres simi-
lar to controls. They also found that serologi-
cal evidence of acute (re)infection (presence
of IgM, a fourfold change in titre, and/or IgG
titre > 1:512) was equal among groups.

These data are in accord with previous evi-
dence suggesting an important role for chronic C pneumoniae infection as a promoter

— continued from page 1096
of asthma symptoms but a lesser role for acute infection as a cause for asthma exacerbations. An additional recent report of positive therapeutic responses to antibiotics in severe steroid dependent asthmatic patients (aged 13–65) further supports the possibility that antibody titres indicative of "previous infection" may also indicate persistent chronic infection.

Acute primary (presence of IgM) or secondary (fourfold change in titre without IgM) C pneumoniae infection has been reported to initiate asthma in previously non-asthmatic individuals. Since the incidence of asthma in adults is very small (around one per 1000 per year), it is likely that most of the acute exacerbations occurred in patients who had had previous wheezing episodes. It would be interesting to know whether Cook et al. can retrospectively identify any patients who had their very first wheezing episode; this might be easier in general practice than in a hospital based study.

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BOOK REVIEWS


This is the third edition of an established book. Aiming to bring together all the recent information on basic mechanisms of asthma and also cover clinical aspects and therapy in depth, this is achieved successfully. The scope of the book provides accessible reviews of all facets of asthma, from epidemiology and physiology to allergen avoidance, including recent developments in these fields. Modifications to the popular second edition include separate chapters on mediator antagonists and immunomodulators with consideration of the potential therapeutic benefits of intervening in the complex inflammatory and pharmacological pathways systematically covered in previous chapters. A new chapter on the pharmacoeconomics of asthma treatment provides a pertinent reminder that, after the wonders of basic science and the development of beneficial interventions, a wider perspective is required to successfully deliver benefits to those who require them. The addition of colour plates provides a welcome change to the previously black and white prints of the old edition which look a little drab in retrospect.

Well written by authorities in their fields and uniformly edited with an attractive presentation, this is an excellent book which succeeds in linking the rapidly developing body of knowledge on asthma with current treatment, while keeping the future constantly in mind.—AF


A large amount of information has been packed into the 184 pages of this new guidebook in the Principals and Practice Series. This is a comprehensive review of the principles of ventilation and gas exchange with special emphasis on the application of pulmonary function measurement during anaesthesia. The book details physiological principles and gives practical measurement guidance, with common sources of error, in the normal circumstances and during anaesthesia. The content is concise, the style direct and occasionally hard going. The text is clear and the diagrams are worth a special mention for their clarity and simplicity. This is not a textbook for beginners and requires a moderate familiarity with the principles of respiratory physiology, and the rules which govern respiratory mechanics and gas measurement. This guide represents excellent value for money and would be equally at home in the pulmonary function laboratory as well as the anaesthetics department.—SR

CORRECTION

Clinical features of non-smokers with α 1-antitrypsin deficiency

The authors of the paper entitled "Clinical features and prognosis of life time non-smokers with severe α 1-antitrypsin deficiency" by N Seersholm and A Kok-Jensen, which appeared on pages 265–6 of the April issue of *Thorax*, regret that some errors occurred in the text and in table 3. On page 267 the first line of column 1 should have read: "... 50 years at entry was 56% compared with 50% for the subjects over 50 years ...". Table 3 is reproduced here with the corrections shown in bold italics.

### Table 3 Mean (SD) FEV, % predicted and FEV/FVC of index and non-index cases stratified by age at entry

<table>
<thead>
<tr>
<th>Age group</th>
<th>All age groups</th>
<th>Non-age groups</th>
<th>p value (t-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV, % predicted</td>
<td>54 (25)</td>
<td>100 (21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>N (%) with FEV, % pred ≤ 70</td>
<td>20 (74%)</td>
<td>3 (8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV, % predicted</td>
<td>56 (37)</td>
<td>100 (19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>N (%) with FEV, % pred ≤ 70</td>
<td>4 (50%)</td>
<td>2 (8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV, % predicted</td>
<td>56 (37)</td>
<td>100 (19)</td>
<td>&lt;0.001</td>
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<td>N (%) with FEV, % pred ≤ 70</td>
<td>4 (50%)</td>
<td>2 (8%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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