LETTERS TO THE EDITOR

“Opportunistic” mycobacterial infections

We were greatly impressed by the Joint Tuberculosis Committee guidelines on the management of opportunistic mycobacterial infections.1 We do, however, wonder why the word “opportunist” has been used to describe the mycobacteria, other than the M tuberculosis complex, that cause human disease. All mycobacteria causing disease, even the M tuberculosis complex, are opportunists. Thus, the latter are often spoken of as causing opportunistic disease in HIV positive persons. Since the causative role of these other mycobacteria in human disease was established in the middle of the 20th century, a wide range of collective nouns has been applied to them—apathetic, anonymous, MOTT (mycobacteria other than tuberculous), non-tuberculous, and tuberculous—as well as opportunists.

The distinguishing feature of almost all mycobacteria other than members of the M tuberculosis complex is that they live freely in the environment. For this reason the expression “environmental mycobacteria” has been used to describe the mycobacteria, other than the M tuberculosis complex. It should also be noted that the nomenclature argument about this group of mycobacteria could have been laid to rest once and for all after these decisions.

1 A CAMPBELL
Chairman of the Joint Tuberculosis Committee’s Working Party on Opportunistic Mycobacteria

1 LP ORMERO
Chairman of the Joint Tuberculosis Committee


Antibiotic prescribing in the community

Macfarlane et al present a comprehensive and thorough review of the multiplicity of factors affecting therapeutic decision making by general practitioners for patients presenting with acute lower respiratory tract symptoms.1 They do, however, pass very briefly over the evidence base for the use of antibiotics in this common and important clinical situation, citing only one original study, one review, and one meta-analysis to justify the statement that “antibiotics have little impact on the duration of symptoms of acute bronchitis”. For such an important and fundamental cause of morbidity in primary care there is an extraordinary dearth of studies to inform evidence-based decision making. The published studies are small, variable in quality, and use various antibiotics, dosage regimens, and outcome measures. In the quoted meta-analysis by Fahey et al1 of randomised controlled trials comparing antibiotics with placebo, only nine studies investigating a total of 700 randomised patients were found for analysis. Only six of these studies were suitable for the analysis of some of the key outcomes. The authors’ conclusion that antibiotic treatment has no effect on the resolution of acute cough was subsequently criticised.2

Although the clinical improvements analysed in the antibiotic treated group failed to reach statistical significance, quite narrowly for some outcomes, the results did favour antibiotics for an effect on both resolution of cough and clinical improvement. A review, suggesting a trend favouring the use of antibiotics over placebo. The wide confidence limits and the small numbers point to the need for further data. The Cochrane meta-analysis of the same data reached very different conclusions, commenting that “the review confirmed the impression of clinicians that antibiotics have some beneficial effects in acute bronchitis”. The benefits are probably labile, more confined to certain patient subgroups, but the quantification of benefit and the definition of the characteristics of responder groups need further studies to delineate.

All responsible clinicians must be in favour of appropriate use of antimicrobial drugs and efforts to “raise the trigger line” for the use of such agents are laudable. The assertion that the majority of British GPs and their European colleagues are ignoring a good evidence base when they prescribe antibiotics in this situation would, however, appear to be premature. Clarification of which patients with acute lower respiratory symptoms will benefit and by how much can only assist us in targeting and restricting the use of antimicrobials. Increasingly well informed patients and GPs attempting to practice evidence-based medicine need such information to make rational decisions on appropriate management options. There is a need for well designed prospective placebo controlled, randomised trials performed in real primary care settings with adequate power to provide definitive answers.

MIKE THOMAS
Manschington,
Brideford, Gloucestershire GL6 9TB,
UK
email: drmthomas@oakbridge.sol.co.uk


7 Shakespeare TP, Bourke RC. Too few subjects provide definitive answers. BMJ 1998;317:1014.


AUTHORS’ REPLY The term “opportunistic” mycobacterial infections agreed by substantial majorities. This decision is also supported by the current and former directors of the Mycobacterium Reference Unit for England and Wales. We had hoped that the nomenclature argument about this group of mycobacteria could have been laid to rest once and for all after these decisions.

1 P D O DAVIES
University Hospital, Aintree, Liverpool L9 1AL, UK

1 J M GRANGE
Imperial College School of Medicine, London SW3 6LY, UK

Correspondence to: Dr J M Grange
email: sophia@hagia.freeserve.co.uk


AUTHORS’ REPLY The term “opportunistic mycobacteria” was suggested by Marks.1 He argued that M tuberculosis, M bovis, and M leprae were obligate pathogens which, if they did get into the environment, could not survive for any significant length of time. The other mycobacteria that cause disease in humans are, as Drs Davies and Grange say, free living environmental organisms and we are all continually exposed to them. However, comparatively few people become infected. Those who do usually have some pre-existing condition which predisposes them to infection—for example, chronic bronchitis and emphysema, bronchiectasis, previous tuberculosis, or some form of immunosuppression. The mycobacteria that are free living in the environment thus need an opportunity to cause disease—hence “opportunistic mycobacteria”. It should also be pointed out that not all environmental bacteria cause disease. The nomenclature was discussed both by the Working Party and the full Joint Tuberculosis Committee; in both it was
Genetic susceptibility to COPD

We read with interest the report by Yim et al of an association between polymorphisms of the microsomal epoxide hydrolase (mEPHX) gene and chronic obstructive pulmonary disease (COPD). 1

This contrasts with the findings of earlier studies. 2 Failure to replicate an initial report of a positive association is common 3 and it is important that the reasons for this are established.

The authors correctly state that their failure to replicate the results of earlier studies may be a reflection of the marked racial differences in the frequency of the mEPHX gene within their population. However, their study also lacks power. Given, for example, their reported frequency of 75% for the wild type homozygous exon 4, a sample size of 80 subjects would only be able to detect a difference of 22% (e.g. 75% versus 53%) between the case and control groups (two tailed p value = 0.05, power = 0.8).

Phenotypic heterogeneity is a problem in the genetic dissection of complex traits and hampers comparisons between studies. The authors are rigorous in their spirometric criteria used to define cases. However, their COPD group also includes never smokers and those with minimal pack-year histories. It is not restricted to adult onset disease, potentially containing chronic asthmatics. This phenotypically heterogeneous group could reduce the likelihood of demonstrating an association. The calculation of pheno-
typic “scores” is one solution to the clinical diversity which the label “COPD” describes.

Finally, the importance of age and sex matching cannot be understated, not only because controls may develop disease, but also to minimise the effects that will occur to the gene pool as the population ages. We would therefore urge caution before abandoning a role for this candidate gene in this population. Further studies in extended populations with rigorously matched controls are clearly needed.

AUTHORS’ REPLY We thank Dr Ruse and colleagues for their interest and comment on our study. 4 They mentioned three points: (1) sample size, (2) the possibility of including asthmatic patients in the COPD groups, and (3) failure of age and sex matching between the disease and control groups.

We agree with them that our sample size was not large enough to detect small differences between the two groups (COPD 83, control 76). The strict criteria used in our study to select patients with disease or healthy smokers made our sample size smaller.

They suggested that the possibility that we may have included asthmatic patients in the COPD groups because of the minimal smoking history in some patients. It is well known that there are risk factors for developing COPD other than smoking history such as environmental tobacco smoking (passive smoking), ambient air pollution, and occupa-
tion. It is therefore possible for non-smokers to develop COPD. Although we vigorously excluded patients with minimal asthmatic features in order to select a phenotypically homogeneous group, it is true that some patients with chronic asthma cannot be differentiated from patients with COPD by any method.

Gene frequencies do not vary according to sex in the general population and the lack of sex matching in our study may not influence the result. When we excluded six women from the COPD group the result was the same. Although we adjusted for the effect of age by stratification, it is clear that an age matched control group would have been better. The first and only study which suggested the role of genotypes of microsomal epoxide hydrolase (mEPHX) in the pathogenesis of COPD also lacked age and sex matching because the control group was nonanonymous.

We agree with Dr Ruse and colleagues that further large scale rigorously matched case control studies are needed to clarify the role of this candidate gene in the pathogenesis of COPD.

C RUSE
Department of Medicine, University of Leicester, Glenfield Hospital, Leicester, UK

S G PARKER
Sheffield Institute for Studies on Ageing, University of Sheffield, Northern General Hospital, Sheffield, UK

P BURTON
Department of Epidemiology and Public Health, University of Leicester, Leicester, UK

A WARDLAW
Institute for Lung Health, University of Leicester, Glenfield Hospital, Leicester, UK

Correspondence to: Dr C Ruse


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evaluate the relationship with COPD in the Asian population.

As mentioned above, the sequencing of the PCR product of exon 3 amplified with an antisense primer outside the original one will clarify this confusion and further research on the functional significance of a single nucleotide polymorphism at codon 119 of mEPHX exon 3 will provide us with a more complete understanding of this polymorphism.

AUTHORS’ REPLY We thank Dr Honour for his valuable comments. We are currently in the process of re-analysing our samples by another laboratory able to perform HPLC measurements with the required quality. We would like to respond as soon as the data are available.

RONALD J MEIJER
HUBA M KERSTJENS
DIEKJE S POSTMA
Department of Pulmonary Diseases,
University Hospital Groningen,
9700 RB Groningen,
The Netherlands
email: h.a.m.kerstjens@int.azg.nl

Correspondence to: Dr HAM Kerstjens.

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C RUSE, S G PARKER, P BURTON and A WARDLAW

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