assay INNO-LiPA Rif.TB[3] was used to detect *rpoB* mutations and an in-house PCR-reverse hybridisation line probe was used to detect mutations in or adjacent to the *katG*, *inhA*, and *ahpC* genes.[4] The isolates were also IS6110 typed.[5]

The single rifampicin and isoniazid resistant isolate had an *rpoB* gene mutation associated with rifampicin resistance (table 1). Four of the five isoniazid resistant isolates had the same single point mutation upstream of the *inhA* gene and the other a single *katG* point mutation. Isolates 3 and 5 had indistinguishable IS6110 types that could represent isolates where recent transmission had occurred. No mutations were detected in the 40 fully susceptible isolates.

PCR-reverse hybridisation methods were highly sensitive and specific at detecting mutations that predict for isoniazid and rifampicin resistance. We also demonstrated that different point mutations can be used to discriminate between isoniazid resistant isolates. We believe that with automation and the addition of oligonucleotide probes designed to detect mutations associated with pyrazinamide (*pncA*)[6] and ethambutol (*embB*)[7] resistance, a system capable of detecting resistance to four front line antituberculous drugs will soon be commercially available. Rapid resistance detection by PCR-reverse hybridisation is likely to have a major impact on patient management and our understanding of the epidemiology of drug resistant TB.

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Lung bullae and marijuana

A previous paper from this hospital described apical lung bullae in four young male marijuana smokers, three West Indian and one Caucasian.[1] Two further cases were recently reported, both in Caucasian men.[2] We describe three further cases (one woman) with large upper lobe bullae. All are Caucasian and had a prolonged history of heavy marijuana smoking with an alpha$_1$-antitrypsin level within the normal range (table). These further cases support the view that marijuana may have a causal role in the development of lung bullae. We suggest that a detailed marijuana smoking history is taken from patients of all ethnic origins with upper lobe bullae.

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Pathophysiology of COPD

The paper by Dentener *et al*[1] is interesting and contributes to the understanding of the pathophysiology of chronic obstructive pulmonary disease (COPD). It is becoming clear that COPD is a systemic syndrome, and this paper suggests some potential mechanisms. However, a number of issues merit further comment.

It is noted that, in healthy controls, there is a wide range of C reactive protein (CRP) values extending well beyond what would be considered to be the normal range. The reason for this is unclear, but it does suggest that these individuals are not as healthy as described. In addition, patients with stable COPD have a range of CRP values that also extend beyond this normal range. This is not consistent with previous studies, which suggests that, in patients with stable COPD, the range of CRP values falls within the normal range.[2] Although patients with bronchiectasis were excluded, it is possible that undiagnosed bronchiectasis may have been present. Previous work has shown that 29% of patients presenting with what appeared to be stable COPD had CT evidence of at least mild bronchiectasis.[3] This could conceivably explain a wider range of CRP levels. In addition, it is interesting that after just 5 days of treatment for an acute exacerbation of COPD the CRP had returned to a level below that of the stable cohort in the study. Since standard treatment for an exacerbation is able to achieve this in just a few days, it suggests that the stable group may have contained individuals that were in fact not so stable.

The authors allude to the potential confounding effect of systemic corticosteroids in the study. The changes in total leucocyte count during the exacerbation are likely to be due to the effect of prednisolone, making it difficult to interpret the changes in leucocyte count. In stable patients the action of corticosteroids may also confound the results. It is possible that, even in patients using inhaled corticosteroids, leucocyte numbers could be affected since there may be significant bioavailability at higher doses. Leucocyte count should therefore not be used as a marker for systemic inflammation in these patients.

Finally, it would appear that the exacerbations of COPD might have been mild, despite the presence of severe COPD on lung function criteria. Although $Paco_2$ was slightly higher and Pao_2 slightly lower than in the stable group, these differences were small in magnitude. The pH was not significantly different and, in fact, the stable group contained individuals with a lower pH (range 7.30–7.50) than in the exacerbated group (pH 7.34–7.49). Although the mean CRP level appears higher than in stable patients, the range does not differ significantly. This may therefore have led to a less profound change in inflammatory markers than might have been expected, and a study looking at more severe exacerbations may be more revealing.

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Table Characteristics at presentation of three cases of apical lung bullae in marijuana smokers

	Case 1	Case 2	Case 3
Age on presentation (years)	33	45	38
Sex	Male	Female	Male
Ethnic origin	Caucasian	Caucasian	Caucasian
Tobacco smoking history	9 pack years	10 pack years	20 pack years
Marijuana smoking history	2–3 joints/day, "heavy" 10 years	Weekends/evenings, "moderate" 10 years	0.25 oz marijuana/week, "heavy" 24 years
Alpha$_1$-antitrypsin (g/l) (normal range 1.1–2.1)	1.4	2.3	1.6
FEV_1 (l) (% predicted)	2.7 (64)	2.4 (96)	3.7 (90)
FVC (l) (% predicted)	4.3 (85)	3.3 (112)	4.7 (94)
FEV_1/FVC (%)	63	73	79
T_{LCO} (% predicted)	9.44 (81)	4.99 (62)	–
K_{CO} (% predicted)	1.44 (88)	1.10 (64)	–

FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; T_{LCO}=carbon monoxide transfer factor; K_{CO}=carbon monoxide transfer coefficient.