Case reports

Commentary

David M Hansell

The common feature of the reports by Franco et al1 and Oliver et al2 is the use of spiral (or volumetric) computed tomography to demonstrate features which would not be readily identifiable on conventional computed tomographic (CT) scanning. The advantages of spiral CT over conventional CT scanning are twofold: increased speed of data acquisition and volumetric (rather than slice by slice) data acquisition. The attribute of speed means that most thoracic examinations can be performed within a single breath hold and the timing of intravenous contrast administration can be precisely tailored, thus allowing reproducible enhancement of any desired part of the vasculature—for example, the pulmonary arteries in cases of suspected pulmonary embolism. Because an entire volume of data is acquired (with almost equal spatial resolution in the three axes) it is possible to reconstruct images in any plane, including three-dimensional (3-D) reconstructions.3 Most examinations acquired with spiral CT scanning are presented as a series of transaxial slices, reflecting the traditional presentation of conventional CT images.

In the report by Franco et al1 the clarity with which the anomalous arteries feeding the sequestrated lung are shown on the 3-D reconstructions is striking. In the past a separate preoperative examination (either aortography or possibly magnetic resonance angiography) to identify the vascular supply would have been regarded as mandatory. Other imaging tests such as radionuclide scintigraphy or ultrasound may answer specific questions in cases of pulmonary sequestration, but the wealth of information now available from a single spiral CT examination is remarkable. Quite apart from their aesthetic appeal, the main benefit of these readily produced 3-D reconstructions is an easy appreciation of what can be complex anatomy. Nevertheless, claims for the increased diagnostic gain from these 3-D reconstructions should not be too extravagant: the anomalous vessels would be identifiable on images presented in the standard transaxial format, although without such immediacy. Furthermore, demonstration of the venous drainage into the pulmonary circulation (for the classic intralobar sequestrations) may not be so readily obtained with a single spiral CT examination. However, the ability to extract so much information from a spiral CT examination represents a substantial advance on conventional CT scanning.

Spiral CT pulmonary angiography is an effective way of demonstrating pulmonary embolism in segmental and larger arteries.4 The basic sign of a filling defect within a well opacified pulmonary artery is straightforward enough. The case report by Oliver et al5 highlights the fact that there may be ancillary signs of pulmonary embolism on spiral CT scanning—in this case shift of the interventricular septum—which corroborates the diagnosis and, more controversially, provides prognostic information. Shift of the interventricular septum and other signs of right ventricular dysfunction are readily demonstrated on echocardiography, but in cases of suspected pulmonary embolism echocardiography does not provide the breadth of information of a spiral CT examination. For example, additional signs of pulmonary embolism, including a mosaic perfusion pattern of the lung parenchyma and radiographically cryptic pleural effusions or small pulmonary infarcts, can be readily picked up on spiral CT scanning. Conversely, because spiral CT scanning provides the “big picture”, an alternative diagnosis may be shown by spiral CT scanning in up to one third of patients investigated for suspected pulmonary embolism.6

The application of image processing to volumetric spiral CT data can be broadly divided into graphic 3-D realisations—for example, virtual reality bronchoscopy5—and the rendering of data so that it is suitable for quantitative analysis. However, progress towards routine volumetric (3-D) depictions of spiral CT data is likely to be slow.7 Even at this early stage of development it is possible to extract very precise volumetric measures of abnormal lung; the most obvious application is in the quantification of low attenuation lung (corresponding to emphysema) on inspiratory and expiratory spiral CT scans. Early results have shown remarkably good correlation between the extent of low attenuation lung derived from 3-D reconstructions of the lungs with functional indices of air flow obstruction and air trapping.8 With this new technique the entire lungs are evaluated, unlike the conventional “density mask” approach which can be applied only to individual CT sections, (which introduces problems with sampling). With the powerful combination of volumetric data from spiral CT scanning and advanced image processing, the excitement has only just begun.

Diagnosis of pulmonary sequestration by spiral CT angiography

José Franco, Roberto Aliaga, María L Domingo, Pedro Plaza

Abstract
The diagnosis of pulmonary sequestration traditionally requires arteriography to identify abnormal systemic vessels feeding the abnormal portion of the lung. Non-invasive imaging techniques have recently been used to replace arteriography. Conventional computed tomographic (CT) scanning is, however, at a disadvantage because of its inability to obtain multiplanar images. The combination of slip ring CT scanning and computerized three-dimensional reconstruction (spiral CT angiography) can be used to visualise the anatomical detail of a wide range of vessels within the lung. Four cases of pulmonary sequestration are reported which were successfully diagnosed using spiral CT angiography. Spiral CT scanning allows simultaneous imaging of anomalous vessels and lung parenchyma in a single examination and is particularly useful in the diagnosis and assessment of pulmonary sequestration.

(Thorax 1998;53:1089–1092)

Keywords: pulmonary sequestration; spiral computed tomography

Pulmonary sequestration is a rare congenital pulmonary disorder defined as an area of dysplastic and non-functioning pulmonary tissue with an anomalous systemic blood supply. It has been classically described in two forms—intralobar sequestrations located within the visceral pleura and surrounded by normal lung, and extralobar sequestrations which have a separate pleural covering. Both types are supplied with blood from the aorta or its branches. The venous return of the intralobar sequestration is usually via the pulmonary veins while extralobar sequestrations generally have systemic venous drainage. Nevertheless, many variations and combinations of these classical patterns have been described.

Traditionally, the diagnosis of pulmonary sequestration requires arteriography to identify abnormal systemic vessels feeding the abnormal portion of the lung. More recently, other procedures have been advocated as a less invasive means of identifying the anomalous artery. Although conventional computed tomographic (CT) scanning can show both abnormal lung parenchyma and the systemic arterial supply, it lacks the multiplanar images which limits its usefulness in the diagnosis of sequestration. With the advent of helical technology, spiral CT angiography is able to delineate the aorta and its branches. The role of CT scanning in evaluating suspected pulmonary sequestration should therefore be re-evaluated.

In this report we describe the use of spiral CT angiography to image the aberrant systemic artery in four cases of pulmonary sequestration.

Methods
We performed four CT angiography studies with a PQ2000S helical scanner (Picker International Inc, Highlands Heights, Ohio, USA). Spiral volumetric CT scanning was performed with 4 mm slide thickness, 4 mm table speed, 3 mm reconstruction index, and smooth reconstruction algorithm. A non-ionic contrast medium (120 ml, iodine 300 mg/ml) was administered at a rate of 3 ml/s via the antecubital vein.

Figure 1  Spiral CT scan of case 1. (A) Contrast enhanced CT axial image showing the small aberrant artery (arrow) adjacent to the upper abdominal aorta (a). (B) Anterior view of helical CT angiogram. The anomalous artery (arrow) feeding the pulmonary lesion (L) arises from the coeliac axis.
A 25 second scan delay was used in order to optimise contrast in the systemic arterial phase of the study. Three-dimensional reconstruction (3D) was performed with a Voxel Q workstation using a shaded surface display (SSD) program with segmentation option.

Case reports

CASE 1
A 32 year old man with a 34 pack-year history of cigarette smoking who still smoked two packs a day was admitted to the smoking cessation programme at our hospital. There was a history of pneumonia at the age of 14. A chest radiograph showed localised air trapping in the left lower lobe. A spiral CT scan (fig 1) revealed a multicystic lesion in the posterior basal segment of the left lower lobe supplied by an artery derived from the coeliac axis; venous return to the pulmonary veins was also demonstrated. The presence of the anomalous systemic artery and venous drainage were confirmed by aortography. The patient was asymptomatic and refused surgery.

CASE 2
A 28 year old man presented with a one month history of recurrent haemoptysis. He smoked one pack of cigarettes daily. Chest radiography showed a mass, 4 cm in diameter, in the right lower lobe. Bronchoscopic examination indicated that the source of bleeding was the right lower lobe but no endobronchial lesions were seen. A spiral CT scan (fig 2) revealed a homogeneous mass in the right lower lobe contiguously to the diaphragm and identified its anomalous arterial supply derived from the upper abdominal aorta just above the coeliac axis; venous drainage into the pulmonary veins was also visualised. Intralobar pulmonary sequestration was confirmed by aortography and thoracic surgery.

CASE 3
A 65 year old male cigarette smoker had a two week history of productive cough and fever. The patient improved with antibiotic therapy but a persistent cough developed. Radiography of the chest showed partial collapse of the left lower lobe and a mass like opacity with an air-fluid level. A CT scan demonstrated a non-homogeneous mass with multiple cystic appearing spaces and cavitation involving the posterior basal segment of the left lower lobe. Fibreoptic bronchoscopic examination disclosed no abnormality. A percutaneous fine needle aspiration biopsy specimen of the lesion revealed non-diagnostic findings. Spiral CT angiography (fig 3) showed a feeding systemic artery arising from the descending thoracic aorta and venous drainage to the pulmonary veins. At surgery an infected intralobar sequestration was found.

CASE 4
A 41 year old man was admitted to hospital with a 48 hour history of fever and pleuritic chest pain. There was no history of use of tobacco. Chest radiography revealed a homogeneous density in the right lower lobe. He was diagnosed as having pneumonia and treated with clarithromycin. One month later he was...
Diagnosis of pulmonary sequestration by spiral CT angiography

The left lung than in the right. The blind end-
the lower lobes. It occurs slightly more often in
predilection for the posterior basal segment of
lungs. Intralobar pulmonary sequestration ac-
characteristically involves the lower lobes of the
Both intralobar and extralobar sequestration
presented.

was not considered at the time this case was
could not identify the venous drainage. Surgery
acquisition, in this case spiral CT angiography
established contrast enhanced helical CT
included in the upper sections of pre-
venous return via the pulmonary veins. Be-
gram showed the anomalous artery and the
right lower lobe supplied by an artery originat-
from the coeliac axis. a = aorta.

Figure 4 Spiral CT scan of case 4. (A) Contrast
enhanced CT axial image showing a systemic artery
(arrowhead) feeding the pulmonary lesion (L) in the right
lower lobe. (B) Right oblique view of helical CT angogram
showing the anomalous systemic artery (arrow) arising
from the coeliac axis. a = aorta.

readmitted with clinical deterioration, unpro-
ductive cough, weakness, anorexia, weight loss,
and fever. Chest radiography showed a diffuse
and bilateral micronodular pattern with per-
sistence of the right lower lobe density. Miliary
tuberculosis was confirmed by histopathologi-
cal examination of a tranbronchial biopsy
specimen and positive culture of bronchial
aspirate. A spiral CT angiogram (fig 4) revealed a focal area of increased density in the
right lower lobe supplied by an artery originat-
ing from the coeliac axis. An abdominal aorto-
gram showed the anomalous artery and the
venous return via the pulmonary veins. Be-
cause the lower pulmonary veins were not
included in the upper sections of pre-
established contrast enhanced helical CT
acquisition, in this case spiral CT angiography
could not identify the venous drainage. Surgery
was not considered at the time this case was
presented.

Discussion

Both intralobar and extralobar sequestration
characteristically involves the lower lobes of the
lungs. Intralobar pulmonary sequestration ac-
counts for 73% of all sequestrations and has a
predilection for the posterior basal segment of
the lower lobes. It occurs slightly more often in
the left lung than in the right. The blind end-
ing bronchi, which may become distended
trapping mucus, are prone to infection. In
about two thirds of the cases the reported first
symptoms occur after the age of 10 years and
are usually secondary to a superimposed infec-
tion. Productive cough, fever, haemoptysis,
recurrent pneumonia, and chest pain are
typical presenting complaints. Extralobar se-
questrations are frequently discovered during
the neonatal period in infants with other
congenital anomalies. The clinical picture is
usually dominated by the associated anomalies
although infection can occur, especially if there
is a communication with the oesophagus or the
stomach. Extralobar sequestrations that are not
diagnosed in newborn infants are often asymp-
tomatic and detected on routine radiography.

In case 1 pulmonary sequestration was
detected by routine radiography, while in case
2 haemoptysis was the presenting symptom of
an intralobar sequestration. Case 3 had an
intralobar sequestration typically manifested
by symptoms of infection and case 4 had con-
comitant disseminated tuberculosis.

Plain radiographs of the chest often show a
single homogeneous opacity or, less com-
monly, a cystic mass in the base of one lung
that can sometimes suggest the diagnosis of
sequestration. Less specific findings include
recurrent pneumonia and focal bronchietatic
changes. The principal objective for diagnosis
of pulmonary sequestration is to identify the
systemic artery supply. With this information,
image can distinguish sequestration from
other causes of lung opacity. Because accessory
arteries, pleural investment, and venous drain-
age are adequately determined intraopera-
tively, at some institutions only the presence
and location of an aberrant systemic artery are
considered essential for preoperative assess-
ment for any symptomatic pulmonary
sequestration.

Imaging strategies for suspected pulmonary
sequestration are based on case reports or
small series since it is a rare congenital disorder
and no study exists that objectively compares
imaging techniques for detection, definition, or
cost effectiveness. Since the definitive step in
the diagnosis of sequestration is the demon-
stration of the systemic arterial supply, for a
long time diagnosis was made by conventional
angiography. More recently all imaging tech-
niques capable of showing the artery have been
implicated in evaluating sequestration. Mag-
netic resonance (MR) imaging and MR angio-
graphy can be used together to diagnose
pulmonary sequestration in a single non-
 invasive examination. Nevertheless, MR can-
not accurately evaluate lung parenchyma and
the airways and must be considered in terms of
cost and availability. Sonography requires a
favourable acoustic window and is ideally
suited for evaluating the chest prenatally and
postnatally. Other non-invasive techniques for
evaluation of sequestration such as scintigra-
phy are only rarely necessary.

In all four cases described in this report spi-
ral CT angiography successfully delineated the
origin and course of the anomalous systemic
artery. Axial images were enough to make the
diagnosis but three-dimensional reconstruc-
tion aided both radiologists and referring cli-
nicians by demonstrating anatomical relation-
ships, particularly for vessels orientated in the z
axis. On the other hand, venous drainage was
also identified in the three cases in which lower
pulmonary veins were included in contrast
enhanced helical CT scans. We have performed
Spiral CT angiography is a minimally invasive technique for vascular imaging that is made possible by combining slip ring CT scanning and computerised three-dimensional reconstruction. Spiral CT angiography has several advantages over other non-invasive vascular imaging techniques. CT scanning, with its superior spatial resolution, yields the most information about the bronchial anatomy and the pulmonary parenchymal lesion. Sonography and MRI cannot evaluate lung abnormalities accurately although MRI can reveal the cystic nature of many intralobar sequestrations as well as the variable solid, fluid, haemorrhagic, and mucus-containing components. MR angiography is hampered by artefacts caused by respiratory motion whereas this problem is generally avoided in helical CT scanning. CT angiography is less expensive than MR angiography and can be used on patients with a metallic device or who do not tolerate the MR examination. Furthermore, helical CT scanning is fast resulting in less sedation and reduced amount of contrast medium. The disadvantages of helical CT scanning are minor and arise from exposure of the patient to ionising radiation and the administration of intravenous contrast material.

In summary, we report four cases of pulmonary sequestration successfully diagnosed using spiral CT angiography. By allowing simultaneous imaging of anomalous vessels and parenchymal lesions in a single examination, spiral CT angiography is a particularly efficacious technique and has the potential to become the procedure of choice in the diagnosis and assessment of pulmonary sequestration.

Interventricular septal shift due to pulmonary embolism on CT angiogram

The initial abrupt rise in pulmonary artery pressure causes increased right ventricular afterload which results in right ventricular dilatation and dyskinesia. Secondary effects of this are tricuspid regurgitation, right atrial enlargement, and loss of respiratory variation in caliber of the great veins. Increased right ventricular wall tension may reduce local coronary blood flow, resulting in ischaemia which impairs right ventricular function further. As the right ventricle dilates, the interventricular septum is displaced towards the left ventricle, the right ventricle assuming a circular axial configuration and the left ventricle a crescentic appearance more typical of the normal right ventricle. This septal shift, combined with the constraining influence of the pericardium, results in reduced left ventricular filling which is already compromised by reduced preload. The cardiac output falls.

Discussion
Massive pulmonary embolism sets in sequence a chain of physiological events that ultimately lead to reduced systemic cardiac output.1 The interventricular septum was displaced to the left, and there was compression of the left ventricle (fig 1A). These features persisted throughout the cardiac cycle. A central venous catheter was placed and tissue plasminogen activator was infused into the central pulmonary arteries. Immediately before treatment the central venous pressure was 22 mm Hg, right atrial pressure was 30 mm Hg, right ventricular pressure was 33/13 mm Hg, and pulmonary artery pressure was 33/20 mm Hg. Five hours after treatment the pulmonary artery pressure had reduced to 20/10 mm Hg and systemic blood pressure had increased to 160/70 mm Hg. A continuing anticoagulation regime was commenced. A venogram showed thrombus within the right popliteal vein. A repeat CT angiogram five days after treatment showed considerable reduction in the load of embolic material within the pulmonary arteries together with a return of the interventricular septum to its normal position and resumption of normal right and left ventricular morphologies (fig 1B).

Figure 1 Computed tomographic (CT) pulmonary angiograms at the level of the interventricular septum in a patient with massive pulmonary embolism. (A) The scan at presentation shows right ventricular dilatation and septal displacement which results in compression of the left ventricle. A filling defect due to an embolus is seen within a segmental branch of the descending right pulmonary artery (arrow). (B) Five days after thrombolysis the pulmonary embolus has resolved. The associated reduction in pulmonary artery pressure has allowed normal septal and ventricular appearances to return. The long axis of the heart now occupies a more normal position. RV = right ventricle, LV = left ventricle, S = interventricular septum.
LETTERS TO
THE EDITOR

Cardiac risks with β-agonists

Martin et al suggest that caution should be exercised when prescribing long-acting oral β-agonists to patients at risk of cardiac failure, based on results from a prescription event monitoring (PEM) study. Firstly, all β-agonists (short and long acting, oral and inhaled) should be used with caution in patients with severe cardiovascular disease, as is pointed out in the package insert for all drugs of this class.

Secondly, the study does not provide any evidence on this issue. PEM studies are not designed to study causal relations but to generate new hypotheses. Although the authors have made an attempt to consider several potential biases in the analyses, the study design is inappropriate compared with, for example, a prospective randomised controlled trial, and the results must be interpreted with great caution.

Thirdly, no support for an association between bumbuterol and an increased risk for cardiac failure has been found in our review of preclinical studies, clinical studies (including >3000 patients/healthy volunteers), or post-marketing surveillance (based on >130 million treatment days).

Fourthly, according to the authors there have been no spontaneous reports of cardiac failure with bambuterol to the Committee on Safety of Medicines. This is in agreement with the WHO database Lntids, with no reports of cardiac failure for bambuterol.

Finally, the paper suggests a doubled asthma mortality in patients receiving salmeterol. In our opinion the reported higher relative risk for non-fatal cardiac failure for bambuterol and the doubled asthma mortality for salmeterol both appear equally explicable by factors other than direct causality, such as confounding by concomitant diseases and disease severity.

Thus, PEM data may be of help in identifying signals with new drugs, but there is little if any merit in comparing drugs used in different populations and introduced to the market at different times.

Table 1 Rates of cardiac failure during the first month of exposure to bumbuterol or a cardiovascular drug studied by prescription event monitoring (PEM)

<table>
<thead>
<tr>
<th>Drug* (ranked by rate)</th>
<th>No. of patients with reported cardiac failure during month 1</th>
<th>No. of patient-months at exposure during month 1</th>
<th>Rate (events per 1000 patient-months of exposure)</th>
<th>Mean (SD) age</th>
<th>Males (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xanamterol</td>
<td>97</td>
<td>4 463</td>
<td>21.7</td>
<td>70.8 (13.9)</td>
<td>53.0</td>
</tr>
<tr>
<td>Nicorandil</td>
<td>73</td>
<td>11 578</td>
<td>6.3</td>
<td>66.9 (11.2)</td>
<td>61.1</td>
</tr>
<tr>
<td>Bambuterol</td>
<td>29</td>
<td>5 891</td>
<td>4.9</td>
<td>58.5 (18.6)</td>
<td>44.8</td>
</tr>
<tr>
<td>Losartan</td>
<td>53</td>
<td>12 900</td>
<td>4.1</td>
<td>63.5 (12.1)</td>
<td>40.2</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>24</td>
<td>8 808</td>
<td>2.7</td>
<td>62.3 (13.9)</td>
<td>59.3</td>
</tr>
<tr>
<td>Enalapril</td>
<td>33</td>
<td>13 544</td>
<td>2.4</td>
<td>61.2 (14.9)</td>
<td>46.1</td>
</tr>
<tr>
<td>Perindopril</td>
<td>17</td>
<td>8 368</td>
<td>2.0</td>
<td>61.8 (12.7)</td>
<td>45.0</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>17</td>
<td>9 517</td>
<td>1.8</td>
<td>62.9 (13.9)</td>
<td>48.4</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>18</td>
<td>11 574</td>
<td>1.6</td>
<td>60.9 (14.3)</td>
<td>44.0</td>
</tr>
<tr>
<td>Ramipril</td>
<td>2</td>
<td>1 277</td>
<td>1.6</td>
<td>60.5 (12.4)</td>
<td>45.1</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>12</td>
<td>12 085</td>
<td>1.0</td>
<td>61.8 (14.7)</td>
<td>46.9</td>
</tr>
</tbody>
</table>

*Betaaxolol, doxazosin, isradipine not shown as number of patients with event was <2, or rate was <1.0 per 1000 patient-months of exposure.


AUTHORS’ REPLY Bertil Lindmark of Astra Draco makes five points about our study on the risk of non-fatal cardiac failure and ischaemic heart disease with long-acting β-agonists. Firstly, he points out that all β-agonists should be used with caution in patients with severe cardiovascular disease. The cardiac effects of β-agonists are well described,1 but there is limited evidence available on whether or not the risks of adverse cardiac effects differ depending on the dose and method of administration of the drug. Clearly, these are important questions for prescribing doctors faced with treating asthmatic patients with concomitant cardiac disease. An observational cohort study formed from health insurance databases from the Province of Saskatchewan, Canada found an increased relative risk of death from cardiovascular disease in users of β-agonists taken orally or by nebuliser, but not in users of β-agonists administered by metered dose inhaler.1 The deaths occurred in patients with significant cardiac disease, suggesting that β-agonists taken orally or by nebuliser should be avoided in patients at high risk of cardiovascular events. We found that the oral β-agonist bumbuterol, but not the inhaled β-agonist salmeterol, was associated with an increased risk of non-fatal cardiac failure. The results from both these studies are plausible as oral β-agonists provide a greater systemic dose than that achieved with metered dose inhalers1 and tachycardia and prolonged QT interval have been reported principally with nebulised or oral β-agonists.1 The advises total daily dose of oral bumbuterol

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(20 mg) is 200 times that of inhaled salmeterol (100 mcg).4

Secondly, Dr Lindmark reiterates our point that the results must be interpreted with caution because the study was observational, and more definitive evidence would come from a prospective randomised trial. Nevertheless, hypotheses about drug safety concerns are often generated from observational studies.5 Such studies drive further research because they provide an “a priori” hypothesis and allow the formulation of a clinically relevant end point. Until results from prospective trials become available, observational research using cohort or case-control techniques remains an important source of evidence about the safety of drugs.

Thirdly, he states that a review by Astra Draco has found no evidence from pre-marketing or post-marketing studies of an association between bambuterol and cardiac failure. In general, pre-marketed drugs have their own limitations,5 as evidenced by the recent withdrawal on safety grounds of two newly launched drugs.6 Similarly, different types of post-marketing surveillance studies, including PEM, have different advantages and disadvantages and, in general, one system cannot be relied upon to provide all the evidence needed.7 This point also applies to the fourth comment. In particular, it should be noted that there is gross under-reporting of suspected adverse drug reactions to the Committee on Safety of Medicines8 and other regulatory authorities, and there are many difficulties associated with interpreting data from spontaneous reporting schemes.9

Finally, as is stated clearly in our paper, it is possible that the association may be explained by factors such as confounding by concomitant disease and disease severity. Interestingly, the rate of cardiac failure associated with bambuterol in the first month of treatment was higher than for 11 other cardiovasculardrugs previously studied by PEM (table 1). Only two cardiac drugs, including the inotropic sympathomimetic xamoterol (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 bambuterol cohort was higher than in cohorts of patients taking cardiac drugs, and the bambuterol cohort was the youngest, these data provide further evidence that an association cannot be discounted. Our findings require further confirmation, but we remain concerned about the size and biological plausibility of the association.

GENETICS AND TUBERCULOSIS

Dr Richard Bellamy alludes to the important fact, frequently ignored by immunologists, geneticists and epidemiologists, that tuberculosis has several different forms.6 Physicians have emphasised the difference between primary tuberculosis, which is comparable to Lurie’s susceptible rabbits with disseminated disease, and post primary tuberculosis, best characterised by smear positive pulmonary tuberculosis and Lurie’s “resistant” rabbits. HLA associations 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 DQ5, was found only in patients with smear positive pulmonary tuberculosis.6 These observations have been refined using DNA based HLA typing and have confirmed a link with the genes DRB1*1501 and DQB1*0502. Antibody levels to epitopes of the 38kDa antigen of Mycobacterium tuberculosis restricted antigens were higher, suggesting an enhanced immune responsiveness in those with HLA-DR15.7 The relative importance of the genes involved in susceptibility 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 population).8

The Lurie experiment suggests that a comparison between patients with different forms of tuberculosis, matched by ethnic origin, may be valuable in identifying candidate genes for susceptibility to tuberculosis. Since smear positive pulmonary 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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Chlamydia pneumoniae and asthma

The paper by Cook et al examines the possible association between Chlamydia pneumoniae infection and asthma. The authors conclude that their data do not support this association. However, we feel that the serological tests performed give important information on the prevalence of infection, but are not sufficiently complete to make definitive conclusions on the incidence of acute C pneumoniae infection in the populations under study. The major pitfall in the study, as pointed out by the authors, is the small proportion of patients from whom a convalescent serum sample was drawn. Moreover, the arbitrary exclusion of IgM positive patients for the diagnosis of acute C pneumoniae infection 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 determination. Nevertheless, notwithstanding these facts, the authors conclude that the study does not support an association between C pneumoniae antibody titres and the incidence of acute asthma attacks.

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 having a female predominance. Both these factors are associated with increased C pneumoniae incidence and prevalence. The authors report using a logistic regression modelling method in which the age value is implemented as a time variable, which is roughly equivalent to the difference in mean age between the acute asthma and control populations.

This study is certainly not informative in that it underlines an association between C pneumoniae infection and severe chronic asthma, particularly “brittle” asthma, which will require further investigation in the future.

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in severe steroid dependent asthmatic pa-
tients (aged 13–65) further supports the
possibility that antibody titres indicative of
“previous infection” may also indicate per-
sonal experience.

Acute primary (presence of IgM) or second-
ary (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 exacer-
bations occurred in patients who had previ-
ous wheezing episodes. It would be interest-
ing to know whether Cook et al can retro-
spectively identify any patients who had had
their very first wheezing episode; this might be
easier in general practice than in a hospital
based study.

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Non-Hodgkin’s lymphoma with CFA

We read with interest the case report by
Orchard et al on non-Hodgkin’s lymphoma
arising in cryptographic fibrosing alveolitis
(CFA).7 Although the authors state that this
has not been described previously, we re-
cently reported six cases of pulmonary B cell
non-Hodgkin’s lymphomas arising in patients
with autoimmune disorders, three of whom
had CFA.8 As in the case described by
Orchard et al, prognosis in these three
patients was much poorer than that in the
patients with high grade pulmonary non-
Hodgkin’s lymphomas unassociated with
CFA, presumably due to the combined
effects of the two diseases.

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In the patient we reported the association
was with cryptographic fibrosing alveolitis
(CFA) alone whereas, interestingly, the three
patients they report had CFA associated with
other systemic autoimmune disorders. The
fact that CFA alone may be associated with
B cell lymphomas, and the poorer prognosis
seen by Nicholson and Corrin in their
patients, as well as ours, supports the hypo-
thesis that chronic local stimulation of the lymph-
oid system may play an important part in
the aetiology and prognosis of these tumours.

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BOOK REVIEWS

Respiratory Measurement. Göran Heden-
strierna. (Pp 184, paperback; £19.95 (UK),
€22.00 (overseas)). London: BMJ Books,
1998. ISBN 0 7279 1207 0.

A large amount of information has been
packed into the 184 pages of this new guide-
book in the Principles and Practice Series.
This is a comprehensive review of the princi-
ple of ventilation and gas exchange with spe-
cific emphasis on the application of pulmo-

ary 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 anaes-
thesia. 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 moder-
ate familiarity with the principles of respira-
tory 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
anaesthetic department.—SR

Asthma: Basic Mechanisms and Clinical
Management. 3rd Edition. Barnes PJ, Rodger
IW, Thomson NC, eds. (Pp 942; hardback; £150.00). London: Academic Press, 1998. 0 12 079027 0.

This is the third edition of an established
book. Aiming to bring together all the recent
information on basic mechanisms of asthma
and also 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. Modifi-
cations to the popular second edition include
separate chapters on mediator antagonists
and immunomodulators with consideration
of the potential therapeutic benefits of inter-
vening in the complex inflammatory and
pharmacological pathways systematically
covered in previous chapters. A new chapter
on the pharmacoeconomics of asthma treat-
ments provides a pertinent reminder that,
with 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 wel-
come change to the previous 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 pre-
sentation, this is an excellent book which suc-
ceds in linking the rapidly developing body
of knowledge on asthma with current treat-
ment, while keeping the future constantly in
mind.—AF

CORRECTION

Clinical features of non-smokers with α1-antitrypsin deficiency

The authors of the paper entitled “Clinical
features and prognosis of life time non-
smokers with severe α1-antitrypsin defi-
cency” by N Seersholm and A Kok-Jensen,
which appeared on pages 265–8 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% com-
pared with 50% for the subjects over 50
years...”. Table 3 is reproduced here with
the corrections shown in bold italics.

Table 3 Mean (SD) FEV1 % predicted and FEV1/FVC of index and non-index cases stratified by
age at entry

<table>
<thead>
<tr>
<th>Age at entry</th>
<th>All age groups</th>
<th>N (%) with FEV1 % pred ≤70%</th>
<th>p value (t test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 years</td>
<td>n = 27</td>
<td>100 (33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>FEV1 (% predicted)</td>
<td>0.57 (0.18)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FEV1/FVC</td>
<td>0.79 (0.13)</td>
<td></td>
</tr>
<tr>
<td>≥50 years</td>
<td>n = 40</td>
<td>3 (8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N (%) with FEV1 % pred ≤70%</td>
<td>20 (74%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 3 continued...

<table>
<thead>
<tr>
<th>Age at entry</th>
<th>All age groups</th>
<th>N (%) with FEV1 % pred ≤70%</th>
<th>p value (t test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 years</td>
<td>n = 8</td>
<td>100 (19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>FEV1 (% predicted)</td>
<td>0.53 (0.20)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FEV1/FVC</td>
<td>0.80 (0.12)</td>
<td></td>
</tr>
<tr>
<td>≥50 years</td>
<td>n = 26</td>
<td>2 (8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>N (%) with FEV1 % pred ≤70%</td>
<td>4 (90%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 3 continued...

<table>
<thead>
<tr>
<th>Age at entry</th>
<th>All age groups</th>
<th>N (%) with FEV1 % pred ≤70%</th>
<th>p value (t test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 years</td>
<td>n = 19</td>
<td>100 (24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>FEV1 (% predicted)</td>
<td>0.58 (0.17)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FEV1/FVC</td>
<td>0.78 (0.14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥50 years</td>
<td>n = 14</td>
<td>1 (7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>N (%) with FEV1 % pred ≤70%</td>
<td>16 (84%)</td>
<td></td>
</tr>
</tbody>
</table>
Chlamydia pneumoniae and asthma

FRANCESCO BLASI, LUIGI ALLEGRA and PAOLO TARSIA

Thorax 1998 53: 1094
doi: 10.1136/thx.53.12.1094b

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