

## OPINION

## The diagnosis of asthma, a clinical syndrome

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**ABSTRACT**

Clinical experience and now genetic data indicate that asthma is a heterogeneous clinical syndrome—clinical cases emerge, proceed and respond to treatments in different ways. Currently the diagnosis of asthma (as enunciated in national guidelines) is based on incisive clinical methods, supported by lung function testing that substantiates labile or reversible bronchial airflow obstruction. But this approach alone is insufficient to address the diagnostic and therapeutic challenges presented by asthma's heterogeneity. This article contends that bronchial pathology (with molecular and morphologic analysis) should be adopted into the mainstream clinical practice of asthma so as to clarify the nature of the bronchial disorder in compliant patients not settling securely on moderate-dose inhaled corticosteroid. This would allow a differentiated approach to appropriate therapeutics—those already available and those yet to be developed.

Physicians agree that chronicity and lability of disorder are characteristic of asthma. There are periods of difficult breathing, noisy breathing, chest 'tightness' and cough, which may produce tenacious sputum. Symptoms are often worse in the very early morning. Triggers of symptoms are often reported—cigarette smoke, perfumes, cold air, exercise, laughter, diverse 'allergens', infections or occupational agents. Periods of remission may occur with change of location or climate, or away from work. On clinical examination, the findings may be quite normal; or there may be mild tachypnoea, irritating cough and polyphonic wheezes on auscultation; or in extremis the patient may be limp and cool, with struggling chest movement, a hyper-inflated chest and silent auscultation. Asthma is thus a clinical diagnosis—based on the above—which entails, through incisive clinical practice, excluding confounder diagnoses (notable in small children is viral bronchiolitis<sup>1</sup>) and addressing aggravating factors. Lung function testing is currently the recommended confirmatory diagnostic, aiming to demonstrate airflow obstruction and demonstrate its reversibility; spirometry, because of its high reproducibility and well defined normal ranges, is the gold standard method for both.

The American and British Asthma Guidelines provide invaluable practical accounts of diagnostic approaches in adults and children, and the sequential therapeutic approaches to be followed thereafter.<sup>2 3</sup>

Yet, there is a conundrum here, which lies around the relegation of definitive bronchial pathology within the recommended diagnostic process. This is

notable when considering that some cases of confounder diagnosis may be clinically deceptive—but especially so when considering that asthma is generally acknowledged to be a heterogeneous clinical syndrome (cases emerge, behave and respond to treatments in quite different ways<sup>4 5</sup>). Moreover bronchial pathology is now ready for the deployment of discriminating molecular as well as morphological analysis. In fact, the acknowledgement of asthma's heterogeneity is (in the context of current mainstream diagnostic practice) tacit because there is no systematic application in clinical practice of definitive pathological characterisation of individual cases of asthma.<sup>2 3</sup> Hence physicians do not formally know how their asthma patients differ or how frequently, and thus there is no differentiated approach to treatments. All cases travel through a cascade of advised therapeutic approaches—some patients responding securely and quickly; some achieving acceptable clinical status dependent on medications; and others struggling despite the same treatments; and others appearing resistant to treatments.<sup>5</sup> This approach results in frequent clinic visits and many treatments not delivering satisfactory patient benefit. Inevitably it is very costly and is frustrating for a significant minority of patients with asthma who remain troubled after multiple trials of treatment.

In clinical medicine at large, pathological study of tissue from the affected organ is recognised as key to secure diagnosis, making the virtual absence of bronchial pathology from standard clinical asthma practice (*pace* efforts such as the Severe Asthma Research programme in the USA,<sup>6</sup> and case series at other centres<sup>7–9</sup>) all the more puzzling. We in mainstream asthma practice only irregularly collect data on the 'phenotype' of our patients' asthma—and then often by indirect methods (eg, sputum eosinophil counts) as surrogates for definitive bronchial pathology.<sup>10</sup> This current position is remarkable considering that Dr Morrow Brown's insisted 40 years ago on demonstrable excess of sputum eosinophils to characterise each case of 'allergic asthma', and when he demonstrated the efficacy of inhaled steroid in difficult cases.<sup>11</sup> Are we, today's respiratory physicians, not overdoing 'lumping' and under-doing precision in our practical diagnostics of asthma—why when we concede that asthma is a heterogeneous clinical syndrome do we not regularly consider bronchial pathology? Our approach certainly contrasts with other specialist clinicians' securing of biopsies for precise morphological and molecular studies. Nephrologists have long and systematically biopsied kidneys to identify distinctive immune/inflammatory diseases and

develop distinctive treatments within broad entities such as glomerulonephritis. Gastro-enterologists require colonoscopy with biopsies to diagnose inflammatory bowel disease in children and adults.

Fibreoptic bronchoscopy is an uncomfortable procedure. But it can be performed safely and swiftly in asthma with the proper expertise and protocols for both diagnostic and therapeutic purposes.<sup>6</sup> It may require general anaesthesia in the child, but prominent among the case series on bronchial pathology are those in childhood asthma.<sup>7–9</sup> Bronchoscopic diagnostics are integral to other areas in respiratory medicine, including very sick patients (eg, microbial diagnosis in pneumonias in immunosuppressed subjects).<sup>12</sup> Of prime importance, the sporadic bronchial pathology case series in asthma already point to the valuable discovery of diverse and unpredictable changes in difficult asthma—including unresolved eosinophilic inflammation, inflammation of different subtype, no inflammation, microbial infection—besides the unearthing of confounding diagnoses such as foreign body or benign tumour.<sup>7–9 13</sup> Is it therefore not timely for us to reconsider the role of bronchial pathology in asthma practice at large? Should we not, at least, be obtaining bronchial biopsy when our clinical methods leave us in doubt and the progress of our patients who are treatment compliant is faltering?

As we stand, our lack of a systematic approach to characterising our asthma cases by direct pathology confines us to a quite imprecise notion of asthma's heterogeneity.<sup>5</sup> We recognise that many patients with asthma also suffer from eczema and rhinitis, show allergy to common antigens, and that their asthma is typically responsive to inhaled corticosteroid. We are aware that T helper 2 immune mechanisms drive bronchitis, including prominent eosinophil infiltration/activation, mucus gland hypertrophy and hyper-secretion, and smooth muscle hyper-reactivity (with remodelling of the airway).<sup>14</sup> We also see that many other asthma cases do not fit this 'allergic' picture—we view them as 'different' and heterogeneous in themselves. A minority have clear cause (eg, occupational isocyanate). But most are obscure in nature—asthma without atopy, asthma with aspirin sensitivity, asthma of later origin in women with obesity, late onset asthma in smokers, asthma with neutrophil-associated inflammation, or asthma with little bronchial inflammation; there is a clinical impression of less secure response to inhaled corticosteroids.<sup>5</sup> We have even less information on how bronchial pathology varies with time in any particular patient with asthma, as a result of variable exposure through inhalation to noxious particulates, gases or microbes.

Moreover, the current position of occasional and fragmentary bronchial pathology data within and across asthma patient populations is also strikingly at odds with the progress being made in fundamental research into asthma. The deficiency in clinical bronchial pathology is limiting the potential of the advances in fundamental research to delineate and characterise the heterogeneity of asthma—and is thus retarding progress towards effective therapies for the whole asthma population.<sup>5</sup> The deficiency is plainly at odds with modern translational medicine which emphasises the necessity to bridge fundamental and clinical science. Fundamental research in asthma has advanced impressively since Dr Morrow Brown's work,<sup>11</sup> its momentum increasing with advancing methodologies. Powerful genome-wide studies of large patient groups affirm the heterogeneity of asthma and now delineate the principal loci where genetic variants promote asthma (emphasising polygenic actions at loci related to epithelial and immune functions).<sup>15</sup> More

realistic models of asthma are being studied in cellular and molecular detail<sup>16</sup> and bronchial biopsy in clinical research has allowed proteomic analysis and morphometric assay of remodelling in asthmatic inflammation and chronic obstructive pulmonary disease.<sup>17 18</sup> Hence, more penetrating descriptions are emerging of the molecular elements underlying immune/inflammatory events and epithelial dysfunction in asthma.<sup>19</sup> There is thus a compelling need to now apply analysis of these elements in the bronchial tissue of patients with asthma in clinical practice—to properly understand the mechanisms, character and clinical epidemiology of heterogeneous asthmatic disorder. There is also the unrealised potential to apply methodologies such as epigenetics, which can define patterns of gene activation and silencing, to bronchial tissue of patients with asthma so that apparently disparate functions can be satisfactorily understood as biological networks.<sup>20</sup>

Surely, it is time to match our acknowledgement that asthma is heterogeneous by adopting bronchial pathology with precise morphological and molecular characterisation (and not any surrogate) into our mainstream asthma practice. This would immediately inform our management of patients with asthma who are struggling. It would transform the understanding of asthma's heterogeneity in practice, as an essential step towards developing targeted therapies.

Details of protocol should be addressed elsewhere<sup>2 3</sup> but this author sees two major alternative clinical time points at which to introduce regular bronchial biopsy into asthma practice—either at the junction of step 1/step 2 or the junction of step 2/step 3 of the British Guidelines.<sup>3</sup> The second may be seen as the more pragmatic time to undertake biopsy, representing the point when patients who are treatment compliant remain troubled by asthmatic symptoms after a thorough trial of moderate-dose inhaled steroid (up to 400 or 800 µg beclomethasone equivalent daily in children and adults respectively) and before treatments are escalated (step 3) in ignorance.

This contention does not deny that clinical skills should remain the starting point and cornerstone of diagnostics for asthma, or that validated symptom questionnaires and robust lung function testing should remain important components of the diagnostic and monitoring process. The contention is simply that we can now do substantially better in our diagnostics and with that lay the foundation for the advances to come in the treatment of heterogeneous asthma.

**Competing interests** JMH has been a Director of Allerna Therapeutics Ltd, and has an ongoing interest in developing anti-STAT6 agents as potential therapeutics in asthma.

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## Journal club

### Using lung cancer screening as an opportunity to diagnose COPD

Early diagnosis of chronic obstructive pulmonary disease (COPD) allows increased opportunity for smoking cessation advice and treatment, which potentially improves prognosis. This single-centre, prospective cross-sectional study investigated whether screening CT scans could diagnose COPD without the need for pulmonary function testing (PFT).

One thousand one hundred and forty men, ex or current smokers (>16.5 pack year history), aged 50–75 years, already enrolled in a lung cancer screening trial, had low dose screening inspiratory CT scans, PFT and an additional expiratory scan. Pre-bronchodilatory forced expiratory volume in one second/forced vital capacity ratio <70% was used to diagnose COPD. Those with advanced disease, self-reported as unable to climb two flights stairs were excluded. CT emphysema, CT air trapping, body mass index, pack years and smoking status formed a diagnostic model to identify those with COPD.

Four hundred and thirty-seven (38%) subjects had COPD on PFT. The diagnostic model correctly diagnosed 274 patients with COPD, falsely identified 85 and missed 163. The model had a sensitivity of 63% and specificity of 88%. Accuracy increased with increasing severity, identifying 100% (25 of 25) patients with severe obstruction, 73% (99 of 135) with moderate obstruction and 54% (150 of 277) with mild obstruction. Model adjustment according to the presence of symptoms did not improve the results.

The authors acknowledge the use of quantitative CT as a primary screening method for COPD is not likely to be beneficial, but suggest that if CT lung cancer screening is widely adopted, this model may be further validated and may be additionally useful for early diagnosis of COPD.

► **Mets OM**, Buckens CF, Zanen P, *et al*. Identification of chronic obstructive pulmonary disease in lung cancer screening computed tomographic scans. *JAMA* 2011;**306**:1775–81.

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