

RESEARCH

Priorities for respiratory research in the UK

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Respiratory diseases are placing an increasing burden on the UK health system

In the past, respiratory research has proved itself effective in vanquishing major killers such as tuberculosis, transforming the lives of patients with asthma and developing life-saving non-invasive ventilation for those with chronic respiratory failure. Now, new problems affect our patients with respiratory diseases and present an enormous burden of ill health that we are currently ill equipped to deal with. The second edition of the *Burden of lung disease* was published by the British Thoracic Society in June 2006¹; it documents that respiratory diseases now kill one in five people in the UK, with the standardised mortality ratio for respiratory diseases showing a threefold difference across social classes. More people die from respiratory disease than from ischaemic heart disease. Respiratory diseases are the most common cause of long-term illness in children, result in the highest levels of consultations with general practitioners and are the second most common reason for emergency hospital admission. Examples of the severity of the situation from UK statistics are as follows:

- respiratory disease kills one in five people
- respiratory disease has the steepest socio-economic mortality gradient of any disease area
- respiratory disease is the most common reason for general practitioner consultation
- the only countries in Europe with a worse mortality rate from respiratory disease than the UK are Ireland, Malta, Kyrgyzstan, Tajikistan, Kazakhstan, Uzbekistan and the Republic of Moldova
- 5-year survival from lung cancer is <8% (only pancreas is worse, 7000 cases/year)
- asthma is the most common chronic illness in children and pregnant women
- there are 10 000 new cases of interstitial lung disease a year.

Although research has undoubtedly contributed to a greater understanding of disease mechanisms, epidemiology,

diagnosis and treatment when compared with other specialities, progress has been slow. In the past 20 years, relative underfunding has meant that there has been less progress. One result of this is that the number of trainees pursuing a career in respiratory research has fallen to a dangerous level, and our ability to exploit the enormous diagnostic and treatment potential of recent advances in biology has been compromised.

This initiative is part of a process designed to change the situation. A broad coalition of groups with an interest in respiratory disease from childhood to old age has come together to develop a common list of priorities that identify those areas where more knowledge is urgently needed.

In October 2005, a large proportion of the respiratory researchers in the UK and those involved in supporting research (Medical Research Council, Wellcome Trust, Department of Health, British Lung Foundation and Asthma UK) and the professional societies (British Thoracic Society, British Association for Lung Research and the British Paediatric Respiratory Research Society) convened a workshop in which the current state of respiratory research was reviewed and possible mechanisms were discussed to consider how the capacity could be built. The first step was to identify the major priorities for research in the near future and then to bring together the various research funders to see how these could be used to help rebuild the capacity. A further highly interactive workshop involving both researchers and funders led to a consensus over those areas where initial effort should be focused. The seven themes that emerged are presented, not in any order of priority.

EARLY LIFE EVENTS: DEVELOPMENT AND LUNG AGEING

Interactions between maturation of immune function and lung growth contribute to the development of airway disease. Both are subject to genetic control, and recent interest has focused on

genes that regulate lung and airway development. The premise that host response to microbial stimuli has altered as a result of changes in the nature, timing or dose of the signals received has gained much attention, but there remains the possibility that changes in the host response are secondary to programming of the immune system by early environmental influences. Two specific areas of interest are the role of pattern recognition (eg, Toll-like receptors and regulatory T cells) in generating antiviral responses in the respiratory tract, and the occurrence and relevance of airway injury and remodelling to disease. One of the greatest challenges will be to identify, with confidence, those infants who have or will go on to develop airway disease in later childhood or adulthood. Several obstacles are yet to be overcome. We know relatively little about the natural history of the intrauterine and immediate postnatal development of the respiratory tract and immune system. Access to peripheral blood or biopsy specimens is severely limited. Measurement of lung function in the very young is also difficult. The ideal technique should have easily transferable technology that is cost effective so that large numbers of children can be studied. Liaison with engineers and nano technologists will be helpful to develop novel approaches. Lung diseases may develop, persist, remit or relapse during adolescence and adulthood, and decline in lung function in adults may be mediated by early life events, but the determination of these outcomes is poorly understood. We need to study the interplay of genetic and early environmental factors that influence the severity of asthma and cystic fibrosis and increased susceptibility to chronic obstructive pulmonary disease (COPD). Changes in the immune system and host response with increasing age may predispose to malignancy and pulmonary fibrosis. Declining lung physiology may precipitate disease, exacerbate existing disease or contribute to disease in other systems (eg, sleep disordered breathing, cardiovascular disease and neurological decline). An improved understanding of development and remission should lead to opportunities for prevention. A better understanding of age-related responses to pharmacotherapy may improve treatment. Key research areas include the natural history of early development of the respiratory tract and immune system and the techniques needed to understand normal airway growth, development and decline in health and disease. It is important to define the normal ontogeny of Toll-like receptors and immunoregulatory T cell function and how this changes

with disease. A prospective birth cohort using an appropriate intervention strategy and including a placebo group could provide an opportunity to do this. For lung disease in adolescence and adulthood, there is a need to identify the factors influencing development, remission, relapse, progression and severity of airway disease, and with this understanding whether the natural history of lung disease can be modified beneficially by early life interventions.

AIRWAY DISEASE AND SLEEP APNOEA SYNDROMES

Asthma, COPD and sleep apnoea syndromes have major health consequences and socioeconomic effects. Each of these diseases is common and constitutes a high proportion of the total respiratory disease burden in the UK. On the basis of recent national consultations, there are major areas where further research could enhance our understanding of the cause, prevention and treatment of disease. Advances in technologies ranging from molecular to whole-body approaches create unique opportunities to make substantial advances in knowledge of these disorders. Key research questions include identifying opportunities for the primary and secondary prevention of acute exacerbations and chronicity of lower airway diseases, the identification of genetic and epigenetic-environmental interactions in susceptibility to all three disorders, the application of pharmacogenetic approaches to improve clinical care and the application of non-invasive imaging and physiological techniques to ascertain normal ontogeny, perturbations in disease and improvement with treatment. These could include the development of technologies for assessing intrauterine development of the lung and immune system, measurement of lung functions from birth to old age, assessment of different lung compartments including airways, parenchymal and vascular structures, and involvement of the central and peripheral nervous system. In relation to the application of new technologies and impact evaluation, there is a requirement to identify unmet clinical needs and for targeted preventive and therapeutic strategies, including palliative care for end-stage disease, accompanied by appropriate outcome measures to evaluate interventions.

RESPIRATORY INFECTIONS

Respiratory infections (excluding tuberculosis) account for >6% of the global burden of human disease, causing more morbidity and mortality than all cancers. Poverty is associated with a >20-fold increase in the relative burden of lung infections, which disproportionately

affect the very young and very old. In the USA, more is spent for research on small pox (US\$324 million in 2004) than on lung infections (US\$287 million); lung infections receive only one tenth of the funding provided for HIV/AIDS, which causes a similar disease burden.²

More infections are spread via the respiratory tract than by any other route. Respiratory pathogens are responsible for a huge worldwide disease burden; they mutate fast, cross species barriers, threaten patients with pre-existing lung diseases, evade antimicrobial treatments and respond rapidly to demographic and economic change. Some (eg, tuberculosis) are on the rise, whereas others (eg, severe acute respiratory syndrome and "avian" influenza) are emerging threats to health and prosperity. There is an urgent need for new vaccines and antimicrobial drugs, and for agents that beneficially modify host immune responses. We need evidence-based approaches to antimicrobial prescribing and to identify situations where combinations of drugs are required. Unnecessary antimicrobial use has led to major problems of antimicrobial resistance, side effects, patient dependence and costs, especially in the community. Appropriate, rational antimicrobial treatments are needed for patients with mild infections. Key research areas include the early "innate" response to microbial invasion, the influence of these responses on T cell and B cell immunity, the role of overexuberant immunity in causing disease and studies of immune evasion, reinfection and persistence. Other important topics include the effects of genetic variation, infection history, coinfections, immune immaturity and senescence. We need a better understanding of the role of infections in chronic inflammatory diseases.

LUNG CANCER

Lung cancer is the most common cause of death from cancer for both men and women in the UK. Its incidence is still rising among women in Britain and will reach epidemic proportions in the Far East, as well as continue to rise in many European countries for years to come. The major cause, tobacco smoking, is well established, and efforts continue to educate populations on the dangers of smoking. This has had success, and, in the USA, there are more lung cancers arising in exsmokers than in current smokers. Exposure to environmental tobacco smoke is also linked to increased cancer, and the success of campaigns to limit smoking in public places is a real achievement.

An urgent need prevails to understand the genetic and environmental factors for

susceptibility to lung cancer, as only a small percentage of heavy smokers contract the disease; the genetic predisposition to lung cancer has only just begun to be studied. The late presentation of most patients has made curative treatment difficult, and studies looking at prognostic symptoms and signs at presentation have been unhelpful. Treatment of advanced disease presentation (the great majority of cases) is unlikely to have much of an impact in the near future. Key research areas include genetic and epigenetic studies of susceptibility and progression; an understanding of how to modify or halt tumour growth, and to identify potential inhibitors of growth; the application of improved technology to identify cancers earlier and at a better stage for potential cure; improve staging of known disease to optimise current available treatment; and evaluation of the potential of screening high-risk populations. It is starkly obvious that current treatments are totally inadequate.

LUNG INJURY, REPAIR AND REGENERATION

The lung is uniquely vulnerable to injurious agents both from the environment, because it exposes a large surface area to the air, and from within the body, because the pulmonary vascular bed receives the entire cardiac output. Tissue injury and the resulting inflammation and repair are processes that underlie most lung diseases. Although the past two decades have witnessed considerable advances in understanding these processes in disease pathogenesis, the mechanisms involved in disease chronicity that are amenable to intervention are largely unknown. Many lung diseases involve complex combinations of epithelial injury, vascular responses and aberrant repair, often in combination with different types of inflammation. For most chronic lung diseases, some understanding has been gained of the cellular and molecular mechanisms underlying disease pathogenesis, but often this knowledge is incomplete and "downstream" of the initiation by noxious agents. The recent rapid development of new in vitro technologies and integrative biological approaches will greatly facilitate future mechanistic studies. Key research areas include the application of cell and molecular approaches as well as genomics, proteomics and metabolomics to identify underlying mechanisms of lung injury, inflammation and repair responses, with a focus on understanding disease chronicity and tissue remodelling. The role of embryonic and adult stem cells in lung repair and regeneration is an important area for study. There is a need to apply

newer technologies to identify biomarkers of chronic disease and acute exacerbations, and to apply these to epidemiological studies to gain a greater understanding of how environmental and other factors can influence the natural history and disease prognosis. There is an important requirement for improved animal models that better reflect chronic lung disease in humans and that can be applied to drug discovery.

PHENOTYPING RESPIRATORY DISEASES

The heterogeneity in clinical features, pathogenic processes and responses to treatment between individuals with respiratory disease is likely to be explained largely by distinct phenotypes that develop because of complex interactions between genetic and environmental factors. In the past, the classification of respiratory disease was largely descriptive, based on symptoms, signs and general functional abnormalities that grouped together individuals with diverse phenotypes. In the future, the accurate phenotyping of disease will have a major effect on the management of respiratory conditions and will lead to the ultimate cure of specific diseases.

The emergence of new investigative techniques, including genomics, proteomics and non-invasive imaging, offers exciting opportunities to classify respiratory diseases more accurately into distinct phenotypes. This approach will help in understanding the pathogenic processes that lead to the initiation and progression of disease, as well as to the development of new targeted treatments. Accurate phenotyping is also important for epidemiological studies of causation, which could lead to prevention. Advances in the identification of specific phenotypes are already being made in several respiratory diseases. Key research areas include determining which respiratory disease phenotypes are important, how they are identified in clinical practice, and their implications for susceptibility, prevention, diagnosis, treatment and prognosis of disease.

DELIVERY OF CARE FOR LUNG DISEASE

Eight million people in the UK have respiratory disease. The medical management of these patients is delivered in primary, secondary and tertiary care by consultants (who may be respiratory physicians or specialists in other fields), by hospital and community-based respiratory nurse specialists or practitioners, by

general practitioners (a minority of whom may have a special interest in respiratory medicine), by practice-based nurses and healthcare assistants, and in future by medical care practitioners. There are also valuable contributions from clinical scientists, pharmacists, physiological measurement technicians, respiratory physiotherapists and others. How this care is delivered and in which sector of the health service is subject to only sporadic evaluation, with evaluation often being undertaken by enthusiasts and with results that cannot always be extrapolated elsewhere. Unlike other specialities, respiratory medicine encompasses a diverse range of disorders. Although some are infectious, short term and self-limiting, most patients with respiratory disorders have long-term non-communicable conditions. Management of those with long-term and disabling conditions should recognise the dominant role of self-care but all too often our patients are not given the skills, training and education they need to effectively self-manage their conditions. Rigorous methods to determine patient preferences, such as discrete choice experiments, are rarely used and benchmarking has not been optimally used, especially in conjunction with standards defined in guidelines.

Key research areas include the rigorous study of outcomes for care delivered in different arenas by different healthcare professionals and by lay people, with such evaluations including full health economic evaluation and benchmarking and educational requirements for healthcare providers (eg, outreach specialist clinics, use of lay educators, nurse prescribing, handover clinics for adolescents with lung disease, nurse practitioner clinics, the role of medical care practitioners). This area is particularly important in long-term respiratory disorders, especially those affecting elderly people, who often also have comorbidities. A further important focus for future research is the rigorous study of patient preferences utilising, for example, discrete choice experiments, especially for long-term disorders where self-care is vital. This should include factors that influence adherence to treatment, such as social needs. There is need for more research to enhance the accurate diagnosis of diverse respiratory diseases, many of which share symptoms with disorders of other systems. Evaluations of one-stop diagnostic centres and population studies are needed to define accurately the true burden and trends of

respiratory illness in the UK. This could be achieved by the Health Survey of England maintaining a focus on respiratory disease, and by monitoring quality and outcomes framework data. For rarer respiratory disorders, continuation and extension of the British Thoracic Society Orphan (Rare) Lung Disease project would be desirable.

Strong social class and ethnic inequalities are associated with some lung diseases (eg, lung cancer, asthma, tuberculosis and COPD). Research is needed to determine how best to reduce these differentials and to reduce inequalities in smoking cessation. Some respiratory conditions are rare, entail high costs and need specialist management. Many others are managed in the community, and there should be a focus on respiratory networks to ensure an optimal research environment to answer questions on the prevention of respiratory disease and optimal management. Rigorous evaluation of the use of new technologies for diagnostic and monitoring purposes is needed—for example, exhaled nitric oxide, telephone and email consultations, and e-learning. Excellent guidelines exist for most respiratory conditions, but implementation is patchy. Evaluations of optimal methods of teaching the correct management of respiratory illness are needed.

By focusing a multidisciplinary effort involving researchers across the full range of respiratory medicine and healthcare, and combining resources from different funders, hopefully, the poor state of research in this major field of unmet clinical need can be addressed, starting with the rebuilding of capacity. A cadre of new young researchers to drive forward understanding and healthcare in lung disease will provide a platform for the subsequent development of this neglected area of human illness. Although this was a UK initiative, we believe that the conclusions drawn are applicable to lung disease in other countries.

Thorax 2007;**62**:5–7.

doi: 10.1136/thx.2006.073882

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Received 23 October 2006

Accepted 31 October 2006

Competing interests: None declared.

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