

Priorities for Respiratory Research in the UK

Summary

On June 28th the Second Edition of the Burden of Lung Disease was launched in Parliament, highlighting once again the enormous unmet clinical need that still exists in lung disease - the UK and worldwide. Set against this is the low level of research in the UK dedicated to lung disease, one of the lowest amongst all the health specific specialities. To begin to address this disparity, respiratory researchers and funders have come together to join forces. The first step has been to identify major priorities for research so that a renewed effort to rebuild capacity is focused on the greatest need. Seven fields were identified which it is hoped will provide a framework for action across the full range of research from basic biomolecular approaches through to clinical and service delivery. This is a unique opportunity to pull together for the benefit of patients with lung disease.

Introduction

In the past respiratory research has proven itself effective in vanquishing major killers like tuberculosis, transforming the lives of patients with asthma and developing life-saving non-invasive ventilation for those suffering from chronic respiratory failure. Now new problems affect our respiratory patients and present an enormous burden of ill-health and suffering that we are currently ill-equipped to address. The Second Edition of the Burden of Lung Disease has been published by the British Thoracic Society in June 2006¹ and documents that respiratory diseases now kill one in five people in the UK, with the standardised mortality ratio for respiratory diseases showing a three-fold difference across social classes. More people die from respiratory disease than from ischaemic heart disease. Respiratory diseases are the commonest cause of long term illness in children, result in the highest levels of consultations with GPs and are the second commonest reason for emergency hospital admission. Respiratory diseases cost the UK over £6 billion in 2004, nearly 25 million certified

sickness absence days and more than 60 million prescriptions were used in their prevention and treatment.

- Respiratory disease kills 1 in 5 people
- Respiratory disease has the steepest socioeconomic mortality gradient of any disease area
- Respiratory disease is the commonest reason for GP 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 less than 8% (only pancreas is worse - 7000 cases per 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.

Respiratory research in the UK is recognised as being world-class and historically has achieved much with relatively modest financial support. However, in the last twenty years relative under-funding has meant that there has been less progress in discovering novel mechanisms, trying new treatments and in managing respiratory diseases generally than other chronic disorders such as cardiovascular and arthritic disorders. As a result the number of younger 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 this situation. A broad coalition of groups with an interest in understanding respiratory disease from childhood to old-age, using tools as varied as basic molecular biology and the evaluation of treatment success, has come together to develop a common list of priorities that identify those areas where more knowledge is urgently needed. The seven themes selected include highly prevalent and frequently lethal conditions that include airways disease, lung cancer and

respiratory infection as well as methodologies of wide application such as the use of new imaging methods and biomarkers to define patients with a different natural history of disease and those who respond differently to treatment. Other approaches include understanding how early life events shape disease in children and adults and developing more understanding of the crucial relationships between pulmonary inflammation and repair which are at the heart of disease progression in many conditions. Whatever treatments we have now or develop in future must be evaluated rigorously if we are to maximise patient benefit at an acceptable cost and this is a further key theme in our research agenda.

In order to achieve the goals outlined in this report, we will need to increase the numbers of researchers that are trained to undertake research in respiratory medicine. The historically low level of funding for respiratory research has meant the research base or “capacity” is smaller than in many other areas of medicine. According to the recent UK Clinical Research Consortium (UKCRC) report², the proportion of combined spend on respiratory research compared to the Disability Adjusted Life Year rates (DALYs) as a measure of disease impact on society, was among the lowest of all the health specific categories¹. Funding to address specific research questions will need to be complemented by personal funding for talented researchers, both clinical and non-clinical, to provide an attractive and achievable career path in respiratory disease. Targeted PhD Studentships and Clinical Fellowships will help recruit young people into respiratory research, with more senior fellowships, such as Career Development and Clinician Scientist awards, required for their further career development.

The subsequent sections of this document discuss in more detail the clinical issues, key questions and some potential research themes that will deliver better respiratory care to more patients more appropriately. Achieving this will be a challenge but it is one that we must meet and there has never been a better time to start this work than now, nor a more pressing need to do so.

Approach Used to Identify Research Priorities

In October 2005 a large proportion of the UK's respiratory researchers and those involved in supporting research (MRC, 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 discussed to address how the capacity could be built. It was decided that a 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 capacity. A further highly interactive workshop involving both researchers and funders led to a consensus over those areas where initial effort should be focused. This process was not designed to be one that restricts research activity in respiratory disease, but to address major areas of unmet clinical need that makes up a significant proportion of the disparity between the disease burden and research need. The seven themes are presented below not in any order of priority.

Early Life Events - Development and Lung Aging

- Interactions between maturation of immune function and lung growth contribute to the development of airways 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 received 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 (e.g. Toll-like) receptors and regulatory T-cells in generating anti-viral responses in the respiratory tract and the occurrence and relevance to disease of airway injury and remodelling. One of the greatest

challenges will be to identify, with confidence, those infants who have or will go on to develop, airways disease in later childhood or adulthood. There are several obstacles 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 biopsies is severely limited. Measurement of lung function in the very young is also very 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 adult decline in lung function 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 severity of asthma and cystic fibrosis and increased susceptibility to COPD. Alterations 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 e.g. 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 placebo group could provide

an opportunity to do this. For lung disease in adolescence and adulthood there is a need to identify what factors influence development, remission, relapse, progression and severity of airways disease and with and with this understanding whether the natural history of lung disease be modified beneficially by early life interventions.

Airways disease and sleep apnoea syndromes

- Asthma, Chronic Obstructive Pulmonary Disease (COPD) and sleep apnoea syndromes have major health consequences and socio-economic impact. Each of these diseases is common and constitutes a high proportion of the total respiratory disease burden in the UK. Based on recent national consultations there are major areas where further research could enhance understanding of disease cause, prevention and treatment.
- 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 airways 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 should include 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 application of new technologies and impact evaluation, there is a requirement to identify unmet clinical needs and for targeted preventative and

therapeutic strategies, including palliative care for end stage disease, accompanied by appropriate outcome measures to evaluate interventions.

Respiratory infections

- Respiratory infections (excluding TB) account for more than 6% of the global burden of human disease, causing more morbidity and mortality than all cancers. Poverty is associated with a more than 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 on smallpox research (US\$324m in 2004) than on lung infections (US\$287m); lung infections receive only on tenth of the funding provided for HIV/AIDS, which causes a similar disease burden ([dx.doi.org/10.1371/journal.pmed.0030076](https://doi.org/10.1371/journal.pmed.0030076)).
- 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 (e.g. tuberculosis) are on the rise, while others (e.g. SARS 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 therapies 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 and B cell immunity, the role of over-exuberant immunity in causing

disease and studies of immune evasion, re-infection and persistence. Other important topics include the effects of genetic variation, infection history, co-infections, immune immaturity and senescence. We need a better understanding of the role of infections in chronic inflammatory diseases.

Lung Cancer

- Lung cancer is the commonest cause of death from cancer for both men and women in the UK. Its incidence is still rising amongst women in Britain and the disease 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 ex- than current smokers. Exposure to environmental tobacco smoke (ETS) is also linked to increased cancer and the success of campaigns to limit smoking in public places as a real success.
- There is an urgent need 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 sufferers has made curative treatment very 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 make much 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 therapy,

and to evaluate the potential of screening high risk populations. It is starkly obvious that current therapies are totally inadequate.

Mechanisms of 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. While the last 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 in large part by distinct phenotypes that develop due to 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 impact 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

- 8 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/practitioners, by general practitioners (a minority of whom may be a GP with 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 by enthusiasts and with results that cannot always be extrapolated elsewhere. Unlike other specialities, respiratory medicine encompasses a very diverse range of disorders. While some are infectious, short term and self limiting, the majority of 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 (e.g. Outreach specialist clinics, use of lay educators, nurse prescribing, hand over 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 often especially affecting the elderly, who also frequently suffer from co-

morbidities. 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 which 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 to accurately define 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 QOF data. For rarer respiratory disorders, continuation and extension of the British Thoracic Society Orphan (Rare) Lung Disease (BOLD) project would be desirable.

- Strong social class and ethnic inequalities exist in some lung diseases (e.g. lung cancer, asthma, TB 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, high cost and need specialist management. Many others are managed in the community and there needs to be a focus upon respiratory networks to ensure an optimal research environment to answer questions on prevention of respiratory disease and optimal management. Rigorous evaluation is needed of the use of new technologies for diagnostic and monitoring purposes, for example exhaled nitric oxide, telephone and email consultations, 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 health care and combining resources from different funders, it is hoped that 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 health care in lung disease will provide a platform for the subsequent development of this neglected area of human illness.

References

1. Burden of Lung Disease Second Edition: A Statistics Report from the British Thoracic Society.
2. UK Clinical Research Collaboration. UK Health Research Analysis.

