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INNATE IMMUNITY TO PULMONARY INFECTION

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Published in 2006 by John Wiley & Sons Ltd,
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Chichester PO19 8SQ, UK

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International (+44) 1243 779777
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Jossey-Bass, 989 Market Street, San Francisco, CA 94103-1741, USA

Wiley-VCH Verlag GmbH, Boschstr. 12, D-69469 Weinheim, Germany

John Wiley & Sons Australia Ltd, 33 Park Road, Milton, Queensland 4064, Australia

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Novartis Foundation Symposium 279
x + 238 pages, 23 figures, 5 tables

British Library Cataloguing in Publication Data

A catalogue record for this book is available from the British Library

ISBN-13 978-0-470-01597-1 (HB)

Typeset in 10½ on 12½ pt Garamond by SNP Best-set Typesetter Ltd., Hong Kong
Printed and bound in Great Britain by T. J. International Ltd, Padstow, Cornwall.
This book is printed on acid-free paper responsibly manufactured from sustainable forestry, in which at least two trees are planted for each one used for paper production.

Contents

Symposium on Innate immunity to pulmonary infection, held at the Wolfson Pavillion, University of Cape Town Medical School, South Africa, 28–30 November 2005

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This symposium is based on a proposal made by Siamon Gordon and Gordon Brown

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Chair's introduction

Siamon Gordon

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To introduce this meeting I would like to list a few topics that we should be thinking about during this meeting, and then at the end we will come back to this list in our final discussion.

Lung infections and to a lesser extent allergies are important diseases in terms of morbidity and mortality. It is not only tuberculosis (TB) that is a problem: this is the second Novartis Foundation symposium in Cape Town, but while TB will be a major focus of this meeting also, we'll be looking at many other important bacteria and viruses.

We have a nice mix here of clinicians and scientists. With input from the different fields represented here, we have a wonderful human 'model' of mucosal immunity. We have experts here who study not only cellular aspects and antibodies, but also the collectins and surfactants, as well as other extracellular factors such as mucus. We want to see what we can learn from the human studies.

Mucosal immunity is an interesting example of interactions between epithelia and haematopoietic cells. Then of course we have something special: we are in the lung, but we also have the interactions with other systemic aspects of host responses. There are not only acute effects (emphasizing the innate aspects), but also long-term sequelae such as the adaptive immune response that follows, and some of the complications such as fibrosis. They are all part of this initial immune response.

The topic of this meeting is of course a worldwide problem, but it is an appropriate problem to be discussed in South Africa. This is a major health problem in this country, but this does provide a laboratory for us to study things that fortunately aren't seen to the same extent elsewhere.

What are some of the issues in terms of host–pathogen interactions? We know that human populations differ. This raises the question of what determines genetic susceptibility of resistance. One breaking topic is whether polymorphisms in, for example, the Toll-like receptors (TLRs) are significant. There is a lot of research in this area, and I've heard of unpublished work on TLR polymorphisms that have a dramatic effect on diseases such as respiratory syncytial virus.

The lower and upper respiratory tracts differ in terms of their commensal organisms. The lower should be essentially sterile, whereas the nose and rest of the upper

respiratory tract are not sterile. This is an interesting problem compared with, say, the gut. There is the popular idea of the hygiene hypothesis; many people are wondering whether the increase in allergy and asthma is in some way related to the increasingly clean environment found in some parts of the world.

Tropism is an interesting question: why are certain agents specifically able to infect certain cells? Is this a property of a particular local cell, or is it something that happens in only some cellular environments? Many cells have the same molecules and only in some is there selectivity of infection. This is particularly relevant to some of the major virus infections. We haven't done justice to the adaptive immune response in this programme. If we had, the meeting would have been a lot longer. Nevertheless, there are some fascinating aspects in which the innate response may or may not be able to influence and skew the adaptive response. The Th1, Th2, T_{regs} and antigen-presenting cells (APCs) all have important roles here, both in terms of inducing an immune response and also suppressing one. This may be a unique property of the airway macrophages. This includes the major biological issue of dormancy. How is it that mycobacteria can persist in some quiescent state within cells? How do we study this? These are issues that are important medically, but difficult to address experimentally.

We mustn't forget we are in the lung. The local environment is something we don't pay enough attention to sometimes. This is an organ of gas exchange, so what is the role of oxygenation in this particular site? What about all those particulates that we inhale? The dust diseases have a long history in South Africa because of the mining industry and also asbestos. There are local surfactants in the lung to consider. And then we have the devastating interaction between the lung and smoking. One of the intriguing issues is whether there is sometimes coinfection between a virus and a bacterium which makes one of the two more virulent or pathogenic. This could be an important issue for influenza. Finally, what are the special features of the vascular bed and the lymphatic drainage?

We also have systemic factors that will influence local disease. There is HIV and infection by opportunistic agents. Again, alcohol is a major and neglected problem in this part of the world, as is poor nutrition. Extrapulmonary parasites are also pervasive and may or may not have an impact on diseases within the lung. A further issue is how emerging infections jump species, and move from one individual in a population to another.

From my point of view this is not only an important subject, but also an opportunity to get research done. We have the opportunity to do translational clinical research in South Africa. We should not ignore animal models, but take advantage of the extensive human material available. The lung is an accessible site. We can obtain sputum, bronchoalveolar lavage, aspirates and even pleural effusions. How can we make the best use of this? A general question is how useful is it to monitor blood when this is not the primary site of infection? Are the cells in the blood

aware of what is happening in the lung, or are they on their way to the lung? With microarrays it is now much easier to get a signature of what is happening in blood cells in systemic and local diseases.

I don't have to emphasize that we are facing a major threat with emerging infections such as avian flu, and I look forward to hearing about this. I'd like to throw out the provocative idea that both avian flu and SARS may be diseases of innate immunity. There are other less nasty, newly discovered (or to be discovered) emerging viruses. There may be more pathogens out there than we know of.

Although it is not a major theme at this meeting, we'll be touching on the development of vaccines, for example, for influenza. The use of drugs and antibiotics is a highly important issue, but let us not forget what we can do about preventing some of these diseases.

Lung diseases in South Africa: an overview

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Abstract. The profile of both infectious and non-infectious lung diseases in South Africa over the past century reflects prevailing sociopolitical and economic forces. The lung, perhaps more than any other organ system is influenced by poverty, occupation and personal habits. These influences are seen in the association between tuberculosis and pneumoconiosis first described in miners, the increasing prevalence of asthma and smoking-related chronic obstructive pulmonary disease, and the current dual epidemics of tuberculosis and infections associated with the human immunodeficiency virus (HIV). The global prediction for developing countries is that by the year 2020 respiratory diseases (including infections) will account for a large majority of deaths and a considerable burden of disability adjusted life years. The country-wide Demographic and Health Surveys of 1998 and 2003 have provided data on symptom prevalence in South Africa. The Lung Health Survey 2002 performed in Cape Town provides disease prevalence and has identified complex interactions between causative factors and disease. Consistent and biologically plausible associations between smoking and susceptibility to tuberculosis and pneumonia in HIV-infected patients have been reported. These findings are relevant both to the planners of public health interventions, and to researchers exploring disease mechanisms and potential remedies.

2006 Innate immunity to pulmonary infection. Wiley, Chichester (Novartis Foundation Symposium 279) p 4–16

The respiratory system, like the skin, serves a unique function at the air-fluid interface between the body and the external environment. Unlike the skin, its function in gas exchange requires it to be delicate and consequently more vulnerable. To compensate for this, it is equipped with a variety of defence mechanisms varying from physicochemical (cough and mucociliary escalator) to immunological. In spite of these it is the target of disease of both infectious and environmental origin which together account for a large proportion of global all-cause morbidity and mortality. In a World Health Organisation (WHO)-commissioned survey of global prevalence of disease in 1990, four diseases of the respiratory system featured amongst the top 10 causes of mortality—lower respiratory tract infections (LRTI) (third place), chronic obstructive pulmonary disease (COPD) (sixth place),

tuberculosis (TB) (seventh) and lung cancer in 10th position (Murray & Lopez 1997). Modelling for the future burden of disease, including estimations of the impact of the rising HIV epidemic, the authors predicted that by the year 2020, COPD would have moved to third position, followed by LRTIs, TB, lung cancer and finally HIV-related deaths (other than chest infections). Since some of these are chronic conditions they are and will continue to be leading causes of lost disability-adjusted life years (DALYs). The authors predicted in developed countries the profile of diseases causing loss of DALYs would be lung cancer (in fourth position) and COPD (ninth position). In developing countries like South Africa, the order and importance of respiratory diseases would be similar to those causing mortality described above (Murray & Lopez 1997). In recognition of the importance of respiratory diseases, especially in developing countries (which comprise the majority of the world population), the World Health Assembly of the WHO resolved in May 2000 to make the prevention and control of chronic respiratory disease (CRD) (World Health Organisation 2000) a priority. This has led to the formation of the Global Alliance Against Lung Disease, launched in March 2006 for the purpose of co-ordinating efforts of the WHO, government and non-governmental agencies and initiatives to address these diseases. Moreover, the twin epidemics of TB and HIV infections have become the focus of intense activity and have been accorded the status of global emergencies. South Africa, in spite of its remarkable and unprecedented political transformation has the misfortune of being, if not in the epicentre, then a major victim of this wave of infectious and chronic respiratory pathology. The origins and forces that have created these waves can be traced through the politics and economics of its colonial period into the modern era, and although the interactions of these forces are many and complex, their combined effect presents a profile of disease that is alarming. First was the creation of fertile soil for spread of the white plague, TB, brought from the 'old world' to the vulnerable populations in Africa. The development of a labour market for unskilled and semi-skilled workers through detribalization into a migrant labour force created conditions that favoured transmission (Packard 1989). Next, but related, was the development of mining, which besides its general pollutant effects exposed the workforce to the fibrogenic and carcinogenic effects of silica and asbestos. In spite of the South African mining industry being a world leader in both deep level mining and in the study of dust-related lung disease (including recognition of increased susceptibility of miners with silicosis to TB, the link between silica exposure and systemic sclerosis, and crocidolite asbestos to mesothelioma), there were unacceptable delays in translating these findings into improvements in working conditions. In the case of asbestos, mining of the highly carcinogenic crocidolite variety continued well after its harmful effects were exposed. The full impact of past mining practices, even those previously considered safe, is only now becoming evident (Churchyard & Corbett 2000, teWaterNaude

et al 2006). One example of this is the very high burden of lung disease including TB amongst retired miners. In 1987 Cowie & van Schalkwyk reported that the prevalence of silicosis among active miners in the Free State goldfields was only 1% (between 0.87 to 1.38%). However studies performed in 1997 (Steen et al 1997) and 1998 (Trapido et al 1998) in retired gold miners who had returned to their homes in Botswana and Lesotho, revealed radiographic, and often advanced stages of silicosis in more than one third of ex-miners and that between one third and one half also had evidence of current or previous pulmonary TB, reflecting the lifelong susceptibility to TB created by silica dust exposure. When one considers that at its height this industry employed more than half a million men, and that the turnover of miners each year was high, it is evident that mining has created a large pool of persons greatly at risk of developing TB and of perpetuating the epidemic (Churchyard et al 2004, teWaterNaude et al 2006).

The next major development that has impacted on the health of the nation and upon respiratory health in particular is the spread of HIV. For the first 80 years of the century, notwithstanding the situation in mines, there was a steady decline in TB notifications in South Africa, suggesting that the National TB Control strategy was beginning to bear fruit (Packard 1989). However, this trend has been reversed and over the past 15–20 years notification rates have risen to record levels, the consequence of the interaction between TB and HIV infections. Amongst miners, according to Corbett et al (2000), notification rates which ranged from 600 to 800 per 100 000 between 1983 and 1991, began to rise in 1992, reaching 3000 per 100 000 by the year 2000. The majority of the increase has been in HIV-infected persons, who now represent more than 70% of patients presenting for treatment of TB. By 2000 the nationwide prevalence of HIV sero-positivity exceeded 20% amongst women attending for ante-natal care, and has continued to rise. By the mid-1990s life expectancy amongst both women and men, which in South Africa as in most African countries had been increasing, began to fall, and has fallen below 50 years in both men and women.

Although silica exposure and HIV infection have had a major impact upon the TB epidemic in South Africa, the pattern of the epidemic in the Western Cape Province has been an enigma. In this province, as there are no mines, the population has negligible exposure to silica, and it was the last to be affected by the HIV epidemic. Yet over the past 30 years TB notification rates have climbed, particularly in low-income communities, and at a time when their income and nutritional status appeared to be improving. Many potential causes for this 'epidemic within an epidemic' have been considered and explored, and there appears to be no single explanation for the phenomenon. Amongst those that have been considered are nutritional factors (particularly vitamin D deficiency, since Cape Town has wet winters with days of overcast skies which might reduce cutaneous conversion of vitamin D to its more active forms) and alcohol abuse (in some

communities alcohol abuse is rife, and often associated with poor nutrition). Genetic susceptibility has also been explored, as has TB strain differences, but without convincing results. More promising has been the study of local factors that favour transmission such as housing and social behaviour. Overcrowding has been a feature of life in the affected areas, the effects of which are aggravated by inclement weather which keeps people indoors. A popular pastime is spending evenings in informal taverns where alcohol is consumed, which results in close contact between residents. Finally, there is the potential impact of smoking, both of tobacco and cannabis. In the Lung Health Survey 2002, performed in two suburbs of Cape Town where the notification rate for bacteriologically confirmed TB was 612 per 100 000 persons (Western Cape Tuberculosis Programme 2002), the prevalence of current smoking amongst males was almost 60% and that among women more than 40%, and cannabis use was recorded in 12% of persons (mainly in males) (Jithoo et al 2003). These levels are well above the national averages for current smoking of 42% for males, and 11% for females aged 15 years and older (Steyn et al 2002).

The association between smoking and TB has received increased attention in recent years, with studies confirming a variety of interactions: risk of infection, transition of infection to disease, severity of pulmonary disease, rate of sputum conversion on treatment, risk of relapse, pulmonary impairment after treatment and mortality. For example, Gajalakshmi et al (2003) performed a case-control study of 78 000 men who had died of disease in rural and urban India. Smokers were at a more than fourfold greater risk of death from TB than non-smokers. In those dying from TB the population attributable fraction, i.e. the proportion of the disease occurrence or mortality in the population attributable to the risk factor (smoking), on the assumption that the association is causal, was more than 50%, higher than that contributed by smoking to the rates of lung and upper respiratory tract cancer, and other respiratory diseases. In the Lung Health 2002 survey, 76% of subjects over the age of 15 years had a positive tuberculin skin test (≥10 mm of induration), and the risk of a positive test was significantly higher in smokers than for never smokers (unadjusted OR = 1.99, 95% CI: 1.62 to 2.45) (den Boon et al 2005). A positive dose–response relationship with pack years was also observed, with those smoking more than 15 pack years having the highest risk (adjusted OR = 1.90, 95% CI: 1.28 to 2.81). Although similar findings have been found in restricted communities like a prison in Pakistan (Hussain 2003), nursing home residents in the UK (Nisar et al 1993), Vietnamese immigrants in Australia (Plant 2002) and migrant farm workers in the USA (McCurdy 1997), this is the first study demonstrating this effect in a cross-sectional survey of an entire community. Moreover, the risk was evident even at very low levels of smoking (1 to 5 pack years), raising the possibility that even passive smoking might be harmful. One previous study has examined the effect of passive smoking on TB infection.

Singh et al (2005) reported a significantly greater risk of infection in children aged 5 years or less who were exposed to an adult with TB if there was concurrent exposure to cigarette smoke.

These interactions between smoking and TB highlight the need for stricter tobacco control, particularly in Africa where TB is out of control, and where communities are being targeted by tobacco companies as promising emerging markets for the sale of tobacco products.

Chronic bronchitis and COPD are further examples of diseases which in Africa and developing nations differ from their counterparts in developed countries. In the latter, the principal cause of with both these diseases—the first characterized by chronic cough and persistent sputum production, without evidence of airflow limitation, and the latter being associated with both respiratory symptoms and lung function abnormality, is considered to be cigarette smoke. However, studies in developing countries confirm major contributions from other factors such as occupational exposures in poorly regulated mines and industries (Hnizdo 1990, 1992), environmental including indoor household pollution (Van Hoorn et al 1996, Grobbelaar & Bateman 1991), TB (Churchyard et al 2001) and other infections, and cannabis use (Chan-Yeung et al 2004). For example in the Demographic and Health Survey of 1998, the first national survey of chronic bronchitis in South Africa, the prevalence was lower than that of countries in Europe (Ehrlich et al 2004). However, in the Lung Health 2002 Survey in Cape Town much higher rates were observed. In the former study the population attributable fractions were 10% for past history of TB, 14% for occupational exposures in men and 14% for smoky domestic fuel exposures in women. Although findings in the Cape Town study were similar, the role of cannabis smoking was found to be important. Perhaps because of its illegal status, there are few data on the impact of cannabis on respiratory disease in South Africa, but it is widely used in some communities and requires further study.

Lack of standardisation of the definition and methods for diagnosing asthma and COPD has made it difficult to compare different studies and sources of information (Ehrlich & Jithoo 2006). This deficiency has been corrected by the formulation of international consensus guidelines by the Global Initiative for Asthma (GINA) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (Pauwels et al 2001) for asthma and COPD respectively, and the development of standardised methods for use in prevalence surveys for these diseases. The Burden of Obstructive Lung Disease (BOLD) methodology developed by the GOLD initiative (Buist et al 2005) involves use of a standardized validated questionnaire, standardized lung function testing and centralized data collection and statistical analysis, and is being promoted for widespread use in order to improve detection of the disease and provide a basis for focused intervention programmes. Its first use in Africa was in Cape Town, in the population in whom the Lung Health

Survey 2002 had been performed. Preliminary results have provided physiological confirmation that the high rates of symptoms recorded in the Lung Health Survey 2002 reflect a high prevalence of COPD in both men and women (Jithoo et al 2006).

Conclusions

The prevalence of respiratory diseases in South Africa reflects its political and social past, and exposures of large numbers of people to harmful environments both in the workplace and in the community, with the added catastrophe of the spread of the human immunodeficiency virus and the rampant resurgence of TB. Examination of associations between risk factors and different respiratory diseases confirms the major impact of environmental factors in respiratory diseases, and the complex relationships between them. Some of these interactions are depicted in Fig. 1. The notion of innate immunity may not apply in this setting where complex exposures occur early in life and even antenatally, and where no population may be viewed as 'naïve'. These considerations are as important for researchers involved in the study of mechanisms of disease, as they are for those responsible for devising policies and designing services for the promotion of health and the prevention and treatment of lung disease.

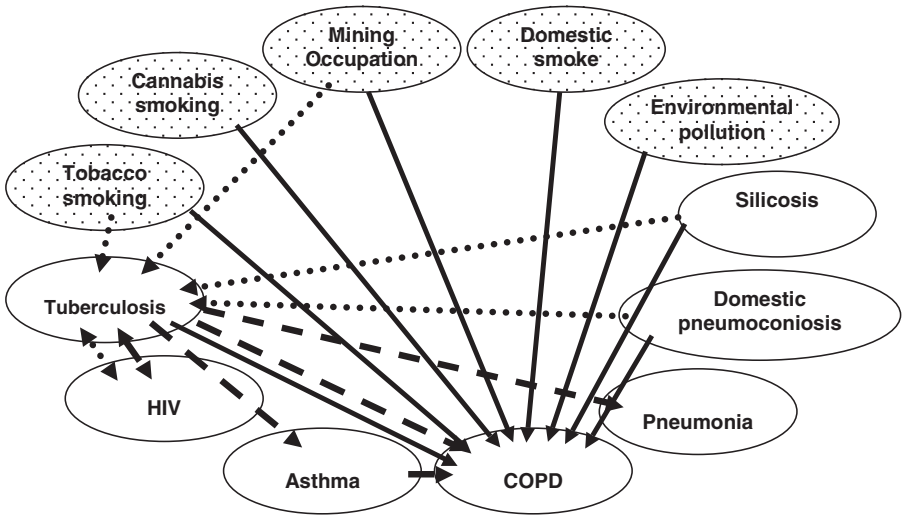

FIG. 1. Recognized interactions between environmental risk factors and common respiratory diseases.

Acknowledgments

Financial support has been obtained from the South African Medical Research Council, Research for International Tobacco Control, and from the South African Thoracic Society through its GlaxoSmithKline Pulmonology Research Fellowship and AstraZeneca Respiratory Research Fellowship for some of the studies in this report.

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DISCUSSION

van Helden: I've done many simple calculations. From my perspective, the estimate of annual risk of tuberculosis (TB) infection of 3.5% is shocking but also probably an underestimate. While I accept that this figure was calculated using the standard methodology, I don't understand one thing. One sees 25% skin

conversion at the age 0–5 to more than 75% at age 15. This means that there is a 50% conversion in 10 years. Purely arithmetically, this is 5% per annum. If you consider that many of these will be dual infections, it must be considerably more than 5%. Can you help me with this?

Bateman: The only correction I would make to your calculation is that the positive tuberculin rate is 75% at age 15 and over: we don't know at which point they convert. The time scale is therefore longer than 10 years. I can't cast additional light on your estimates because the ARI work is not mine. I had hoped that you might have more information on that study. You are correct, though: this calculation was utilizing the standard measure for ARI, which is percentage conversion to positivity in the period of one a year in a susceptible group.

Schoub: I was interested in what you said about the interaction of various factors. Clearly there is a striking relationship between climate and acute respiratory infection. There may be various 'arrows' linking these factors. There may be an epidemiological arrow which you alluded to; there may be a viral triggering factor, and, with relevance to this symposium, there may also be innate immunity factors. I think the climatic factor is one we may want to look into with regard to mechanisms.

Bateman: Climate is one of the most difficult things to study. Keatinge and colleagues have examined the effects of thermal extremes upon mortality. They have demonstrated that people in the colder countries of Europe protect themselves better from cold stress, than those in warmer countries (Keatinge et al 2000). In another study the authors found an inverse association between cold-related mortality figures across six regions of Europe (warmer and colder) and the wearing of gloves, scarves and hats (Donaldson et al 2001). Perhaps what our grandmothers said about dressing warmly, is correct, particularly if you have a weak chest, are frail or elderly. This is indirect evidence and may sound unlikely, but the data are impressive.

Feldman: With pneumococcal infections, there are two studies looking at the influence of ambient temperature. There is a close correlation between the appearance of pneumococcal infections and outside air temperature (Dowell et al 2003). It was thought that one of the risk factors would be viral infections occurring mainly in winter. The question is, why do viral infections occur more commonly in winter? But even if you control for this, and also for the fact that in winter people tend to gather together indoors more, there is still a much higher incidence of pneumococcal infections with cooler air temperature. Meteorological data correlate very closely with this incidence. Even if you factor in HIV, the peak of pneumococcal infections occurs in winter. In HIV-positive individuals the peak still occurs in winter. As a risk factor HIV doesn't overwhelm the effect of ambient temperature on lower respiratory tract infections.