10 Immunology of the Lung

Margaret Turner-Warwick

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Margaret Turner-Warwick,
D.M., Ph.D., F.R.C.P.
Professor of Medicine (Thoracic Medicine),
Cardiothoracic Institute, Brompton Hospital, London

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General Preface to Series

The impact of immunological thought on medical practice has been increasing at a steady rate now for nearly twenty years. There appear to be very few fields to which the immunologist cannot contribute. Initially the immunological approach was limited to assistance in diagnosis and in sera and vaccine production. New approaches in the field of therapy are not only in the use of vaccines, sera and immunosuppressive agents, but also in the more rational use of conventional therapeutic agents. Immunological knowledge is especially necessary in the field of tumour therapy, particularly in the balanced use of surgery and radiotherapy. Moreover, immunological knowledge in other fields has allowed us to understand more readily the mechanisms whereby a single aetiological agent can produce a wide range of different clinical manifestations. Different disease patterns occur depending on the nature of the immunological reaction causing tissue damage. A completely different symptom complex from reactions involving soluble immune complexes reacting with the complement cascade will be found in those involving the reaction of specifically sensitized lymphocytes with antigen as part of a cell-mediated or delayed hypersensitivity reaction.

As a massive amount of new scientific material accumulates in this field, the clinician is frequently left behind and perplexed. Each year a new scientific journal is published specializing in fields as diverse as immunogenetics, immunochemistry or immuno-logical techniques. We have journals emanating from continents as well as countries. The wealth of material is often bewildering. Simple textbooks of immunology are often too simple, whereas review articles may be too complicated for the specialist physician or surgeon who wants a treatise on those aspects of the subject particularly relevant to his own field of interest. It is hoped that this series will fulfil some of these needs by giving comparatively short reviews that will lay emphasis on immunological subjects which should appeal to both clinicians and those working in clinical laboratories. The aim is to provide the busy clinician in a particular field of medicine with a short volume relevant to his practice written by a specialist. It should introduce the reader to the immunological approach to his subject and indicate how modern immunological thought might influence his day-to-day work in the wards or clinical laboratory.

JOHN TURK

The Royal College of Surgeons of England
London

Preface

Many physicians find immunology confusing. This is often due to terminology. The number of new and technical terms is enormous, sufficient in fact to fill a dictionary of its own (Herbert and Wilkinson, 1971, *A Dictionary of Immunology*; Blackwell, Oxford). The problem is compounded because the same word is used by different workers to mean different things. Moreover, the concepts themselves are often difficult to follow for those not familiar with the laboratory techniques upon which they depend.

It is also a fact that many technical terms or jargon are used to express very simple concepts and there is obvious room here for better communication between immunologist and physician. Perhaps one of the most misleading aspects of immunology is the frequent implication that when a new laboratory technique demonstrates a new function within some immunological system, a new substance or factor has thereby been identified. It is well known in other disciplines that a single substance has many different properties, and it would be wise to simplify immunology using a similar approach, until there is evidence that a certain function can indeed be identified with a definably distinct chemical component.

Why should anyone try to write a book on the immunology of respiratory diseases? More particularly, why should they try to do it now, at a time when even the basic concepts of the individual components of the immunological responses are changing and expanding so rapidly? The purpose of this book is to help physicians who deal with lung diseases and who may not have much background knowledge of immunology to understand the clinical applications of this relatively new subject. It is not intended to be an advanced treatise for specialist immunologists.

Immunology is important to medicine because it focuses on, and attempts to analyse, the interrelationships between agents potentially damaging to the body and the host's response to them. Further, by analysis of the *mechanisms* involved in this interaction, it enables us to study and sometimes to understand the changes occurring in body tissues. This is fundamental to the understanding of disease, its logical prevention and to its management.

Immunology is of particular importance in respiratory medicine because of the special vulnerability of the lung both to the external environment with all its contaminants and to the internal environment, through the pulmonary and bronchial circulations.

The modern history of immunology and lung disease covers the last 100 years and its beginnings can be identified in the studies of microbiologists on the one hand and with those of allergists upon the other. The struggle to

reinterpret observations made by allergists more than half a century ago, into terms of modern immunological theory has often been both stormy and contentious, but in spite of, and perhaps because of, this dialogue, a series of hypotheses have emerged which attempt to explain the mechanisms of pulmonary damage ranging over almost the whole spectrum of lung disease (Fig. Pr. 1). Much detailed immunological work has already been done on asthma, infections, and the acute and chronic forms of alveolitis. Fields of study are now rapidly expanding to cover lung tumours and the pneumoconioses.

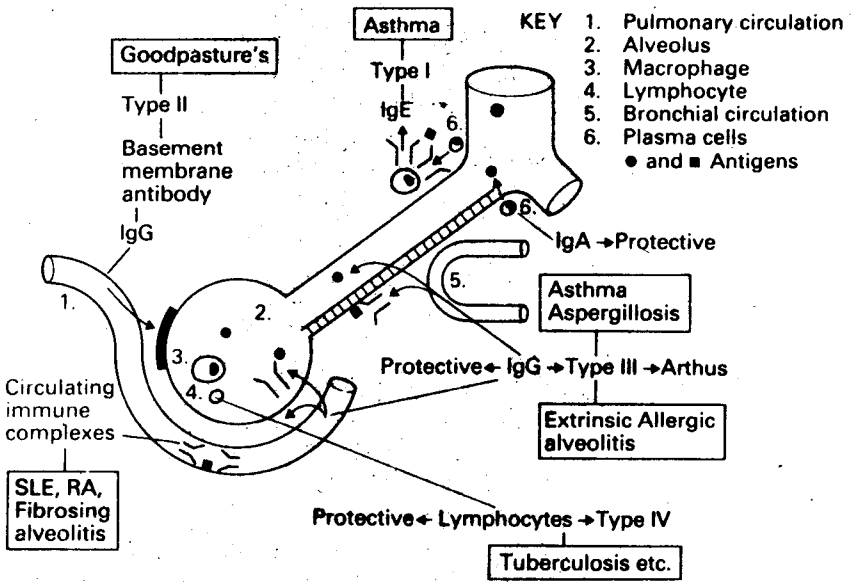

Fig. Pr. 1 A demonstration of the range of protective and tissue damaging immunological mechanisms operative in the lung.

The object of writing this book at the present time is to collect together, in a condensed form, the currently available information on respiratory immunology. It is hoped that this may form a background of basic understanding upon which the vast array of new data may in the future be assembled in some sort of comprehensible order. As the new order emerges, the base may well have to change, but this is true of any evolving subject. In one sense this book will certainly be obsolete even before it is completed, but, in being so, it may yet have achieved its aim.

The primary object here is to review the immunological information relevant to lung diseases in man, recognizing that the mechanisms of injury are usually complex and that much is still unknown. Basic immunological concepts will be mentioned briefly, and somewhat didactically, to form a relevant background to the understanding of clinical problems. The immunology of tuberculosis has been excluded from this edition.

The references have been selected in an attempt to provide an easy source for those wishing to refer to earlier developments in the subject as well as to

cover some of the more recent contributions. Complete references are clearly impossible within a relatively short text and the omission of many important papers has been inevitable, but much regretted. Books written in 'spare' time almost always include errors and for these too, I apologise.

A large amount of work has properly been done in animals, where the components of immunological reactions can be manipulated under controlled conditions in a way never possible in man. While the advantages of animal models are obvious, their relevance to human disease has to be challenged constantly, because species differences are so great and the exact conditions of exposure are often very distant from those inducing disease in humans. Clinical and experimental immunology are complementary and cannot be used as substitutes for each other. Hence there is ample justification for clinicians to limit themselves to the natural model of disease occurring within the species of their primary responsibility and this precept is expressed in the clinical emphasis throughout this book.

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Above all I must acknowledge my indebtedness to the very many patients whose problems form the essence of this text and for whom I have had the privilege to care.

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While all errors and omissions are entirely my own responsibility, I am grateful to Dr Patricia Haslam, Dr Peter Cole, Professor Jack Pepys, Dr Wallace Fox, Dr Janet Darbyshire and Dr David Girling for reading the text and for their advice. I thank Miss Lindsey Pegas for help with illustrations, Miss Milena Potucek and Mr Ken Moreman for the photographs. I am especially grateful to my secretary, Miss Heather Rolls, for so much indefatigable support besides the typing, and to my family who have been exploited yet again.

M.T.W.

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Basic Concepts of Pulmonary Immunology

Introduction

Historical landmarks

Studies undertaken during the nineteenth century mainly by microbiologists, sought to unravel the fundamental mechanisms responsible for the development of inflammation in tissues. These studies gave an early indication of important factors present in the serum, the role of the cellular components of inflammation and the vascular responses to it. They demonstrated the fundamental fact that successful elimination of noxious agents from the internal environment of the body was often achieved only at the cost of a variable amount of damage to host tissues.

The lungs received focused attention more than half a century ago from quite another source. In 1916 Cooke and Vander Veer published their now classic observations on 'human protein sensitization' to common environmental agents and its association with asthma, thus initiating interest in the rapidly expanding subspecialty of clinical allergy in lung disease.

The science of immunology received renewed impetus some 40 years ago with the development of methods to separate serum proteins electrophoretically (Tiselius and Kabat, 1938). The subsequent development of new and often relatively simple techniques within the capacity of routine clinical laboratories, allowed improved identification of the components of the immune system. Thus techniques were developed to demonstrate the interaction of antigen with specific serum protein components by immunoelectrophoresis (Graber and Williams, 1955), and a simple precipitation test was developed to identify specific antibody in serum by double diffusion in agar plates (Ouchterlony, 1948).

The recent explosion of immunological knowledge has in part depended upon, and in part stimulated, the development of a wide range of ingenious techniques to analyse, both quantitatively and qualitatively, components of the immune response.

Advances have, for instance, been made using a range of procedures to 'tag' antibody or antigen so that their qualitative or, in some cases, quantitative involvement in immune responses can be followed *in vitro* as

well as *in vivo*. Tagging procedures have been devised using fluorescent dyes (Nairn, 1969), peroxidase, ferritin in association with electron microscopy, radiolabelled materials and a variety of particles from both biological (e.g. red cells) and synthetic sources (latex, Sephadex, bentonite, etc.). Quantitative techniques to measure specific antibody, not amenable to standard agglutination or complement fixing methods, have been developed (e.g. radioallergosorbent tests — RAST). The rate of development of immunology in clinical medicine depends, at least in part, on the relevant tests being simple enough to be within the capacity of most routine clinical laboratories.

Great advances have been made possible following the elucidation of the molecular structure and configuration of antibody gamma globulin (Porter, 1963). Purification of the antibody molecule has allowed its function and that of its biochemical components to be studied in great depth; its interaction with specific antigens has been analysed in detail as well as its interaction with complement. Analysis of the multiple components of the latter has identified many important controlling factors involved in the inflammatory response.

Impetus for the formulation of fundamental ideas on the methods by which the body distinguishes foreign materials, especially proteins from 'self' components (Burnet, 1959), was stimulated partly from work unravelling the determinants of tissue graft rejection (Medawar, 1958) and partly following the recognition of disease in man, apparently resulting from immunological reactions involving his own tissues. Focus on graft rejection, and the development at about the same time of techniques to study the characteristics of lymphocytes, allowed great progress to be made on the function and role of these cells in the immune response (Gowans, 1970). The heterogeneity (i.e. functional and structural differences) of the population of circulating lymphocytes was soon recognized and the basic concept of the different properties of thymus-dependent T cells and Bursar-equivalent dependent B cells (Miller, 1972) was soon overtaken by the further identification of many functionally different lymphocyte subpopulations within these two major groups.

While the major advances in immunology have been concerned with systemic responses, it is now recognized that these contrast in many ways with the special host defences apparently designed for the protection of mucosal surfaces. Although this fact has been recognized for many years, a major stimulus to interest in local immunity of the respiratory tract stemmed from the characterization of secretory IgA (S IgA) antibody and its identification as the main local source of immunoglobulin (Chodirker and Tomasi, 1963). This subject is, however, still very young and, as will be shown in later chapters, much more work has to be done in clinical fields.

Still more recently, another component of the inflammatory response has begun to receive focused attention. The importance of macrophage *activation* in processing antigen for appropriate presentation to immunologically responsive cells (of both T and B cell type) and in amplifying its capacity to ingest and kill noxious agents and eliminate immune complexes has further extended the horizons of immunology.

Throughout the period during which the host-derived components of the immune response have been studied (be they antibody, complement, lymphocytes or macrophages), much systematic work has also continued on the physical and chemical nature of antigens and their influence on different types of host response.

The lung as a target organ

The lung is developed from the foregut pouch and, in this, has features in common with the gastrointestinal tract. It is uniquely vulnerable to invasion by noxious agents for two reasons. First, even at rest, it is exposed to some 9000 litres of air every 24 hours: an environment containing all manner of contaminants, including inorganic particles, smoke, fumes and organic material, such as animal and vegetable products contained in dusts, pollens and moulds. Second, the lung is the only organ to receive the entire cardiac output and there is therefore maximum opportunity for circulating agents, be they antigen or immune complexes, to reach the pulmonary capillary bed.

From the immunological standpoint, the lung may be considered in two major compartments. (1) The mucosal lined airways containing in their walls mucus-secreting cells, smooth muscle and, in part, cartilage: these structures have specially adapted systems for clearance of particles and possess a special local system for antibody production. (2) The gas-exchanging parts of the lung, composed of alveoli having an extensive air/blood interface: in this region, the cellular and humoral responses in normal individuals are derived almost entirely from the circulation.

The lung, like most other organs, has only a limited range of responses to damaging agents. This is so because the final common path of inflammation and repair involves a fairly limited range of cells. Thus a very wide range of initiating agents cause damage to host cells in a much more limited number of ways. The uniformity of the final common path response is even more striking when the late healing stage of widespread lung damage is considered. Thus, a very wide variety of quite different acute inflammatory reactions, if persistent, will result in a uniform pattern of fibrous scarring. At this late stage there may be no remaining immunological clues as to the initiating events (see chapter 9).

The purpose of this chapter is to introduce very briefly some of the concepts basic to immunology, partly to introduce in context some essential terms and in part so that discussion in later chapters is more readily understood without digression into basic facts or constant reference to other works. The diagrams and tables in this chapter have been deliberately oversimplified, but it is hoped that by doing so the major components of reactions will stand out more clearly and will aid understanding. I apologize if this offends the purist.

Obviously such a section can only cover the barest outline of the subject and the interested reader is referred to many useful textbooks now available (Gell *et al.*, 1975; Good and Fisher, 1973; Hobart and McConnell, 1975; Roitt, 1974; Turk, 1969; Humphrey and White, 1970).

Terminology

Like many other rapidly growing branches of medicine, immunology has its own heritage of terminological problems.

Not only is the language of immunology rich in difficult words for simple things, but identical terms are used by different workers in different ways. Thus, for instance, 'allergy' is frequently used to imply an immunological tissue damaging process, but is often defined as 'an altered state of immunological reactivity' which includes tissue damage on the one hand and protective immunity on the other.

Herbert and Wilkinson (1971) have published a most useful dictionary of immunological terms in which is included the uses of many words where agreement is lacking, as well as an indication of preferred definitions. Hobart and McConnell (1975) also provide a useful glossary.

Figure 1.1 sets out the use to be made in this text of some very common terms. If this scheme is adopted, then the use of words such as 'immunity', 'allergy', 'allergen' and 'antigen' becomes clear. It will be seen that some of the distinctions are methodological, while others can only be discriminated in a relative and not in an absolute way.

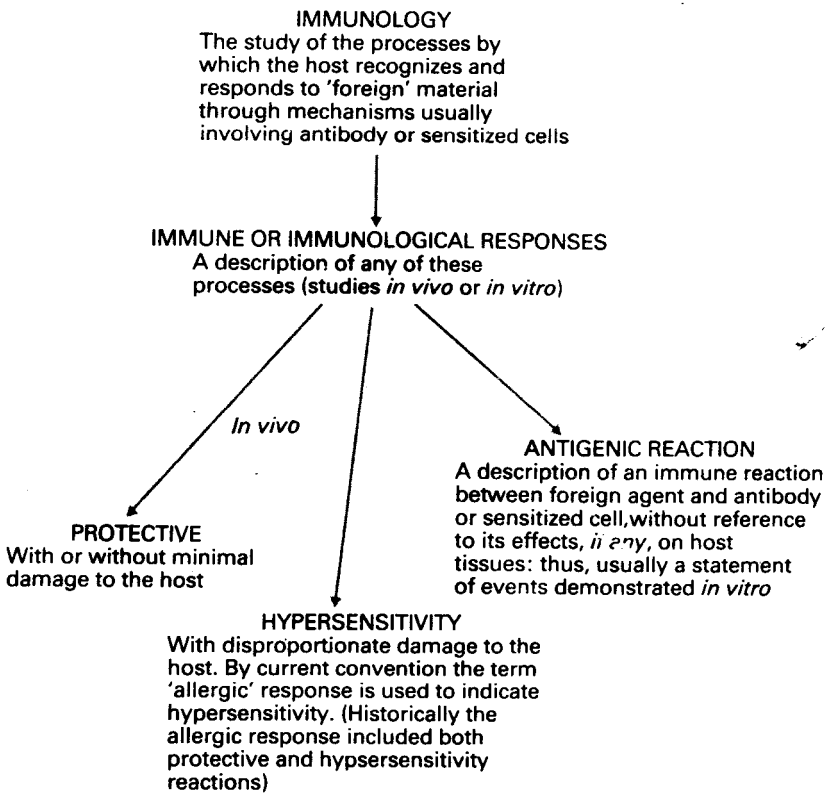

Fig. 1.1 Definitions: immunological responses.

For practical purposes, therefore, we may define *antigen* as an agent which can be demonstrated to react with various components of the immune system, especially with antibody or immunologically competent cells. This demonstration is normally conducted *in vitro*. A similar reaction may or may not be demonstrable *in vivo*. An *allergen* may be defined as an agent which can be demonstrated to react *in vivo* with components of the immune system — leading either to protection of the host or to hypersensitivity tissue-damaging responses. In practice, many authors limit the words 'allergy' and 'allergen' to hypersensitivity reactions.

It has to be conceded that some licence in terminology must be accepted in part out of respect for common usage and in part as a sop to style. These concessions will, however, be limited as far as possible.

Protection and hypersensitivity

These two major aspects of the allergic response will be the main brief of this monograph. *Protective 'immunity'* in relation to the respiratory tract, (common usage!) concerns those processes determining resistance to organisms invading the lungs. The discussion on *hypersensitivity* will include an analysis of those processes leading to a disproportionate damage of host tissue. The distinction between the mechanisms inducing inflammation in order to rid the body of a noxious agent and thus restore health, and those causing undue damage to host and tissue disease, is often more one of quantity than of quality, the components of the immune response being similar in both instances. The tissue-damaging cell-mediated hypersensitivity response seen in the lungs of a patient successfully overcoming an infection by *Mycobacterium tuberculosis* is a classic example of this fine quantitative distinction.

Immunological stimuli

The nature of an observed immunological response in the lung depends not only upon the extent to which the major components of the immune system are involved (i.e. antibody, lymphocyte, macrophage and complement) but also upon a very large number of qualitative and quantitative variables concerning the antigen on the one hand and host responsiveness on the other (Table 1.1).

Antigen penetration into the lung

Penetration of antigen into the airways or alveoli is a prerequisite for immunological interaction. Some of the non-specific defence mechanisms will be mentioned further in relation to host protection in Chapter 5. The effectiveness of these will be greatly influenced by particle dimensions. Particles greater than about 10 μm diameter are deposited in the upper respiratory tract, trachea or large airways by gravitational sedimentation or impaction. Particles of less than 0·1 μm reach the alveoli because of their

high diffusion coefficient, and particles of about 1 μm tend to be deposited in gas-exchanging parts of the lung. Particles of about 0·5 μm have the least probability of being deposited in the airways; they remain airborne and are expelled from the lung on exhalation (Muir, 1972). The total dose of material absorbed will depend upon the minute ventilation of the subject and will thus increase on exercise. Mouth breathing allows greater penetration into the lung than breathing through the nose, so that heavy manual work as well as the environment may influence the risk of disease caused by inhaled agents.

Table 1.1 Some of the variables to be considered in order to understand the effects of potentially damaging agents on the lung

Antigen	
Types	Bacterial, plant, viral, tissue, etc.
	Toxicity to tissues, e.g. toxins.
	Allergizing potential, e.g. protein or polysaccharide structure, complete antigen or hapten associated with carrier protein.
Physical and chemical structure of antigens.	
	Particle size, density, shape, solubility, susceptibility to enzyme breakdown.
Conditions of exposure	route, dose, single, multiple, intermittent or continuous exposure.
Host responsiveness	
Genetic	
Acquired factors modifying host response, e.g. age, nutrition, previous exposure.	

The mean particle size of many pollens is greater than 20 μm and these will, under normal conditions, be trapped in the nose. Although many pollens are remarkably uniform in size, grains smaller than the mean may nevertheless penetrate further down the respiratory tract and larger particles may reach the main bronchi on hyperventilation and mouth breathing.

Many fungal spores are much smaller than pollen grains (around 1—5 μm in diameter) and may reach and be retained in the smaller airways and alveoli, from whence clearance is slow.

The house dust mite is about 300 μm in size but its products may be much smaller.

Antigens

Foreign material acting as complete antigens and able to stimulate antibody formation as well as participate in immune responses is mainly protein or