Recent Advances in RESPIRATORY MEDICINE

EDITED BY

D. C. FLENLEY

NUMBER TWO

Recent Advances in **RESPIRATORY MEDICINE**

EDITED BY

D. C. FLENLEY

NUMBER TWO

CHURCHILL LIVINGSTONE
EDINBURGH LONDON MELBOURNE AND NEW YORK 1980

CHURCHILL LIVINGSTONE
Medical Division of Longman Group Limited

Distributed in the United States of America by
Churchill Livingstone Inc., 19 West 44th Street, New York,
N.Y. 10036, and by associated companies,
branches and representatives throughout
the world.

First published 1980

ISBN 0 443 02012 4
ISSN 0308 6623

British Library Cataloguing in Publication Data
Recent advances in respiratory medicine.
2.
1. Respiratory organs – Diseases
I. Flenley, D C
616.2 RC731 80–41003

Printed in Great Britain at The Pitman Press, Bath

Preface

The rapid decline in deaths from tuberculosis in the West following the efficient deployment of effective chemotherapy led many to suspect that the specialty of chest diseases would atrophy. However, it now seems probable that the increasing affluence which led to the slow but steady fall in tuberculosis mortality before chemotherapy has also created our present-day abundance of chronic bronchitis and lung cancer, without much reduction in pneumonia deaths, at least in the elderly, and the continued emergence of new environmental hazards. Non-neoplastic diseases of the respiratory system are now second only to mental disorders in their burden of sickness on the British economy, and when lung cancer is added it seems clear that the physician with a special interest in respiratory medicine is not going to lack for patients in the foreseeable future.

The obvious necessity for solutions to these apparently intractable problems remains the mother of invention, so that there is a plethora of research output to be assimilated. The choice of topics for this account of recent advances in respiratory medicine is necessarily personal, but I hope that they do reflect growing points of importance for the the practising clinician—both the specialist in respiratory medicine, and also the general physician who deals with most patients with respiratory disorders. New understanding of pathogenesis, as in immunology, the granulomatous disorders, occupational medicine, and in chronic bronchitis and emphysema, has in the past led to more rational diagnosis, therapy and prevention, and it seems very probable that this will continue. New diagnostic techniques, as in fibreoptic bronchoscopy and CAT scanning, appear to provide a precision of both anatomical location and the pathological nature of disease, which may yield similar advances to those gained by physiological studies of respiratory function over the last two decades. Advances in treatment continue to attract much attention, as in lung cancer, pneumonia (where Legionnaires' disease has shown that the germ theory of disease is still very much alive), as well as in bronchial asthma, chronic bronchitis and emphysema, and in the possibility of even shorter courses of anti-tuberculosis chemotherapy. New ideas to allow the patient with chronic impairment of respiratory function to make the best use of his diminished exercise tolerance are discussed in the chapter on rehabilitation. Finally, as all respiratory physicians meet the ravages caused by cigarette smoking, every day, a discussion of the attempts to prevent this major epidemic of self-inflicted disease seems appropriate. I hope that the reader will find this mixture as informative and exciting as has the editor!

I am grateful to my wife for compiling the index.

Edinburgh, 1980 D.C.F.

Contributors

JONATHAN J.K. BEST MB ChB MSc MRCP FRCR
Professor of Medical Radiology, University of Edinburgh, Royal Infirmary, Edinburgh

I. R. CAMERON MA DM FRCP
Professor of Medicine, St Thomas' Hospital Medical School, London

PETER COLE BSc MB MRCP
Senior Lecturer in Medicine (Thoracic) at Cardiothoracic Institute, and Honorary Consultant Physician to Brompton Hospital, London

J.V. COLLINS MD MRCP
Consultant Physician, Brompton Hospital, London

H. D. DANIEL Prof Dr rer nat
Head of Department of Medicinal Chemistry, CH Boehringer Sohn, Ingelheim, and Professor, Technical University of Munich, Germany

D. C. FLENLEY BSc MB ChB PhD FRCP(Ed) FRCP(Lond)
Professor of Respiratory Medicine, University of Edinburgh, City Hospital, Edinburgh

WALLACE FOX CMG MD FRCP FFCM
Director, MRC Tuberculosis and Chest Diseases Unit, Brompton Hospital, London

NIGEL GRAY AM MB BS FRACP FACMA
Director, Anti-Cancer Council of Victoria, East Melbourne, Australia

GUNNAR GRIMBY MD
Professor of Physical Medicine and Rehabilitation, University of Göteborg, Sweden

DAVID HILL MA MAPsS
Education Director, Anti-Cancer Council of Victoria, East Melbourne, Australia

IAN ISHERWOOD MB ChB MRCP FRCR
Professor of Diagnostic Radiology, University of Manchester, The Medical School, Manchester

HAROLD L ISRAEL MD MPH
Professor of Medicine, Thomas Jefferson University, Philadelphia, U.S.A.

D. M. MITCHELL MA MB MRCP
Medical Registrar, Brompton Hospital, London

D. C. F. MUIR MB PhD FRCP
Director, Occupational Health Programme, McMaster University, Hamilton, Ontario, Canada

JOHN F. MURRAY MD
Professor of Medicine, University of California, San Francisco; Chief, Chest Service, San Francisco General Hospital Medical Center, San Francisco, California, U.S.A.

I. PHILLIPS MA MD MB BChir MRCP MRCPath
Professor of Medical Microbiology, St Thomas' Hospital Medical School, London

K. SCHROMM Dr phil
Department of Medicinal Chemistry, CH Boehringer Sohn, Ingelheim, Germany

HAMISH SIMPSON MD FRCP DCH
Consultant Paediatrician, Royal Hospital for Sick Children, Edinburgh

BENGT-ERIC SKOOGH MD
Associate Professor of Respiratory Medicine, Lung Clinic, University of Göteborg, Sweden

M. F. SUDLOW MB BS MRCP
Consultant Physician, Department of Respiratory Medicine, University of Edinburgh, City Hospital, Edinburgh

PATRICIA M. WARREN BSc PhD
Research Fellow, Department of Medicine, University of Edinburgh, City Hospital, Edinburgh

ANN J. WOOLCOCK BS MD FRACP
Associate Professor of Medicine, Department of Medicine, University of Sydney, New South Wales, Australia

Contents

1. Immunological mechanisms in lung disease

Peter Cole

INTRODUCTION

Man's evolution as an air breathing mammal required the development of a system of local defences in the lung to guard against infective and parasitic agents. Although the living nature of the invader posed a need for its initial killing, the essential feature of this defence system of the respiratory tract was an efficient clearance mechanism which could operate in the face of gravity, as man had assumed the upright posture. Man thus permitted himself to breathe air in safety, but at the price of a complicated network of lung defences which was therefore liable to malfunction with usually embarrassing, but occasionally disastrous, effects. Major strides have occurred in respiratory immunological medicine in the past decade through realization that a protective pulmonary response to infective agents exists, and that its function against non-infective, particularly inorganic, agents may actually harm the host. In this way lung defence abnormalities have taken their place alongside defects in gas exchange and defects in the metabolic/biochemical functions of the lung. It is only against this background that the significance of individual advances can be appreciated in what, until recently, have seemed to be highly specialized areas of immunolgy. We have entered an era where threads are rapidly being drawn together to form a pattern which promises to show the interrelations of pathogenetic mechanisms of a number of seemingly unrelated disorders of the lung. More important, perhaps, this broad pattern promises to point to areas where newer concepts of therapeutic intervention could influence previously untreatable diseases.

Although the general classification of this chapter is clinical, discussion will focus on the mechanisms underlying syndromes and diseases, so that the interplay of mechanisms causing such clinical entities will become apparent. Particular attention will be paid to allergy and infection because of the common nature of these conditions in clinical practice.

Immunology shares with many other scientific disciplines in being considerably affected and rapidly advanced by development of new techniques. Perhaps the most significant of these developments in the last decade has been radioimmunoassay and the use of fibreoptic bronchoscopy to explore the bronchial tree. The former has been applied particularly to measure the small quantities of immunoglobin (IgE) in serum, so 'making allergy respectable' as it has allowed more objective measurements to be made in this area than was formerly possible. The advent of fibreoptic bronchoscopy has allowed safe segmental broncho-alveolar lavage under direct vision to obtain living free lung cells from man, and has provided a mirror of pulmonary events which can be manipulated 'in vitro' without harm to the individual from whom such cells were obtained. The technique of whole lung lavage previously used in

animals has therefore become applicable to man on a regional basis under safe direct vision.

Not all advances stem from technological development, however, as for example in the use of drugs to study the host's response. Thus the painstaking work to demonstrate the value of disodium cromoglycate (DSCG) has changed the face of treatment of allergic asthma and rhinitis. Simple keen observation still opens doors in this age of complex technology. The clinical observation that asthma and other syndromes could be associated with certain occupations has accounted for numerous patients' symptoms on a rational immunological basis, where formerly they would have contributed to the large pool of idiopathic disorders.

LIMITATIONS OF THE CLASSICAL APPROACH

The classical types of immunological reaction (immediate hypersensitivity type I, cytotoxic type II, immune complex-mediated type III and delayed hypersensitivity type IV) have for years dominated the minds of immunologists and have allowed a maze of different reactions to be neatly classified. This has certainly aided teaching, and perhaps also in vitro immunological experimentation. However, this rigid classification can obscure the breadth of inflammation from the immunologist by focusing his attention on narrower areas. It is now apparent that many events in the lungs can be traced to evolution of local defence mechanisms, so that each narrowly classified type of immunological reaction can be seen in a broader context of its place in the production or reduction of inflammation — which is the final common pathway of most such reactions. The study of mediators of inflammation released by, and affecting, immunological cells has sprung from this broad approach, and provides a potential biochemical 'loop hole' to exploit in treatment. Such a broad view also shows that in any given pathological situation several classical immunological reactions may interact in a very complicated manner. It avoids the dogmatic assertion that a particular pathological appearance is purely, simply and only caused by a type I, II, III or IV reaction.

ALLERGY

IgE antibody

The painstaking isolation and characterization of the special class of reaginic antibody, IgE, by the Ishizakas was the most significant advance in allergy research since von Pirquet first coined the term 'allergy' in 1906, and Prausnitz & Küstner demonstrated that allergic diseases were due to reaginic antibodies in 1921. Their work was aided by Johansson & Bennick's discovery of an IgE myeloma, which also provided sufficient material to allow specific antisera to IgE to be raised, thereby paving the way for development of an in vitro radioimmunoassay of serum IgE as a diagnostic aid. These advances, together with a series of controlled clinical evaluations of various treatments and appropriate in vitro models of allergic response, led to objective measurements. These have resulted in rapid progress in a diversity of clinical problems, and also understanding of pragmatic approaches to therapy which obscured the nature of immunopathological events causing immediate hypersensitivity.

The atopic state

Coca & Cooke first proposed the word 'atopy', from the Greek meaning strange, to describe the state of a group of patients with asthma, hay fever or allergic eczema, in many of whom similar disorders were found in the family. As such patients have the propensity to produce IgE (detected by positive prick skin tests and raised serum IgE levels) more readily than is usual in response to everyday allergens, Pepys proposed that this latter form the basis of the definition of atopy. This has not been universally accepted as many individuals possess this propensity, yet are not clinically affected.

Genetics of atopy

Study of the genetics of asthma and atopy is of clinical importance because of the potential reward that it might indicate predisposed persons who should be cared for prophylactically, as by antigen avoidance.

The epidemiological aspects of inheritance of atopy reviewed by Schwartz in 1952 show a higher prevalence of eczema and hay fever in allergic asthmatics than in a non-allergic population, although he pointed to the differences between the two populations, and in the diagnostic methods used. In 1964, Schade compared monozygotic and dizygotic twins for concordance in atopic diseases, and found 59 per cent concordance in the former as compared to 12 per cent in the latter. Edfors-Lubs found lower concordance in a large study, which suggested that although genetic factors contributed to the predisposition for development of allergies, they did not appear to determine which disorder was expressed in each patient.

More recent experiments have been directed toward answering the question as to whether immune response (Ir) genes (that is genes coding for immune responsiveness) in man play a role in the generation of allergic diseases, and whether they form a discernible linkage with the histocompatibility HL-A locus so that conventional tissue typing techniques could define markers for either the atopic state or its component conditions. In a study of ragweed hay fever, which is accompanied by an IgE response to antigen E (a ragweed antigen), Levine et al found a highly significant correlation between clinical symptoms and intense IgE response to antigen E, and also with HL-A haplotype in successive generations of seven families. This implied a close genetic linkage between the HL-A system and a genetic locus controlling immune responsiveness to a particular antigen of ragweed. Subsequent experiments suggested that this gene also controlled IgG response to the antigen, and showed antigen specificity. It must be emphasized that in these studies the haplotype linking cases was different between families, although the same within each family. Also, although necessary for clinical expression of the hay fever, the presence of the Mendelian dominantly inherited Ir gene was not sufficient in itself for such expression — other factors being necessary but unclear. Other workers have also indicated Ir genes in man specific for other antigens.

The problem of finding more universal haplotype markers for individual atopic diseases which are not restricted to individual families remains, although claim for an HLA A1 B8 marker for childhood asthma has been made, and HLA A3 A9 for atopic dermatitis. Soothill, Stokes, Turner, Norman & Taylor (1976) studied infants prospectively for one year after birth and although they showed HLA A1 B8

haplotype to be associated with development of skin test positivity they could not show it to be associated with development of infantile eczema.

Mediators

Except for a few immunopathological reactions in which the inflammatory response and tissue injury arise from direct cell contact between lymphocytes and target cells, most reactions resulting in tissue damage do so because of the induction of inflammation. Humoral and cellular immune responses trigger release of a complex series of mediators which result in localized accumulation of inflammatory cells and plasma factors causing tissue injury. The two crucial elements of such an inflammatory reaction are vasopermeability changes and arrival of circulating leukocytes, but there are less obvious important elements such as fibroblast activation to produce collagen and endothelial cell proliferation to form new capillaries.

Many mediators are described (Ward, 1979) with in vivo activity in spite of their often rapid destruction by plasma factors. Important ones are the prostaglandin (PG) system, the kinin-forming system, the leukokinin-forming system, the basophil and mast cell factors, and the complement system.

A variety of control mechanisms ensure inflammation does not 'get out of hand', as in the two types of control of the complement system — inhibition of activation of enzymes (e.g. Cl esterase inhibitor), and inactivation of the system's products (e.g. C3b inactivator).

The mechanism of mediator release seems to depend upon control of cell secretory changes by intracellular cyclic adenosine monophosphate (cAMP) in immediate hypersensitivity reactions. ß-adrenergic agonists which stimulate adenylate cyclase inhibit histamine release from basophils. Target cells for the allergic response have surface ß-adrenergic receptors which, if stimulated, block the fall in cAMP induced by antigen. Other receptors have been defined, and dose-response and kinetic changes induced by various agonists have been shown to parallel the inhibition of mediator release. Mast cells are virtually bathed in fluid which may contain these agonist 'hormones', so that such hormone-receptor interactions are crucial in determining the outcome of antigenic challenge. Similar interactions control almost all aspects of the inflammatory response, and in each case increased cAMP levels lead to a diminished response. This is in direct contrast to almost all other cellular secretory responses where an increase in cAMP increases response. The acute allergic response can now be divided into at least two stages; the first antigen dependent and calcium independent involving cAMP and the second dependent on both energy and calcium involving microtubule-associated events with release of mediators.

Pathogenesis

Even if an associated Ir gene is present clinical allergic disease will only result if other less well understood factors operate, including those regulating antibody avidity, mediator release, vascular response to mediators, neurohumoral target organ responsiveness, metabolic processes, etc.

There are several possible pathogenetic pathways which may result in expression of clinical atopic disease — all of which account for the increased production of IgE antibody. The two hypotheses which have received the most attention recently are:

1. excessive stimulation of IgE-forming B cells, and
2. faulty regulation of IgE synthesis by B cells.

The 'overstimulation' concept proposes that excessive amounts of antigen enter the system, as might occur if mucous membrane permeability were increased. Salvaggio suggested this might occur when he found an increase in nasal absorption of protein antigens by atopic individuals; but this could not be confirmed. The concept is important as it has led to considerable collaboration by immunologists interested in both respiratory and gastrointestinal systems, gastroenterologists interested in food absorption, and virologists interested in vaccination by the oral route.

It is well established that potentially immunogenic molecules can cross the mucosal barrier of the gut via the epithelium overlying lymphoid nodules, and also via the columnar epithelium covering the villi. Hemmings & Williams have recently found that up to 5 per cent of a dose of ingested protein can be found in the blood of rats, with up to 46 per cent protein-bound in the tissues and 20 per cent retaining the antigenic characteristics of the original protein. The immunogenicity of such molecules can be reduced, either by hindering absorption via antigen combining with secretory IgA antibody in or at the mucosal surface (Swarbrick, Stokes & Soothill, 1979), or by suppression of the immune response to such antigens in local lymphoid tissue through suppressor T-lymphocytes in Peyer's patches. Antigen may be complexed with IgA at the enterocyte surface and degraded by pancreatic enzymes. Whatever the mechanism of inhibition of antigen transport across gut mucosa, serum IgA deficiency occurs in a significantly higher proportion of persons with atopy than in the normal population. Therefore, in 1974 Soothill proposed that atopic disease was a consequence of IgA deficiency, leading to defective handling of allergens coming into contact with mucosal surfaces.

There are three main criticisms of this hypothesis. First, the reports of serum IgA deficiency in atopy are contradicted by others who find similar serum and secretory IgA concentrations in atopic and non-atopic individuals. Also, serum concentrations of secretory IgA, which might reflect mucous membrane permeability, are not elevated in atopic children, and the distribution of all classes of immunoglobulin in mucosal biopsy specimens is similar in atopic and non-atopic subjects. Moreover the IgA deficiency may only be transitory during the neonatal period or with gastrointestinal disease in early life. The second major criticism of the hypothesis is based on animal experimentation. Jarrett (1977) pointed out that activation of IgE suppressor T-cells is achieved more by intense antigenic stimulation (as would occur in increased mucosal permeability) than by smaller quantities — which tend to activate IgE helper T-cells. In other words increased absorption of antigen from the gut should decrease, rather than increase, IgE response. Third, insects introduce allergen parenterally and not through mucous membranes when they sting, so that allergy to these stings should, by this hypothesis, be equally common in atopics and non-atopics. However, atopic patients do have a higher prevalence of this type of allergy.

A second possibility for the pathogenesis of atopy is faulty regulation of IgE production. There is evidence in man that there is T-cell deficiency and depression of delayed hypersensitivity in atopic subjects and certain immunity deficiencies are associated with high IgE levels. In animals, IgE production appears to be dependent on distinguishable antigen-specific and antigen-non-specific suppressor T-cells, a

deficiency in either causing increased IgE antibody. Evidence for a suppressor T-cell deficiency in atopic persons has been put forward. In addition, IgE T-helper cells have been shown to be more sensitive to T-suppressor signals that IgG T-helper cells in the mouse. Thus a small deficiency in non-specific suppressor T-cell function could preferentially enhance IgE helper T-cell function, with excessive IgE production. Both of these hypotheses probably play a role in the pathogenesis of atopy.

However, IgE overproduction in itself is not the whole explanation for atopy, for although most atopics have raised IgE levels, some who display indisputable clinical atopic disease appear to have normal IgE levels. Again prick skin tests may be positive yet serum IgE normal, so it may be that increased mucosal permeability in some cases has led to clinical atopic disease but relative suppression of the IgE response. The relationship of clinical disease to IgE regulation requires much further work.

Treatment

Therapy of allergic disease has been of two types—immunotherapy and drug therapy. In general, hyposensitisation has been shown to be of clinical value in pollen-induced rhinitis but not convincingly so in asthma, and the situation with regard to house dust mite is far from clear.

Mice which respond to antigen with a large rise in IgE (high responders) can be used as a model for immunotherapy. There is a decline in helper T-cell function after immunization, with a consequent depression of IgE formation and suppression of secondary IgE responses. Suppressor T-cells are also induced by the treatment. This model again underlines the importance of cellular regulation of IgE response, manipulation of which may in future considerably advance specific therapy.

Drug therapy has proved more effective in control of asthma and, besides agents which have pharmacological actions totally independent of immunological events (see Ch. 10), disodium cromoglycate (DSCG) and locally administered corticosteroids have revolutionized treatment of allergic asthma and rhinitis in recent years. The mechanisms of action are not clear, but the major result of DSCG treatment is to inhibit histamine release from mast cells and possibly to inhibit the formation of slow reacting substance of anaphylaxis. Its action may be non-immunological, as it is effective in the prevention of asthma induced by exercise, hyperventilation and certain chemical irritants. Corticosteroids affect target cells in many ways, but may restore the diminished response of the β-receptor in asthmatics to normal. Regular local administration of corticosteroid to the airways and nose is now known to prevent asthma and rhinitis (Second Report of the Brompton Hospital/Medical Research Council Collaborative Trial). The local doses required result in minimal absorption and therefore few systemic side-effects.

Bronchus-associated lymphoid tissue (BALT)

Hypotheses as to the nature and pathogenesis of atopy have been influenced recently by recognition of a peculiar anatomical distribution of T-lymphocytes which control the IgA response (Elson, Heck & Strober, 1979). T-lymphocytes may help or suppress antibody production of the various classes by B-lymphocytes. T-cells from gut-associated lymphoid tissue (GALT, Peyer's patches) suppressed IgG and IgM antibody synthesis, but enhanced IgA synthesis. Therefore oral immunization would

theoretically stimulate IgA response and suppress IgG and IgM response. This has been confirmed in the mouse by Swarbrick et al (1979). This important work, even at first sight in an organ of little interest to the respiratory physician, not only provides a clue to the possible pathogensis of atopy (and to its prophylaxis by antigen avoidance at the critical period of IgA deficiency), but also underlines the urgent need to look at the nature of T-lymphocyte helper/suppressor function in the lung's own local lymphoid tissue (BALT).

Antigen processing in the lung is vitally important, as the lungs are an important portal of entry of antigen, like the gut. As far back as 1958, lung was shown to be the most important tissue source of antibody after intravenous hyperimmunization with particulate antigen. The significance of these results in terms of the lung's immunocompetence in host response to inhaled antigens has not been fully realized until recently.

The term BALT was first coined by Bienenstock, and is similar to GALT in being composed of lymphoid tissue covered by a layer of lymphoepithelium, which possesses microvilli but not cilia. It is more dense at bronchial bifurcations and develops in germ-free animals although proliferating to a far greater extent in conventionally-reared or wild animals. Although up to 25 per cent of its cells may be T-cells, the remainder are either B-cells or cells lacking these markers. Absence of plasma cells in BALT despite presence of B-cells strongly suggests that BALT is different from other peripheral lymphoid tissue, and may serve as a site of differentiation for B- and T-cells. The destination of the cells in BALT could be the bronchial lumen, either directly or after recirculation, as sometimes the overlying epithelium can be seen to be breached. These lymphoid patches may 'monitor' antigens in the bronchial lumen, and in some way aid immunological sensitization to them. However, cell transfer studies suggest that BALT cells can repopulate the lamina propria of both gut and lung with IgA-producing cells (as also can GALT cells), although the stimulus for this in the intact animal is unknown. There is clearly need to study the function of T-lymphocytes in BALT to see whether these, like those of GALT, are IgA-helper, but IgG- and IgM-suppressor in function.

The importance of the discovery of this lymphoid system which is peculiar to the airways, but similar to that of the gut, arises from the facts that both organs are subjected to constant challenge by potential pathogens, both possess a local secretory IgA system, and both are derived from endoderm. Therefore, these lymphoid aggregates lying just below a modified mucosa are in a sentinal position in the bronchial tree, and would be an excellent priming system — to direct cells which are proliferating in response to specific antigen to other mucosal sites, where they may protect not only against invasion by pathogens, but also against antigen entry at a time when it may cause atopy.

'Late' immunological reactions in skin and airways

'Late' reactions to antigen (that is later than immediate hypersensitivity responses, but sooner than delayed cell-mediated hypersensitivity) have been designated as type III Arthus reactions (in classical terminology) which are thought to be mediated by complexes of antigen, antibody and complement. Such reactions were shown, using avian or *Aspergillus* antigens, to result in bronchial reactions which corresponded in time course to the appearance of a 'late' reaction in the skin. Biopsies of these skin

reactions showed IgG and complement around small blood vessels in the dermis. These late skin and bronchial reactions can both be blocked by corticosteroids, which have no effect on immediate hypersensitivity reactions.

Recent work, however, has thrown doubt on whether all such 'late' reactions are mediated by immune complexes. Dolovich, Hargreave, Chalmers, Shier, Gauldie & Bienenstock (1973) provoked identical reactions in the skin by increasing doses of anti-whole IgE or anti-$(Fab)_2$IgE (a part of the IgE molecule) alone, and this has subsequently been confirmed. Therefore they feel that IgE-mediated events can be 'late' as well as immediate. This opens a whole new area of research into the underlying mechanisms. It may be that an immediate reaction is a prerequisite for the development of such 'late' reactions in some way, which would explain their blockade by DSCG. However, in some bronchial reactions to small molecular weight chemicals inducing occupational asthma no immediate reactions may be detected.

Occupational asthmas

One of the major and continuing advances in the field of immunological respiratory medicine has been the recognition that a large number of allergens to which persons are exposed during the course of their occupation or hobbies can provoke immunologically-mediated asthma (see Ch. 4). Nevertheless, one must be aware that non-immunological mechanisms of provoking reversible airways obstruction can closely mimic immunological mechanisms, which is hardly surprising as all share the final common pathway through production of mediators of inflammation.

Such agents may cause asthma by irritation (particularly in atopic persons with a 'lower threshold' to histamine liberation); endotoxin contamination; immediate hypersensitivity (e.g. furs in furriers; contaminant weevils in wheat, affecting millers); 'late' reactions (e.g. alcalase enzyme of *Bacillus subtilis* in detergents); and hapten formation (small molecular weight chemicals, e.g. amino-ethanolamine in aluminium soldering flux). These asthmas are reviewed by Newman-Taylor (1979).

Pulmonary eosinophilias (PE)

These include the extrinsic non-atopic and atopic asthmas (notably allergic bronchopulmonary aspergillosis) and idiopathic asthma, besides those without, or with less, asthma (including helminthic and drug-induced varieties), also the rarer polyarteritis nodosa and variants with vasculitis.

The important recent immunological advance in this area is greater understanding of the induction of the eosinophil response—although its significance is still a mystery. The heterogeneous group of conditions composing the PE possessd few common denominators until four different mediators, all attracting or stimulating eosinophils, were identified as linking the conditions and termed eosinophil chemotactic factors (ECF).

The peptide ECF of anaphylaxis (ECF-A) was found by Kay and colleagues to be released from anaphylactically-triggered mast cells, and in particular from the human lung. Parish demonstrated its release from human basophils, and Wasserman and his co-workers its release from a large cell anaplastic human lung tumour associated with local and peripheral eosinophilia. This factor explains the local eosinophilia in allergic states.

ECF derived from complement (ECF-C) was discovered by Kay in 1970 following

observations by others that several complement components were chemotactic for eosinophils. This factor was found to be C5a, and accounts for the eosinophilia seen in non-allergic conditions where complement is activated by antigen-antibody reactions, immune complexes, polysaccharides, denatured or aggregated proteins, endotoxin, bacterial products, etc.

Cohen & Ward detected an ECF derived from lymphocytes which required activation by antigen-antibody complexes to attract eosinophils. This was subsequently characterized and accounts for eosinophilia when delayed hypersensitivity co-exists with antibody production and antigen.

Lastly, Colley defined a second lymphokine stimulating eosinophilia (eosinophil stimulation promoter, ESP).

It is challenging that nobody has shown the significance of the eosinophil in respiratory pathology, although there are a number of hypotheses including the possibility that the eosinophil, in being evolved to constitute an excellent defence mechanism against parasites, has become involved in other host responses in which allergens trespassing on the respiratory tract broadly mimic parasitic invasion.

Chronic bronchitis

Fletcher, Peto, Tinker & Speizer have recently concluded from a prospective longitudinal study that there are two distinct features of chronic obstructive lung disease—the development of airflow obstruction and hypersecretion of mucus—both, however, associated with smoking. Turnbull, Turnbull, Crofton & Kay (1978) have found the sputum from chronic bronchitis to contain histamine, SRS-A, IgE and eosinophils whose concentrations vary inversely with peak expiratory flow. Furthermore, mediators of immediate hypersensitivity have been found in sputum from young cigarette smokers with just cough and early morning sputum. The presence of mediators does not prove an immediate hypersensitivity reaction to tobacco smoke as has been hypothesized, but the observations are extremely interesting as will be the follow-up of the young smokers and their response to drugs such as DSCG.

INFECTION

Much recent work has defined the extent and mechanisms of the protective local response of the respiratory tract against infection, including defences which are non-immunological, such as clearance mechanisms, surfactant, interferon, etc. Immunologically specific mechanisms include local antibody production, and the local lymphocyte system (BALT) discussed above. The pulmonary alveolar macrophage (PAM), although largely non-specific in its role as a phagocyte, is intimately concerned with immunological lymphocyte function—both in terms of influencing it and being influenced by it. This cell is fully reviewed by Hocking & Golde, 1979.

Pathogenesis and treatment of recurrent and chronic respiratory infections in adults

In a study of over 400 adult patients suffering from recurrent and/or chronic respiratory infection two principal groups have emerged (Cole, 1979). The first consists of patients suffering recurrent episodes of acute respiratory infection (usually viral upper respiratory tract illness rapidly affecting the chest) with production of

purulent sputum but little radiographic shadowing, slow to respond to antibiotics, but who are normal between episodes. The second is composed of patients with chronic purulent sputum production, who are mainly bronchiectatic.

Immunologically, the first group has a significant prevalence of deficiencies or absence of serum and secretory IgA, and several other immunity deficiencies. The second group has a significant prevalence of deficiency/absence of all circulating antibody classes (hypogammaglobulinaemia), but if this is excluded they tend to have a exuberant response with immunoglobulin levels which are usually higher than normal; a significant prevalence of autoantibodies and associated 'autoimmune' disease in the patient or his family; inhibitory factors for lymphocyte function in the serum, and increased titres of circulating immune complexes (often containing IgA). In a small subgroup of patients who had recurrent acute pneumonia there was a highly significant prevalence of hypogammaglobulinaemia. Associated upper respiratory tract disease tended to parallel lower respiratory tract disease in its recurrent or chronic nature. Bronchiectatic patients with disease which progresses rapidly, despite exemplary physiotherapy and antibiotic therapy, appear to be those with both the highest serum immunoglobulins, and also the highest titres of serum inhibitory factors and circulating immune complexes. In the few cases in which bronchial biopsies are available, local deposits of stainable immunoglobulin (principally IgA) and complement are present.

It would appear, therefore, that the most important routine screening test for patients with protracted respiratory infection problems is estimation of serum immunoglobulins. This detects total deficiency, selective IgA deficiency/absence, and an exuberant antibody response, all of which may be important in treatment.

The evidence suggests that immunity deficiencies account for one group of infective problems (mainly recurrent ones), whereas excessive response (probably to persistent bacterial antigens) may conceivably cause bronchial tissue-damage and eventual bronchiectasis. What triggers this latter response is unknown, but some patients have a suggestive history of proven severe viral respiratory infection (e.g. influenza) immediately prior to development of their disease. One small group of patients gave a history of ulcerative colitis developing during bronchiectasis, or of total colectomy for this condition immediately before development of bronchiectasis. All these patients possessed smooth muscle antibody.

Immunity deficiencies requiring more sophisticated tests to uncover (in the group of patients with recurrent infections) include low antibody affinity (despite normal immunoglobulin levels), deficient antibody response to primary and recall antigens, deficient opsonization for peripheral blood phagocytic function, and rare complement deficiencies. It is possible that patients with infective pulmonary problems, who appear normal in peripheral blood tests, may suffer from deficiencies in local respiratory defence mechanisms. In vitro study of the function of PAM lavaged from the bronchoalveolar tree (Cole, 1979) has shown some patients to have opsonin defects for PAM function, and a small number appear to have an intrinsic PAM defect in bacterial phagocytosis and killing, which can be partially rectified by incubating the cells in vitro with an immunostimulant drug, levamisole. However a clinical trial of levamisole in such patients has revealed an unacceptable frequency of toxic effects. Nonetheless in a controlled trial De Loore, Heck, Van Eygen & Casneuf (1979), following a similar report by Van Eygen in 1976, reported a reduction in the number,