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New perspectives on basic mechanisms in lung disease · 3

Drug intervention in asthma: present and future

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In Western industrial countries asthma affects about 5% of the adult population and 10–15% of children. Asthma is now the most common chronic respiratory disorder seen in general practice in Britain, with over 1 million consultations a year.[1] Epidemiological studies suggest that its prevalence, severity, and mortality are rising and, although redefinition of diagnostic criteria and a greater awareness of the disease may contribute to the increase, there is evidence that environmental factors, such as increased exposure to allergens and atmospheric pollutants, may be a contributing factor.

Drug treatment in asthma has changed during recent years, reflecting the increased awareness that asthma is not just a disease of reversible bronchoconstriction and that the underlying inflammation occurring in the airways contributes in a major way to the pathological processes and progress of the disease. Over the past few years knowledge of the basic mechanisms underlying the inflammatory process has greatly increased and a plethora of chemical substances have now been identified that are known to be released from a wide range of different inflammatory cells. These chemical substances (now totalling 25–30) could all potentially have a role in the inflammatory process. The predicament for the drug discoverer is that the possibilities for drug intervention in the inflammatory process appear endless and are increasing as new knowledge emerges. This article aims to cover the current thinking on asthma treatment and to look to the future, both immediate and more long term, from the viewpoint of the discovery of drugs in the pharmaceutical industry.

Current asthma treatment
Histological studies of lungs from patients who died of asthma show profound inflammatory changes with occlusion of major airways with inflammatory cells, epithelial cells, and mucus plugs.[2] Biopsy specimens from patients with asthma who have minimal symptoms, however, also show characteristic features of inflammation, including shedding of ciliated epithelium, eosinophil infiltration, partial mast cell degranulation, and collagen deposits beneath the epithelial basement membrane.[3] During the past 10 years there has been an increased realisation that airway

inflammation is a major pathological feature in asthma and is likely to contribute to the symptoms and bronchial hyperresponsiveness that is characteristic of the disease. This has led to the recommendation that anti-inflammatory treatment should be started at an early stage.[4 5] Of the commonly used drugs, inhaled and orally administered corticosteroids appear to be the most potent anti-inflammatory agents. Although systemic steroids are of benefit for patients with severe or refractory asthma their side effects limit their general use. Introduction of the inhaled corticosteroids (beclomethasone, triamcinolone, flunisolide, and budesonide) provided a major advance in the treatment of asthma. When these agents are administered before an allergen challenge to sensitised patients, the late phase bronchoconstrictor response and increase in bronchial hyper-responsiveness are inhibited whereas continued administration will also reduce the immediate response to allergen[6] and reduce bronchial hyperresponsiveness and symptom scores in patients with asthma.[7] This therapeutic effect of topical steroids is likely to be multifactorial, resulting from the suppression of the actions of several types of inflammatory cell, including macrophages, eosinophils, lymphocytes, and mast cells.[7 8] Therapeutic benefit can be obtained by inhaling doses below 800 μg/day, generally with minimal side effects, in adults and children.[9] Some patients, however, respond only to higher doses, which may result in adrenal suppression, growth retardation, osteoporosis, and haematological changes.[10] Other local effects, such as dysphonia and oral candidiasis, may limit the dosage.[11] To improve on the currently available inhaled steroids, drugs with higher topical activity and reduced local and systemic effects are needed. One such recently introduced agent is fluticasone propionate, which has negligible oral bioavailability as a consequence of limited absorption from the gastrointestinal tract and virtually complete first pass metabolism.[12] These properties could be highly advantageous for inhalation in man, where a substantial fraction of an inhaled dose is normally ingested by swallowing.[12]

Alternative anti-inflammatory preparations are available in the form of cromolyn and nedocromil. The mechanism of action of these drugs is unknown, but may include stabilisation of inflammatory cells and effects

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on local nerve endings.[13] Cromolyn has no appreciable bronchodilator activity, but given long term (for more than 12 weeks) will reduce airway hyperresponsiveness in patients with asthma, and in shorter term use (for under six weeks) is effective in preventing seasonal increases in bronchial hyperresponsiveness.[13] Cromolyn appears to be a less effective anti-inflammatory agent, however, because improvements in bronchial hyperresponsiveness may be variable and may not be maintained;[4 6] moreover, the dosing regimens (2 mg four times a day) may not be convenient.[6] Although cromolyn has been claimed to be equieffective in children and adults[13] it is prescribed more usually in children because of concerns about the growth retardation produced by steroids. Nedocromil has a clinical profile similar to that of cromolyn and may provide a sustained decrease in bronchial hyperresponsiveness. Unlike steroids, they give no appreciable improvement in FEV_1 with prolonged usage.[6]

Although an inflammatory basis for asthma is now widely recognised and inhaled prophylactic anti-inflammatory agents are increasingly prescribed, there still remains the need to achieve acute relief of symptoms by the use of bronchodilator agents. The inhaled β_2 adrenergic agonists (salbutamol, terbutaline, fenoterol) are by far the most effective bronchodilators in current use.[2] These agents have a rapid onset of action and are indicated as first line treatment for the short term relief of bronchoconstriction and acute exacerbations of asthma symptoms.[2 4] New long acting inhaled β agonists (salmeterol, formoterol) are now becoming available, but in view of the debate about continued regular use of β agonists[14] as opposed to on demand treatment the place of these agents in the treatment of asthma cannot be certain. The twice daily dosing regimen and long acting effect, however, will no doubt benefit many patients,[15] though the clinical relevance of earlier claims for an anti-inflammatory effect of salmeterol is at present unclear.[15]

Anticholinergic bronchodilators, such as ipratropium or oxitropium, are also used in asthma, and have utility in certain subsets of patients. Subtypes of muscarinic receptors have now been recognised in the airway; agents selective for the smooth muscle (M_3) receptor should prove to be useful and have a greater potential than non-selective agents for increased effect.[2]

Novel drugs in early clinical development

Over the past 20 years research on asthma has focused on the identification, elucidation, and synthesis of chemical substances released from mast cells, neutrophils, and eosinophils during antigen challenge. This led to the design and development of several antagonist drugs as potential drugs for asthma. Histamine antagonists proved to be disappointingly ineffective and research effort then turned to the three groups of potentially important mediators derived from activation

of membrane phospholipids by phospholipase A_2, the cyclooxygenase products, lipoxygenase products, and platelet activating factor (PAF)—see figure 1. Lung tissue can metabolise arachidonic acid either via the cyclooxygenase pathway, giving metabolites that can be proinflammatory (prostaglandin (PG) $F_{2\alpha}$, PGD_2, PGH_2, and thromboxane A_2) or anti-inflammatory (PGE_2 and PGI_2), or via the 5-lipoxygenase pathway, giving bronchoconstrictor and proinflammatory leukotrienes. The prostanoids, leukotrienes, and PAF have all been shown to be released in appreciable amounts during an allergen challenge, though the profile of products changes in the early or late reaction. Nonsteroidal anti-inflammatory drugs that inhibit the enzyme cyclooxygenase and prevent formation of the prostanoid precursor PGH_2 have been evaluated in asthma. Conflicting results have been produced and, although most studies suggest that indomethacin or flurbiprofen have some small beneficial effects,[16] a few patients become worse with this treatment. It has been suggested that these compounds cause a shunting of arachidonic acid metabolism to the lipoxygenase pathway, with a subsequent increase in leukotriene concentrations. More promising targets were considered to be intervention further down the arachidonic acid cascade—namely, inhibition of thromboxane A_2 (TXA_2), leukotrienes (LT), and PAF.

THROMBOXANE SYNTHETASE INHIBITORS
AND ANTAGONISTS

Thromboxane receptors are widely distributed in airway smooth muscle of various species. In man they mediate constrictor responses not only to TXA_2 but also to other prostanoids, such as PGD_2 and $PGF_{2\alpha}$. Two classes of compounds have been developed, compounds that inhibit the synthesis of TXA_2 and compounds that block the action of prostanoids on the thromboxane receptor. The potential of thromboxane synthetase inhibitors is now considered to be limited because synthesis of endoperoxide still occurs, with the consequent transformation to other prostanoids, which activate the thromboxane receptors just as thromboxane does. Nevertheless, the thromboxane synthetase inhibitor OKY-046 (ozagrel) has been reported to show some inhibition of bronchoconstriction in allergen challenge studies,[17] and is being developed in Japan for the treatment of asthma. Conceptually thromboxane receptor antagonists hold more promise and two such antagonists have been tested in asthmatic patients, GR32191 and ICI92605. The results of early allergen challenge studies were promising because GR32191, for example, produced modest reductions in allergen induced bronchoconstriction.[18] In a subsequent four week study, however, the compound had no effect on morning and evening peak expiratory flow rates, subjective symptom scores, or nocturnal dyspnoea.[19]

These results suggest that prostanoids act-

Membrane phospholipid

Phospholipase A₂

Lyso-PAF

Arachidonic acid

PAF

Cyclooxygenase

5-Lipoxygenase

PGG₂, H₂

LTB₄   LTC₄, D₄, E₄
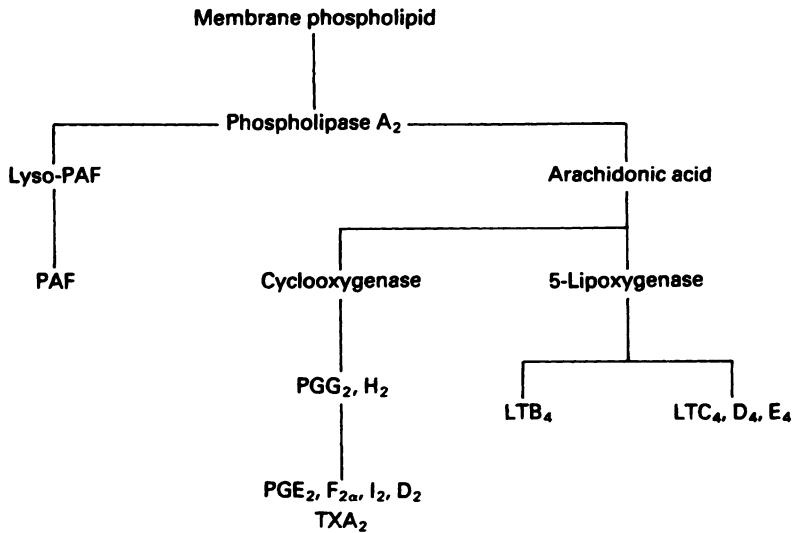
PGE₂, F₂ₐ, I₂, D₂
TXA₂

Figure 1   Formation of platelet activating factor (PAF), prostaglandins (PG), and leukotrienes (LT) during the allergic response. TX—thromboxane.

ing via the thromboxane receptor do not have a key role in asthma. Further evidence will, however, come from studies with another, more potent, thromboxane antagonist, BAY u3405, which is currently being evaluated in patients with asthma.[16]

LEUKOTRIENE SYNTHESIS INHIBITORS AND ANTAGONISTS

Arachidonic acid metabolised via 5-lipoxygenase initially forms the unstable LTA_4, which may be hydrogenated to form the chemotactic LTB_4; or glutathione is incorporated to form the *peptido* (cysteinyl) leukotrienes LTC_4, LTD_4, and LTE_4, which are potent smooth muscle contracting substances. LTC_4 and D_4 are 1000 fold more potent than LTE_4, which is in turn 100 times more potent than histamine in producing contractions in strips of human lung.[20] The clinical utility of the first generation of leukotriene antagonists was limited by low potency and poor pharmacokinetics, but more potent compounds are now available—for example, ICI 204219 and MK571. Early studies with these compounds are very encouraging. For example, in allergen challenge studies ICI 204219 reduced the early phase bronchoconstriction by 80% and late phase bronchoconstriction by about half and attenuated the accompanying increase in bronchial hyperreactivity.[21] MK571 has also shown good results in exercise induced asthma.[22] Studies in chronic asthma are ongoing and although early reports are encouraging[23] the role of these agents as anti-inflammatory agents in chronic asthma remains to be defined.

As LTB_4 is a potent chemotactic agent for inflammatory cells, greater efficacy may come from compounds that inhibit the enzyme 5-lipoxygenase, thus inhibiting the synthesis of all the cysteinyl leukotrienes as well as LTB_4. One such agent is zileuton (A-64077), which has a direct effect on the enzyme.[24] More recently a compound, MK886, has been

described that has an indirect blocking effect by inhibiting the translocation of the enzyme from the cytosol to the cell membrane.[25] These compounds are only partially effective at inhibiting leukotriene synthesis in man and appear to have limited efficacy in early clinical studies.[26] More effective compounds are required that will achieve and maintain more than 90% inhibition of leukotriene production throughout the dosing period.

PLATELET ACTIVATING FACTOR ANTAGONISTS

Of the many mediators suggested to have a role in asthma, platelet activating factor, an ether phospholipid released from membrane phospholipids by activation of phospholipase A_2, was considered to have excellent scientific credentials as a potential inflammatory mediator, as its effects mimic the pathophysiology of asthma more closely than any other single mediator. Exogenous PAF induces profound bronchoconstriction and bronchial hyperreactivity, increases recruitment and activation of inflammatory cells, increases vascular permeability, and induces epithelial damage.[27 28] Extensive research during the 1980s has documented the release of PAF from various cells, including macrophages, eosinophils (containing the largest quantities), neutrophils, and platelets. It has shown that PAF not only releases various mediators and cytokines, including prostaglandins, leukotrienes, and interleukin-1, but additionally can prime cells and induce amplification of inflammatory responses.[28 29]

As the knowledge of the complex interactive biological profile of PAF increased, a stronger scientific rationale for a role for PAF in the development of the chronic inflammation associated with asthma became apparent.[30] In response, many companies focused on this target and several potent and selective receptor antagonists of PAF are now available and are currently being evaluated clinically. Data from early clinical studies have, however, been disappointing. Thus apafant (WEB 2086), given by inhalation[31] or orally,[32] and oral MK-287[33] and UK-74,505[34] failed to show any effect on antigen induced early and late reductions in FEV_1 or on the subsequent increase in airway hyperresponsiveness to agonist challenge.

Data from longer term studies on natural asthma are awaited. The current view, however, is that inhibition of PAF may not produce effective treatment for asthma, though more potent antagonists with a different selectivity profile (for example, inhibition of intracellular as well as membrane extracellular sites) may prove to be of more benefit.

Potential for drug intervention in allergic inflammation

The response of the asthmatic airways to inhaled allergen is extraordinarily complex. A range of inflammatory cells is known to be present in the airways of patients with asthma, including mast cells, macrophages, lymphocytes, and eosinophils.[2] A complicated

network of cytokines and immunological stimuli orchestrates recruitment and activation of these cells in response to allergen. The release of preformed and newly synthesised mediators, with attendant epithelial damage, neural stimulation, and plasma extravasation, maintains and amplifies the entire allergic cascade.

A scheme of likely events in the allergic response of the airways is shown in figure 2. Inhaled allergens are ingested and processed by antigen presenting cells (for example, macrophages) and the attendant release of inflammatory mediators and chemotactic cytokines assists recruitment of other inflammatory cells to the airways. A specific subset of T lymphocytes, CD4 T cells, after activation, produce a range of proinflammatory cytokines, which play a part in the recruitment and activation of mast cells and eosinophils.[35] Additionally, in response to the dual signal of T cell contact and interleukin 4 (IL-4) B lymphocytes produce antigen specific IgE.[36] This binds, via its Fc portion, to specific high affinity IgE receptors on the mast cell surface[37] and to low affinity receptors on the surface of other inflammatory cells, such as the eosinophil.[38] Re-exposure to antigen cross links the surface bound IgE, triggering cellular degranulation[37] and release of further proinflammatory mediators and cytokines as well as certain tissue destructive enzymes and basic proteins.[2] The pathophysi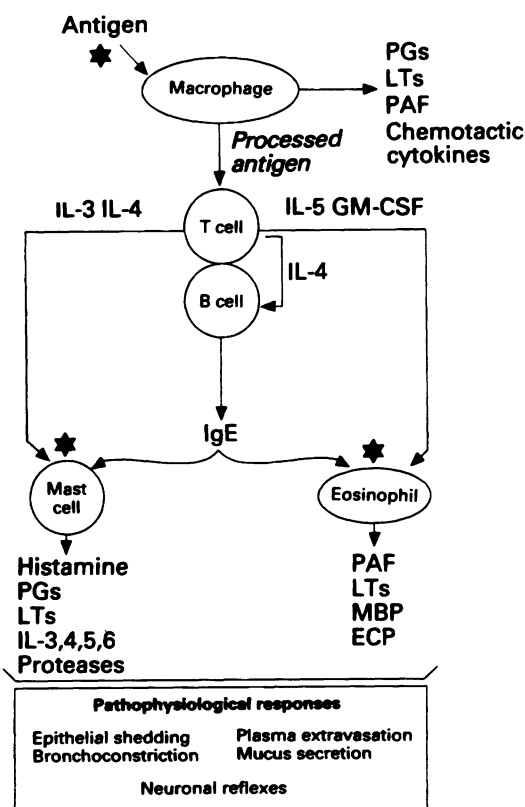ological responses to this inflammatory cascade include shedding of epithelium, extravasation of plasma, secretion of mucus and bronchoconstriction, while increased stimulation of sensory nerves may evoke release of bronchoconstrictor and inflammatory neurotransmitters (for example, acetylcholine, substance P), which further exacerbate the inflammation.[2]

How can the drug discoverer exploit the knowledge of the early inflammatory events in asthma to design novel, effective drugs for the treatment of this disease?

There is good evidence, for example, that intervention by means of a drug directed at the T cell may offer possibilities for novel treatment. Activated CD4 T lymphocytes are found in bronchial biopsy specimens from patients with asthma in numbers that correlate with disease severity. Moreover, an increase in CD4 cells in bronchoalveolar lavage fluid is observed in patients who develop a late phase response to allergen challenge.[35] Additionally, cyclosporin, which acts mainly through inhibition of activation of T lymphocytes, showed improved lung function and steroid sparing effects in chronic severe asthma.[39] Cyclosporin itself, however, has undesirable side effects (such as nephrotoxicity), and improved safety and efficacy profiles would be essential for this novel approach to the treatment of asthma to be more widely applicable.

Inflammatory cell cytokines represent another target for drug intervention as they have several key functions; IL-5 and granulocyte-macrophage colony stimulating factor (GM-CSF) are important for the differentiation, recruitment, and activation of eosinophils whereas IL-3 and IL-4 influence the growth and differentiation of mast cells.[40] IL-4 is also required for IgE synthesis by B cells.[36] Any one of these cytokines may be a target for intervention by a novel drug, though rational design of new drugs will require still further advances in our basic biological knowledge of the mechanisms of cytokine production and of their interactions at specific receptors. Difficult though this challenge is, it is further complicated by the pleiotropic nature of cytokine action and considerable emphasis would have to be placed on identifying new treatments for asthma that would not produce unwanted immunosuppressive effects.

Increased attention is also being given to the possibility of selectively modulating second messengers. For example, five isoenzyme classes of cyclic AMP and cyclic GMP phosphodiesterases have been defined biochemically[41] and, because the distribution of isoenzymes between different cells varies substantially, an excellent opportunity is available for developing highly isoenzyme specific, and possibly cell specific, phosphodiesterase inhibitors. Until relatively recently research into the potential utility of phosphodiesterase inhibitors in asthma was confined to the airway smooth muscle. Certain phosphodiesterase inhibitors, however, inhibit functional responses in some mast cells,

Figure 2   Mediators released in asthma. PAF—platelet activating factor; LT—leukotriene; IL—interleukin; GM-CSF—granulocyte-monocyte colony stimulating factor; PG—prostaglandin; MBP—major basic protein; ECP—eosinophil cationic protein.

eosinophils, and lymphocytes.[42] Further work is required to identify the functional role of individual isoenzymes in different cell types, and this could lead to the development of bronchodilating and anti-inflammatory phosphodiesterase inhibitors without the effects on the cardiovascular and central nervous systems that are produced by the currently available inhibitors.

Modulation of IgE production or function has also been suggested as a possible target for intervention.[36 37] IgE plays a part in propagating the allergic reaction via binding of its Fc portion to specific high affinity receptors on mast cells and basophils. The binding of IgE does not induce any apparent cell activation, but in sensitised individuals re-exposure to the sensitising allergen cross links the surface bound IgE, triggering mast cell activation and degranulation.[37] The mast cell is a source of a range of preformed mediators, such as histamine and proteases, as well as lipid mediators, such as PAF, leukotrienes, and prostaglandins, and possibly also newly synthesised cytokines, such as IL-3, IL-4, IL-5, IL-6, and GM-CSF.[43] Interference with IgE binding or with triggering of cell degranulation could lead to novel anti-inflammatory drugs. Already much is known about how IgE binds to its receptors, and there is growing information regarding the intracellular processes that trigger release of mediators. Much more detailed and extensive basic scientific knowledge of these processes is still required, however, and the discovery of new drugs remains a long way off.

Another potentially important inflammatory cell in asthma is the eosinophil.[44] Surface bound IgE molecules may also prime the eosinophil to degranulate in response to allergen exposure, though the specific surface receptor differs structurally from that on the mast cell and has lower affinity for IgE.[38] Eosinophils release a mixture of inflammatory mediators and highly basic proteins (major basic protein, eosinophil cationic protein) plus oxygen derived free radicals, all of which may be associated with the characteristic shedding of epithelium observed in asthma.[45] Drug strategies targeting the eosinophil may therefore be beneficial in asthma. As there is an increasing awareness of the role of cell surface adhesion molecules in migration of inflammatory cells into the tissues, one possibility could be to interfere with the migration of the eosinophil into the airways. Cell adhesion and migration are mediated through several different families of adhesion receptors. For example, ICAM-1 (intercellular adhesion molecule 1) is induced and expressed on epithelial and endothelial cells in response to certain inflammatory mediators and cytokines.[46] Indeed, in a primate model of allergic asthma a monoclonal antibody to ICAM-1 reduced infiltration of eosinophils into the lungs and bronchial hyperreactivity.[46] The application of monoclonal antibodies to the treatment of asthma, which would be a new departure for the drug industry, could be important with regard to inhibition of key processes for which no drug moieties of small molecular weight are known.

As the understanding of the pathology of asthma increases and more is known about the mechanisms of the inflammatory process more opportunities open up for discovering drugs that act at different points in the allergic cascade. The table summarises some of these possible anti-inflammatory targets; other mechanistic targets have been described elsewhere.[47] There are many exciting and challenging ideas for the discovery of future drugs, but this also poses the dilemma for the drug discoverer in the pharmaceutical industry of how to decide which is the most accessible target that is likely to yield a major therapeutic advance.

What intervention will give the best chance of success in terms of efficacy in treating and preventing asthma? How can we determine what are primary events and what are consequences of the disease? Animal models, such as sensitised guinea pigs and sheep, may help to guide research, but they do not mimic human asthma entirely and cannot therefore reliably predict the potential clinical efficacy of drugs. Drug discovery and assessment of therapeutic potential represent a long and costly process. For example, it was suggested in the early 1980s that PAF may be an important mediator in asthma,[48] but it has taken 8–10 years to identify and progress PAF receptor antagonists and to set up phase II studies for assessing their potential efficacy. As the discovery of novel drugs becomes progressively more complex and challenging the time scale will necessarily lengthen and research investment must increase proportionally.

Future research
To reduce the risk of failure and to increase the probability of designing drugs with activity against asthma we need more knowledge of the sequence of events after initiation of the allergic response and the way different mediators and cytokines interact with each other and with different cells and of the positive and negative feedback systems. For example, an antagonist of a particular mediator will be

Possible mechanistic targets for inhibition of the inflammatory cascade in asthma

Drug target	Desired action
T cells	Inhibition of activation/recruitment of T cells
Interleukins	
IL-3, IL-4	Inhibition of mast cell growth and differentiation
IL-4	Inhibition of IgE production
IL-5	Inhibition of eosinophil activation and recruitment
IgE	Inhibition of binding to mast cells and eosinophils
	Inhibition of triggering of mediator release
Phosphodiesterase inhibitors	Inhibition of inflammatory cell degranulation
Adhesion molecules	Inhibition of inflammatory cell recruitment

effective only if that mediator is released early in the inflammatory cascade and contributes in a major way either directly or indirectly, through release of other mediators, in the initiation and propagation of the allergic response. Many of the potential mediators described presumably do not fall into this category but contribute variously and independently to the inflammatory process.

Consequently many drug companies are focusing on the early events in the allergic response to try to increase the chances of success. Modulation of the function of inflammatory cells, either directly by targeting cells or indirectly by inhibiting the production or action of appropriate cytokines, represents an attractive approach. Selectivity, however, must be feasible—that is, the agent would need to have activity against asthma without compromising other aspects of the immune response.

Undoubtedly over the next few years advances in the knowledge of basic mechanisms of the allergic response, at both cellular and molecular level, will play a major part in guiding the discovery of drugs. The future offers challenging and exciting opportunities and a range of drugs with novel mechanisms will eventually be available for clinical testing. Some of these agents, however, are likely to be not efficacious antiasthmatic drugs but possibly important pharmacological tools that will help to unravel the complexities of the inflammatory process and basic mechanisms in the pathophysiology of asthma. Further advances in the knowledge of the molecular biological and cellular processes that underlie the initiation of disease may lead to a new era of targeting drugs to cure asthma rather than treating the symptoms.

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Adventitia

Dusts and lungs

Following up a nascent interest in occupational and environmental lung diseases during my first few faculty years I embarked on an academic visit to several centres in Britain. It was during the late 1960s, and my "hangouts" (besides the King's Road) were primarily the Brompton, the London School of Hygiene and Tropical Medicine, and the Medical Research Council Pneumoconiosis Unit. Britain was a spectacular place for learning how to investigate occupational lung diseases. Among many leaders in this field were Richard Schilling and Molly Newhouse at Keppel Street and Gower Street, Margaret Turner-Warwick and Jack Pepys on the Fulham Road, and John Gilson and colleagues in Penarth. Since then, happily, there have been many opportunities for return visits and scientific collaboration with overseas colleagues. I have repeatedly gained knowledge and insight from these relationships. Here are two such examples.

About 10 years ago, my colleagues at Tulane and I began a large, multi-mill longitudinal study of cotton textile workers in the South eastern United States. A major objective was to test Richard Schilling's hypothesis that, besides periodic symptoms of byssinosis, cotton textile workers were at risk of chronic progressive airways obstruction. Cumulative dust exposure estimates for each individual were based on air sampling data and job histories. After five years of data collection analyses taking smoking into account and using the individual exposure estimates failed to provide convincing relationships between dust exposure and annual change in lung function. It was time to discuss our difficulties with Richard Schilling on my next visit to Britain. By the time we sat down to talk he had already figured out that we were probably trying to "fine tune" the individual exposure estimates excessively—beyond the realities of the data from mills, where jobs were most often not clearly physically separated. He had calculated that if the average exposure of the mill were assigned to the workers of that mill the dose dependency of the annual change in FEV_1 was clearly seen in yarn manufacturing workers, particularly if they smoked. Richard's experience in assessing exposure in an industry that he knew so well allowed us to complete the analyses and interpretation and show the potential for an adverse exposure related effect on the airways (in smoking workers who produced yarn), even at the low levels of exposure now mandated by regulation.

The chest radiograph was recognised as a useful tool in diagnosing pneumoconiosis in the 1930s, but its role in epidemiology awaited the development and several refinements of a standardised international classification. The resulting system has repeatedly been shown to quantify responses to (and, of course, retention of) mineral dusts and has produced dose-response relationships useful in the setting of workplace standards around the world. No person has contributed more to these methods than John Gilson. In my research unit it was always a special occasion when John was in residence for a fortnight, spending many full days classifying survey films (while Margaret was producing marvellous water colours of industrial scenes along the Mississippi River). On the occasion of John's last visit, however, he was particularly unhappy about the technical quality of the radiographs and the variability of this quality, as they had been obtained from laboratories situated in the different locations of the man-made mineral fibre plants under study. As we drove home each evening his frustration was clear—I, only half jokingly, wondered aloud whether a bad bout of hay fever and its attendant watery eyes, induced by the New Orleans allergenic environment, contributed to John's poor opinion of the film quality!

He was, as usual, absolutely correct, as the analyses showed unexpectedly high interobserver and intraobserver variability of the readings, undoubtedly due to the combination of the variable quality and minimal abnormality. His repeated emphasis on films of uniformly high quality for epidemiological research is to be heeded now more than ever before as investigators survey populations in which abnormalities on the chest film are at the "margin," the central question being "Is there an effect?"

These have been great years, in no small way a consequence of the extraordinary professional guidance that I have received from my British colleagues.

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