Introduction

There is a co-evolutionary relationship between microbe and host in their mutual aim to survive. The microbe always has the evolutionary ‘edge’ by virtue of its ability to replicate rapidly and adapt. Man’s respiratory defences are compromised by their derivation from those previously defending the foregut from which the respiratory tract is derived. The microorganism’s best strategy for survival is quiet persistence rather than dramatic invasion, and it is from the states of chronic microbial colonization and infection that we can learn most about microbial tactics to achieve this state. Bronchiectasis, irreversible dilation of a bronchus or bronchi, is an important cause of chronic bronchial infection, is a well-defined entity, and represents the ideal parasitic state for bacteria within the (normally sterile) bronchial tree. As such it provides an ideal model for examining man’s interrelationships with microorganisms.

Human and experimental models of bronchiectasis

Bronchiectasis is the final common pathway of inflammatory consequences of a number of known causes but in the UK over 60% of cases are idiopathic. Paradoxically, the vast majority of patients with bronchiectasis appear to be immunocompetent but to expectorate secretions containing microorganisms regarded as non-invasive. Such opportunistic bacteria are exemplified by non-typeable, unencapsulated Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis and mucoid Pseudomonas aeruginosa. Some of these are normal commensals in the oropharynx.

The answer to why such immunocompetent patients should be persistently colonized or infected with apparently non-invasive microorganisms may lie in the observation that the first-line sinobronchial defence mechanism of mucociliary clearance is severely impaired in patients with bronchiectasis. A review of the known causes of bronchiectasis suggests that most could have their primary effect by reducing mucociliary clearance in the respiratory tract. So it is conceivable that such causes might result in a pathogenetic mechanism which is entirely independent of the presence of microorganisms in the normal sterile respiratory tract, the organisms being merely passengers as a result of compromised mucus clearance. However, an experimental model of bronchiectasis produced by partial ligation of the apical lobe of a rat clearly demonstrates that the evolution of bronchiectasis requires persistence of viable microorganisms. Moreover, the microorganisms most readily achieving this disease in the model are those bacteria which are commonly isolated from the sputum of patients with bronchiectasis.

A hypothesis for the pathogenesis of bronchiectasis can be constructed from the observations in such models, based on initial reduction in mucociliary clearance by a variety of causal agents or underlying diseases.
Vicious circle' hypothesis of the pathogenesis of bronchiectasis

A 'vicious circle' of events can explain the known facts about patients with bronchiectasis. A initial triggering insult with or without underlying genetic disease compromises the first-line bronchial defence mechanism, mucociliary clearance, allowing bacteria to remain for longer in the bronchial tree. This allows those microorganisms which are able to damage such clearance mechanisms directly to colonize the mucus, then stimulate the host to an inflammatory response. The inflammation becomes chronic because it fails to eliminate the colonists. It damages 'innocent bystander' lung and further impairs mucus clearance. Hence, microorganisms first use the tactic of direct damage to the host's respiratory tract and subsequently they subvert the host's normally protective inflammatory defence into one which damages the host's own respiratory tract—and so the bacteria achieve a parasitic state in the bronchial tree.

Direct microbial damage

A variety of mechanisms exist by which the non-invasive microorganisms commonly isolated from the sputum of patients with bronchiectasis are able to damage the respiratory mucosa directly by production of exotoxins—including inhibition of ciliary function and damage to bronchial epithelium, inhibition of mucociliary transport, alteration of respiratory epithelial ion transport, and stimulation of mucus secretion.

The phenazine pigments of P. aeruginosa, pyocyanin and 1-hydroxyphenazine, slow cilia in a dose-dependent manner. Pyocyanin causes gradual onset of progressive ciliary slowing and ultimately ciliostasis and epithelial damage. 1-Hydroxyphenazine causes rapid onset of ciliary slowing and dyskinesia with subsequent recovery. These toxins slow tracheal mucus velocity in the anaesthetized guinea pig.

Pseudomonas phenazine pigments interact in a pro-inflammatory manner with neutrophils, intensifying bacterial and neutrophil-mediated injury to epithelium. Pseudomonas proteases and rhamnolipids also inhibit ciliary beating and damage the epithelium.

Pneumolysin, the protein toxin of S. pneumoniae, has cytotoxic and complement-activating domains. The cytotoxic region of the molecule is associated with ciliated epithelial damage. Pneumolysin alone induces the salient histological features of lobar pneumonia without the requirement for the live bacterium. Interestingly, prior immunization with pneumolysin in Freund's adjuvant reduced the severity of the pneumonia.

Although these in-vitro observations cannot be extrapolated to man directly, the P. aeruginosa phenazine pigments can be found in the respiratory secretions from patients with bronchiectasis and cystic fibrosis, colonized with the organism, in concentrations sufficient to inhibit ciliary function in vitro.

Microbial persistence

Recent work has shown that the majority of bacteria in bronchiectasis appear to persist in mucus and that the organisms do not adhere to normal respiratory epithelium but only to damaged cells— which are extruded out into the mucus. Bacterial fimbriae may confer an advantage in allowing adherence to mucus and damaged cells, but they do not do so with normal respiratory epithelium.

Initially, S. pneumoniae adheres to a thick gelatinous mucus layer and slows ciliary beating by release of pneumolysin but does not adhere to epithelial cells or cilia, nor does it cause much epithelial damage. Later, separation of epithelial cell tight junctions occurs with disruption of the epithelium and invasion by the bacterium.

Indirect microbial damage

Bacterial colonists can be shown to stimulate a chronic inflammatory response in the host, e.g. by chemo-attraction of granulocytes to the bronchial tree in sufficient numbers to cause tissue damage. There is also evidence for elaboration of molecules by H. influenzae which inactivate neutrophil granulocytes at the site of infection. The host also mounts a florid cell-mediated immune response (consisting mainly of activated CD8 lymphocytes and both antigen-presenting and mature macrophages) in the bronchial wall.

A nalysis of bronchial secretions expectorated as sputum reveals high concentrations of the cytokines interleukin 1α
(IL-1α) and IL-1β, tumour necrosis factor α, IL-6, IL-8 and granulocyte colony-stimulating factor, the levels of IL-8 being particularly high. This cytokine response is held to be responsible for the incessant neutrophil traffic to the bronchial tree. Initially it is likely that this migration of neutrophils is in response to release of chemo-attractants from bacteria but with the passage of time the chemotactic signal almost certainly becomes host-mediated via such cytokine production. This may cause the neutrophil migration to become largely autonomous of the presence of bacteria as suggested by the observation that bacteria but not the IL-8 level can be reduced by successful antimicrobial therapy.

Neutrophil migration through the bronchial wall in severe bronchiectasis has been shown by whole body counting to approximate to 50% of circulating cells. This very large cell traffic has significant damaging potential, via released contents such as elastase, for the epithelium and bronchial matrix proteins. Neutrophil elastase also increases the number of mucus-secreting goblet cells in the bronchial tree and is the most potent secretagogue for mucin secretion so far found. Other neutrophil products such as active oxygen radicals may also play a part in the progressive lung damage seen in bronchiectasis. Some bacterial products appear to be pro-inflammatory in interaction with neutrophils and hence may intensify neutrophil-mediated tissue damage.

Hydrogen peroxide (H₂O₂) and hypochlorous acid cause ciliary dyskinesia and slowing. The pneumococcus produces H₂O₂ and it may therefore be a virulence factor for this bacterium. However, phagocytes are likely to be the most important source of the molecules.

Bioactive phospholipids cause significant dose-dependent slowing of ciliary beating and epithelial damage in vitro, and PMNLs enhance these effects probably by enhanced reactive oxygen radical production. Guinea-pig eosinophils activated by platelet activating factor (PAF) disrupt tracheal epithelium probably by a related mechanism.

In the experimental model of bronchiectasis a similar immunopathology develops and this promises to be a useful tool for testing whether such cell-mediated immunity has a damaging role in the natural history of bronchiectasis and what treatments might intervene in the process.

Mucus transportability

The basic underlying abnormality of decreased mucociliary clearance in chronic respiratory infection could be due to defective ciliary function, or to inferior mucus qualities making the latter unsuitable for clearance by cilia, or to both. Recently, an intrinsic abnormality of expectorated mucus has been defined which renders it more slowly transported by cilia. A mucus-depleted bovine tracheal model has been instrumental in demonstrating this abnormally slow-moving mucus to be present in cystic fibrosis, bronchiectasis and chronic bronchitis. Mucus movement appears to be abnormal because of low osmolality which, if rectified, produces a change in the rheology of the mucus, allowing cilia to transport it at normal rate. This might be a route by which the mutated cystic fibrosis gene product has its effect in predisposing to respiratory infection.

Modes of protection

From a knowledge of the mechanisms underlying the pathogenesis of bronchiectasis, it is possible to devise more successful management of chronic lung infection than previously possible.

Management consists of: (i) suspecting the presence of bronchiectasis in all patients persistently coughing purulent sputum (but excluding eosinophils as the cause of purulence) and proving it by an imaging technique; (ii) establishing the cause of the bronchiectasis, if possible; (iii) assessing the inflammatory activity of the disease; (iv) treating the patient; and (v) monitoring the result of treatment and modifying treatment if necessary.

Treatment

Conventionally, treatment consists of: (i) specific treatment for the cause, if known (e.g. immunoglobulin reconstitution in hypogammaglobulinaemia); (ii) considering curative surgical resection if disease is localized, and there is no underlying causal or associated disease (including sinusitis) to indicate underlying propensity to develop further bronchiectasis; (iii) postural physiotherapy employing gravity to assist bronchial mucus clearance; (iv) reducing bronchial inflammatory activity with local and/or systemic anti-inflammatory agents; (v) achieving bronchodilatation with bronchodilators; (vi) killing bacteria in the airway secretions using antibiotics, preferably those penetrating mucus efficiently; (vii) treating associated rhinosinusitis to prevent post-nasal drip; (viii) treating associated gastric acid reflux if this is causing reflex or direct stimulation of mucus secretion; (ix) treating other associated disease (e.g. ulcerative colitis); and (x) considering palliative surgical resection of any sump of pus hindering response to medical treatment.

Antimicrobial strategies consist of reducing the microbial load colonizing the airways (which stimulates host-mediated damage) in various ways: (i) antibiotic cover for viral upper/lower respiratory infections in those whose infective exacerbations only occur following these; (ii) elective intermittent ("pulsed") oral or intravenous antibiotic to reduce microbial load and prevent infective exacerbations; (iii) continuous inhaled antibiotic to prolong remissions between infective episodes; and (iv) continuous oral or intravenous antibiotics for the most severely affected patients whose first line clearance mechanisms are insufficient to protect at all against microbial recolonization (such therapy is often achieved through an implanted venous access device).
More recent treatments that have been considered are discussed in the following sections:

Epithelial cytoprotection. Subinhibitory concentrations of macrolide antibiotics can be shown in vitro to protect the epithelium by a mechanism as yet undetermined although mediates an increase of intracellular adenine nucleotides but probably mainly by stabilizing the cell membrane.

Modulation of neutrophil function. Salmeterol stabilizes the cell membrane of neutrophil PMNLs, reducing their activation and respiratory burst, and their reactive oxygen radical production. (Feldman et al., personal communication).

Direct anti-inflammatory effect on epithelium. A recent controlled pilot study of inhaled fluticasone in a dose of 1500 mg/day has shown that, in those clinically responding with reduced symptoms of bronchiectasis, there is a significant reduction in inflammatory indices in biopsied bronchial epithelium in bronchiectasis and, in some cases, reduction in the number of bronchiectatic changes on CT imaging. (Wells et al., personal communication).

Mucokinetic agents. A gent that thin the mucus so as to render it more easily coughed up (e.g., recombinant human DNase) have been shown to be effective in cystic fibrosis but not in bronchiectasis from non-cystic fibrosis origin. More promise is held for agents that alter the rheology of mucus by altering its osmolality thus restoring normal transport of it by cilia.

References

Chronic lung infection

human neutrophils exposed to *Pseudomonas aeruginosa* pigment 1-hydroxyphenazine. *Journal of Infectious Diseases* **166**, 568–73.


