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Clinical aspects of protective immunity of the respiratory tract[1]

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Bacteriologists of the 19th century were aware of the host's capacity to overcome bacterial and other types of infection and their capacity to resist further infections. Early theories of immunity were particularly concerned with circulating antibodies and their mode of interaction with, and elimination of, infective agents. These studies identified a number of ways in which host factors were able to destroy invading organisms. Such mechanisms included direct bacterial lysis by antibody, usually occurring in association with complement and, under other conditions, agglutination of bacteria, which rendered them more susceptible to the phagocytic action of macrophages and polymorphs. More subtle changes could sometimes be demonstrated where antibody reacting with the antiphagocytic outer coating of certain capsulated bacteria also predisposed them to phagocytosis.

Early bacteriologists were also aware that protection was sometimes provided when no antibodies could be demonstrated. Early classic studies on infections caused by *Mycobacterium tuberculosis* demonstrated the importance of lymphocytes in protective immunity against certain organisms, and it is now known that suitably sensitized lymphocytes are able to cause direct cytotoxic effects on cells as well as to secrete a range of lymphokines, affecting many different components of the inflammatory response which may aid, directly or indirectly, antigen elimination.

During early years, most attention was focussed upon circulating factors promoting antigen elimination, particularly as they influenced systemic rather than local infections.

Around the turn of the century, studies were performed which demonstrated the antibacterial inhibitory properties of various external secretions, but techniques were not available at that time to distinguish between specific antibody, natural antibody or nonimmunological antimicrobial activity (now known to include such substances as lysozyme, lactoferrin, and interferon).

[1]The 1974 Marc Daniels lecture at the Royal College of Physicians

Some of the milestones in the advance of our knowledge concerning local protection of surfaces exposed to the outside environment are worth recalling, because they emphasize the fundamental distinction between immunological protection from surface invaders and the immunological processes responsible for the elimination of damaging organisms which have already gained access to the internal environment of the body.

For example, as early as 1919, Besredka demonstrated that the oral administration of enterobacteria could successfully afford protection from the damaging effects of a further bacterial challenge, and Davies in 1922 was able to show that specific antibodies to Shigella could be found in the stools of patients recovering from dysentery.

The classic experiments of Burrows and Havens in 1948, studying cholera in pigs, showed that the degree of immunity was related to the titre of antibody found in the faeces (coproantibody) and correlated poorly with serum antibody levels. They showed that parenteral inoculation of organisms gave protection against parenteral infection, but protection from an oral challenge with cholera was obtained only if coproantibodies (local antibody) were present.

Early studies on the respiratory tract were made by Bull and McKee (1929), who showed in rabbits that immunity to further challenge by pneumococci administered by the nasal route was associated with mucoantibodies detectable in the nasal secretions. Only some 20 years ago were detailed studies on the respiratory tract undertaken. Fazekas de St. Groth (1950), using mice, showed that, following instillation of influenza virus antigen into the nose, the ratio of antibody in the nasal secretions to that found in the serum was 10 times greater than that following the subcutaneous injection of virus. They also demonstrated a strong positive correlation between haemagglutinating activity of bronchial washing sand the degree of specific immunity. They further showed that local inoculation of an unrelated virus or nonantigenic irritant injected intraperitoneally increased the titres of secreted antiviral antibody obtained

from the nose—the so-called 'pathotopic potential'. They explained this effect on the basis of increased permeability of the mucous membrane allowing circulating antibody to escape into the secretions.

The modern era of understanding concerning mechanisms of immunity of the respiratory and gastrointestinal tract may be linked with the isolation of a separate class of immunoglobulin (Heremans, Heremáns, and Schultze, 1959) termed gamma A and now called, by international agreement, IgA, and its identification as the major immunoglobulin in colostrum (Gugler *et al.*, 1958). That IgA was the predominant immunoglobulin in most external secretions was demonstrated only some 10 years ago by Chodirker and Tomasi (1963), and that plasma cells in the lamina propria were mainly of the IgA type was shown a few years later (Tomasi *et al.*, 1965; Tourville *et al.*, 1969).

Over the past decade a large amount of information has accumulated concerning secretory immunoglobulins in general, and several detailed and excellent reviews have been published (Secretory Immunologic System, 1971; Tomasi and Grey, 1972). However, much information is still needed concerning protective immunity of the respiratory tract in man and its implications in clinical respiratory medicine.

One of the reasons why study of protective local immunity of the respiratory tract has been relatively neglected may in part be due to the exciting developments in other fields of immunology, particularly immunopathogenesis or the tissue-damaging processes induced by various types of antibody and sensitized cells. This field of study was stimulated, at about the same time as the discovery of secretory IgA, by the now classic classification proposed by Gell and Coombs (1968) and its application in the field of respiratory medicine, particularly by Pepys (1969).

Theories about immunopathogenesis of disease, however, have often failed to answer the very important questions as to why only a small proportion of an exposed population develop hypersensitivity reactions to infective or non-infective agents and what immune responses protect the majority.

The object of this Marc Daniels lecture is to review certain aspects of protective immunity of the respiratory tract studied over the past decade in the hope that this will stimulate further systematic clinical work which is now long overdue.

The respiratory defences against external agents are multiple; they involve specific and non-specific mechanisms and include physical as well as humoral and cellular mechanisms of defence (Fig. 1). Some relate particularly to the airways and others to the gas exchanging parts of the lung.

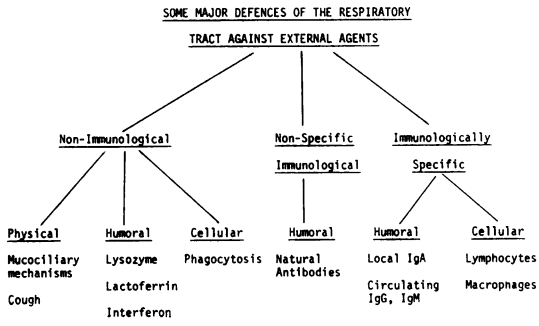


FIG. 1.

NON-SPECIFIC AGENTS

A very large literature now exists on the mechanisms of physical clearance of particles from the lungs by mucociliary action in normal human subjects and their deviations in smokers, in various forms of chronic bronchitis, and in those exposed to a range of organic and inorganic dusts (Walton, 1970; Muir, 1972).

NON-SPECIFIC HUMORAL AGENTS

A variety of non-immunological chemical substances are found in bronchial secretions, and these are probably derived from bronchial glands or epithelial cells. They include lysozyme capable of lysing bacteria, particularly in the presence of complement (Inoue *et al.*, 1959) and lactoferrin, a glycoprotein which binds iron and is bacteriostatic to certain bacteria (Masson *et al.*, 1966).

Interferon is another protein substance of low molecular weight which may be detected in both serum and respiratory secretions and is stimulated especially by viruses, bacteria, and endotoxins and has recently been observed following injection of transfer factor from peripheral lymphocytes (Emodi, Just, and Grob, 1973).

Thus, even before we consider specific immune mechanisms, any condition leading to abnormalities of the bronchial epithelium, alteration of the secretory properties of bronchial glands, or paresis or overwhelming of the phagocytic functions of tissue macrophages can be expected to predispose to bacterial, fungal, and viral infections, on the one hand, or access of allergens with hypersensitivity reactions on the other.

From this it might seem reasonable to suggest that in conditions where macrophage activity is overwhelmed, as perhaps in some cases of desquamative interstitial pneumonia, inorganic dust diseases, or haemosiderosis, bacterial and viral infection might occur commonly. This, however, is not usually the observed fact.

Again, in those cases where florid allergic reactions occur, grossly disturbing the structure and function of mucous membranes, it might be assumed that secondary infection would inevitably occur, but once again this is quite uncommon in clinical practice.

From these observations it would seem that specific protection may be able to overcome even grossly impaired non-specific mechanisms of the respiratory tract.

THE LOCAL SPECIFIC SECRETORY SYSTEM OF THE RESPIRATORY TRACT

External secretions of the respiratory tract, including nasal and bronchial secretions, show several unique properties (Newcomb, Normansell, and Stanworth, 1968):

1. IgA is the predominant class of immunoglobulin present.
2. Secretory IgA differs from serum IgA both chemically and antigenically.
3. IgA in the secretions is mainly produced locally from plasma cells (Figs 2 and 3).
4. There is a lack of quantitative correlation between local and circulating IgA both during normal development and after certain infections.

The predominant form of IgA in external secretions has a sedimentation co-efficient of 11S and contrasts with 7S IgA found in serum. The difference is due to the structure of secretory IgA which consists of two 7S IgA molecules linked by an additional polypeptide chain of molecular weight 60 000, called the secretory or 'T' piece. There may be some species difference in the exact chemical composition of secretory IgA and its relation to secretory piece, and the precise spacial configuration of human secretory IgA has not yet been completely established. Recently, another junctional small molecular weight protein has been identified and termed 'J' chain by Halpern and Koshland (1970).

SITES OF ORIGIN OF SECRETORY IgA

Tourville *et al.* (1969) demonstrated plasma-like cells in the interstitium of bronchial glands and in the lamina propria. No epithelial immunofluorescence was obtained using 7S anti IgA but was obtained using anti-secretory IgA.

The site of origin of secretory piece is somewhat controversial because many antibodies prepared against secretory piece cross-react with lactoferrin. However, the general view is that this is formed in the epithelial cells of bronchial glands (Fig. 4) and becomes attached to IgA produced from local plasma cells either as this is transported through the epithelial cells or after it has been secreted in the bronchial lumen.

Secretory IgA has been shown to be stimulated locally by intranasal inoculation of various respiratory viruses (Artenstein, Bellanti, and Buescher, 1964; Chanock *et al.*, 1966; Smith *et al.*, 1966 and Smith, Bellanti, and Chanock, 1967; Alford *et al.*, 1967; Perkins *et al.*, 1969), and many other workers have shown that secretory IgA levels are closely related to protection from natural and experimental virus infections but that serum levels correlate poorly.

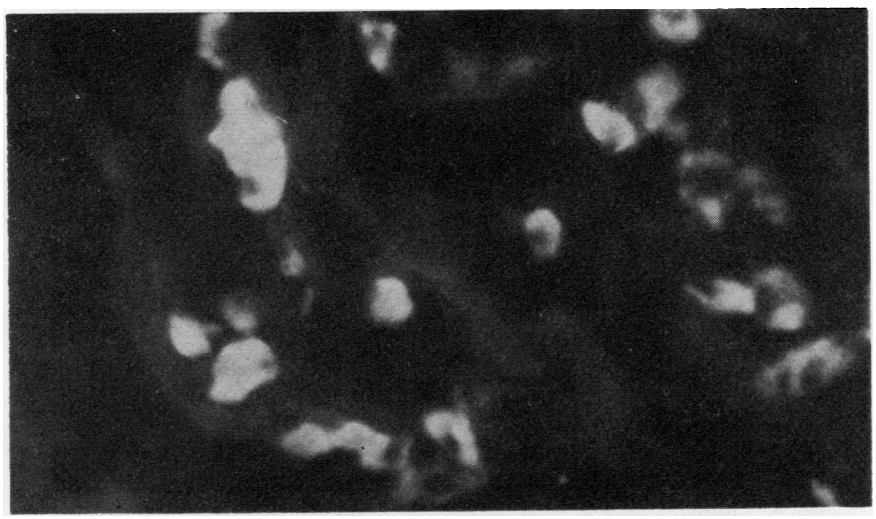


FIG. 2. *IgA containing plasma cells in submucosa of normal human right main bronchus, demonstrated by immunofluorescence with goat antihuman IgA.*

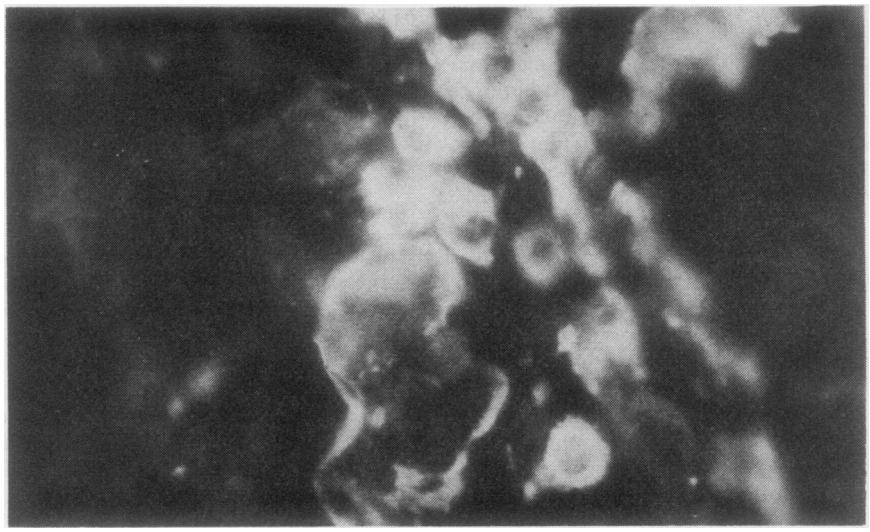


FIG. 3. *IgA containing plasma cells clustered round bronchial mucous glands. Taken from the same preparation as Fig. 2.*

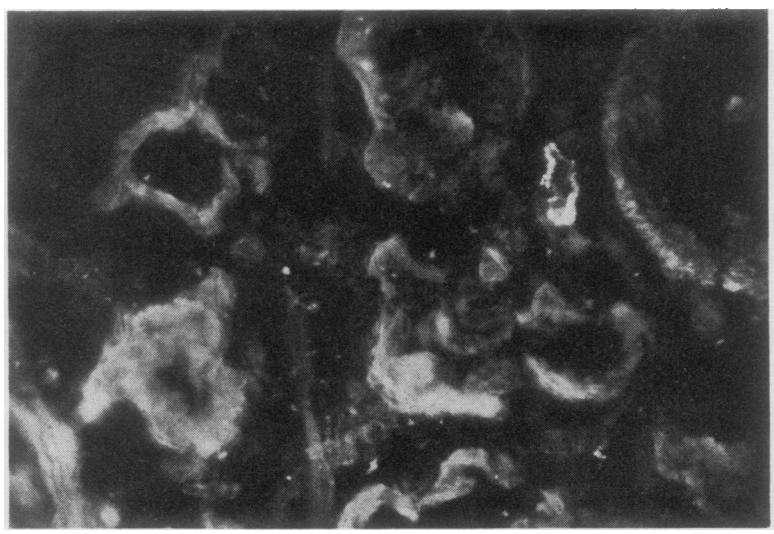


FIG. 4. *Secretory piece in bronchial mucosal glands demonstrated by double layer immunofluorescence using antibody to secretory piece (sheep) followed by fluorescein conjugate anti sheep globulin.*

This is evidence that the secretory IgA system is at least partially independent of serum IgA (especially when challenged locally) and is chemically distinct. Although some controversy continues, secretory IgA is more stable than serum IgA in the presence of a number of agents, including proteolytic enzymes (Brown, Newcombe, and Ishizaka, 1970), and should therefore be more capable of retaining its immunological capacity in the presence of lytic enzymes when the latter are secreted, for instance from local pus cells. Further, secretory IgA in the presence of lysozyme and complement is able to cause bacterial lysis, whereas serum IgA is probably non-complement fixing by the classic pathway and has no such lytic action (Adinolfi *et al.*, 1966; Ishizaka *et al.*, 1966).

On the evidence of experimental challenge with viruses and bacteria, the case for stimulation of local specific antibody of the IgA class in secretions appears to be substantiated. The essential questions now to be answered are, what is the role of such local antibodies in normal protective immunity of the respiratory tract, and can other immunological systems defend the lungs from invaders when local IgA production is deficient?

These questions are particularly pertinent when we turn to the natural experiments of clinical medicine where a number of inconsistencies have to be recognized. At this point we also have to accept that detailed clinical studies on the local immune status of patients with recurrent respiratory disease are sadly incomplete.

Most of the experimental work on stimulation of specific secretory IgA of the respiratory tract is based on studies with viruses, and it might be assumed that in severe antibody deficiencies, where there is an absence of both serum and secretory IgA, virus infections would be a predominant clinical problem. However, as we shall see, virus infections are apparently less common in antibody deficiencies than are bacterial infections.

In spite of the obvious importance of protection of the respiratory tract from bacterial pathogens, little work has been done on the common organisms such as *Haemophilus influenzae*, staphylococci or streptococci. For instance, we have little idea about the factors allowing normal commensals to flourish in the upper respiratory tract while pathogens fail to thrive or, extending the argument, the reason for the frequency of *H. influenzae* infections in chronic bronchitis but the prominence of other pathogens such as *Escherichia coli*, *Pseudomonas pyocyanea* or *Staphylococcus aureus* in cystic fibrosis or bronchiectasis (Burns and May, 1967).

In the absence of detailed and systematic studies, I shall draw on the natural experiments of clinical medicine to explore the answers to some of these questions.

These can be looked at from two points of view—the evidence obtained from patients with established IgA serum deficiencies, and that obtained from assessing the frequency and type of local and general immunological disturbances in various chronic bronchial diseases.

IMMUNE DEFICIENCIES

The commonest presentation of immune deficiencies is infection of the upper and lower respiratory tracts—sinusitis, recurrent bronchitis, bronchiectasis or recurrent pneumonias (Squire, 1962). Squire noted that, of 518 episodes of infection, the lungs were involved in 152 and the upper respiratory tract in 109.

Detailed and systematic bacteriological studies on patients with total and selective antibody deficiencies still need to be done. However, from the cases we have seen over the past few years it appears that infections with *H. influenzae* and Gram-positive cocci are the most frequent, but *Ps. pyocyanea* and other Gram-negative organisms are also found, particularly in those with established bronchiectasis.

In antibody deficiency syndromes there is either a total, or virtually total absence of all immunoglobulin classes, or the deficiencies may be selective and affect a single class. In the present context, selective IgA deficiencies, both absolute and relative, are of particular interest. When serum IgA is undetectable, secretory IgA is usually absent as well (South *et al.*, 1965; Tomasi, 1968). However, where there is a partial deficiency only, then there may be a disparity between deficient serum levels and relatively normal secretory levels. This has been described in a case of malabsorption syndrome (Swanson *et al.*, 1968) and in ataxia telangiectasis (McFarlin *et al.*, 1965). This disparity will be exemplified later when asthma and bronchitis are discussed.

The disparity between low serum levels and normal secretory levels may be particularly important in explaining the finding of isolated IgA deficiencies in about 1 in 600 healthy adults (Bachmann, 1968). A study of secretory IgA in these healthy individuals is now urgently needed. Where secretory IgA is also found to be low in healthy people other explanations for adequate local protection have to be sought, and here local IgG or IgM may compensate (Stobo and Tomasi, 1967). Alternatively, local IgA may be less important in the maintenance of local immunity than is often assumed.

SERUM ANTIBODY DEFICIENCIES AT BROMPTON HOSPITAL

Dr Bill Wood from North Carolina and I are cur-

rently reviewing the clinical patterns of patients in whom serum antibody deficiency has been detected on routine testing at the Brompton Hospital. I am indebted to my physician colleagues for allowing me to include some of their cases. I have excluded the children under 5 years old in whom lower levels may obviously be found. We have studied 43 patients who have attended over the past two years and in whom low immunoglobulin levels (less than 126 mg/dl) have been detected on routine investigation.

The great majority had selective but partial deficiencies of IgA (Table I), and the main respiratory disorders could be classified into five groups: recurrent infections, asthma, lymphomas, sarcoidosis, and miscellaneous (Table II).

TABLE I

TYPES OF IgA DEFICIENCY IDENTIFIED ON ROUTINE SCREENING 1971–73

Deficiency	No.	%
IgA alone	36	84
IgA + IgM	4	9
IgA + IgG	2	5
IgA + IgG + IgM	1	2·0
Total patients with serum IgA < 126 mg/dl	43	100

TABLE II

IgA DEFICIENCY 1971–73

	M : F	Age (yr)		IgA (mg/dl)	
		Mean	Range	Mean	Range
Infections:					
Bronchiectasis	4 : 2	29	12–60	108	98–115
Recurrent 'bacterial' infection	2 : 4	21	6–30	83	25–126
Cystic fibrosis	1 : 0	13	–	72	–
Asthma:					
'Extrinsic'	4 : 4	25	7–36	84	30–126
'Intrinsic'	2 : 4	51	24–73	89	50–126
Lymphoma	4 : 5	57	16–72	79	25–120
Sarcoidosis	1 : 2	30	23–40	54	20–115
Miscellaneous lung disease (adenoma, pulmonary fibrosis, chronic cavitating Tb)	3 : 1	63	50–74	82	27–120

Review of the 43 cases suggested that, on clinical evidence, recurrent recognizable viral infections were not especially common, although in this retrospective survey, systematic attempts at virus isolation were not made. Substantial fungal infections were also uncommon. Only one patient with a selective IgA deficiency developed an infection with *Pneumocystis carinii* over the two years of this survey, and he had a lymphosarcoma and had received massive immunosuppresant therapy.

Stobo and Tomasi (1967) have shown that in immune deficiency states, local IgG and IgM are produced and perhaps compensate for loss of IgA, but these immunoglobulins do not appear to be associated with secretory piece. IgM and IgG secretions into the respiratory tract may thus provide a replacement form of protection, but their lack of resistance to proteolytic enzymes might render them a poor substitute for IgA, and might also make their detection in bronchial secretions more difficult. IgG and IgM will nevertheless afford important protection from organisms once they have gained access to the body, and this may account for the rapid response to systemic infections, although the predisposition to recurrent infections continues. It also might account for the normal development of bacterial IgG precipitins seen in some of these cases, although we have noted the absence of such precipitins in other patients and this feature may be another manifestation of a more subtle form of immune deficiency in some patients; this defect might depend upon inadequate T cell cooperation or inadequate IgG antibody formation. The frequency of respiratory symptoms in isolated IgA deficiency, sometimes associated with an absent IgG response on immunization challenge, has been described previously by Hobbs (1968).

Isolated IgA deficiencies are also seen rarely and sometimes apparently as an acquired disorder in association with a number of diseases including lupus erythematosus, cirrhosis of the liver, malabsorption syndrome, including coeliac disease and cystic fibrosis, and asthma. This diverse list suggests that there is more than one cause for the low serum level. Moreover, in many of these conditions respiratory infections are not a prominent feature. This fact raises two questions. First, how far is *local* IgA immunity intact, and, second, how far does local IgA production contribute to serum IgA levels? Complete answers to these questions are not known.

Before leaving the natural model of immune deficiencies, the predisposition to viral, fungal, and protozoal infections in cases showing combined deficiency of cellular and antibody deficiency must be mentioned. Cellular defences are particularly important in normal protection against these types of organisms and demonstrate the differential system of defence relating to different types of invaders. It may be an over-simplification to suggest that IgA antibody is especially important in protecting mucous membrane surfaces, that IgM and IgG antibody are particularly important once the membranes have been penetrated, and that cellular immunity may be particularly important in the defence against intracellular organisms and persistent particulate antigens.

However, it is worth re-emphasizing at this point that there remains an unexplained gulf between the evidence *in favour* of local IgA playing an important role in local immunity, especially from experimental studies with respiratory viruses, and evidence *against*

its importance from the examples in clinical practice where low IgA levels are found quite incidentally in the absence of any form of respiratory infection.

CHRONIC BRONCHITIS

Early studies have emphasized the importance of *H. influenzae* as a pathogen in this condition (May, 1968). Serum IgG precipitins to the H_1 antigen of *H. influenzae* are very common in infective chronic bronchitis, occurring in some 69% of one series of cases reported by Burns and May (1967), and relating to clinical exacerbations with purulent sputum. The role of circulating precipitins in defence mechanisms or hypersensitivity tissue-damaging responses is so far unestablished.

Recent work on immune responses in chronic bronchitis has included studies on IgA in the serum, IgA in the saliva (where secretory IgA can be measured without the complicating features of secondary infection and its associated pathology), and IgA in sputum which is relevant to the actual site of disease (see Fig 5).

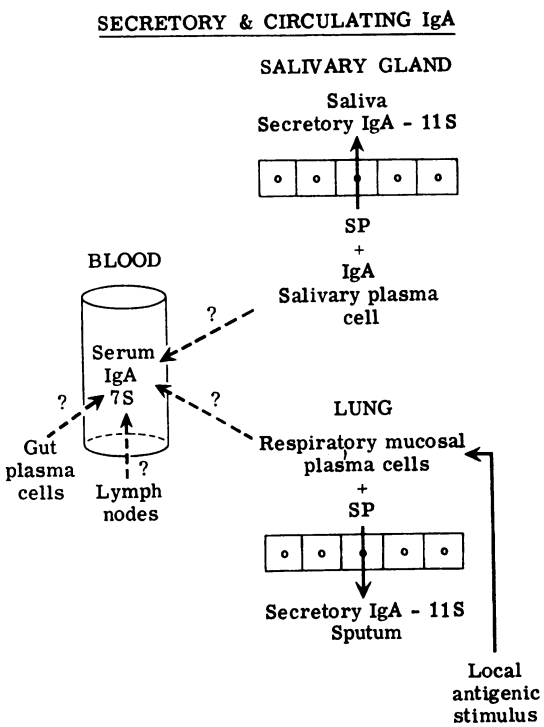


FIG. 5.

SALIVA Siegler studied 86 chronic bronchitics from Citron's bronchitis clinic and, working in our laboratory, found 6% to have serum levels of IgA less than 125 mg/dl (Siegler and Citron, 1974). This incidence is more than twice as great as would be expected in a random population. IgA levels in saliva obtained after maximal stimulation of flow were found to lie within the normal range, having a normal mean value of 2·6 mg/dl. The relationship between the serum and salivary levels was not close although all of the cases with low serum IgA levels had salivary levels less than 4 mg/dl. Salivary IgA levels did not apparently differ in simple chronic bronchitis compared with the infected 'complicated' cases.

From this study it appears that there is no abnormality affecting the entire secretory IgA system in chronic bronchitis. This conclusion supports the findings of Lewis, Lapp, and Burrell (1970), studying saliva, and of Alford *et al.* (1967), who found normal IgA levels in the nasal secretions of bronchitics.

SPUTUM Quantitative measurements of IgA in sputum are difficult to interpret partly because of the wide variation in the concentration in sputum obtained at different times and also because the contribution from serum through inflammatory exudate is variable and may be great.

To allow for these difficulties, Medici and Buergi (1971) graded the extent of inflammatory change by relating it to sputum lactate dehydrogenase levels and studied mild, moderate, and severe chronic bronchitics through infective exacerbations. In mild bronchitics, IgA levels were shown to increase with inflammation, but in advanced cases, the IgA levels were low initially and failed to rise at times of infection. Low IgA levels in sputum have also been reported in a small number of chronic bronchitics after allowance was made for serum contamination (Deuschl and Johannson, 1973). On the other hand, Falk, Okinaka, and Siskind (1972), using bronchial washings, were unable to demonstrate a difference in IgA production between controls and those with chronic airways obstruction.

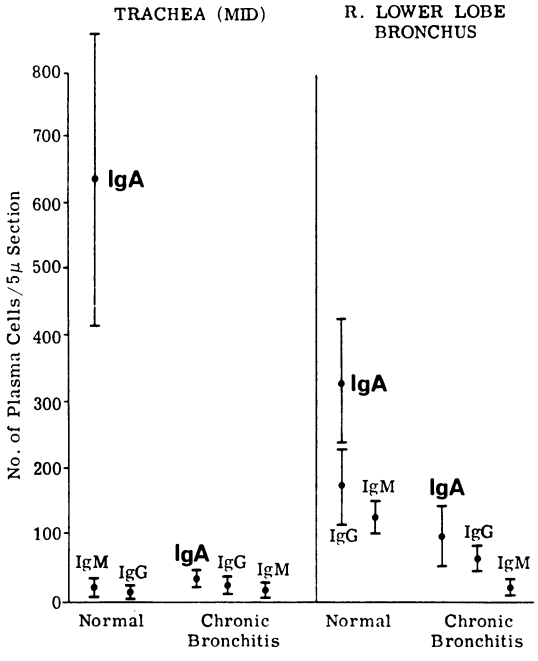
PLASMA CELL COUNTS To overcome the problems of serum dilutional factors, a more direct approach has been to perform differential counts using immunofluorescent techniques on local plasma cells forming specific classes of immunoglobulin.

Preliminary data reported by Gerber, Paronetto, and Kochwa (1971) showed fewer IgA and IgG cells in random bronchial wall sections from bronchitics than in normals.

Soutar (1974), working in our laboratory, has developed a technique for counting plasma cells in entire rings of bronchi at standard levels throughout the bronchial tree. He has shown that, in normal

subjects, IgA plasma cells predominate over IgG and IgM, and the greatest number are seen in the main bronchi. Lower in the bronchial tree a predominance of IgA cells continues but there is less difference between the numbers of IgA and IgG cells. These findings are similar to those of Tada and Ishizaka (1970).

In contrast to the normal, grossly reduced numbers of IgA plasma cells were found in the trachea and bronchus in advanced and fatal chronic bronchitis (Fig. 6). In smokers without cough, an increase in IgA was demonstrated (Soutar and Turner-Warwick, 1974; Soutar, 1975), and this finding correlates well with Medici and Buergi's data on sputum in mild and moderately severe bronchitis. An increased number of IgA plasma cells has also been observed in patients with cystic fibrosis and recurrent bronchial infections (Martinez-Tello, Braun, and Blanc, 1968).



(Soutar & Turner-Warwick 1974)

FIG. 6. *Local IgA plasma cell counts in normals and chronic bronchitics.*

The full explanation of these observations must depend upon further work. Many interesting questions are posed. What factors control the local repopulation of local IgA plasma cells? Are these 'directed' from local lymph nodes or perhaps by the lymphoid collections sometimes seen in bronchial epithelium (Bienenstock, Johnson, and Perey, 1972) and believed to be the equivalent to Peyer's patches in the gut. Is the depletion of IgA plasma cells in the late stages of chronic bronchitis related to cigarette smoking, as suggested by the experimental work of Roszman and Rogers (1973)? Alternatively, the explanation of scanty IgA plasma cells in severe bronchitis may simply reflect the very extensive degree of disruption of bronchial walls. If this is the explanation, the secretory piece might be expected to diminish, and this has been reported by Medici and Buergi (1971).

Thus we may offer a tentative hypothesis on the sequence of events in chronic inflammation of the bronchi due to cigarette smoke (Fig. 7). This hypothesis is based on the concept of an initial and a later deficiency in local IgA production, the initial depletion perhaps dependent on a water-soluble fraction from cigarettes (Roszman and Rogers, 1973) and the secondary depletion dependent on local changes in the mucosa.

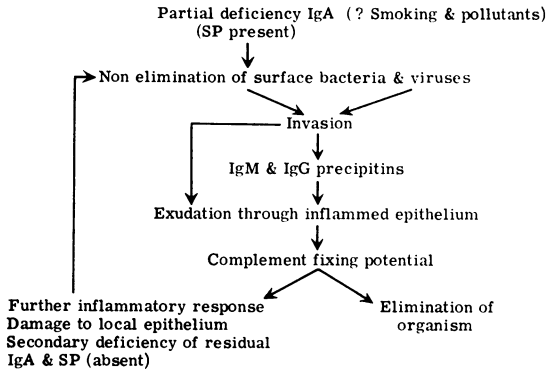


FIG. 7. *A tentative hypothesis relating certain facts to the development of chronic bronchitis.*

ASTHMA

Kaufman and Hobbs (1970) have suggested that some 12% of atopic asthmatic children have IgA deficiencies, and Soothill and his colleagues (Taylor *et al.*, 1973) have suggested that atopic status may develop when there is a transient and delayed maturation of the IgA system. Both these groups of workers studied mainly children.

If this thesis is extended to look at adults with asthma, one might predict that life-long asthmatics with IgA deficiency severe enough to persist into adulthood would show atopic features and heightened IgE values. The thesis could be further tested by comparing the frequency of IgA deficiencies in atopic (extrinsic) and non atopic (intrinsic) asthmatic patients.

In our survey of patients seen over a two-year period with low IgA values, 14 had asthma, and of this small number eight had extrinsic and six intrinsic asthma (Table I). A larger series selecting only those adults in whom asthma started in childhood would form a particularly interesting group to study. In Siegler's series of 50 asthmatics obtained from our asthma clinic, 8% had low serum IgA levels. Salivary levels were within the normal range and showed no difference between the two types of asthma. Salvaggio *et al.* (1973) also demonstrated normal salivary, nasal washing, and sputum IgA in atopic and non-atopic adult asthmatics. Callerame *et al.* (1971) found no depletion of IgA cells in bronchial wall plasma cell counts.

Further evidence of the normal local production of specific antibody in asthmatics has been demonstrated by Waldman, Newman, and Grunspan (1970), who found that aerosol immunization with killed influenza vaccine in asthmatics was normal.

Preliminary studies in our laboratory have shown that in a few asthmatic patients with bronchorrhoea, secretory piece is present, and this contrasts with the findings in advanced bronchitis.

Normal antibacterial defences of the respiratory tract are also suggested indirectly by the early studies of Burns and May (1967), who showed that only 6% of asthmatics had precipitins to H_1 antigen, presumably because these organisms were dealt with by effective local mechanisms before invasion occurred.

In advanced cases of chronic bronchitis with asthma, the situation may become more complicated. Not only do circulating precipitins increase, but there is some evidence to suggest that complement and IgG may be found in the basement membrane of the respiratory epithelium (Callerame *et al.*, 1971; Gerber *et al.*, 1971). If these immunological events result in local destruction, then a secondary reduction in local defence might be expected.

CORTICOSTEROIDS, IMMUNOSUPPRESSANTS, AND LOCAL IMMUNITY

In relatively small doses and with otherwise healthy local immunity, steroids and immunosuppressant agents have rarely resulted in bacterial, fungal, or viral invasion of the lungs in clinical practice.

However, when these drugs are used in very large doses, as in the management of organ transplant, these forms of therapy may be associated with serious invasive infections in the lung by bacteria, fungi, and protozoa.

When these drugs are used in patients with pre-existing deficiency of immune mechanisms (as in lymphomas), then serious respiratory infections are notable, especially miliary tuberculosis, invasive aspergillosis, candidiasis, and *Pneumocystis carinii*.

A recent special opportunity to study the effects of corticosteroids on local defences has arisen with the use of beclomethasone diproprionate now frequently used in the treatment of asthma. Superficial candidiasis is very frequent (Brompton Hospital/MRC Trial, 1974) and has been reported in over 70% of cases on high-dose, long-term therapy. Systemic invasion has not been reported, and the presence of this superficial infestation has not so far interfered with the management of asthma. Candidiasis occurs most frequently in those having pre-existing precipitins, suggesting that the superficial infection is an exacerbation of a pre-existing state; the appearance of precipitins for the first time after local oral thrush was also found, but much less frequently. The relationship between this and local antibody production is now being studied.

CONCLUSION

Much has yet to be learned about the precise immunological responses protecting the respiratory tract. The exact role of locally produced IgA antibody and its interdependence (if any) on antibody produced in local lymph nodes remains to be clarified.

Due to the multiple systems of non specific and immunologically specific defences, penetration by organisms to the internal environment of the body can be prevented even when one or another of these systems is grossly compromised.

An hypothesis has been presented that as these barriers are broken down, so circuits of local damage may become established, which not only result in further local disruption but will also themselves destroy other defences.

I am particularly grateful to my colleagues at the Brompton Hospital who have allowed me to see and study their patients, and to Dr. Soutar and Dr. Siegler, who undertook most of our own studies. Work in our laboratory has been supported by grants from the Medical Research Council, the Wellcome Trust, and the Tobacco Research Council.

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