Respiratory Tract Reactions in Young Bovine Animals and Their Significance

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Introduction

Understanding the pathogenesis of a disease is a prerequisite to developing measures to combat it. Most of the respiratory diseases affecting young bovine animals, indoors or outdoors, are considered to be due primarily to micro-organisms or parasites. However, not only have micro-organisms been isolated from the respiratory tracts of calves without clinical disease but striking morphological changes in the respiratory system, producing clinical disease, have not been linked with causal agents. A fundamental component of the pathogenesis of any disease is the morphological reactions involved in the affected system; these are the structural damage caused by the agent directly and the ensuing immunoinflammatory response accompanied by a repair reaction. The significance of some of these reactions and the difficulties associated with identifying and interpreting them will be considered here. The limited space precludes quoting many appropriate references.

The Upper Respiratory Tract

Inflammatory reactions in the nasal passages and pharynx are common in cattle. In general most rhinitis and pharyngitis is either subclinical or is clinically detectable but has no immediately recognizable significance. The exception is infection with infectious bovine rhinotracheitis (IBR) virus since this can not only cause serious upper respiratory tract disease but also involve extensively the lower respiratory tract. A spectacular variety of organisms has been recovered from the bovine upper respiratory tract. Several types of viruses e.g., rhinovirus, adenovirus, parainfluenza type 3 (PI3) virus and respiratory syncytial (RS) virus, as well as bacteria e.g., *Micrococcus luteus, Acinetobacter lignieresi, Pasteurella haemolytica, Pasteurella multocida, Corynebacterium pyogenes, Actinobacillus actinoides* and mycoplasmas e.g., *Mycoplasma bovirhinis, Mycoplasma bovis, Mycoplasma dispar, Ureaplasma spp.* and fungi e.g., *Aspergillus spp.* seem to be able to colonize the nasal and pharyngeal mucous membrane. Presumably some of these are responsible for the simple acute inflammatory reactions with their associated immune component that are frequently seen in the nasal and pharyngeal mucosae.

Inflammation of the larynx does not appear to be common except during outbreaks of IBR when a proportion of cases may develop a severe necrotising laryngitis. Sometimes the necrotic debris obstructs the airway and is a significant factor contributing to the clinical signs and to the death of the animal.

Individual cases of chronic laryngitis are found in which foci of necrosis or suppuration with fibrosis within the mucous membrane or the cartilages cause laryngeal distortion; this results in the animal having snoring respirations.

There appears to be no common allergic upper respiratory tract reaction in cattle comparable to hay fever in man. However the condition called "nasal granuloma" which develops in young adult cattle at pasture and produces a nasal discharge, has been attributed to allergy (19).

If it is accepted that economically and clinically the most important component of the bovine respiratory disease problem is lower respiratory tract damage the significance of most upper respiratory tract infections is (i) they provide a reservoir of potential lower respiratory tract pathogens to infect other susceptible animals, (ii) in any individual they may spread to lower respiratory tract and (iii) they will induce a serological response which may make the interpretation of data, collected for studying lower respiratory tract diseases, very difficult.

Tracheitis and Bronchitis

Excluding incidents associated with either the aspiration of infected necrotic debris from oral or pharyngeal lesions e.g. bovine papular stomatitis, or the accidental administration of liquids into the trachea, severe necrotising tracheitis is invariably due to IBR virus and occurs with upper respiraory tract disease. Mild tracheitis and bronchitis, which can only be detected microscopically, are not uncommon findings in calves, even in those without obvious pneumonia. The reactions can be subclinical and the remarks made earlier about rhinitis and pharyngitis are equally applicable to these.

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Bronchitis may be described as regional when it is localized to one part of the lungs or generalized when bronchi in several lobes are involved. In the U.K. and some other parts of the world the most important cause of severe generalised bronchitis is infestation with *Dictyocaulus viviparus*. In these locations this is the most frequent cause of clinical respiratory disease in calves and young adult cattle at grass. The bronchi affected are principally those in the caudal lobes of the lungs but in severe infections segmental and lobar bronchi in all the lobes can be involved. In addition to the presence of the parasites in the airways, the reaction is characterised by a cellular infiltrate which includes eosinophils in the bronchial wall. Hypersecretion of mucus occurs; the exudate in the lumen not only has eosinophils but is light and frothy compared with that seen in other forms of bronchitis. If parasites succeed in infecting a partially immune animal the exudate in the lumen of the bronchi may be greenish-yellow due to the presence of very large numbers of eosinophils. Interstitial emphysema is frequently associated with lungworm infection probably because the larger bronchi are involved in the reaction; this is likely to produce a more significant increase in airway resistance than involvement of small bronchi. Bronchitis classically causes coughing and this is a cardinal clinical sign of parasitic bronchitis even when small numbers of worms are present.

A regional bronchitis affecting the cranial and middle lobes of the lungs often develops in association with the pneumonias commonly found in calves indoors and is probably a major cause of the persistent coughing which occurs. The reaction is often a simple acute bronchitis with immunoinflammatory cells accumulating in the bronchial wall and with increased amounts of mucus secreted onto the epithelial surface. Neutrophils are often prominent in the lamina proporia and migrating through the epithelium whereas plasma cells predominate in the lamina propria and the submucosa around the mucous glands. Lymphocytic aggregates also appear in the submucosa and in some cases coalesce to form a major part of the cellular response.

In chronic cases the increased activity of the mucous secreting apparatus is reflected in the large amount of viscid thick mucus lying in the airways, the enlargement of the bronchial submucosal glands, and the increased numbers of goblet cells in the bronchial epithelium associated with the presence of goblet cells in the bronchiolar epithelium (4). Bovine bronchial mucus is a mixture of glycoproteins. Most goblet cells secrete sulphated glycoprotein but in bronchitis some cells containing sialylated glycoproteins are seen. In bronchitis the proportion of cells secreting acid glycoprotein in the glands increases.

Immunoglobulin A secreted into bronchial mucus is important in the defense of the bronchial mucous membrane, IgA containing plasma cells can be found in the mucosae of normal and inflamed bronchi, but plasma cells containing other immunoglobulins are also present. Although the plasma cells containing IgA increase in number during bronchitis large numbers of IgA_1 containing plasma cells can also be found and these often exceeded the number of IgA plasma cells (3). In addition plasma cells containing IgG_2 and IgM are present in the walls of normal bronchi and those that become inflamed.

Prolonged immunoinflammatory reactions in the bronchi in the cranial and middle lobes of the lungs often lead to bronchiectasis and this is one cause of intractable chronic pulmonary disease with unthriftiness.

Petecchial haemorrhages or severe diffuse congestion of the tracheal and bronchial mucosae occur with the complex of lesions described as atypical interstitial pneumonia (AIP) or the bovine acute respiratory distress syndrome (ARDS), (6,7). Hypersensitivity has been incriminated as a cause of these reactions in young cattle indoors and hemorrhages do occur in the tracheal and bronchial mucosa during experimental systemic anaphylaxis in cattle, however pneumotoxic materials such a 3 methylindole may also have this effect.

Bronchospasm is difficult to identify *in vivo* in cattle but probably occurs when calves develop interstitial emphysema e.g. parasitic bronchitis, ARDS, systemic anaphylaxis. The exact immunological and pharmacological basis for this complex reaction is not fully understood although there is a considerable amount of information available about the mediators (10). It seems likely that the role of histamine in causing bronchospasm in cattle has been over-emphasized and that mediators like slow reacting substance of anaphylaxis (leukotrienes) or kinins are more important. The role of IgE is not known although one might expect it to be important in parasitic bronchitis. The syndrome known in man as bronchial asthma, recurrent generalised airways obstruction which is paroxysmal and reversible, at least in the early stages, has not been documented in cattle.

Pneumonia

Definitions of pneumonia vary in the criteria they use. In our work pneumonia was considered to be a disease characterised by abnormalities, primarily affecting both bronchioles and alveoli, that resulted from an inflammatory reaction, often with an immune response, in the lobules of a lung. The classification of pneumonia in any species is difficult. There is a tendency now not to use the older anatomically based names such as bronchopneumonia and lobar pneumonia; these have been replaced by nomenclature based on aetiology. This approach presents problems in dealing with bovine pneumonias since the aetiology is often in dispute. Morphological changes are still useful for grouping these lesions in cattle although they should not be interpreted too rigidly and the following considerations should be kept in mind (i) was the pneumonia fully developed and the cause of death or was it coincidental? (ii) chemotherapy and immunity can significantly alter the appearance of lesions (iii) the number of tissue samples used to assess the lesion and (iv) more than one type of reaction may be present

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in an individual animal.

It would probably be better to stop using the following terms since they are either inaccurate or misleading. Br nchopneumonia is not useful since it encompasses assumptions about the development of the lesion which often cannot be confirmed by the morphological changes. Enzootic pneumonia tends to suggest that there is only one pneumonia affecting calves indoors whereas there are probably several pneumonias from any point of view i.e. aetiological or morphological. Atypical interstitial pneumonia is now considered to be a readily identifiable typical reaction that does not primarily involve the interstitium of the lung.

Two main forms of inflammation are recognized, acute and chronic, therefore we should attempt to group pneumonias under these reactions with further subdivision based on the morphological features of the inflammatory processes that are considered to be outstanding. In some cases these features are useful pointers to aetiological agents. Nevertheless it is always preferable to confirm these either by the morphological demonstration of the agent or its antigens in the lung or by its isolation from lung tissue. An attempt to group the acute and chronic pneumonias of young bovine animals using this approach is shown in *Table I.*

TABLE 1. A classification of bovine pneumonias based on morphology.

ACUTE PNEUMONIA	EXUDATIVE	Simple Epithelial Fibrinous Haemorrhagic Necrotising Suppurative Eosinophilic
	PROLIFERATIVE	Epithelial Eosinophilic
CHRONIC PNEUMONIA	NON-SUPPURATIVE	Simple Lymphocytic Granulomatous Eosinophilic Interstitial
	SUPPURATIVE	

The term acute exudative pneumonia is used for a pneumonia whose basic features are those of acute inflammation and the term acute proliferative pneumonia for a lesion with proliferation of the alveolar or bronchiolar epithelium in addition to the other acute inflammatory changes. Variations in the nature of the inflammatory exudate or the inflammatory cellular response were used to further subdivide the lesions. It is not possible to deal with all of these here. However the following examples are important. A fibrinous pneumonis is one in which there is a very large amount of fibrin found in the alveoli, or the interstitial lymphatics or on the pleura and this is invariably associated with *Pasteurella haemolytica* or *Pasteurella multocida* infection (5,16). However, as with many of these reactions, the converse is not true. In other words a simple exudative pneumonia may also be associated with *Pasteurella spp.* infection. Acute epithelial pneumonias are those with significant changes in the bronchiolar or alveolar epithelium. This usually takes the form of viral inclusion bodies e.g. PI3 virus or syncytia e.g. RS virus; the latter should be differentiated from miltinucleated macrophage syncytia which are quite common in many calf pneumonias (17). Acute eosinophilic pneumonia is invariably associated with lungworm infection (12). Acute proliferative pneumonias may have some of the features associated with infection by one of the paramyxoviridae as described earlier but in a significant number of cases it is neither possible to demonstrate viral antigens nor to isolate the virus.

Chronic pneumonias, characterised by the presence of many cells of chronic inflammation e.g. macrophages, lymphocytes, fibroblasts are usefully subdivided simply into non-suppurative and suppurative *Table I.* The non-suppurative lesions can be further identified by the outstanding cell type seen e.g. chronic lymphocytic pneumonia is used to refer to the lesion of "cuffing" pneumonia, a lesion with large follicular accumulations of lymphocytes around the bronchioles. Although lymphocytes and plasma cells accumulate in chronic pneumonias they do not always form large follicular groups. The presence of lymphocytes and plasma cells in a lesion can be difficult to interpret particularly when the animal has not died from the pneumonia. They may represent either the late phase of an acute pneumonia going into resolution or a slowly progressive non-suppurative chronic lesion such as that caused by mycoplasmas.

Very young calves have virtually no lymphocytes in their peribronchiolar tissues. During infection plasma cells and lymphocytes appear in the interstitial connective tissue of the lung lobule, particularly around the bronchioles, and presumably reflect a local immune response. Single follicular aggregates occur but these should be differentiated from the extreme development of a "cuffing" lesion (14). By analogy with this reaction in other species it seems likely that many of the lymphocytes in the "cuff" are T cells. Lymphocytes also appear within the airways during pulmonary infections and these, obtained from broncho-

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alveolar washings, have been shown to be T cells and B cells (13). The very striking peribronchiolar lymphocytic development in some pneumonias may reflect the nature of the agent stimulating the response e.g. a mycoplasma or it may simply be due to a persistent antigenic stimulus. These lymphocytic pneumonias are longstanding and probably represent lesions that are at least six weeks old. In one outbreak of calf pneumonia this type of change was found during the late phase of the outbreak six weeks after an earlier acute proliferative pneumonia (15).

The term granulomatous pneumonia describes any lesion in which macrophages predominate whether or not they take the form of classical granulomas. A common important pneumonia of this type is that, due to lungworm eggs and larvae, found in association with bronchitis during the patent phase of *D. viviparus* infection.

Bronchiolitis obliterans is frequently seen in chronic non-suppurative pneumonias either simple, lymphocytic or granulomatous. In the third example lungworms are usually considered to be responsible for the severe damage to the bronchial epithelium that leads to this response. In simple or even lymphocytic chronic pneumonias the lesion may be a pointer to previous virus infections since it has been found in experimental PI3 infections (8) and also during the late phase of natural cases of RS virus infection (15).

Fatal Acute Pulmonary Disease

The death of a calf from acute pulmonary disease either as an individual clinical case or during an outbreak of respiratory disease in a group of animals, is usually due to one of the following reactions (i) acute pneumonia, (ii) diffuse acute proliferative alveolitis or (iii) pulmonary oedema. Any one of these lesions may be complicated by interstitial emphysema which will contribute to the respiratory failure.

Acute Pneumonia:

The acute pneumonias listed in Table 1 can involve enough lung tissue to kill calves; when this happens 60-80% of the lungs are consolidated. Calves with this degree of consolidation may have respiratory distress without developing interstitial emphysema. In keeping with the traditional concept that a virus infection may interfere with lung clearance mechanisms and lead to secondary bacterial infection morphological evidence for two acute exudative pneumonias, one due to virus and the other due to a bacterium, can be found in some cases. In indoor calves fatal acute pneumonia complicated by interstitial emphysema, particularly with bulla formation, is suggestive of infection with RS virus or PI3 virus. There are however a substantial number of cases in which it is not possible to demonstrate the antigens of these viruses. In another group of cases, consisting of animals dying indoors and outdoors, the acute pneumonia is complicated by a second reaction which can be described as a diffuse acute proliferative alveolitis (DAPA).

Acute pneumonias due to *P. haemolytica* or to *P. multocida* are also important causes of death in young cattle indoors. In calves outdoors in the U.K. pneumonia affecting the caudal lobes of the lungs and complicated by interstitial emphysema is often due to *D. viviparus infection.*

Diffuse Acute Proliferative Alveolitis:

An important reaction, characteristically affecting lobules diffusely, and frequently widespread throughout the lungs, is alveolar epithelial hyperplasia with hyaline membranes, pulmonary oedema and pulmonary congestion. The hyperplastic alveolar epithelial cells are type 2 pneumocytes whose proliferation may be to replace damaged type 1 pneumocytes (1), or be due to an endogenous or exogenous mitrogen. Since the changes appear to be primarily a reaction of the alveolar wall and the bronchioles are relatively uninvolved, the reaction can justifiably be called an alveolitis. Diffuse acute proliferative alveolitis is found in fatal cases of pulmonary disease as either (i) the major pulmonary lesion (ii) with a concomitant pneumonia or (iii) with interstitial emphysema to form the complex described as AIP or ARDS. Although both DAPA and interstitial emphysema can occur together it is useful to consider the changes separately since DAPA reflects damage to alveoli whereas interstitial emphysema probably reflects a reaction in the bronchi.

The aetiology of the lesion is not known. Toxic damage to the alveoli by an agent absorbed from the alimentary tract e.g. 3 methyl indole could be responsible but this has not been identified yet in natural cases in young adult cattle indoors. Hypersensitivity has also been proposed for the aetiology and restricted lesions like this can be produced by experimental aerosol exposure to antigen (9). If hypersensitivity is involved, in natural cases, it could be hypersensitivity to inhaled material acting simply as an allergen, as in farmer's lung, or to a micro-organism already established in the lung e.g. a virus, bacterium or mycoplasma; cases have been associated with PI3 and RS virus infection.

Pulmonary Oedema:

The only pulmonary lesion found in some calves that die with signs of respiratory distress is widespread pulmonary oedema. In a proportion of cases the oedema is due to acute left heart failure from a congenital heart lesion e.g. ventricular septal defect. In other cases there is no obvious explanation and once again hypersensitivity is often suggested. It is usually very difficult to confirm this although it may be strongly suspected, particularly if the reaction follows the injection of potentially antigenic material e.g. a vaccine or a drug. There is no doubt that systemic anaphylaxis in the bovine species results in pulmonary oedema that can be fatal (2); this oedema may or may not be associated with interstitial emphysema. In some cases the oedema may be due to an anaphylactoid reaction rather than true anaphylaxis.

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Interstitial Emphysema:

Interstitial emphysema is not uncommon in young cattle with severe respiratory disease whether they are indoors or outdoors. The emphysema takes the form of small bubbles of gas within the interlobular, peribronchial, perivascular and subpleural connective tissue; in some cases one or more large bullae, up to ten cm in diameter develop. This lesion in the bovine animal is not identical with the common forms of emphysema in man which are defined by some authorities as an increase in the size of the airspaces distal to the terminal bronchioles with destruction of the alveolar walls; these conditions are not reversible. There is no unequivocal evidence that persistent coughing or a persistently raised respiratory rate or even increased respiratory efforts *per se* will produce interstitial emphysema in normal lung tissue unless the bronchi supplying it are affected in some way. A link between bronchial reactions and interstitial emphysema is suggested by the fact that interstitial emphysema can occur in lungs in the absence of pulmonary consolidation or widespread alveolar congestion and oedema. It is likely that there is some intrinsic change in the bronchi leading to increased airway resistance. This might be bronchospasm, congestion or oedema of the bronchial wall or exudate in the bronchial lumen. The increased airway resistance leads to overinflation of the part of the lung that is still being ventilated and rupture of alveolar walls in these lobules allows gas to escape into the interstitium. The accumulation of gas in the interstitium inhibits inflation of the adjacent lobules and around large bullae the alveoli may be collapsed. All these changes will interfere with pulmonary ventilation and cause respiratory distress. It is important to realize that interstitial emphysema is potentially reversible, the gas being absorbed over a period of several weeks. From a diagnostic point of view, interstitial emphysema is a useful marker when considered along with the other lesions in the lungs it occurs commonly in lungworm infection and has been associated with cases of RS virus and PI3 virus infection (11, 18).

Severe Chronic Pulmonary Disease

Severe chronic pulmonary disease due to immunoinflammatory lung damage produces a chronic clinical syndrome lasting one to six months or longer. Affected animals usually fail to gain weight, may even lose weight, and eventually die from respiratory failure or cardiac failure. Cor pulmonale leading to congestive cardiac failure is less frequently seen in young cattle than in adult cattle with diffuse fibrosing alveolitis. Animals with chronic pulmonary disease may ostensibly be presented clinically as cases of acute pulmonary disease due to a flare-up of the original condition or infection of the damaged lungs by another agent. It can be very difficult to elucidate the initial events that take place to produce chronic pulmonary damage since they may have happened months prior to the lungs of the animal becoming available for examination.

The most severe form of chronic pulmonary disease in groups of young animals grazing is the chronic granulomatous pneumonia, due to aspirated lungworm eggs that occurs with bronchitis in patent lungworm disease. This combination of lesions can be fatal. The chronic pneumonias occurring in young animals indoors, particularly the non-suppurative pneumonias, may eventually resolve but take months to do so. Chronic suppurative pulmonary disease (CSPD) is a term that has been applied to the clinical syndrome produced by three types of pulmonary lesions which occur separately or in any combination; it is useful since it is very difficult in most cases to distinguish between them clinically. The three lesions leading to CSPD are (i) chronic suppurative pneumonia (ii) chronic pulmonary abscesses and (iii) bronchiectasis. With these conditions there may be extensive adhesive pleurisy with strong fibrous connective tissue adhesions developing between the lobes of the lungs and adjacent structures. When this degree of lung damage has occurred there is virtually nothing that can be done to reverse the pulmonary disability.

Conclusions

The reactions that occur in young bovine animals during respiratory tract disease are diverse and complex even from a morphological point of view. Nevertheless it is possible to group them into several readily identifiable broad categories which are useful since they supply clues about the aetiology of the reactions and about the functional disturbances associated with them. Although the reasons for some of the cellular and tissue reactions that make up these lesions are better understood now, there is still a lot to discover, much of it related to the bovine equivalent of fundamental problems inflammation, immunology and microbiology.

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