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Animal models for diseases of respiratory system

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ABSTRACT

Latest trends in understanding of respiratory diseases in human beings can be derived from thorough clinical studies of these diseases occurring in man, but conducting such studies in man is difficult in terms of experimental manipulation. In the last 2 decades, various types of experimental respiratory disease models has been developed and utilized by investigators, which have contributed a lot to the understanding of respiratory diseases in man, but only little investigation has been done on the naturally occurring pulmonary diseases of animals as potential models which could have added to our knowledge. There are certain selected examples of spontaneous pulmonary disease in animals that may serve as exploitable models for human chronic bronchitis, bronchiectasis, emphysema, interstitial lung disease, hypersensitivity pneumonitis, hyaline membrane disease, and bronchial asthma.

1. Introduction

An animal model is a living, non-human animal used during the research and investigation of human disease, for the purpose of better understanding the disease without the added risk of causing harm to an actual human being during the process. The animal chosen will usually meet a determined taxonomic equivalency to humans, so as to react to disease or its treatment in a way that resembles human physiology as needed. Many drugs,

treatments and cures for human diseases have been developed with the use of animal models. (Chakraborty *et al* 2009; Kari *et al* 2007).Animal models serving in research may have an existing, inbred or induced disease or injury that is similar to a human condition. These test conditions are often termed as animal models of disease. The use of animal models allows researchers to investigate disease states in ways which would be inaccessible in a human patient, performing procedures on the non-human animal that imply a level of harm that would not be considered ethical to inflict on a human. In order to serve as a useful model, a modeled disease must be similar in etiology (mechanism of cause) and function to the human equivalent. Animal models are used to learn more about a disease, its diagnosis and its treatment. Animal models have physical characteristics or suffer from illnesses similar to those seen in humans. They allow comparisons to be drawn between animal and human physiology, and help our understanding of how the human body functions. Comparative biology studies the differences and similarities between species, allowing predictions to be made, and concepts to be extrapolated from one species to another. There are many respiratory ailments of humans for which certain naturally occurring diseases of animals have been chosen in the hope to yield certain clues to understand pathological and clinical investigations.There is a list of naturally occurring respiratory disease conditions in animals which have been used as a model for parallel conditions in humans, among which certain conditions need be discussed.

2. Canine Chronic Bronchitis

It has been seen that chronic bronchitis occurring in the dog closely resembles, both clinically and pathologically, the disease of chronic bronchitis in man. (Pirie & Wheeldon 1976). This condition has been defined in clinical descriptive terms similar to the definition used in humans. Chronic bronchitis in the dog refers to the condition of subjects with chronic or recurrent excessive mucus secretion in the bronchial tree. This is a disease of adult dogs and is found from middle age onward. Although larger breeds, such as German shepherds, can be affected, chronic bronchitis typically occurs in smaller breeds, such as poodles and terriers, and is commonly seen in obese animals. The disease has an insidious onset and a progressive course: usually by the time the dog is presented it has been coughing for several months. Coughing is often precipitated by exercise or excitement, and in a number of cases it is productive, with gagging and expectoration. The dominant feature at postmortem examination is the excess amount of mucus present in the airways; the mucus extends throughout the tracheobronchial tree, and there is often pooling at the tracheal bifurcation. Beneath the mucus, the mucosa appears roughened and opaque; microscopically, it is thickened by irregular and diffuse fibrosis, edema, and mononuclear cell infiltration. Most importantly, the mucus-secreting apparatus is increased in size, tracheobronchial mucous glands proliferate and enlarge so that they completely surround the airway lumina, and there is marked increase in the number of epithelial goblet cells. In addition, there is qualitative change in the mucus, with a shift in the production of the different types of mucosubstances. The epithelial mucosubstances of the healthy canine bronchial system have been studied by Spicer *et al,* 1971 and Wheeldon *et al* 1976. The goblet cells of the canine bronchial epithelium were found to contain largely sulfomucins, but the mucous glands produced both sulfomucin and sialomucin as well as neutral mucins. In man, nearly all the goblet cells contain some acid mucosubstances that consist of periodate-reactive sulfomucins and sialomucins. The mucous glands of the human bronchial system contain mostly acid mucosubstances, the majority of which are sialomucin. The sialomucins in human respiratory mucus are of two types, one susceptible to neuraminidase and the other resistant to it. Both types of sialomucin have been identified in the canine respiratory tract. Generally speaking, the mucosubstances of the canine and human respiratory tracts are similar; however, there are differences in distribution, notably the predominance of sulfomucin in the goblet cells of the epithelium of the canine tracheobronchial tree. Dogs with naturally occurring chronic bronchitis have decreased amounts of epithelial sulfomucins together with a corresponding increase in epithelial sialomucins.

3. Chronic bronchitis and bronchiectasis in rats

Chronic bronchitis in man is defined as a clinical disorder characterized by excessive mucus secretion in the bronchial tree manifested by chronic productive cough not due to other known specific causes. Enlargement of the tracheobronchial mucous glands is the characteristic morphologic finding, together with an increase in the number of mucus-secreting cells in the surface epithelium at all levels of the airways. The clinical signs are difficult to detect and evaluate in most animal species, therefore the morphologic changes of chronic mucus hypersecretion

are relied upon heavily in defining an animal model of chronic bronchitis. When studying chronic bronchitis in rats, one important factor must always be kept in mind. Rats are very susceptible to a serious contagious syndrome referred to as chronic respiratory disease (CRD). Many agents have been suggested as causing chronic respiratory disease, with *Mycoplasma pulmonis* infection being frequently mentioned. Young rats appear perfectly well, but by early adulthood (1 or 2 months), clinical signs (such as abnormal breathing sounds) may be apparent. Many rats develop catarrhal rhinitis and suppurative otitis media. Varying numbers develop pneumonia characterized by peribronchial infiltration of lymphoid cells, sometimes with distention of bronchi and bronchioles by mucus and polymorphonuclear leukocytes. Severe bronchiectasis with squamous metaplasia of bronchial epithelium may develop, with one or more lobes of the lung being converted to a mass of multiple large abscesses. Chronic bronchitis, characterized primarily by chronic mucus hypersecretion, as in man, does not occur spontaneously in rats. As discussed above, chronic respiratory disease characterized by bronchitis and bronchiectasis does occur in many rat colonies. In general, this disease, because of the more inflammation and involvement of the pulmonary parenchyma, does not qualify as a good animal model for chronic bronchitis, but it may be a useful model for describing the destructive airway changes leading to bronchiectasis. "Bronchitis" in rats, however, have been used in a number of studies such as mucus transport in the tracheobronchial tree and the effect of exposure to irritant gases. Lindsey *et al* (1971) have provided the most definitive study of chronic respiratory disease in rats and have firmly implicated Mycoplasma pulmonis as the primary microbial cause. In their study, dramatic hyperplasia of bronchial epithelium accompanied lesions in peribronchial lymphoid tissue. This resulted in marked increase in height and piling up of epithelium along bronchial walls. Mucus production increased markedly. As the process continued, epithelial cells along the luminal surface underwent squamous metaplasia with loss of cilia. Simultaneously, neutrophils continued to accumulate in the bronchial lumens. Peribronchial lymphoid cuffing, hyperplasia of bronchial epithelium, and continued influx of neutrophils into the bronchi seemed to provide a vicious cycle for development of advancing lesions along the bronchial arborizations and in the surrounding parenchyma. The accumulation of lymphoid cells in bronchial walls and marked hyperplasia of bronchial epithelium often appeared directly related to stagnation and progressive accumulation of purulent exudate in more distal bronchi and bronchioles. As these changes increased in severity, the more distal parenchyma became atelectatic, and often the purulent exudate extended into terminal bronchioles and alveolar spaces. When neutrophils were present in alveolar spaces they were always found to be mixed with macrophages. Both of these cellular elements were sometimes so densely packed into the collapsed alveoli as to give the appearance of a solid tissue. Accumulation of peribronchial lymphoid cells often was accompanied by lesions in adjacent alveoli. These alveoli were lined by cuboidal epithelium and filled with neutrophils and macrophages.

The occurrence of bronchiectasis is clearly associated with extreme accumulation and subsequent impoundment of purulent exudates anywhere along the bronchial tree. As the exudate continues to accumulate distally, the hyperplastic bronchiolar epithelium appeares to invade alveolar spaces, thus forming bronchiectatic airways in close association with the pleural surface. In a few instances, discrete abscesses can be found in lung parenchyma.

It is entirely possible that the contributions that properly studied rats with CRD might make to our understanding of the pathogenesis of chronic airway damage and bronchiectasis in times to come.

4. Emphysema

Pulmonary emphysema is defined as an anatomic alteration of the lung characterized by abnormal enlargement of air spaces distal to terminal, non-respiratory bronchioles and accompanied by destructive changes of alveolar walls. The term has also been applied to abnormal increases in distal airspace size due to hyperinflation atrophy, or hypoplasia. There are four major types of emphysema, based on the primary anatomic location of lesions. The centrilobular (centriacinar) type primarily involves the respiratory bronchioles. Panlobular (panacinar, diffuse or diffuse generalized) emphysema is a general involvement of respiratory bronchioles, alveolar ducts, and alveoli. Paraseptal emphysema is the destruction of respiratory epithelium along lobular septae. A fourth type is one in which the lobule is irregularly involved, an example being paracicatricial emphysema, in which destruction is found adjacent to scars in the lung.

Emphysema is occasionally seen in any species of animals, but the details are often lacking. Clearly, some horses develop destructive emphysema, and elegantly detailed pathophysiologic studies are available (Gillespie & Tyler 1969). Emphysematous changes have been observed in lungs of most species in association with other

disease processes. Inflammatory changes in bronchioles of dogs may extend into alveolar ducts, leading to alveolar wall destruction and formation of large bullae at edges of lobes (Suter & Ettinger 1975). "Spontaneous" emphysema has been observed in rats in the presence of inflammation of airways and parenchyma (Casarett 1953; Palecek & Holusa 1971). The Blotchy Mouse presents a spontaneous model that may be useful for certain studies of emphysema, although the condition is not age-related and occurs in immature subjects. These mice have a genetically determined effect that prevents the generation of the lysine-derived aldehyde necessary for cross-linking of collagen and elastin (Rowe *et al* 1974; Hunt 1974; Starcher *et al* 1977). Their lungs have enlarged terminal airspaces, attenuated alveolar walls, and functional characteristics typical of emphysema (Fish & Kuhn 1976).

An important question before choosing an animal model of emphysema is to ask whether the pathogenesis of the disease of the model closely mimics the pathogenetic pathways of the human disease, whereas for the study of a therapeutic approach a model that is characterised by a well defined end-stage of the disease may be more attractive.

5. Bronchial asthma models

Bronchial asthma occurs as either the IgE-mediated (extrinsic) or non-IgE-mediated (intrinsic) type of asthma which does not occur in animals, with the possible exception of certain dogs. Dogs seem to be the only animals in which a defined hypersensitivity disease related to aeroallergens occurs. The clinical disease is most commonly ragweed pollenosis, although hypersensitivity to grass, tree, house dust, and cat antigens has been identified. The clinical manifestations include conjunctivitis, rhinitis, and an intensely pruritic dermatitis. In contrast to seasonal pollenosis in man, dermatitis, rather than ocular and respiratory symptoms, constitutes the major canine seasonal symptom. The only immune response defined has been the presence of reaginic antibody and the percutaneous absorption of pollen protein antigens has not been demonstrated.

A clinical syndrome in dogs similar to asthma does occur in pollen-sensitive dogs manifested by cough, dyspnea, and production of thick ropey mucus. This is rare and, although its incidence has not been adequately documented, it appears to have a much lower rate of occurrence in allergic dogs than does asthma in allergic humans. Canine respiratory responses have been induced by immunologic stimuli in both the anesthetized and unanesthetized animal. When the allergic animal is exposed to the appropriate aerosolized antigen in a chamber, acute dyspnea will develop. That is, increased frequency of respirations and labored breathing will occur. If the animal is removed from the test chamber, gradual recovery occurs, and if the dog is treated with epinephrine, there is more rapid resolution of these respiratory changes. There is also an evidence of eosinophilic bronchiolitis with many morphologic similarities to the lesions seen in long-standing human asthma. These lesions are characterized by marked smooth muscle proliferation in distal airways, glandular hyperplasia, eosinophil infiltrates in the hyperplastic mucosa, bronchospasm, and abundant plugging of smaller airways by mucoeosinophilic debris. These changes suggest that further exploration of this bovine disease is indicated.

6. Hyaline membrane disease models

The syndrome of hyaline membrane disease (HMD) is believed to be an expression of a basic defect in elaboration and secretion of pulmonary surfactant, developing when the lung has not been exposed in utero to hormonal stimuli necessary for lung maturation, or because the surfactant producing cells have been damaged, as may occur during episodes of hypotension or hypoxia. Not only is its pathophysiology carefully documented, but major advances have occurred in therapy, and prenatal prediction and prevention of the disorder are possible in some instances. Although considerable research effort has been directed at various experimentally induced models of HMD, little attention has been paid to the potential research applications of naturally occurring HMD in domestic animals. HMD has been reported and detailed largely in two species, the foal and the piglet (Slauson 1979). Foals born with HMD are usually carried to term and have been referred to as "barkers" because of a characteristic expiratory grunt (Rossdale & Leadon 1975; Rossdale *et al* 1967; Rossdale 1972; Mahaffey & Rossdale 1959). Affected foals may be hypoxemic and have respiratory distress, as indicated by reduced tidal and maximal tidal volumes, increased respiratory rate, and low arterial blood oxygen saturation. Signs of cardiac dysfunction, as evidenced by a marked jugular pulse, rapid heart rate, and a hard peripheral pulse, may be present in some foals. Histologic changes in the lungs include uneven airway expansion, edema, and hemorrhage. A marked surfactant

deficiency can usually be demonstrated in these foals (Rossdale *et al* 1967). Central nervous system signs, presumably related to growing anoxia, are clonus, generalized convulsions, loss of the sucking reflex and affinity for the mare, apparent blindness, opisthotonos and extensor rigidity of hind and fore limbs, loss of righting reflexes, incessant chewing, sneezing, asymmetric pupillary apertures, muscular flaccidity and coma, and wandering or dummylike behavior. (Mahaffey & Rossdale 1957; Palmer & Rossdale 1975).

An almost invariably fatal condition of newborn piglets, characterized by respiratory distress and, in some instances, subcutaneous edema and a short, fine haircoat, was first observed in England in 1973. Affected piglets produced characteristic expiratory grunting sounds reminiscent of the so-called "barker" syndrome of foals, and consequently they were called "barker" piglets. Very soon after birth, affected piglets develop respiratory distress and at necropsy they have a distinctive array of lung lesions that includes uneven expansion of the airways, epithelial necrosis, hyaline membrane formation, and hemorrhages. Lungs were also characterized by the presence of abnormal, probably immature alveolar epithelium, and by very marked deficiency of surfactant. Gross pulmonary lesions consisted of atelectasis and edema. Histologically the lungs showed an uneven expansion of alveoli; dilatation of bronchioles; subpleural, interlobular, peribronchial, and peribronchiolar edema and hemorrhage. Some alveoli had a glandular appearance or fetalization similar to that seen in the lungs of 90-day-old fetuses. The glandular appearance was due to the presence of large, rounded, or polygonal cells containing cytoplasmic PAS-positive material and lipid free vacuoles. Hyaline membranes containing blood cells and cellular debris were common features of small respiratory passages. Subsequent electron microscopic studies confirmed that the pulmonary lesions are characterized by immaturity of the distal airways and of alveoli, by severe alveolar epithelial hyperplasia and hypertrophy, by increased width of the blood-to-air barrier, by alveolar and bronchiolar epithelial degeneration and separation, by the production of alveolar and bronchiolar hyaline membranes, and by alveolar hemorrhage and alveolar and peribronchial edema (Bradley & Wrathall 1977). Many of the hyperplastic cells of the alveolar epithelium are pyramidal, rest on a basement membrane, have microvilli on their luminal surfaces, form tight junctions with their neighbors, and contain reduced numbers of lamellated electron-dense inclusions in the cytoplasm. These cells are dystrophic Type 1 or Type II pneumocytes. Both types contain large amounts of cytoplasmic carbohydrate material and are deficient in lamellated inclusions associated with Type II pneumocytes of normal piglets. These two animal species can thus be regarded as potential models for hyaline membrane disease.

7. Hypersensitivity pneumonitis models

Hypersensitivity pneumonitis (extrinsic allergic alveolitis) has been identified as a naturally occurring disease in cattle and horses, although it is presumed that other domestic species may also develop the disease. The bovine form of farmer's lung was, interestingly enough, first described in cattle from the same district of Britain in which the first human cases were recognized (Pirie *et al* 1971; Wiseman *et al* 1973). Both acute and chronic forms have been identified. Precipitating antibodies (precipitins) to *Micropolyspora faeni* can be demonstrated in the sera of cases of bovine "farmer's lung" by double diffusion tests (Pirie *et al* 1972; Hawbowrne *et al* 1970; Nicolet *et al* 1972). Intradermal injection of *M faeni* antigen produces skin thickenings that reach maximum size after about 4 hours and slowly decline over the next 72 hours. Biopsy of the skin test site at 4 hours reveals that the swelling is mostly due to local edema in the dermis, and many neutrophils can be seen within small blood vessels, emigrating through their walls and accumulating around them; this histologic appearance is consistent with that of an Arthus reaction.

In acute cases the lungs are superficially normal, but closer inspection reveals the presence of a number of small gray spots on the pleural surface of many lobules. The peripheral acini of each lobule are overinflated, and this produces a raised pale edge around a darker-red central portion. On microscopic examination, however, widespread pulmonary lesions can be observed. There is diffuse infiltration of alveolar septa by lymphocytes, plasma cells, and interstitial cells, and intraseptal aggregates of lymphocytes without germinal centers are present. The exposure of horses to dusts derived from avian excreta can produce hypersensitivity pneumonitis. An allergic reaction may take place in the small airways rather than in the alveoli as is typical of farmer's lung (extrinsic allergic alveolitis may also involve the bronchioles). The presence of pulmonary eosinophilia in some animals could be related to exposure or allergy to inhaled fungi, as in allergic bronchopulmonary aspergillosis or the pulmonary eosinophilias of man. There are several factors that suggest that the disease in these horses is at least partially a Type 3 immune response. Biopsy specimens from the areas of intradermal tests to chicken serum resemble Arthus-

type reactions induced experimentally in normal horses. There is no eosinophilia in the blood or bronchial secretions. Circulating precipitating antibody can be demonstrated and can be shown to increase and decrease relative to exposure to the specific antigen. The clinical signs can be reproduced some 4 hours after inhalation of chicken antigen. Other immunologic reactions, specifically the Type 1 and Type 4 immune reactions, have been related to hypersensitivity pneumonitis in man. Thus horses can be used as suitable models to study hypersensitivity pneumonitis.

8. Interstitial lung disease models

ILD is characterized by spontaneously occurring primary or idiopathic pulmonary fibrosis and diffuse fibrosing alveolitis and such a condition may exist in bovines (Pirie & Selman 1972). Diffuse fibrosing alveolitis in the bovine species seems to be a distinct clinical and pathologic entity. Clinically, these cases can be readily detected because, although the animals are usually bright, they have a persistently high respiratory rate, widespread adventitious sounds over both lung fields, and a cough. At rest hyperpnea is obvious, and even mild exercise is not readily tolerated (exercise intolerance).

The lesions seen microscopically are distributed widely in all the lobes of the lung, and the fibrosis is characteristically within the interstitium of the respiratory acinus. The cellular thickening and fibrosis of the alveolar septa conform to the criteria suggested for diffuse fibrosing alveolitis. The second criterion is the presence of large mononuclear cells in the alveolar space, although in most cows the interstitial reaction predominates. Hyperplasia and metaplasia of the glveolar epithelium are not considered essential features of the disease in man, but they are present in many bovine cases. Although the predominant changes in the lungs are in the alveoli, there is also a reaction in the bronchial tree. It has been suggested that one form of human fibrosing alveolitis could be due to farmer's lung, and it is possible that a similar pathogenesis is responsible for the disease in the cows with precipitins against *M faeni*, although there are some differences between the changes in these lungs and those in bovine farmer's lung (Breeze *et al* 1975; Pirie *et al* 1976). This potential model for ILD obviously awaits further definition.

9. Conclusion

Most of the diseases, syndromes, lesions, and occurrences mentioned are usefulness as models for parallel human diseases of the respiratory tract. All of them seem to have reasonably direct corollaries in diseases of human beings viz they are naturally occurring diseases in animals of sufficient size to permit patho-physiologic detailing, and they are of common enough occurrence to be easily induced in different animal species. For instance, Hypersensitivity pneumonitis has been best detailed in cattle and in horses and is clinically, etiologically, immunologically, and morphologically similar to the disease in man. Hyaline membrane disease has been poorly documented in animals, with the possible exception of the neonatal respiratory distress syndromes of foals and piglets. So these animal species can be used as potential spontaneous models for such conditions. Hence we can conclude here that there many respiratory disease conditions in different animals which are clinically and pathomorphologically similar to disease conditions in humans and their true potential as comparative pulmonary disease models can be realized.

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