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Review

Animal models of bronchial asthma

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Abstract. Due to the continuous increase in prevalence and morbidity in asthma, there is an urgent need to improve present therapy by drugs with new modes of actions. In contrast to many human diseases, allergic asthma does not occur in the animal world. Therefore, we have to mimic some characteristic feature of asthma in animals. For this reason, a wide variety of animal models have been developed and are employed in the search for new chemical entities for asthma therapy. In the present paper, the experimental models of the most characteristic asthma symptoms are critically reviewed.

Key words: Animals – Models – Asthma – Allergy

Introduction

The growing seriousness of asthma in the general population has been recognized by increased prevalence, morbidity, and mortality rates in the past 20 years. From 1980 to 1987 the prevalence rate of asthma in the United States increased 29% [1]. But asthma is also increasing in severity and mortality throughout the world. It has been estimated that 3–10% of the population worldwide suffer from asthma. Of more than 150 million asthma patients across the world, more than 100,000 die every year. In Germany alone, asthma is responsible for 6,000 asthma deaths per year – nearly as many as the AIDS death toll.

The continuous increase in prevalence, severity, and mortality in industrialized countries highlights the deficiency of suitable treatment. Of the several drugs currently available neither doctors nor patients are completely satisfied with their effects. There is no doubt that we urgently need new and effective drugs which are able to treat or even possibly cure the allergic inflammation.

In contrast to other disorders such as epilepsy, heart insufficiency, arthrosis, etc., allergic asthma does not occur in the animal world. To mimic bronchial asthma in animals, a wide variety of animal models have been developed. A growing dilemma for those of us interested in the discovery and development of new drugs for the treatment of asthma is that the more we learn about this increasingly complex disease, the more difficult it has become to find appropriate animal models. The use of an appropriate model could help us to make the development of new chemical entities (NCEs) for the treatment of human allergic disorders more predictable. Over the past 5 years there has been a marked increase in the number of publications appearing in the literature which describe different models of allergic airway disease in which mechanisms, thought to be relevant to asthma in man have been explored. There have been many attempts to develop and characterize animal models that approximate human allergy or asthma. Each model has its own inherent advantages and shortcomings and unfortunately, no model is identical to the conditions found in human disease. Nonetheless, the development of relevant animal models continues in anticipation that they will aid in the examination of underlying processes that contribute to asthma or allergy, or will assist in the identification of novel therapies that can be used to treat these diseases. In the present paper I review the experimental models of asthma in different animal species.

What should we and what can we model?

Acute bronchospasm (early phase, immediate reaction)

An asthmatic patient's lower respiratory airways respond to an appropriate allergen by narrowing. This airway reaction often consists of two stages. The first is an immediate reaction upon allergen contact. The second phase is a delayed reaction ("late phase" bronchospasm) and occurs several hours after allergen challenge.

To our knowledge, there is no mouse model of acute bronchoconstriction.

Rats are relatively seldom used. A model of allergic bronchoconstriction has been described in the Donryu rat which

This paper is dedicated to Prof. Dr. med., Dr. h. c. Kay Brune in honour of his 60th birthday and in recognition of his work on inflammation.

is apparently more sensitive than the Wistar rat. After i.p. sensitization with ovalbumin, intravenously administered antigen induces an acute airway response [2].

Bronchial anaphylaxis in sensitized guinea pigs is a popular model of early, "immediate-type" allergic bronchoconstriction. Guinea pigs are actively sensitized, mostly with ovalbumin. The acute bronchoconstriction can be induced in either conscious or anesthetized animals. In anesthetized animals, the most widely used model is the often modified so-called Konzett-Rössler method [3]. Guinea pigs are usually challenged by aerosolized antigen. Beside the measurement of all practically important respiratory parameters (e.g. respiratory rate, tidal volume, R_L, C_{dyn}) and the control of blood pressure, this model also allows us to apply compounds via different routes. Drugs can be administered i.p., i.v., s.c., i.m. or p.o. but also directly intrapulmonary as an aerosol or dry powder [4]. In actively sensitized conscious guinea pigs, aeroallergen-induced dyspnoe or a reduction in specific airway conductance (sGaw) can be recorded by a noninvasive whole body plethysmographic technique [5, 6].

Until now, there has been only one attempt to induce acute experimental bronchospasm in ferrets. In our department, Hahn (personal communication) actively sensitized ferrets with house dust mite. Animals could be repeatedly challenged by mite containing aerosol. Ferrets responded with an early phase increase in airway resistance. Despite a less pronounced contractile response to histamine in comparison with guinea pigs, ferrets do have some advantages which maybe of use including relatively large lung size, long trachea, more human-like histological structure of the trachea, etc. [7]. According to our opinion, the ferret could prove a useful animal species and should be more frequently used in the respiratory pharmacology.

Immediate bronchoconstrictor response can be induced by antigen-challenge in actively sensitized rabbits [8].

As part of the reaction of the sheep naturally sensitized to Ascaris suum antigen, an immediate airway reaction (bronchconstriction) develops upon allergen provocation. Both rabbits and sheep can be challenged repeatedly on several occasions each >14 days apart [9, 10].

Lower airway disease in cats is a syndrome resembling chronic bronchial asthma with episodes of acute, life-threatening bronchoconstriction [11].

To study drug effects on acute bronchoconstriction, dogs naturally sensitized to Ascaris antigen have already been used in the 70ies [12–14]. In conscious Ascaris-sensitive dogs, Hahn and his co-workers [15] demonstrated that antigen challenge of the upper airways appears to elicit a significant increase in pulmonary resistance. Young animals can also be immunized with ragweed or other antigens [16].

Actively sensitized domestic pigs [s.c. injection of Ascaris suum allergen in a suspension of $Al(OH)_3$] developed an acute bronchocontraction following topical challenge with the antigen [17–19]. Weanling pigs were sensitized to ovalbumin (i.p. and s.c.) and were subsequently challenged three times with antigen aerosol. Animals exhibited immediate bronchoconstriction to ovalbumin [20]. Our aim was to develop a chronic model of asthma in domestic pigs or micropigs. Domestic pigs actively sensitized with Ascaris suum antigen showed the expected increase in airway resistance upon aerosol antigen challenge. However, their sensitivity to the antigen declined rapidly after antigen challenge was performed repeatedly with an interval of two weeks. After this desensitization, pigs could be sensitized with ovalbumin again. But the repeated challenge again resulted in a quick attenuation of airway responses to allergen. For immunization of micropigs, we used the scheme described by Metzger and his co-workers [21]. Briefly, micropig litter mates were injected i.p. with Ascaris-antigen within 24 h of birth. Afterwards, the micropigs were repeatedly treated with the antigen (i.p. injection) 4 times in 4 months. Unfortunately, there was no consistent response to allergen. In some animals, airway obstruction occurred after allergen challenge. There was, however, no response in some pigs. Apparently, young domestic pigs develop a rapid desensitization and micropigs are generally relatively resistant against sensitization. To develop a chronic asthma model in this species, there is probably only one possibility which should, however, be investigated: similarly to sheep, animals naturally sensitized by Ascaris worm should be selected for allergen-challenge studies. However, the use of domestic pigs in asthma research is limited by the rapid growth of these animals.

In monkeys sensitive to Ascaris immediate bronchoconstriction developed after inhalation of the antigen [22, 23].

Different classes of drugs are active on the acute phase bronchoconstriction in animals. Of course, β_2-adenoceptor agonists and antimuscarinic drugs prevent antigen-induced bronchoconstriction in actively sensitized guinea pigs in a dose-dependent manner. However, some drugs are also able to inhibit the development of this bronchoconstriction. First of all, histamine H_1-receptor antagonists are capable of attenuating the acute pulmonary airway narrowing [24]. This observation led to a false interpretation of the role of antihistamines in the treatment of bronchial asthma. A bronchodilatory effect was expected that was, however, not fulfilled in the therapy. Other drug classes such as leukotriene antagonists, PDE3 inhibitors showed more or less pronounced dilatory effects both in animals and in humans. Thus, the bronchodilatory effect of this type of new chemical entities (NCEs) can be "foreseen" in an animal experiment. With a few exceptions, such an effect can be predicted on the basis of animal data. Since the basic mechanisms of bronchodilation are relatively well understood, the knowledge of the mode of action may contribute to the realistic judgement of a possible human effect. Therefore, there might be no doubt that compounds increasing intracellular cAMP content are able to dilate bronchi. The false positive results with antihistamines are based on the different involvement of mediators in the development of the acute bronchoconstriction. Histamine is the major mediator in guinea pigs but not in humans. Therefore, it is evident that antihistamines can inhibit allergen-induced bronchoconstriction in guinea pigs where histamine is the dominant mediator of bronchoconstriction. Since histamine's role as mediator of bronchospasm in man is limited, the efficacy of classical antihistamines such as mepyramine, diphenhydramine in humans is practically zero.

Early phase allergic bronchoconstriction can be induced in a number of animal species. Due to the involvement of mediators that are not deterministic in humans, false positive judgement of NCEs can occur.

Late phase bronchospasm

In some asthmatics, an acute bronchoconstriction is followed by a second bronchoconstriction that appears 5–8 h after antigen contact. This is the so-called late-phase bronchoconstriction and can be induced in various species.

Similarly to the immediate bronchoconstrictor response, we did not find any data on the late phase bronchospasm in mice.

In anesthetized actively sensitized Brown Norway rats (ovalbumin in aluminium hydroxide gel + Bordetella pertussis), aerosolized ovalbumin induces both early and late phase bronchospasm (increase in lung resistance) [25]. Interestingly, ovalbumin-specific IgE level did not correlate with the magnitude of either the early or the late phase responses. An inverse correlation was, however, found between the specific IgG level and the late phase bronchospasm [26].

Guinea pigs were sensitized by i.p. injection of ovalbumin. 14 to 21 days after sensitization, animals were exposed to 1% ovalbumin inhalation for 2 min (macroshock) or 0.01% ovalbumin inhalation for 60 min (microshock). Late phase bronchoconstriction peaked variably between 17 and 24 h. Interestingly, the late phase is associated with an influx of eosinophils in both models but neutrophils only appeared after an inhalation of the high concentration of ovalbumin (macroshock) [27]. Zaagsma and his co-workers [28] showed that actively sensitized and challenged guinea pigs display early (0–5 h) and late phase (8–23 h after antigen challenge) bronchoconstrictor responses. Conscious actively sensitized (ovalbumin or Ascaris) guinea pigs challenged with aerosolized antigen produced late phase responses in only 50% of animals. These results failed to substantiate literature reports of a high incidence of late responses in the guinea pig [29]. An interesting model was developed by Heuer et al. [30]. Briefly, guinea pigs were actively sensitized with ovalbumin in alum and treated once with cyclophosphamide. Weekly inhalations of polymyxin B were additionally performed before and during sensitization. Under cover of mepyramine, all animals exhibited a pronounced early phase bronchoconstriction. Nine of 15 animals demonstrated a second phase (late phase – 4–8 h after challenge) bronchospasm. Based on their results, both methylprednisolone and WEB 2347, a platelet-activating factor (PAF)-antagonist inhibited the late phase development. The authors suggested the inflammatory nature of the late phase reaction. In the meantime, it has become obvious that PAF may be involved in inflammation in this model but not in human asthmatic inflammation. This difference might also explain why PAF-antagonists were highly effective in animal models but unfortunately not in man.

Some investigators have developed a method to sensitize newly born rabbits with booster injections at certain intervals afterward. Allergen exposure induced an acute bronchoconstriction, which fully resolved itself after 30 min to 1.5 h. About four hours after aerosol challenge a late phase bronchoconstriction was observed [31, 32].

Allergic sheep can be challenged repeatedly on several occasions each >14 days apart and classified on the basis of their airway response to Ascaris suum antigen aerosol as acute or dual responders. Acute responders show only an immediate increase in R_L whereas dual responders have an immediate and late phase (6–8 h after challenge) increase in airway resistance [9, 10]. The sheep model is well suited to mimic long-term therapy with drug inhalation [33]. Sometimes, the sheep model can also delivers false positive results. For example, it was shown that PAF antagonists were effective in the inhibition of late phase reactions [34]. Later it turned out that PAF antagonists are not effective in the treatment of human asthma.

In mongrel dogs with inherent sensitivity to Ascaris suum antigen, a late phase response to antigen aerosol can be induced [35].

It is known that in some aspects the pig seems to be more related to man when compared to the rat and guinea pig. Active sensitization of domestic pigs with s.c. injections of Ascaris antigen resulted in a bronchoconstrictor reaction after local antigen-challenge [17]. Alving's group uses pathogen free domestic pigs which are actively sensitized with Ascaris suum antigen. In order to achieve a pronounced allergic response, pigs are treated before and after allergen challenge with metapyrone, a cortisol-synthesis inhibitor, because endogenous cortisol controls the development of allergen-induced late phase reactions in pigs [18].

Use of primates is gaining popularity and significance in the development of new anti-asthma drugs [36]. Rhesus monkeys can be sensitized with Ascaris or they are naturally sensitized to Ascaris [37](. IgE-mediated asthma in rhesus monkeys has individual characteristics that are analogous to the individual responses of human patients [38]. Some monkeys (so-called dual responders) sensitive to Ascaris show early and late phase responses after inhaling the antigen [22, 23]. Cynomolgus monkeys are also suitable and useful [39].

Based on results obtained with NCEs in this model of asthmatic symptoms, it is likely that non-rodent species may have higher predictability than rodents.

Bronchial hyperresponsiveness

Bronchial hyperresponsiveness (BHR) is a major feature of bronchial asthma characterized by an exaggerated response to a wide variety of stimuli that can induce an increased resistance to air flow in the lung. In daily practice, it is always a warning of an ongoing bronchial asthma, if an apparently "healthy" asthmatic coughs at the change from warm to cold air ambience. There are several provoking stimuli that are used to demonstrate BHR. The list of these agents is long and includes, for example, cold air, histamine, 5-hydroxytryptamine (5-HT), adenosine, nebulized saline, etc. The pathogenesis of BHR remains to be fully elucidated, but it is considered to be closely linked to airway inflammation. Animal models might provide us with useful data for a better understanding of the interrelationship between these phenomena. It is evident that BHR in animal models should be produced by similar mechanisms to those producing BHR in patients suffering from bronchial asthma.

To investigate the mechanisms underlying BHR several murine models were developed. Mice can be sensitized with different antigens. Animals are usually intraperitoneally sensitized with ovalbumin and after 4 weeks challenged via an ovalbumin aerosol. BHR can develop via mechanisms independent of an inflammatory infiltrate. Since mast cell degra-

nulation occurs after antigen exposure, it was hypothetized that mast cells are involved in the induction of BHR in this mouse model [40]. Recently, Nijkamp and his colleagues [41] have demonstrated that both histamine and serotonin play a role in antigen-induced bronchial hyperresponsiveness in the mouse. By contrast, it is well known that serotonin does not play any role in the pathogenesis of human asthma because human mast cells, in contrast to murine mast cells, do not contain any serotonin. There are obviously strain variations in BHR in inbred mice. Konno et al. [42] found that the C57BL/6J strain is a low responder and that the A/J strain is a high responder. Apparently, the development of BHR is genetically determined and cannot be predicted by levels of pulmonary eosinophilia, airway inflammation, total IgE, or antigen-specific IgE. As shown in an elegant study by Brewer et al. [43], ovalbumin sensitization and repeated challenge caused no BHR to methacholine in some strains (e.g. A/J, CBA, C57BL/6), but induced pronounced BHR in more susceptible strains (e.g. Balb/c, FVP, SWR). BHR to methacholine was observed in ovalbumin-sensitized Balb/c mice, but not in C57BL/6 or B6D2F1 mice. It is interesting that the authors observed BHR in Balb/c mice in the absence of airway eosinophilia [45]. Miyabara et al. [46] employed high IgG responder (C3H/He) and high IgE responders (Balb/c) mice. Animals were immunized with i.p. administered ovalbumin (in alum) and treated with intratracheally instilled diesel exhaust particles (once a week for 5 weeks). Ovalbumin aerosol induced airways hyperresponsiveness in C3H/He mice. Surprisingly, the changes were very weak in Balb/c mice. Vargaftig and his co-workers [46] developed a murine model of antigen-induced BHR and airway eosinophilia. The special mouse strain named BP2, "Bons Producteurs 2" for High Line of Selection 2, produces large amounts of IgE. With regard to reproducibility, this strain appears to be stable and produces well-recognizable BHR to i.v. administered methacholine.

In actively immunized (ovalbumin) Brown Norway rats, repeated antigen challenge at 5-day-intervals led to an increased response to inhaled methacholine [47]. There is a tendency to desensitization in guinea pigs and rats when they undergo repeated challenge [48]. The Brown Norway rat can be sensitized with trimellitic anhydride (TMA). In these animals, the repeated low-dose allergen challenges (for 7 consecutive days) produce slight epithelial damage and BHR to i.v. acetylcholine. BHR was independent of ongoing eosinophilia in the airways [49]. Similar results were found by Kips et al. [50]: In actively sensitized Brown Norway rats, airway inflammation is not always associated with BHR. In contrast, Elwood et al. [51] demonstrated that BHR after allergen challenge is associated with the presence of airway inflammation and persists despite the regression of inflammatory cells in the bronchoalveolar lavage (BAL) fluid after multiple antigen (ovalbumin) challenge. Glucocorticoids (e.g. dexamethasone) abolished BHR and increased inflammatory cell count. In contrast, cyclosporine A had no effect on BHR to inhaled acetylcholine and only inhibited eosinophil and lymphocyte influx. Similar results were found in a recent study [52]. However, we could not confirm the dissociation of airway hyperreactivity lowering and anti-eosinophil effects of cyclosporine A. In BP-2 mice, we found that cyclosporine A is able to abolish both i.v. methacholine-induced BHR and eosinophil migration as also shown by Nagai et al. [53] in Balb/c mice. Airways of inbred rat stains varied in their responsiveness to i.v. injections of carbachol or 5-HT [54, 55]. Interestingly, Brown Norway and Lewis rats were poor responders to both stimuli [54]. In an excellent study, Fisher and Lewis rats were compared. Lewis rats exhibited a significant effect on maximal lung resistance and elastance, whereas Fisher rats did not [56]. Environmental poisons can also elicit BHR. In rats, ozone induces BHR to acetylcholine and significant neutrophilia in bronchoalveolar lavage fluid at 24 h after exposure [57]. There are strain dependent differences in ozone-induced BHR in some inbred rat strains. Lewis and Long-Evans rats develop BHR to i.v. serotonin after ozone exposure, whereas other strains such as Wistar, Sprague-Dawley, Brown Norway, Fisher 344 rats do not. Genetic factors are likely to account for this variability in sensitivity of airways to ozone [58]. Although there was no change in pulmonary resistance in Long-Evans rats treated chronically with cigarette smoke, the animals exhibited BHR to methacholine [59]. Allergen-induced BHR in an appropriate rat strain is a suitable model for studying drug effects on BHR. The model has many characteristics of human allergen-induced BHR. It is likely that Th2 lymphocytes may play a regulatory role in the development of BHR in the rat. The majority of the above-mentioned BHR models in rats have several disadvantages. Non-specific stimuli (mediators, cholinergic agonists, etc.) are usually given intravenously. This is a common practice. Inhaled stimuli are exceptions [60–62]. The cardiovascular effects of i.v. administered stimuli such as serotonin, carbachol, methacholine which may indirectly influence lung mechanics, are largely ignored. Probably, the choice of non-specific stimuli may also have profound influences on the outcome of BHR studies because different agonists cause bronchoconstriction via different mechanisms. Additionally, certain mediators (e.g. serotonin) are not involved in human asthma pathogenesis.

Guinea pigs are relatively often used to study the influence of drugs on BHR. Aoki et al. [63] demonstrated BHR to i.v. administered histamine in actively sensitized (ovalbumin) and challenged guinea pigs. Repeated ovalbumin challenge by aerosol (twice weekly for 4 weeks) of previously sensitized guinea pigs produced striking BHR to inhaled acetylcholine [64]. There are several other possibilities to immunize guinea pigs and to elicit BHR. Western red cedar asthma is the most common form of occupational asthma in the Pacific Northwest. Plicatic acid is the chemical component of Western red cedar that causes asthma. In guinea pigs, an asthma model has been developed using plicatic acid conjugated with $Al(OH)_3$ as an adjuvant given bi-weekly for a period of 6 months [65]. Repeated exposures to toluene diisocyanate results in BHR in guinea pigs [66]. BHR and eosinophilic inflammation can also be induced by trimellitic anhydride in sensitized guinea pigs [67]. Although sensitized conscious guinea pigs showed lung dysfunction (increase in airway resistance, decline in airway conductance) upon repeated allergen challenge, no BHR to aerosolized acetylcholine was observed [68]. General caution should be exercised in using non-invasive measurements when changes in the upper airways (nose and larynx) cannot be excluded. In rats and guinea pigs, the upper airways constitute the domi-

nant portion (about 80%) of the total airway resistance [69]. Thus, in conscious animals, experiments should be carried out bypassing the nose.

Certain compounds can induce BHR in guinea pigs directly without immunization and challenge. Platelet activating factor (PAF) induces BHR to histamine, probably via activation of capsaicin-sensitive sensory fibres [70]. However, PAF did not induce bronchial hyperresponsiveness in atopic non-asthmatic patients [71]. IL-8 rapidly causes BHR via TxA2 release in guinea pigs [72]. Repeated intranasal administration of IL-5 results in a BHR to histamine that is associated with an accumulation of eosinophils [73]. When guinea pigs were exposed to sulfur dioxide gas, they showed BHR to i.v. serotonin [74]. Endotoxin administered as an aerosol or intraperitoneally induces neutrophilic airway inflammation and BHR to substance P in guinea pigs [75, 76]. The latter is more likely a model of BHR present in COPD.

In general, it is likely that BHR can be induced in guinea pigs. However, we do not believe that this is the best model to mimic human airway hyperresponsiveness. Based on our experience and that of others, it is obvious that the mouse and the rat are more suitable for studying BHR and the effect of NCEs on BHR than the guinea pig.

Apparently, the ferret is not a frequently used experimental animal species in asthma research. In vivo models of BHR in sensitized ferrets were not found. However, certain mediators (e.g. PAF) can induce BHR to methacholine in this species, as well [83]. But ferrets could be suitable for investigations of BHR induced by toxic compounds. Acrolein is a ubiquitous air pollutant that can cause adverse lung effects. Tracheas excised from ferrets treated with acrolein aerosol showed increased contractile responses to carbachol and acetylcholine indicating that acrolein can cause BHR in this species [84].

Allergic rabbits develop early and late phase asthmatic responses and subsequent BHR to histamine [31, 85]. This rabbit asthma model is basically a chronic model because animals can repeatedly be challenged [86]. Interestingly, isolated bronchi obtained from actively sensitized rabbits were not hypersensitive to methacholine in vitro [87].

The sheep represents a species that can also be used repeatedly for studying drug effects on BHR. It has been demonstrated that BHR can be induced by inhaled carbachol or histamine in challenged sheep [33, 88]. Pulmonary hyperreactivity can also be produced in sheep by inhalation of noxious substances (e.g. sulphur dioxide) or by PAF [89, 90].

Padrid and co-workers [91] have developed an asthma model in cats, a species that spontaneously develops idiopathic asthma ("lower airway disease"). The animals were repeatedly sensitized with i.m. injection of Ascaris suum antigen. Cats responded with increased airway resistance to aerosolized antigen and also demonstrated BHR to methacholine [92].

Dogs naturally sensitive to Ascaris suum were challenged with an aerosol of antigen. This produced a moderate increase in BHR to inhaled PGF2α but no change in BHR to methacholine, histamine or 5-HT [93, 94]. The BHR produced in dogs by inhalation of different stimuli is clearly different from that which occurs in asthmatics. A marked increase in neutrophils in the bronchoalveolar lavage fluid (BAL) is found. Accumulation of neutrophils is characteristic for COPD patients but not for asthmatics. It is, however, well known that BHR can also occur in COPD patients. Basenji greyhounds have a hereditary BHR to various environmental or pharmacological stimuli such as hypotonic solution, citric acid, methacholine [95]. But they can also be sensitized with Ascaris by weekly exposure over 4–6 months [96]. Their hereditary BHR has some similarities to the changes found in asthmatics. However, there are no clinical symptoms, a fact that represents a big difference from asthma in man.

BHR in immunized and challenged pigs was not measured. Recently, Sephadex suspension was instilled intratracheally into pigs in order to induced BHR in this species. Although Sephadex beads produced the usual focal peribronchial granulomatous reaction, no BHR to acetylcholine was observed [97].

Recurrent airway obstruction or heaves is an asthma-like condition of horses occurring naturally and relatively often in sensitive animals precipitated by exposure to moldy hay. As early as in 1964, it was reported that COPD in horses affects the small airways and is associated with hay dust exposure [98]. Around 12–50% of all horses in Europe and the United States suffer from this disease [99]. The predominant cell in BAL is the neutrophil. The number of neutrophils in BAL and in lung tissue sections correlates well with the severity of the disease [100]. Thus, the characteristics of this disease have more similarities with COPD than with bronchial asthma. There are several reasons why the horse is not a suitable experimental animal for studying COPD. One of them is their price. The expense of horses obviously reduces their use as a model of asthma or COPD.

In naturally sensitized atopic cynomolgus monkeys (*Macaca fascicularis*), BHR develops after multiple challenge with Ascaris-antigen and it is accompanied by a massive infiltration of eosinophils in the BAL [23, 36].

The use of transgenic animals will certainly contribute to an increase in the predictability of experimental animal asthma models. In IL-9-expressing transgenic mice, markedly increased BHR to inhaled methacholine was observed [62]. Furthermore, these mice show some impressive pathological changes that were not observed in actively sensitized and challenged animals: epithelial cell hypertrophy, increased subepithelial deposition of collagen, increased number of mast cells, accumulation of mucus-like material within non-ciliated cells. In immunized IL-5 transgenic mice, allergen provocation induced massive eosinophil influx which was suppressed by dexamethasone. Despite the high eosinophil counts, no BHR to methacholine was detected [101]. Based on these results the authors concluded that eosinophil overproduction and lung infiltration are apparently not sufficient to induce BHR, even in constitutively hypereosinophilic IL-5 mice. In other studies using IL-5 transgenic mice, antigen-induced lung eosinophilia was, however, associated with a BHR that was dependent on the recruitment and activation of eosinophils [64, 102].

The model of Sephadex-induced eosinophilia and BHR in rats was developed at the end of the 80ies [77, 78]: BHR to serotonin accompanied by peripheral and pulmonary eosinophilia was induced by i.v. administration of Sephadex particles. Interestingly, it has recently been published that

Sephadex-induced BHR may not be directly associated with recruitment of eosinophils [79]. An interesting study was performed in actively sensitized Brown Norway rats by Rossi et al. [80]. They demonstrated that Sephadex-induced eosinophila is associated with an increase in the late phase allergic response (increase in pulmonary resistance). In my opinion, the use of Sephadex spheres (usually G200) to induce blood and lung eosinophilia is more than problematic. The small beads obliterate capillary vessels, induce a local inflammation mostly in the lung tissue and consequently change the lung mechanics that may result in a non-physiological airway response. As in rats, following i.v. administration of Sephadex, BHR developed to acetylcholine in the guinea pig [81]. Although there is evidence that Sephadex induced BHR in guinea pigs could be related, at least in part, to blood eosinophilia and eosinophil activation [79]. This type of BHR cannot be considered to be of classical allergic pathogenesis.

There are several possible ways to investigate the effect of test compounds on bronchial hyperreactivity. In my opinion, sensitized and challenged mice are the most suitable species. At present, our experience with transgenic animals is relatively limited. However, the future definitely lies in the use of these animals. Due to changes in pulmonary mechanics, I advise against the use of Sephadex-treated animals when the effects of NCEs on BHR are to be studied.

Spontaneous increase in airways resistance

Spontaneous increases in airways resistance throughout the life are one of the most important characteristics of human asthma. Unfortunately, to our knowledge, there is no animal model which demonstrates a continuous increase in airway resistance to airflow after repeated antigen challenge. Neither in rabbits, sheep, dogs, nor in monkeys was this phenomenon observed although these species can be used and challenged repeatedly. Due to the disadvantages of the non-invasive techniques and differences in the nose-lung proportionality between small rodents and man [69], neither guinea pigs nor rats are suitable for measuring the spontaneous increase in airways resistance.

One key response of human asthma is wheezing, a response not elicited in most animal models. In 1995 Corcoran et al. [103] reported about the feline asthma syndrome characterized by recurrent bouts of coughing, wheezing and/or dyspnoea. Sometimes, mild or predominant eosinophilia in the airways was also observed.

Recruitment of inflammatory cells in the lungs

Bronchoalveolar lavage and mucosal biopsy studies in asthma patients provide strong evidence for prolonged eosinophil infiltration, mast cell and T cell activation. The progression of the disease and disease severity is apparently T-cell driven. More severe asthma, requiring steroids or proving resistant to corticosteroid therapy, is dominated by numerous activated T cells infiltrating the airways [104]. By contrast, mild asthma is associated with only low levels of T-cell activation [105].

Balb/c mice sensitized with ovalbumin and challenged by repeated exposure to ovalbumin yielded marked eosinophilia in bronchoalveolar (BAL) fluid [106]. Actively sensitized (ovalbumin) C57BL/6 and DBA/2 mice responded differently to aerosolized antigen: C57BL/6 mice were more susceptible to ovalbumin-induced pulmonary eosinophilia than DBA/2 mice. The allergic reaction is apparently mediated in C57BL/6 mice via a Th2-response, while a Th1-response was predominant in DBA/2 mice [107]. There is evidence that in ovalbumin-sensitized A/J mice pulmonary eosinophila develops to inhaled allergen via Th2-type mechanisms [108, 109]. It has also been shown that eosinophil influx can also vary dramatically in mice of the different strains. Strains such as 129/SV, CBA belong to non- or low responder. Strains as SWR, FVB, C57BL/6 responded to antigen-challenge with a marked increase of eosinophils both in the BAL and in the lung tissue [43]. A novel sensitization procedure was also been described in mice in 1997. Instead of i.p. injection of ovalbumin in alum, heat-coagulated egg white was implanted subcutaneously. 14 days later, the mice were challenged intratracheally with heat-aggregated ovalbumin. 48 h after antigen challenge, the eosinophil peroxidase activity in the lung was higher than in mice sensitized classically [110]. Based on their results, Balb/c mice appear to be the most sensitive strain. Regrettably, with regard to susceptibility, there is no clear differentiation between the strains. After repeated intratracheal challenge with house dust mite extract (HDM), there was a chronic inflammation characterized by increased numbers of eosinophils and lymphocytes in the lung of sensitized Balb/c mice [111]. In B10.RIII mice sensitized with HDM extract, the intranasal allergen challenge resulted in an eosinophil infiltration in the lung tissue [112].

Rats with a different immunization schedule are also frequently used to mimic airway eosinophilia. In Sprague-Dawley rats sensitized with ovalbumin (i.p.) and challenged by aerosol 14–21 days later, lung eosinophilia was detected [113, 114]. However, Brown Norway rats are usually employed to study drug effects on airways eosinophilia. Inhaled antigen (ovalbumin) causes an influx of eosinophils into the lung tissue and airway lumen [115]. Schneider et al. [116] quantified eosinophil migration into the lung parenchyma and into the bronchoalveolar space in three inbred rat strains. 14 days after immunization with ovalbumin in alum (s.c.) and ovalbumin with Bordetella pertussis (i.p.), animals were challenged with an ovalbumin aerosol for 60 min. In Brown Norway rats, eosinophil accumulation peaked at 48 h in lung parenchym and at 72 h in BAL. In contrast to Brown Norway rats, no pulmonary inflammation was observed in Lewis and Fisher rats indicating the eosinophil model in Brown Norway rats is useful for investigating changes in and influences on allergen-induced eosinophil migration into the lung. As in mice, a new sensitization method has recently been described that does not require adjuvants nor multiple boosters [117]: Wistar rats were sensitized with a single s.c. implant of a fragment of heat-coagulated ovalbumin and challenged 21 days later with intratracheal instillation of heat-coagulated ovalbumin. For comparison, they used the classical schema: intraperitoneal injection of ovalbumin in $Al(OH)_3$ as adjuvant, one booster injection on day 14 and challenge on day 21. The new sensitization technique resulted in a significantly higher number of eosinophils in the BAL 24 h after anti-

gen challenge. Thus, the authors believe that their novel sensitization procedure without adjuvant represents a significant improvement over existing methods.

There are several models of pulmonary eosinophilia using guinea pigs. Intraluminal eosinophilia usually develops between 18 h and 7 days after challenge in actively sensitized guinea pigs [118]. Underwood et al. [119] found that eosinophil influx was demonstrable at 4 h and peaked after 24 h following aerosol ovalbumin challenge. It persisted for at least 8 days. In general, actively sensitized guinea pigs are used. On day 15–30, the animals are challenged with aerosolized ovalbumin. 20 to 24 later the animals are sacrificed and a BAL is performed. Orally administered mepyramine (histamine H1-receptor antagonist) provides complete protection against immediate, often lethal, asthmatic response without influencing the late phase associated lung eosinophilic infiltration [120]. Sometimes, airway eosinophil accumulation elicited by allergen challenge was observed without accompanying BHR [121]. Hsiue et al. [122] developed an animal model of mite-induced allergic airway inflammation in guinea pigs. In our opinion, guinea pigs can be considered as a less appropriate species for studying drug effects on eosinophilia for several reasons. The number of eosinophils in the bronchoalveolar lavage fluid often undergoes seasonal variations. Similar seasonal changes are well-known this species [131]. Indeed, it was observed that the number of eosinophil granulocytes in the BAL is lower during the summer months (Achterrath-Tuckermann and Chand, personal communication). The major reason is that naive guinea pigs have a high proportion of eosinophils in their BALF in comparison with other animals including man. Constitutive levels of eotaxin observed in guinea pig lung may be responsible for the basal lung eosinophilia in this species [132]. Therefore, I recommend the use of other species, such as mouse or rat instead of guinea pig.

Neonatal rabbits sensitized with Alternaria tenuis or ragweed antigen in alum demonstrated a significant increase in eosinophils and neutrophils in the BAL after allergen challenge [133, 134].

In allergic sheep, there is an apparent increase in eosinophils and neutrophils in the BAL fluid obtained 24 h after challenge [88, 135, 136].

I did not find any publication about pulmonary eosinophilia in sensitized and challenged dogs. It is, however, known that LTB_4 and PAF increased eosinophila in in vivo perfused canine tracheas indicating an interesting model for in vivo chemotaxis [137]. An interesting model of airway eosinophila has recently been described: a dog under general anesthesia receives dry air through a bronchoscope every 48 h for two weeks. This procedure results in a persistent airway obstruction and eosinophilic inflammation not unlike that found in asthma [138].

Pigs that had been actively sensitized with repeated s.c. injection of Ascaris antigen were challenged with topical antigen in the lower airways under pretreatment with metapyrone, a cortisol-synthesis inhibitor. There was a marked eosinophil infiltration into the lung tissue at 8 h after challenge [139].

In atopic (Ascaris- or house dust mite-sensitive) rhesus or cynomolgus monkeys, the number of eosinophils increased 24 h after aerosol antigen challenge [140–142].

The use of Sephadex particles is a simple way to investigate the effect of drugs on BHR and eosinophilia, though strain-related differences can occur. Pulmonary eosinophilia in BAL fluid developed in each strain, and the magnitude of the response was Brown Norway > Lewis > Wistar > Fisher 344. With regard to BHR, only the Lewis strain exhibited a significant BHR [123]. On the other hand, one should take into consideration that Sephadex particles could fundamentally change the lung mechanics (development of pulmonary granulomas) resulting in a "non-physiological" response. Intratracheal instillation of Sephadex also caused eosinophil infiltration in rats that could be induced by upregulation of eotaxin [124]. Pulmonary eosinophilia can also be induced by different mediators or cytokines or Sephadex beads in naive guinea pigs. Administration of IL-5 to guinea pigs by intratracheal instillation induced a significant increase in the number of eosinophils in the BAL [125, 126]. Subcutaneous or intraperitoneal injection of recombinant human GM-CSF or mouse TNFα or recombinant guinea pig TNFα (intratracheal instillation) caused selective eosinophilia in the airways of guinea pigs [127, 128]. Intranasal administered anti-guinea pig IgE induced remarkable eosinophil infiltration in the airways of normal guinea pigs 6 h after challenge [129]. Airway eosinophilia in guinea pigs can also be induced by intravenous injection of Sephadex beads [130].

Among rodents and other small species, mice and rats are suitable species to study cellular changes in the lungs. Due to the relatively high number of eosinophils in normal animals, guinea pigs are less suitable. Sephadex-induced eosinophilia is a rapid and simple method but not suitable for studying allergic changes.

A further characteristic feature of the allergic airway inflammation is the extravasation due to increased microvascular permeability. It is likely that damage of the bronchial epithelium in asthmatics is caused by extravasation of plasma proteins, inflammatory cells, enzymes, and other mediators. These changes may further prime nerve receptors in the airway resulting in BHR.

In actively sensitized animals, antigen challenge results in increased vascular permeability. Appropriate mediators generated in the blood and airways of asthmatic patients can also induce plasma exudation when administered experimentally to animals. The extent of microvascular leakage is usually investigated using Evans blue dye or other markers (e.g. albumin) of plasma exudation. Antigen (ovalbumin) challenge in actively sensitized Brown Norway rats results in both early and late phases of plasma leakage as measured with Evans blue [143]. It is likely that increases in microvascular permeability induced by antigen challenge occur independently of eosinophil infiltration in the Brown Norway rat [144]. Intravenous PAF also causes dose-related increases rat airways [145]. Topical capsaicin or histamine induced leakage of plasma from guinea pig tracheal mucosa [146]. Bradykinin instillation into airways of guinea pigs induces microvascular leakage which can be inhibited by B2-receptor antagonists [147]. In guinea pigs, bilateral vagal stimulation results in the so-called neurogenic plasma extravasation [148]. I.v. administered substance P or LPS induce microvascular plasma leakage in various vascular beds, including the lung [148, 149]. Environmental factors such as

tobacco smoke can also cause an increased plasma leakage [150].

Disodium chromoglycate (DSCG, applied topically), theophylline (i.v.) or budesonide (i.p.) attenuated histamine- or capsaicin-induced plasma leakage in guinea pigs [146], indicating a possible advantageous therapeutic effect. PDE4 inhibitors are also capable of inhibiting antigen-challenge induced plasma leakage in sensitized Brown Norway rats and guinea pigs [151]. Corticosteroids had an inhibitory effect on plasma leakage both in upper and in lower airways of sensitized and challenged rats [152], which may make a contribution to their efficacy in preventing late phase responses to allergen and reducing bronchial hyperreactivity. As a consequence, it is to be expected that some of the new compounds under development will have a certain degree of predictability as they act in a comparable way to corticosteroids. An interesting model is represented by the hamster cheek pouch, which is used extensively for studies on inflammation. It has been shown that anti-asthma drugs such as budesonide and theophylline counteract histamine-induced permeability increase [153].

Peripheral blood eosinophilia

Peripheral blood eosinophilia is a typical feature of allergic disorders in humans. It can also be observed in animal models.

Balb/c mice were sensitized with Aspergilus fumigatus. Peripheral blood eosinophilia and pulmonary inflammation with an influx of eosinophils into the lung was detected in animals exposed to antigen [154]. B6D2Fl/J mice were immunized with alum-precipitated ovalbumin i.p. and challenged with aerosolized antigen. A significantly increased number of eosinophils was observed in the peripheral blood that lasted for four days after the challenge [155]. In BDF1 mice sensitized with alum-precipitated ovalbumin i.p., peripheral blood eosinophilia was observed after aerosol antigen challenge [156]. Already in 1982, Vadas [157] clearly demonstrated that cyclophosphamide-pretreated mice given keyhole limpet hemocyanin in Freund's adjuvant develop eosinophilia in the blood. Due to the different genetic control of eosinophilia in mice, strains demonstrated blood eosinophilia to a varying extent: Balb/c and C3H are high responder strains, CBA and A/J are low responders.

We used actively sensitized male Brown Norway rats. They were exposed to an ovalbumin aerosol. An increase in the number of eosinophils in the arterial blood obtained from ovalbumin challenged Brown Norway rats was detected 48 h after allergen-challenge (saline control: 110 per µl vs. ovalbumin challenge: 340 per µl) as observed by others [114]. The simplest way to induce blood eosinophilia is to administer Sephadex beads. Sephadex particles administered i.v. to rats induce a granulomatous tissue inflammation with peripheral blood eosinophilia [158, 159].

Alwing and his co-workers have demonstrated that blood eosinophilia occurs simultaneously with late phase airway obstruction in the actively sensitized and challenged domestic pig [18, 139].

Of non-human primates, owl monkeys (Aotus trivirgatus) have gained interest in the last decade. They are used to model several human diseases such as malaria, virus infection, leishmania, etc. [160, 161]. Interestingly, parasite-free K-VI monkeys (Aotus azarae boliviensis) consistently have more eosinophils than other non-primates [162]. The clinical significance of this finding is yet unknown. To my present knowledge, no attempt to immunize these non-primates has been undertaken.

It is true that peripheral blood eosinophilia is one of the characteristics of bronchial asthma and other allergic disorders. However, this is seldom used as a parameter in experimental pharmacology. It can, however, be observed both in sensitized and challenged rodents and non-rodents.

Changes in mucus quality

In humans dying from asthma, extensive mucous plugging occurs in the airways associated with goblet cell hyperplasia. Similar to man, excessive mucus in the lumen of airways was observed in a simple mouse model of asthma [163]: B6D2F1/J mice were sensitized with alum-precipitated ovalbumin and challenged 12 days later by aerosolized antigen. Recently, Blyth et al. [164] and Braun et al. [165] described a murine model of atopic asthma in which a marked, extensive hyperplasia of airway goblet cells is induced by repeated intratracheal challenge with ovalbumin. They used ovalbumin-sensitized Balb/c mice. Animals were challenged by ovalbumin aerosol over several days (8x). Similar results were observed in the model described by Temelkovski et al. [166]. In rats and guinea pigs, instillation of PAF induced goblet cell hyperplasia [167].

Due to the presence of submucosal glands, ferrets are suitable animals for studying changes in mucus production and quality. For example, it was demonstrated that chronic inhalation of nicotine induces a shift from serous to mucous glands in the airways of ferrets [168].

Relatively few publications have appeared dealing with the changes in mucus secretion and quality. Therefore, a clear recommendation for a given species cannot be given.

Histological changes

In high IgE responder Balb/c mice, systemic (i.p.) sensitization to ovalbumin and chronic challenge with intratracheally applied antigen resulted in a progressive inflammatory response in the airways characterized by typical features of human asthmatic changes, such as infiltration of lamina propria with mononuclear cells, goblet cell hyperplasia, epithelial thickening, subepithelial fibrosis [164, 166]. De Siqueira et al. [169] also found epithelial shedding and eosinophilic inflammation in sensitized and challenged mice. The airways of IL-11 transgenic mice manifest nodular peribronchiolar monnonuclear cell infiltrates and impressive airway remodeling with subepithelial fibrosis [170].

In sensitized Brown Norway rats exposed repeatedly to ovalbumin aerosol, structural changes as observed in human asthma such as increased subepithelial collagen deposition, eosinophil and lymphocyte accumulation, smooth muscle thickening, airway remodeling developed. Additionally, increased incorporation rate of a DNA marker was also

observed [171]. Cui and co-workers [172] sensitized Brown Norway rats with trimellitic anhydride (TMA) and exposed them to TMA conjugated to rat serum albumin for five consecutive days each week for 9 weeks. BHR to acetylcholine was accompanied by airway wall remodeling (increased thickness of bronchial smooth muscle, goblet cell hyperplasia). These models with chronic and repeated inhalation exposure to antigens seem to be appropriate for studying structural changes in experimental asthma. In another model, the lungs of rats infected with Toxicara canis showed pulmonary interstitial infiltrates of eosinophils with airway and vascular remodeling [173].

In guinea pigs, intravenously administered PAF induced a transient bronchoconstriction and a severe inflammatory reaction accompanied by desquamation of bronchial epithelial cells, an histological change typical of bronchial asthma [174].

In actively immunized cats, increase in smooth muscle thickness, epithelial shedding, eosinophil infiltration and hypertrophy of submucosal glands and goblet cells were observed [91]. In several respects, the histopathological changes in cats resemble those of human asthma.

Epithelial shedding after antigen-challenge was also observed in adult cynomolgus monkeys [175].

In the lungs of asthmatics, several morphological changes can be seen, including bronchial muscle hyperplasia and thickened basement membrane (collagen deposition). These together lead to the so-called remodeling often associated with angiogenesis. It is known that collagen homeostasis is controlled by matrix metalloproteinases (MMPs). An increased release of MMP-2 and MMP-9 in bronchoalveolar lavage fluid was observed in ovalbumin-sensitized and challenged mice [176]. Chronic environmental pollutants such as prolonged ozone exposure increased the deposition of lung extracellular matrix [177]. Even though some models are reminiscent of remodeling effects, a model of pulmonary angiogenesis is still to be described.

There is no preferred species for histological studies. Rodents have the advantage that immunological probes are available. Possible errors in the assessment of the efficacy of drugs for the treatment of asthma can be avoided by additional histological investigations. It is highly likely that systemic treatment with steroids or other anti-inflammatory drugs reduces all of the challenge induced changes, but the reduction, for example, of eosinophilia, is much less in the lung tissue than in the airway lumen. As a consequence, the testing of drugs based purely on counting cells in BAL may be liable to serious error, since it will fail to disclose the tissue damage that may already have occurred, and which is much harder to cure. Thus, an additional histological investigation could confirm the results obtained by counting the cells in the BAL.

Are there any species with certain preferences? General remarks

Animal models of asthma are necessary and irreplaceable for the further understanding of the pathophysiological mechanisms and development and preclinical evaluation of new chemical entities in the search for new treatments. As mentioned earlier, there are a number of animal asthma models. However, several questions arise: How can asthma and its symptoms be induced in a given species? How useful are animal models of asthma? What can we model? (Table 1)

It is usual to subdivide asthma into extrinsic forms in which an environmental inducing agent can be identified and intrinsic in which an environmental cause cannot be found. The majority of asthma is found in association with atopy derived from such environmental sources as house dust mite, pollen grains, animal dander and fungal spores. Patients suffering from extrinsic asthma are sensitive to certain antigens.

Table 1. Animal models in asthma research

Symptoms	What kind of asthma symptoms are available?										
	Monkey	Horse[1]	Pig[2]	Dog	Cat	Sheep	Rabbit	Ferret	Guinea pig	Rat	Mouse
Early phase broncho-constriction	yes	yes	yes	yes	yes[3]	yes	yes	yes	yes	yes	?
Late phase broncho-constriction	yes	?	yes	yes	?	yes	yes	?	yes	yes	?
Bronchial hyperreactivity	yes	yes	?	yes	?	yes	yes	(yes)[4]	(no)	?	yes
Inflammatory cells in the lungs	yes	yes[6]	yes	yes[6]	yes[5]	yes	yes	?	yes	yes	yes
Peripheral eosinophilia	(yes)[7]	?	?	?	?	?	?	?	?	yes	yes
Pathological changes in the lungs	yes	yes	?	?	?	?	?	?	yes	yes	yes

[1] COPD-like symptoms; [2] domestic and micropig; [3] lower airway disease; [4] non-allergical BHR; [5] dominated mainly by eosiniophils; [6] dominated mainly by neutrophils; [7] in owl monkeys.

As a consequence, experimental animals should also be made sensitive to an antigen.

Passive sensitization is seldom used in animal studies. It is preferred in in vitro experiments. For in vitro studies serum can be obtained from an atopic donor or an actively sensitized animal. Mice are very seldom passively sensitized. Hamelmann and co-workers [178] have recently described a passive sensitization in mice. In rats, it has already been described in 1988. Briefly, animals were passively sensitized with a murine monoclonal IgE-anti-dinitrophenol (DNP). 48 h later rats were challenged intravenously with mouse serum albumin conjugated to DNP. The animals became cyanotic, but they did not die [179]. Guinea pigs are often sensitized passively. Vargaftig and his co-workers [180] described an interesting procedure. Guinea pigs were passively sensitized with mouse ascites fluid containing DNP-specific IgE antibodies. 5 h after sensitization, maximum bronchoconstrictor response was evoked by i.v. administered DNP coupled to bovine serum albumin. Passively sensitized guinea pigs are still in use [181].

Active immunization is a more frequently used procedure than passive sensitization. Details have been given previously. In general, it is obvious that practically each antigen can induce asthma-like changes in animals. Ovalbumin is the most frequently used antigen followed by certain environmental pollutants, chemicals such as 2,4-toluene diisocyanate, trimellitic anhydride, etc. Sensitization protocols are extremely different. It is likely that sensitization protocols are a "denomination": Certain research groups swear by a definite protocol and they consider it gives the best "human-relevant" results. Others believe the opposite. Therefore, it is impossible to give a general, widely acceptable immunization protocol. It is not necessary to use human-relevant antigens such as house dust mite or cat dander. The antigenicity of ovalbumin is high enough and the pathological changes induced by ovalbumin-sensitization do not differ from those induced by other antigens. However, one should probably use species-relevant antigens which are more frequently used in a definite species or occur naturally in animals. We basically use Ascaris-antigen in our pig studies because pigs can be sensitized easily to Ascaris. However, we have clearly demonstrated that pigs can also be immunized with ovalbumin to the same extent as with Ascaris. It is very difficult to judge the relevance of the use of adjuvant. In certain species (e.g. guinea pig) it can help to change the type of immunization (drift from IgG to IgE). According to our experience, the use of adjuvant leads to a more pronounced allergic response: Brown Norway rats were sensitized with ovalbumin suspended in alum. Some animals received Bordetella pertussis additionally. Mucosal extravasation in the nasal cavities followed by topical ovalbumin challenge was measured by Evans blue. In rats additionally treated with Bordetella pertussis, dye leakage after allergen challenge increased by 35% in comparison to animals sensitized without Bordetella pertussis. The route of immunization may also have an important role in the development of allergic responses in animals. If Brown Norway rats are sensitized with i.p. administered ovalbumin (in alum), the number of eosinophils in the BAL 48 h after aerosol challenge amounts to 1.22 million. If ovalbumin was given subcutaneously, the number of eosinophils increased up to 4.36 million indicating that the subcutaneous route of sensitization may induce a more pronounced allergic reaction than intraperitoneal administration.

In atopic and sensitive patients inhalation contact with corresponding antigens results in bronchoconstriction. Unfortunately, in actively sensitized mice and rats, no bronchoconstriction develops following aerosol administration of antigen. This phenomenon can only be induced by intravenous administration of antigen. In all other species, aerosol administration of antigen results in bronchospasm. Thus, in actively sensitized mice and rats we have to take into consideration that asthma-like changes in airways caliber follow a non-human-like provocation. Another question is the number of challenges. It is obvious that animals can only be challenged once when the antigen is given intravenously. In the case of aerosol challenge, the number of provocations with antigen is practically unlimited. Mice or rats can be challenged several times on consecutive days. It has, however, not definitely been proven that repeated challenge of rodents results in a more serious allergic "disease": Histological changes were only slightly worse or unchanged when animals were repeatedly challenged. Other species such as rabbits, sheep, dogs, monkeys can also be challenged repeatedly at different time intervals. However, repeated challenge does not lead to a worsening of asthmatic symptoms or histological signs. Actively sensitized domestic pigs can also be challenged repeatedly. However, they are desensitized very rapidly.

According to our knowledge and experience, the guinea pig is the only species in which allergen challenge should be carried out under histamine protection. We use a histamine H1-receptor antagonist, azelastine at an extremely low dose (0.01 mg/kg, p.o.) which has no effect on late phase eosinophilia but protects the animals from acute lethal bronchoconstriction. But it is likely that other antihistamines are also usable at a corresponding dose.

With regard to aerosol challenge, one should bear in mind the different anatomical relationships in rodents (long upper airways in comparison to human). Delivery of aerosol by this route presents a problem in small animals that are obligate nose breathers. It has been shown that more than 80% of the aerosol inhaled by conscious guinea pigs is deposited in the nose [182]. To overcome this problem, techniques of delivering an allergen aerosol directly to the lower airways by endotracheal intubation have been developed [183]. However, the nose-only inhalation as aerosol challenge in conscious animals is even better than the widely used box in which the animal does not only inhale but licks the antigen from the fur.

Since all allergic diseases are characterized by early and late phase symptoms we have to model the symptoms of both phases. Furthermore, it is also necessary to investigate mediators and cells involved in early and late phase of an allergic reaction. Additionally, the increased airway responsiveness should also be modeled. In animals, inflammatory changes should be induced that result in pathological changes including airway remodeling.

A murine model for asthma presents numerous advantages when compared with the use of other animal species. This model offers the opportunity to explore mechanisms of allergic reactions because of the existence of nume-

rous immunological reagents specific for murine cytokines, adhesion molecules, etc. Murine models have provided fundamental information regarding certain features of asthma such as involvement of lymphocytes. Because mice are extremely useful for immunological studies, a suitable murine model of allergic pulmonary inflammation can be invaluable to study drug effects on it. There are several transgenic or knock out strains available. On the other hand, because of considerable physiological dissimilarities with primates, the ability to extrapolate murine findings to humans will be difficult. However, I do not believe that the poorly developed airway musculature will be a disadvantage. It is well known that there are excellent models of BHR using mice.

The rat has received considerable attention during recent decades. Experimental data suggest that the most characteristic features of human asthma including pathological changes can be duplicated in rats. Certain strains such as Brown Norway rats produce IgE as the major anaphylactic antibody. Since a large number of corresponding immunological reagents are available, the role of cytokines and chemokines in allergic inflammation can also be studied in a rat model. In contrast to guinea pigs, allergic sensitization requires use of adjuvant such as alum or Bordetella pertussis. From the drug development point of view, this is not a disadvantage. Another disadvantage of this species is that an early phase bronchoconstriction cannot be induced via inhalation of the antigen. It should be given intravenously. There are several inbred strains with different types of immunological reaction to antigen that should be taken into consideration. The rat also offers economical advantages.

The guinea pig was or perhaps is still the most popular animal model of allergic reactions. There is no doubt that the lung is the major allergic target organ in this species. Anaphylactic (early, immediate-type) bronchoconstriction in sensitized guinea pig is the most frequently used model for testing antiallergic, bronchodilatory agents, despite large differences between this species and humans. There are several good reasons for employing guinea pigs as models of asthma, ranging from the pragmatic benefits of economy and ease of animal handling to the features which allergen-induced bronchoconstriction and human bronchial asthma have in common. Such features include the bronchoconstrictor response to antigen-contact, the hyperresponsiveness of the airways to mediators and the eosinophilic nature of allergic bronchial inflammation. Campos and Church [184] wrote in 1992 that "the guinea pig is a useful animal in which to model features of the asthmatic response in order to probe their possible mechanisms". The scarcity of inbred strains is a disadvantage with regard to studying genetic influence but not for drug development. However, there are some really considerable disadvantages. The lack of species-specific immunological reagents makes it difficult to identify particular cell types, cytokines, etc. Guinea pig anaphylactic responses usually involve IgG1 antibodies, even though the model can be tailored for the production of IgE by additional adjuvant such as alum [185]. Despite methodological variations, many interesting findings have emanated from guinea pig models.

The hamster is seldom used in asthma research. Its oral mucosa is well suited for intravital microscopy and therefore for studying microcirculation. It is sometimes employed for testing in vitro effects of kinins [186].

The rabbit provides an interesting animal model in that the lung is the target organ for anaphylactic response. This species can demonstrate early and late phase responses with accumulation of eosinophils. BHR is also available. A further advantage of this species is the production of IgE. In my view, with regard to mediator involvement, there is a great disadvantage: rabbit airways have adenosine A_1-receptors, a receptor type that probably does not occur in human lung tissue. With regard to the presence of adenosine A_1-receptors in human airways, there are contradictory results. Bjorck et al. [187] demonstrated the presence of A_1-receptors in bronchi of asthmatics by using old-fashioned adenosine A_1-receptor antagonists. Rabbits are small, docile animals and relatively inexpensive. They can apparently be used repeatedly without danger of desensitization.

The sheep represents a species in which sensitization to Ascaris occurs naturally. The antigen-response consists of an early and a late phase bronchoconstriction. The latter is accompanied by cell infiltration. BHR to carbachol can also be induced in sheep. An advantage of this method is that sheep are not sedated and relatively unrestrained.

Cats represent an interesting possibility. Actively immunized cats show several responses that are similar to human asthmatic changes. However, they are not very popular experimental animals. So their use is limited.

Dogs can be sensitized by natural exposure to Ascaris, but they can also be immunized by other antigens. Basenji greyhounds have persistent marked BHR. But in contrast to asthma in man, BHR in Basenji greyhounds is not associated with clinical symptoms. According to our opinion, dog studies can be replaced by other species, not only for economic reasons.

Airway disorders including clinical symptoms can naturally occur in horses which are hyperreactive to inhaled mediators. As a model species, they are not used, not only because of their price.

In asthma research, little attention has been paid to domestic pigs or mini- or micropigs. From an anatomical point of view, pigs have several similarities to humans. Few research groups are dealing with this species. Doubtless, problems with sensitization may exist. We should reinforce our activities to immunize micropigs by changing the sensitization schedule. The high endogenous cortisol level may also be a disadvantage that can, however, be overcome. The real handicap with pigs is their size. Therefore, micropigs would be preferred.

The non-human primate model is rapidly gaining popularity in the characterization of novel anti-inflammatory drugs in asthma. The classic allergen challenge model in this species is exposure to extracts of Ascaris suum, but it requires naturally sensitized animals, as laboratory sensitization remains problematic. Monkeys demonstrate an IgE-mediated early and late phase respiratory response to antigen. They have shown BHR. Monkeys are considered to have an immune system very similar to that of humans in comparison to mice, rats, and guinea pigs.

In summary, it should be emphasized that any animal model will have both strengths and weaknesses, and its value in answering particular research questions must be evaluated

with respect to its relevance to human diseases. Unfortunately, this relevance becomes more difficult to determine when the cause of the underlying disease is unclear, or potentially complex, as in asthma. Thus, many species have been utilized in the development of animal models of asthma, including mice, rats, guinea pigs, ferrets, hamsters, rabbits, dogs, sheep, pigs, horses and non-human primates. Each possesses certain advantages and disadvantages as a model of asthma. Therefore, certain caveats must be recognized in using animal systems. It must, however, be appreciated that animals are only surrogates. Results from such studies must be compared with information obtained from experiments performed with human materials in order to minimize or even to avoid faulty extrapolations. It is also important to recognize that no single model is sufficient to draw therapeutic conclusions on the value of new chemical entities. Prudent employment of well-designed animal models can provide valuable information on drug effects. Undoubtedly, in vitro investigations will receive greater attention in the future.

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