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PERTUSSIS SENSITIZATION AS AN ANIMAL MODEL FOR THE ABNORMAL BRONCHIAL SENSITIVITY OF ASTHMA†

For half a century anaphylaxis has served us as the animal model for bronchial asthma, and it has served us very well, generating many substantial contributions to the understanding of the pathogenesis of the disease and to its treatment. We have just heard Patterson describe extensions of this model which offer promise for still further developments, but as a matter of fact anaphylaxis has been such a successful model that for years we have been inclined to ignore facets of asthma that it does not explain. The purpose of my presentation is to list some features of asthma which I think a model should explain, to call your attention to a different animal model which could help explain these features and to discuss briefly how well the model and the disease correspond.

We are all painfully aware of the difficulties in the terminology of chronic obstructive lung diseases, so for the purpose of the present discussion I will use the following operational definition of asthma.[1] Bronchial asthma is characterized by diffuse airway obstruction which is virtually completely reversible, either spontaneously or with treatment. It is often familial and is associated with eosinophilia in the blood or sputum. It is further characterized by a remarkable bronchial sensitivity to various kinds of stimulation, notably including cholinergic drugs and histamine.

Asthma has often been considered to be a syndrome like hypertension produced by many agents, but we can also consider it a disease like diabetes which has a common definable, though complicated, metabolic abnormality. My argument starts with the premise that "asthma is asthma is asthma," and that the variety of etiologic features we recognize in our patients has a single final common pathway of pathogenesis. The most important of those features are allergic reactions, respiratory infections, air born irritants, emotional disturbances and familial influences, and a major reason for considering them provocative factors of a disease with a common underlying pathogenesis is that individual patients present all varieties of permutations and combinations of them. A unifying hypothesis of asthma should account for all of these factors and also explain the eosinophilia, the

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therapeutic benefit of small doses of corticosteroids, and the typical occurrence of attacks at night.

Attacks of asthma do, of course, sometimes follow exposure to pollen or other allergens to which the patient has anaphylactic type of allergy. As an end result of this allergic reaction a number of mediators such as histamine, slow reacting substance, and kinins are released which cause bronchospasm and increased mucus production. The problem in considering that asthma is fundamentally an allergic disease is that all patients with asthma do not have demonstrable allergy, and all patients with allergy do not have asthma. In fact, most people allergic to ragweed, for example, just have hayfever, and bronchospasm is generally not part of the anaphylactic reaction in non-asthmatic persons to insect stings or penicillin.[2] The difference between asthma and allergic rhinitis cannot be explained by known differences in the antibody response or in the release of the mediators of anaphylaxis. But there is a difference in the bronchial response to stimulation. Bronchi of asthmatics respond excessively to acetylcholine and the mediators of anaphylaxis.[3-7] Bronchi of patients with hay fever are considerably less sensitive than those of asthmatics although somewhat more so than those of normal persons.[7,8] People who have recovered from anaphylaxis to penicillin or insect stings respond normally.[8] For these reasons if there is a single basic abnormality in all patients with asthma it must be related, not to allergy itself, but to this excessive bronchial response to stimulation of any kind, including stimulation by mediators released by an antigen antibody reaction or to homeostatic reflex vagal activity.

Several years ago Andor Szentivanyi suggested that pertussis sensitization represents an experimental model for human asthma. Mice or rats innoculated with *Bordetella pertussis* vaccine also have greatly increased sensitivity to histamine, serotonin, acetylcholine, and anaphylaxis.[9,10]

Szentivanyi and others have studied the mechanisms of pertussis sensitization in considerable detail and while all students of the phenomena do not agree, most of the evidence points to the conclusion that pertussis vaccine produces a blockade of beta adrenergic receptors.[11-14] One of the most striking features of this adrenergic blockade of pertussis-sensitized animals is absence of elevation of blood sugar and free fatty acids after epinephrine injection. Anaphylaxis, histamine, serotonin, or acetylcholine all mobilize epinephrine, but in the pertussis-sensitized animal, unlike the normal animal, this mobilization of epinephrine is not followed by the expected rise in blood sugar and free fatty acids.

The pertussis model then, suggests that patients with asthma have as their underlying disorder a partial beta adrenergic blockade. Normally the tendency to bronchoconstriction from cholinergic or other stimulation is

balanced by bronchodilitation from adrenergic activity. In asthma this normal homeostatic defence fails at the target cell level and airway obstruction develops as a consequence. In this hypothesis emotional disturbances are viewed as causing trouble either by inhibiting adrenergic or increasing cholinergic impulses. Cold air, dust, and fumes would provoke bronchospasm through vagal reflexes which act unopposed by counterbalancing beta adrenergic activity. Respiratory infections are known to increase the sensitivity of the bronchial tree of both normal and asthmatic subjects to cholinergic stimulation[9] and in asthmatics killed influenza virus vaccine also has this effect.[15] The mechanism of influenza-vaccine increased bronchial sensitivity is unknown, but it is possible that influenza vaccine and other viruses increase the degree of beta adrenergic blockade.

The eosinophilia of asthma could be explained not only by the increased production of eosinophiles as a consequence of the allergic reaction, but also by a blockade of a normal beta adrenergic action of epinephrine in lowering the number of these cells in circulation. Asthma is often controlled by corticosteroids in small doses which are not effective in other diseases like lupus erythematosus in which cells are injured by allergic mechanisms. The mechanism of the therapeutic benefit of steroids in asthma is unknown so the field is open to the speculator. It is known that corticosteroids are necessary for epinephrine to exert its action[16] and that they antagonize the effect of adrenergic blocking drugs[11] as well as partially reversing the effects of pertussis vaccine in mice.[11-14] Some of the therapeutic effects of corticosteroids in asthma could be explained as a restoration of the normal response to adrenergic stimulation. Recumbent posture increases airway resistance and also increases the bronchial response to histamine.[17] These observations partially explain nocturnal attacks, but asthma is often worse in the evening before the patient lies down. It has been found that the sensitivity to histamine increases greatly at night.[18] An additional explanation for nocturnal attacks might be that both catecholamine and corticosteroid blood levels are at a low ebb at this time of day,[19,20] thus reducing effective beta adrenergic stimulation at night.

A familial incidence of asthma is well established but it is not certain whether the tendency to develop asthma is inherited or acquired in the close setting of family life.[21,22] In any case according to the β-adrenergic blockade hypothesis the lesion that runs in families is either the blockade itself or a genetic predisposition to develop the blockade.

It is evident, then, that β adrenergic blockade could explain much about asthma and the hypothesis is at least superficially plausible. The next question is how well does asthma correspond to the pertussis model? The Table lists some relevant points of correspondence. I should say straight-

TABLE 1. COMPARISON OF BRONCHIAL ASTHMA IN MAN AND PERTUSSIS SENSITIZATION IN RATS AND MICE

	Asthma	*Pertussis*
Exaggerated response to:		
Antigen challenge	Yes	Yes
Histamine	Yes	Yes
Serotonin	Yes?	Yes
Bradykinin	Yes	Yes
SRS-A	Yes	No data
Acetylcholine	Yes	Yes
Response to epinephrine:		
Reversal of the abnormal state	Diminished in status	Diminished
Hyperglycemia	Diminished?	Diminished
Peripheral uptake of glucose	Diminished?	Diminished
Mobilization of FFA	Diminished?	Diminished
Vasodilitation	Diminished	No data
Tachycardia	Not affected	Diminished
Eosinopenia	Diminished	Diminished
Reduction of abnormality by corticosteroids	Yes	Yes
Reproduction of pharmacological sensitivity in normal subjects by beta blocking drugs	No?	Yes
Eosinophilia	Present	Present
Lymphocytosis	Absent	Present
Antibody production	Increased	Increased
Reagins	Often present	Present transiently

away that few if any of the clinical studies have been conducted with the rigor of the studies on pertussis sensitization in animals, and to date there is no conclusive evidence of adrenergic blockade in asthma. At best studies of subjects with intact autonomic nervous systems can only show autonomic imbalance and cannot provide evidence of the site of the abnormality. In the items followed by a question mark conflicting results have been reported by different investigators.

I have already mentioned the similarity in sensitivity to anaphylaxis and its mediators. The response of the pertussis-sensitized mouse[11-18] and of asthmatic patients[23-28] to epinephrine has been studied extensively. Epinephrine does not prevent fatal anaphylaxis in pertussis-sensitized animals, but does in normal animals.[14] While epinephrine is usually effective in terminating an attack of asthma it is not effective in status asthmaticus. Airway obstruction by mucus plugs, and diminished cellular response to

epinephrine because of respiratory acidosis are probable explanations for the lack of effect, but in a few patients epinephrine injection actually increases the airway obstruction. In other words the usual bronchodilating effect of epinephrine is reversed and bronchoconstriction occurs. A similar reversal occurs in animals after beta adrenergic blockade.[29] Blockade of beta receptors allows the stimulation of alpha receptors to become evident, and reversal of the expected epinephrine effect in severe asthma suggests that beta blockade is present.

There is not time to discuss fully epinephrine-induced hyperglycemia, but there are two major mechanisms involved. Epinephrine stimulates the release of glucagon which in turn promotes hepatic glycogenolysis and release of glucose into the circulation.[30] Epinephrine also activates muscle glycogenolysis directly and prevents glucose from entering the cell.[31] The end result of both is an elevation of blood sugar. In mice sensitized with pertussis or given beta blocking drugs, the hyperglycemic effect of both glucagon and epinephrine is reduced, and the peripheral uptake and utilization of glucose is increased.[11] The effects of beta blockade on blood sugar levels in man are less definite, but in our species, too, they block the effect of epinephrine on peripheral utilization of glucose and lactic acid production.[32]

There have been several studies on the hyperglycemic effect of sympathomimetic drugs in asthma and the results are conflicting.[23-25,27,33] None of the studies is free of flaws in experimental design but some investigators have concluded that asthmatics have a diminished hyperglycemic response to glucose due mainly to increased peripheral uptake. The response to glucagon was not abnormal.

Mobilization of free fatty acids by epinephrine is impaired in the pertussis-sensitized animal.[33] The data on asthma are conflicting, one study reporting normal[25] and two reporting impaired response.[27,33]

Asthmatic patients show a diminished vasodilator response to beta adrenergic stimulation, but the chronotropic cardiac response is normal[34,35] or even exaggerated.[35]

Corticosteroid drugs are effective in treating asthma and in preventing death from anaphylaxis, histamine, and serotonin in pertussis-sensitized mice. But they do not reverse the abnormal bronchial sensitivity of asthmatics to methacholine, although I have found they do potentiate the effect of ephedrine on the methacholine response.

Increased sensitivity to anaphylaxis and the mediators can be produced in mice and guinea pigs with beta blocking drugs,[36] and propranolol increases the airway resistance in asthma[37] as well as in normal man,[38] and also increases the bronchial response of hay fever subjects to ragweed

aerosol.[39] But Zaid and Beall[34] reported propranolol does not increase the response of normal subjects to histamine or methacholine and Sly and coworkers[40] found it did not increase the exercise-induced bronchospasm of asthmatic patients. The question of whether beta blockade can or cannot reproduce the asthmatic state cannot yet be considered settled, however. The beta receptors for inotropic and chronotropic cardiac activity have important differences from the receptors for trachobronchial dilatation.[41] The pattern of apparent adrenergic blockade in asthma more closely resembles the blockade produced by methoxamine derivatives than propranolol. The methoxamine derivatives block the metabolic and smooth muscle beta receptors more effectively than the cardiac receptors.[42,43] Propranolol, on the other hand, more effectively blocks the cardiac receptors.[44] A similar dissociation of the cardiac and smooth muscle beta receptors can be achieved with dichloroisoproterenol and alpha methyl-dichloroisoproterenol.[45] Butoxamine should be examined as a possible asthmogenic agent before we accept the conclusion that pharmacologic beta blockade does not reproduce asthma. It is quite possible that asthma is associated with a greater degree of blockade in the bronchi than can be readily achieved in man with customary doses of propranolol.

Eosinophilia is a prominent feature of both asthma and pertussis sensitization, and in both the eosinophiles are resistant to the eosinopenic effect of epinephrine.[36]

Lymphocytosis is as prominent in pertussis-innoculated animals[46] as it is in whooping cough, but lymphocytosis is not present in asthma.

Pertussis vaccine is an excellent adjuvant for increasing antibody production in all species studied, including man.[47] In rats and mice this increased antibody response includes a gamma$_1$ antibody which has many of the characteristics of the human reagin frequently associated with asthma.[48-51] Patients with asthma also have a modest increase in antibody response to bovine serum albumin[52] and dextran,[53] but increased antibody response of asthmatic subjects seems to be found only when the antigen is introduced through mucus membranes.[54-55]

The resemblance can be summed up by saying that in pertussis sensitization there appears to be an intense and widespread beta blockade, but it is transient, disappearing after about two weeks. The blockade in asthma, if it exists, is partial and involves only some organs, notably the bronchi, but lasts for years. The pertussis model, it seems to me, is valuable in provoking a fresh approach to the old idea of autonomic imbalance in asthma. The beta blockade hypothesis is testable, indirectly at least, and possibly directly. Many intriguing questions come to mind. What could bring on the beta blockade in the first place? Do respiratory infections in fact produce a

blockade? Is the bronchospasm of chronic bronchitis related to asthma and mediated by a similar mechanism? And most important of all, will this model stimulate any new ideas for treatment of asthma?

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