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Szentivanyi A. The beta adrenergic theory of the atopic abnormality in bronchial asthma. *J. Allergy* 42:203-32, 1968.
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The theory postulates that the basic abnormality in bronchial asthma may lie in an inherited or acquired lesion of the beta-adrenergic receptor-coupled adenylate cyclase-cyclic AMP complex. The resultant malfunctioning produces a unique pattern of bronchial hyperreactivity to a broad spectrum of nonspecific stimuli. If this theory can be proved, then most, if not all, of the significant characteristics of this disease can be accounted for by one single defective mechanism. [The *SCI*® indicates that this paper, the most cited ever published in this journal, has been cited in over 805 publications since 1968.]

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Historically, the interpretation of the symptomatology and the underlying reaction sequence of asthma was patterned after those of the anaphylactic guinea pig. However, the range of atopic responsiveness in asthma includes a variety of stimuli that are nonimmunologic in nature. Foremost among these are pharmacologic mediators that are the chemical organizers of autonomic regulation.

Therefore, I believed that anaphylaxis could not be used as a model for the investigation of the constitutional basis of atopy in asthma. Such a model, if it was to be meaningful, must be able to imitate both the immunologic and the pharmacologic abnormalities of the disease.

Thus, the beta-adrenergic approach to asthma was the outgrowth of two consecutive series of experiments chosen and designed with these assumptions in mind. In the years from 1952 to 1958, I collaborated with G. Filipp[1] (University of Saarland, Federal Republic of Germany) on an experimental series that utilized hypothalamically "imbalanced" anaphylactic animals. A second series of experiments employed bacterially (*Bordetella pertussis*) or pharmacologically (beta-adrenergically blocked) sensitized animals. The latter experiments were started in collaboration with the late C.W. Fishel and D.W. Talmage[2] at the University of Colorado in the years from 1959 to 1962.

The critical common feature of the two models was an alteration of autonomic regulation accomplished through two different preparatory procedures in an attempt to produce conditions that could conceivably result in the altered immunologic and pharmacologic reactivities seen in asthma. These experiences led me to formulate the theory in 1962.

The theory postulates that the constitutional basis of atopy in asthma lies in an inherited or acquired lesion of the beta-adrenergic receptor-coupled adenylate cyclase-cyclic AMP complex. Alternatively, the lesion may occur at a point beyond the cyclic AMP generation step, in a related pathway, or in an interacting or modulating system. The resultant beta-adrenergic malfunctioning produces a unique pattern of bronchial hyperreactivity to a broad spectrum of immunologic and nonimmunologic stimuli.

This theory was first presented on February 21, 1962, at the annual dinner of the Rocky Mountain Allergy Society and in subsequent years on many other occasions. But it was in this article that a comprehensive review of the theory was first published. The reason for the delay was my reluctance to commit myself to a frame of thought potentially just as dogmatic as the immunologic scheme was. Nevertheless, because of the growing interest and increasing pressure by many investigators requesting that a definitive exposition of the theory be published, I finally went ahead.

The significance of the theory and why it has been so frequently cited may be explained as follows. Most importantly, it was the first all-inclusive theory capable of accounting for most, if not all, of the significant facts (immunologic and nonimmunologic) surrounding this disease. Second, it offered a pathway to action by directing attention to a specific effector system that is chemically defined and can be tested. Third, it can serve as a theoretical basis for the interpretation of the clinical pharmacology of asthma. Fourth, by determining the chemical nature of the basic abnormality in this disease, it could serve as a basis for designing new approaches to an ultimate cure.

While the ultimate validity of the theory is as yet undetermined, it is clear that it was the major triggering development of current research directed at exploring the role of adrenergic mechanisms in this disease.[3-6]

1. **Filipp G & Szentivanyi A.** Anaphylaxis and the nervous system, part III. *Ann. Allergy* 16:306-11, 1958.
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3. **Szentivanyi A, Heim O & Schultze P.** Changes in adrenoceptor densities in membranes of lung tissue and lymphocytes from patients with atopic disease. *Ann. NY Acad. Sci.* 332:295-8, 1979.
4. **Szentivanyi A.** The radioligand binding approach in the study of lymphocytic adrenoceptors and the constitutional basis of atopy. *J. Allerg. Clin. Immunol.* 65:5-11, 1980.
5. **Szentivanyi A & Szentivanyi I.** Neuester Stand der Rezeptoren-Theorie bei Atopie. *Allergologie* 6:155-9, 1983.
6. **Krzanowski J J & Szentivanyi A.** Reflections on some aspects of current research in asthma. *J. Allerg. Clin. Immunol.* 72:433-42, 1983.