Development of "Resistance" in Beta-Adrenergic Receptors of Asthmatic Patients*

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Complete in vitro dose-response curves for l-isoproterenol (isoprenaline) sulfate showed no functional defects in bronchial muscular β-adrenergic receptors in three patients with chronic intrinsic asthma, as compared to 60 patients with normal pulmonary function. Complete in vivo dose-response curves for intravenously infused isoproterenol were obtained in eight outpatients with chronic intrinsic asthma to register effects on bronchial muscle (forced expiratory volume in one second), heart rate, blood pressure, and skeletal muscular tremor. The isoproterenol test was performed before and also during oral treatment with a long-acting selective β-adrenergic stimulator (terbutaline sulfate, 5 mg three times daily).

At the end of the 1960s in Great Britain, the publication of data suggesting a connection between the increase in acute deaths due to asthma and the sale of β-adrenergic stimulators in spray form focused attention on the development of resistance to these drugs. Various causes for this connection have subsequently been proposed. In 1971, Conolly et al1 suggested development of "resistance" in the β-adrenergic receptors of bronchial muscles, thus leaving the parasympathetic nervous system and other bronchoconstrictor factors free to take over, which might lead to death. It was also suggested that the risk of developing resistance might be even greater when long-acting selective β-adrenergic stimulators were used.

According to the theory proposed by Szentivanyi2 in 1968, β-adrenergic blockade is the cause of asthma; and prior to any treatment, constrictor impulses will produce a pronounced effect and may cause bronchospasm.

This theory has received further support during recent years, as it has been shown that a certain degree of β-adrenergic blockade is present in the leukocytes of patients during acute asthma attacks.3-6 Since one of the therapeutic effects of the β-adrenergic stimulators is inhibiting liberation of spasmogens from the mast cells, adrenergic blockade could lead to increased liberation of spasmogens. β-adrenergic blockade in the leukocytes can to some extent be diminished by an α-adrenergic blocker2 and also by corticosteroids.7

The normalizing effect of α-adrenergic blockers on β-adrenergic blockade in leukocytes demonstrated by Alston et al8 is interesting in the light of our previous findings9,9 that bacterial endotoxin markedly increased α-adrenergic receptor-mediated bronchospasm in isolated bronchial muscles from patients with airway obstruction.

We should, however, distinguish between the β-adrenergic effect in the bronchial muscle and other β-adrenergic effects, including that involved in liberation of spasmogens, the clinical significance of which is not proved.

No studies have been published on the function of the β-adrenergic receptors in isolated bronchial muscles from asthmatic patients. We have, therefore, performed in vitro studies on bronchial muscles from patients with normal pulmonary function and...
from patients with chronic asthma. Furthermore, for more than one year, we have carried out a study aimed at establishing whether resistance really does develop in the \( \beta \)-adrenergic receptors of the bronchi, heart, and skeletal muscles during treatment with normal doses of a long-acting \( \beta \)-adrenergic stimulator in patients with chronic asthma not previously treated with \( \beta \)-adrenergic stimulators. In addition, we performed an overdosage investigation at the end of the study. Preliminary data from the first three months of this study were recently published.\(^{10,11}\)

**Material**

The *in vitro* studies were performed on segmental bronchi obtained from lungs resected for bronchial carcinoma. A total of 67 bronchial muscles from 80 patients with normal pulmonary function and six bronchial-muscle preparations from three patients with asthma were used for the *in vitro* studies. The muscle preparations were removed in connection with surgery for lung cancer but were taken from uninvolved areas of the lung.

The *in vivo* investigation was performed in eight outpatients aged 29 to 66 years; seven were men. The mean body weight was 73 kg (161 lb; range, 58 to 92 kg [128 to 203 lb]). All patients had endogenous asthma of many years' duration, with relatively constant airway obstruction. Some patients also had chronic bronchitis. In a preliminary trial, all patients had been found to have an increase of at least 15 percent of their control value for the forced expiratory volume in one second (FEV\(_1\)) after two puffs of \( l \)-isoproterenol (isoprenaline) sulfate (160 \( \mu \)g). No patients had signs of cardiac disease. None was receiving cortisone therapy or antibiotic treatment, none was receiving any therapy other than that given due to the study.

The patients were informed of the purpose of the investigation and told that they could demand interruption of the study at any phase. The design of the study was approved by the ethical committee of the University of Göteborg, Sweden.

**Methods**

The *in vitro* bronchial muscular tests were performed as described by Svedmyr et al.\(^{12}\)

In the *in vivo* studies, the patients arrived at the laboratory in the morning after having eaten a very light breakfast. An intravenous catheter was immediately inserted into a cubital vein, and the patient lay comfortably in a reclining chair throughout the investigation. The basal values for the several variables were determined after 90 minutes of rest. Isoproterenol was then infused intravenously during ten-minute periods in increasing doses at intervals of 30 minutes. The lowest dose had a negligible bronchodilator effect, while the highest dose produced almost maximal bronchodilation.

The following variables were recorded: FEV\(_1\), vital capacity, heart rate determined by continuous electrocardiogram, blood pressure (auscultatory), and skeletal muscular tremor, determined with an accelerometer attached to the middle finger of one hand and using a carefully standardized technique.\(^{13}\) Except for the ECG, which was recorded continuously, the variables were recorded during the last four minutes of each isoproterenol infusion, when the "steady state" was reached.

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**FIGURE 1.** Effects on ventilation (FEV\(_1\)) of increasing doses of \( l \)-isoproterenol (isoprenaline) sulfate infused intravenously (isoproterenol test) in patients with chronic asthma not previously treated with \( \beta \)-adrenergic stimulating drugs (thick solid curve) and after 1, 2, 3, 6, 9, and 12 months (I, II, III, VI, IX, and XII) of treatment with terbutaline sulfate (5 mg three times daily per os). Study was ended by new isoproterenol tests after additional treatment for three days each with terbutaline by inhalation, two inhalations four times daily (2 \( \cdot \) 4) and six inhalations four times daily (6 \( \cdot \) 4), respectively.

After the initial isoproterenol test (heavy solid curve in Fig 1), all patients were treated with 5 mg of terbutaline sulfate orally three times daily. After 1, 2, 3, 6, 9, and 12 months of treatment with terbutaline, the isoproterenol test was re-

![Graph](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/20979/)

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**FIGURE 2.** Relaxing effect of \( l \)-isoproterenol (isoprenaline) sulfate on human bronchial muscle obtained from normal and asthmatic patients and contracted with carbachol (carbacholine) *in vitro*. Thick curve represents mean dose-response curve of 67 bronchial muscles from 60 patients without asthma; *diagonally lined area* indicates \( \pm 1SD. * Other curves represent six dose-response curves from three patients with severe chronic asthma.*

![Graph](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/20979/)
peated using exactly the same method. Prior to each isoproterenol test, bronchodilator therapy was interrupted for 12 hours. The study was performed over 12 months in an attempt to avoid seasonal variations in the basal degree of obstruction. After the test at 12 months, the patients were treated for three days with two inhalations of terbutaline sulfate (0.50 mg) four times daily (8 AM, 12 noon, 4 PM, and 8 PM) in addition to the oral terbutaline therapy. On the fourth day, a new isoproterenol test was performed. During the following three days, the patients were given six terbutaline inhalations four times daily, and this was followed by a final isoproterenol test.

RESULTS AND DISCUSSION

In Vitro Tests

The six bronchial-muscle preparations from the three asthmatic patients showed normal dose-response curves for isoproterenol (Fig 2). This shows that there were no signs of β-adrenergic blockade, despite the fact that these patients had pronounced airway obstruction and died after surgery in respiratory failure.

In the early phase of an acute asthma attack, when bronchospasm dominates, patients also respond excellently to β-adrenergic stimulators. This pronounced bronchodilation indicates that β-adrenergic blockade is not present in the bronchial muscle at this stage. Treatment with β-adrenergic blocking drugs does not cause asthma in healthy individuals. Beta-adrenergic receptor blockade cannot, therefore, be the cause of asthma.

Figure 3 shows an experiment from one of our previous studies,5,9 in which an α-adrenergic receptor stimulator, phenylephrine, did not initially cause contraction of untreated human bronchial muscle, while a small dose of bacterial endotoxin increased the bronchoconstrictor effect of the α-adrenergic stimulator several thousand times. It would be of great interest to know whether endotoxins increase α-adrenergic mediated liberation of spasmogens in the bronchial muscle and, thereby, oppose the action of β-adrenergic stimulators. This might be one of the causes of the so-called resistance to some β-adrenergic stimulators.

In Vivo Studies with Terbutaline

All patients stated improvement of their pulmonary function throughout the period of oral treatment with terbutaline. Sometime during the year of the study, most patients suffered from an acute infection, with deterioration for about a week, but conventional antibiotic therapy produced a rapid cure without necessity of changing the patients' basic therapy for asthma. In some cases a period of infection occurred at a time when the patient would otherwise have undergone an isoproterenol test; this was then postponed until the infection had disappeared. Figure 1 shows the pulmonary function expressed as FEV1.0. As may be seen, the patients had a relatively mild basal obstruction, which was a prerequisite for admittance to the study; one would otherwise not have expected them to be able to carry out a year's treatment without alteration of therapy. The thick solid curve shows the effect of the initial isoproterenol test; FEV1.0 increased with the dose of isoproterenol.

During treatment with terbutaline, the basal FEV1.0 values were equal to or higher than those in the initial test. This, in itself, suggests that the patients had not become resistant to their own epinephrine (adrenaline) or norepinephrine (noradrenaline), which, according to the resistance theory, might be the cause of the increase in acute deaths. When isoproterenol was subsequently infused intravenously, the FEV1.0 rose in the same way as in the initial test, thus clearly demonstrating that resistance had not developed in the β-adrenergic receptors of the bronchi during long-term terbutaline therapy.

Two curves (2-4 and 6-4) in Figure 1 show the results when the patients had added treatment with terbutaline by inhalation, two inhalations four times a day and six inhalations four times a day, respectively. All patients stated that they experienced a further improvement in their pulmonary function throughout. Three of the patients stated that they felt a transient mild irritation of the throat when they took six inhalations each time. Figure 2 also shows that basally the patients were objectively improved during inhalation therapy. This is in accordance with our previous findings14 that the addition of inhalation therapy improves bronchodilation. When isoproterenol was infused after the inhalation series, the same normal isoproterenol effect was obtained again. There were no signs of development of resistance in the β-adrenergic receptors of the bronchi. There was no significant difference between the

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effect of isoproterenol infusions after two inhalations four times daily and that after six inhalations four times daily.

All patients developed pronounced muscular tremor towards the end of the initial isoproterenol test. The tremor was clearly visible to the eye. Objective registration (Fig 4) showed that the tremor was more than quadrupled with the highest dose of isoproterenol. The isoproterenol-induced muscular tremor decreased in all patients during the course of treatment with terbutaline and was significantly less pronounced at all the subsequent isoproterenol tests. On the average, tremor decreased by 50 percent. All patients also stated that tremor was most pronounced during the first two to three weeks of treatment with terbutaline.

The effect on heart rate is shown in Figure 5. All patients had almost constant basal heart rates at the various times of investigation, probably due to the fact that optimal basal conditions were achieved during the performance of the tests. During the initial isoproterenol test, a pronounced increase in heart rate was recorded in all patients. During treatment with terbutaline, the isoproterenol-induced increase in heart rate was less pronounced than during the initial test, but the difference was not very marked.

In studies in healthy subjects in the same age group, we have always found greater increases in heart rate with the same doses of isoproterenol than in patients with airway obstruction. This suggests that the patients in the present study may have some initial resistance in the β-adrenergic receptors of the heart, possibly due to high sympathetic activity in order to counteract their airway obstruction.

It is possible that resistance may also develop in the β-adrenergic receptors of the bronchi if the patient very often takes large doses of a β-adrenergic stimulator; however, in our opinion, the so-called resistance found in patients with very severe airway obstruction is in most cases due to other factors causing obstruction, such as mucosal edema and secretions, as pointed out previously. Beta-adrenergic stimulators do not, of course, affect these factors. This development of “false” resistance warrants treatment with other agents, such as steroids, antibiotics, and mucolytic agents.

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REFERENCES

Kinetic Art

The kinetic art of the present day includes works in virtual and in actual movement in two or three dimensions. A sense of movement has been established through the active participation of the spectator—principally by his movement in front of the work or by his manipulation of the elements involved in the work. In the case of three-dimensional works in real movement, there is an important division between machines and mobiles, which depends upon their greater or lesser degree of predictability. The majority of the machines move in response to electro-magnetic forces. But human forces, hydraulic and magnetic forces, even solar forces and cybernetic devices also play their part. Other forces of the physical universe were also being used in the creation of works of art that featured unpredictable movement. Water, fire and various acids made a somewhat unexpected entry into the field of movement in art. The last group of important works within the overall field of kinetic art is concerned with light and movement. Works of this kind can be traced back to three different sources, the color organs, the cinema and the mobile theatre set. On a relatively small scale there were the "cinechromatic apparatuses," luminous pictures, the "chromokinetic" works and light mobiles, which were equivalent to traditional paintings in motion.