Lung Diseases of the National Heart, Lung, and Blood Institute.  

In all, 203 patients were enrolled in NOTT. All had severe COPD with resting arterial oxygen tensions \(\text{PaO}_2\) < 50 mm Hg (room air) when they were clinically stable. Exceptions include patients with \(\text{PaO}_2\) between 56 to 59 mm Hg if there was also evidence of physiologic dysfunction which could be attributed to hypoxemia: right atrial hypertrophy, erythrocytosis, or right heart failure. (The protocol may be obtained by writing to the Division of Lung Diseases, National Heart, Lung and Blood Institute, Bethesda, MD 20205).

The scientific design of NOTT included a careful randomization scheme so that one-half of the patients would receive supplemental oxygen 24 hours daily, and the other half for only 12 hours to include their usual period of sleep. The two groups are virtually identical with regard to their demographic and physiologic characteristics, supporting the adequacy of the randomization process.

The most detailed analyses were done after a stabilization phase of three weeks without supplemental oxygen (to assure that the \(\text{PaO}_2\) did not improve to a value > 50 mm Hg), and again at six months after the initiation of home oxygen therapy. Since much of the existing literature about the value of supplemental oxygen concerns hemodynamic improvement, better exercise tolerance, and improved neuropsychological functioning and quality of life, we placed major emphasis on these areas as we chose tools to include as a part of the protocol.

In view of the known hemodynamic benefits from oxygen in some, but not all, patients, right-sided heart catheterization was of fundamental importance to detect possible differences between the 12- and 24-hour groups. Predictably, this one testing procedure took the greatest amount of time to explain to patients and their families; some candidates refused to participate in NOTT because of the requirement for cardiac catheterization.

The exercise testing employed in the study design was noninvasive, and adequacy of oxygenation with and without supplemental oxygen was measured with an ear oximeter. Each patient was tested semiannually intervals under steady-state conditions, and his/her maximal performance was assessed with a progressive multistage test until unacceptable dyspnea, fatigue, or a target heart rate was reached. By and large, cessation of exercise was at a subjective end point.

Because of interest in possible cerebral correlates of COPD, extensive neuropsychological assessments (Halstead-Reitan Battery and Lafayette Repeatable Battery) were undertaken. These evaluations should provide evidence for the effect of oxygen treatments on various cognitive functions, which, in turn, might relate to quality of life. Indeed, quality of life issues were felt to reflect the most important salutary effect of oxygen on the NOTT participants. Care was taken to collate data on the frequency and reasons for hospitalization among the two groups, as well as activity levels and tests designed to measure emotional attitude—both as judged by the patient and another close associate (usually a relative).

Nursing personnel visited patients in their homes at weekly intervals during the first six months of their participation, and monthly thereafter. There were several purposes of these visits: assessment of physical (physiological) status by clinical means; quality of life approximations through standardized assessment tools; and reinforcement of educational material regarding medications, oxygen equipment, how to manage acute problems, etc.

We hope that NOTT will answer the fundamental question: will 12 hours of supplemental oxygen for hypoxemic patients with COPD be as good as, or better than, 24 hours of oxygen a day? However, we also hope to learn more about the physiologic, psychologic, and sociologic characteristics of these patients and how an adjunctive treatment modality such as supplemental oxygen affects the lives of such people. NOTT is rapidly approaching its final data collection day (June 1980), and we eagerly await the collation and interpretation of these data so that our conclusions can be shared with the scientific and lay communities.

The NOTT Study Group*

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Reprint requests: Dr. Paul Kcoe, Division of Pulmonary Medicine, 2799 West Grand Blvd, Detroit 48202

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Antihistamines and Asthma
Do They Have a Role in Therapy?

The role of antihistamines in the therapy of asthma has been controversial from the beginning, over 30 years ago. It was only natural that
after histamine was demonstrated to cause bronchospasm, and was closely related to the allergic phenomenon, the antihistamines should be expected to be effective in the therapy of asthma. In practice, however, the effectiveness of the histamine antagonists appeared to be disappointing to most investigators, although a few were enthusiastic.

Antihistamines, first introduced by Bivet and Staub in 1942, have proven their worth in allergen-induced hay fever. No controversy exists in this area. A variety of chemical variants and analogues have multiplied over the years. Each new analogue has affected one element or another of the effects of antihistamines but, in general terms, they all demonstrate the following characteristics: they are well absorbed from the gastrointestinal tract, they have local anesthetic effects, antagonize histamine with varying degrees of specificity, block histamine-induced contraction of smooth muscle, decrease secretions from lacrimal and salivary glands, have an atropine-like effect, tend to create sedation, dizziness and incoordination with varying degrees of intensity, sometimes hypersensitize individuals, especially evident as skin rashes and photosensitivity. They occasionally even cause anaphylaxis.

Investigations over the past years have concentrated on the effects of antihistamines directed towards the H1 receptor sites, in relationship to their therapeutic possibilities for asthma. By all accounts, antihistamines should be very effective in blocking antigen-induced mediator (histamine) release and thus relieving the resulting bronchospasm.

Why, then, the controversy? The asthmatic patient whose bronchospasm is related to histamine alone must be very uncommon. The factors shown to precipitate attacks of asthma are varied and diverse. True allergy (antigen-antibody, IgE or possibly an IgG4 combination) results in the release of a host of mediators from mast cells and circulating basophils. Only one of these is histamine. The prostaglandins of the F class, SRS-A (which now appears to be a prostaglandin itself) thromboxanes and superoxides are examples1 of the others which are unaffected by antihistamines. Exercise-induced asthma (EIA)2 is present in 80 percent or more of asthmatic patients. The possible mechanisms involved have taken a step forward in that inhaled air temperature (cooling)3 in the bronchi seems to be an initial step resulting in the production of bronchospasm. There must be a next step which may eventually be histamine release or may not. The ability of certain viruses4 to produce severe bronchospasm has been demonstrated, but the underlying mechanism remains uncertain. Pure irritants derived from the environment or from certain occupations5 appear to act mechanically on irritable airways. Some drugs6 (organic iodides for example) may precipitate an anaphylactic phenomenon through the nonimmunologic alternative pathway resulting in mast-cell mediator release. The role of the parasympathetic pathways7 has been shown to play a prominent role by numerous investigators. Changes in weather for reasons that are, at present, inexplicable, can precipitate asthma. Emotional factors aggravate asthma that is already there. (For that matter, what disease do emotions not aggravate?) Exposure to cold may have the same mechanism as EIA and, finally, the ubiquitous "intrinsic" asthma which merely underlines our inadequacies, as does the present position of gastrointestinal reflux8 and asthma.

Given all these mechanisms, so many of them unrelated to each other, and the fact that many of them are present in all asthmatic patients and sometimes all of them are involved in a very small minority, what should be expected of an antihistamine?

It is hardly a surprise, to this author at least, that antihistamines appear to be of little value in the treatment of asthma. They can only be expected to affect problems caused by histamine (and, at this time of writing, by the H1 antihistamine groups). To go back 30 years, Herxheimer9,10 investigated an antihistamine (Anthisan) and found it effective in the treatment of asthma. He used monthly vital capacity measurements and diarized historic data. He considered its use a major advance. He went further with another study in the same year, demonstrating that an antihistamine (Phenergan) blocked acetylcholine and histamine-induced bronchospasm produced by inhalation. One can admire his pioneering spirit as one of the early "inhalation challengers" and respect his ignorance at that time of so many other mechanisms involved. Schild et al11 proceeded to show blocking effects produced by an antihistamine in experiments utilizing tracheal rings from an asthmatic patient who died, as well as similar results from sensitized tracheas derived from animals. Herxheimer was one of the investigators.

It is interesting that in 1948 Curry and Lowell12 published an extensive paper dealing with antigen-induced asthma, presuming that histamine was the ultimate pathway to bronchospasm, but added an astute comment which I quote verbatim: "... the great majority of our patients whom we have seen, though they exhibit sensitivity to one or more allergens, have asthma at odd times, apparently unassociated with exposure to a recognizable allergen.

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and very frequently brought on by exposure to cold air, steam, extremes of temperature, fits of laughter, coughing or crying, emotional upsets, respiratory infections, inhalation of smoke, particulate matter, soap flakes, strong odors or irritating gases.” This was 31 years ago—so much for progress!

Casterline and Evans,13 using histamine by inhalation challenge, showed that bronchospasm could be blocked by pre-treatment with an inhaled antihistamine, dephenylamine HCL. In 1978, Göbel14 showed that an antihistamine (clemastine), which is specific for H₁ receptor sites, was relatively ineffective in controlling his asthmatic subjects while ketotifen, a drug with antihistamine and cromolyn-like properties in regard to effects on mast cell stabilization, was very effective.

Nogrady and co-workers15 used the same specific antihistamine H₂ blocker (clemastine) by inhalation (as opposed to oral form used by Göbel) in a comparative test against inhaled salbutamol, a beta₂ sympathomimetic agent. Equal bronchodilation occurred, but over a longer time period than that obtained by salbutamol.

In this issue of Chest, Popa (see page 442) demonstrates that an intravenous injection of chlorpheniramine (Chlortrimeton) initially effectively blocked an antigen challenge, but did not prevent bronchospasm from occurring when the amount of antigen inhaled was doubled.

What can one make of all this? Unquestionably, histamine is a cause of bronchospasm and hence a cause of asthma. There seems every indication that, given the right antihistamine such as clemastine, and administering it by inhalation, antihistamines may have a significant role in the treatment of asthma. However, at this Center (NJH/NAC), Koepke (unpublished data) has shown that only one subject out of ten effectively blocked an antigen challenge after pre-treatment with inhaled Chlortrimeton.

Antihistamines, by whatever route of administration, face stiff therapeutic competition. The beta₂ sympathomimetics, either oral or inhaled, and the present effectiveness of controlled theophylline therapy around the clock, together with cromolyn sodium and the new oral cromolyn-like analogues being developed, as well as the prospect of an inhaled atropine analogue becoming available in the future, are so much easier to manage and are very effective synergistically when used together. They will be difficult to replace for the physician in daily practice. The possibility that a combination of H₁ and H₂ antihistamines might act synergistically in the treatment of histamine-induced asthma was somewhat dashed by Shocket (personal communication)16 who found that combination of H₁ and H₂ antihistamines did nothing to block asthma induced by histamine inhalation challenge in adults. In fact, the H₂ antihistamines given alone appeared to have increased bronchial sensitivity to histamine.

The outlook for antihistamines becoming a prominent feature in the management of asthma is not very bright. Time will tell.

Hyman Chai, M.D., F.C.C.P.
Denver

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