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# Update

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## **Behavioral and psychological changes in asthmatic children taking theophylline**

by Bruce G. Bender, Ph.D., and Stanley J. Szeffler, M.D.

*Controversy has surrounded the use of theophylline for several years because of concerns that it can cause psychological changes and behavioral problems in asthmatic children. However, a comparison of recent scientific publications about theophylline side effects reveals inconsistent results, and most studies have been conducted for only a few weeks. Therefore, we undertook a carefully controlled study to assess theophylline effects over a six-month period.*

Theophylline, a methylated xanthine closely related to caffeine, is a commonly prescribed medication for the treatment of childhood asthma. Behavioral and psychological side effects have been linked to theophylline, including: poor attention, hyperactivity and impulsivity, impaired memory and learning, conduct problems, poor motor control, anxiety, irritability and sadness.

While this list may seem to present a compelling case against continued use of theophylline, the collection of studies and reports published to date is marked

by striking inconsistencies. Different studies often reported different problem behaviors. Some studies found no detrimental side effects, while others found a

### **Behavioral Complaints Previously Linked to Theophylline**

- impaired attention
- hyperactivity/impulsivity
- impaired memory and learning
- conduct problems
- poor motor control
- anxiety
- irritability/sadness

few adverse effects accompanied by a long list of negative findings. Most studies only followed children receiving theophylline for a few weeks.

Our study was designed to remedy some of these deficiencies while evaluating changes caused by theophylline over six months.

### **Methodology**

To do this, we selected three groups of children, all 8 to 16 years of age. The first group consisted of 21 asthmatic children who received theophylline. The second comprised 48 asthmatic children who did not receive theo-

*(Continued on page 2)*

## **Audiotape answers patient questions about "Living with Asthma"**

A new audiotape, entitled "Living with Asthma," contains answers to 100 questions most commonly asked of LUNG LINE® nurses about asthma.

The patient education tool allows asthmatics or family members to review a message as often as they wish, at their own convenience and at their own pace.

Side One explains the nature of asthma, while Side Two covers treatments

and preventive measures.

Copies of "Living with Asthma" can be purchased by sending a check or money order payable to "BIOCOM Asthma Tape" to BIOCOM, P.O. Box 0647, Planetarium Station, New York, NY 10024. The price for each cassette is \$7.60. Reduced rates for bulk orders may be arranged by calling BIOCOM at 212-769-0703.

## Theophylline...

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phylline. The third was a selection of 26 non-asthmatic children.

Patients were excluded from the study if they were psychiatrically disturbed, had other known illness or neurological disorder or had received steroids in the previous month. Subjects had to remain steroid-free to be included in the six-month protocol.

Subject characteristics, including

*“Self-reported mood, impulsivity and hyperactivity showed no significant changes, but parents reported increases in these symptoms.”*

intelligence, psychological history, age, sex, socioeconomic status and asthma severity, were used as corellative variables.

A battery of standardized and innovative measures were used to document potential changes in both psychiatric and neuropsychological characteristics of the children.

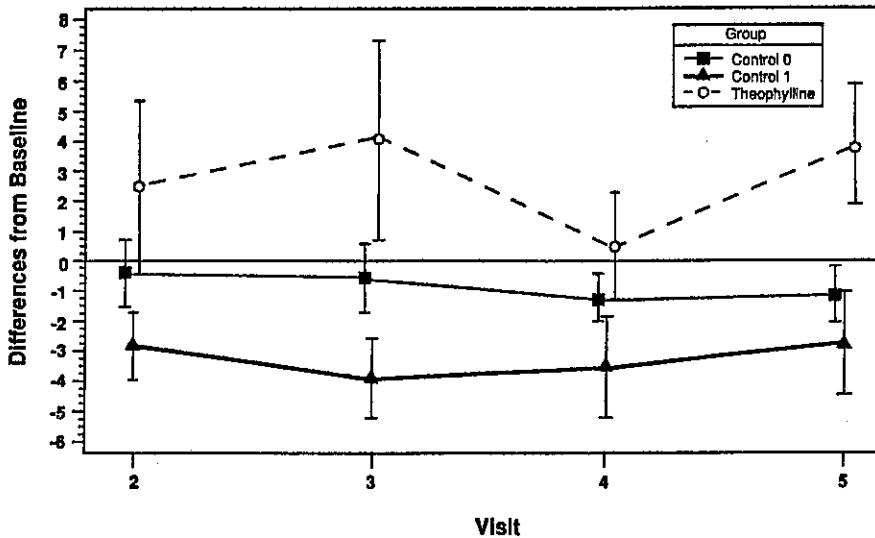
Each child was evaluated on five occasions. Baseline testing for the theophylline group was conducted before theophylline treatment was begun. The remaining four visits occurred at one week, one month, three months and six months after beginning theophylline. The other two groups were tested at the same intervals, although they did not receive theophylline.

Because of the long duration involved, this was an open label study. Theophylline dose was adjusted to provide concentrations between 8-20 micrograms/milliliter. On each of the five visits, subjects participated in pulmonary function and psychological testing, and blood was drawn to assess serum theophylline concentration.

Instruments used in the behavior test battery included measures of:

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### Conduct Problems (Parent-Reported)



Parents of the theophylline group reported a consistent increase (with some fluctuation) in conduct problems over six months, while the non-asthma (Control 0) and asthma-without-theophylline (Control 1) groups remained constant or showed decreased behavior problems.

## Other studies in progress on theophylline side effects

Dr. Bender and Henry Milgrom, M.D., are conducting further studies on adverse side effects of theophylline in children.

One three-month investigation focuses on children with a history of reduced attention span or other problems attributed to theophylline. Half of the subjects will get theophylline first, the other half will get placebos first in the double-blind crossover study. Measurements similar to those described in the accompanying article, such as impulsiveness, changes in attention span and hyperactivity, will be used. "What we're trying to find out is, can we predict which kids will have problems," Dr. Bender said.

Another Bender/Milgrom study is designed to determine whether children on theophylline have fewer side effects with a single dose of sustained-release medication at night before bed compared to the more common practice of taking it twice during the day.

"If we can identify kids who are at increased risk, is there a different way to treat them?" Dr. Bender asked. "Would they do better on an evening dose or do they need to be off theophylline and on something else?"

Dr. Bender and Dr. Milgrom also are beginning an investigation to see if a sustained-release dose of theophylline at night before bed reduces adverse side effects in adults with nocturnal asthma.

# Theophylline...

(Continued from page 2)

self-reported anxiety and depression, impulsivity, attention, memory, fine motor control, body movement and behavior problems. The measurements were conducted with the child in the testing laboratory, with the exception of behavior problems, which were measured by the Conners Parent Rating Scale completed by parents at each visit.

The first four laboratory measures were administered by computer. An examiner tested verbal memory. Fine motor control and hyperactivity were measured by an electronic steadiness tester and an ultrasonic motion detector specifically constructed for this study.

Change scores were derived by subtracting the baseline test score from the test score at one week, one month, three months and six months.

## Findings

As expected, a striking improvement in pulmonary function was seen in the

group receiving theophylline. Pulmonary functions of this group were equal to those of the two control groups beginning one week after initiation of theophylline treatment.

No significant changes for any of the groups were found across the time intervals in the laboratory measures of self-reported mood, impulsivity or hyperactivity. On the Conners Parent Rating Scale, however, parents of the theophylline study group reported increasing symptoms of hyperactivity, impulsivity and difficult behavior after one month and over the six-month course of the study.

Of the covariates studied, lower IQ and a history of behavior problems were

*"The group receiving theophylline demonstrated improved attention and memory."*

associated with a tendency toward behavior change while taking theophylline.

On the Continuous Performance Test, which measures attention, only the theophylline group recorded a significant change. Improved attention was found in these patients after receiving theophylline for one month and over six months.

Similar results were recorded on the Verbal Memory Test. After one month and over six months, the group receiving

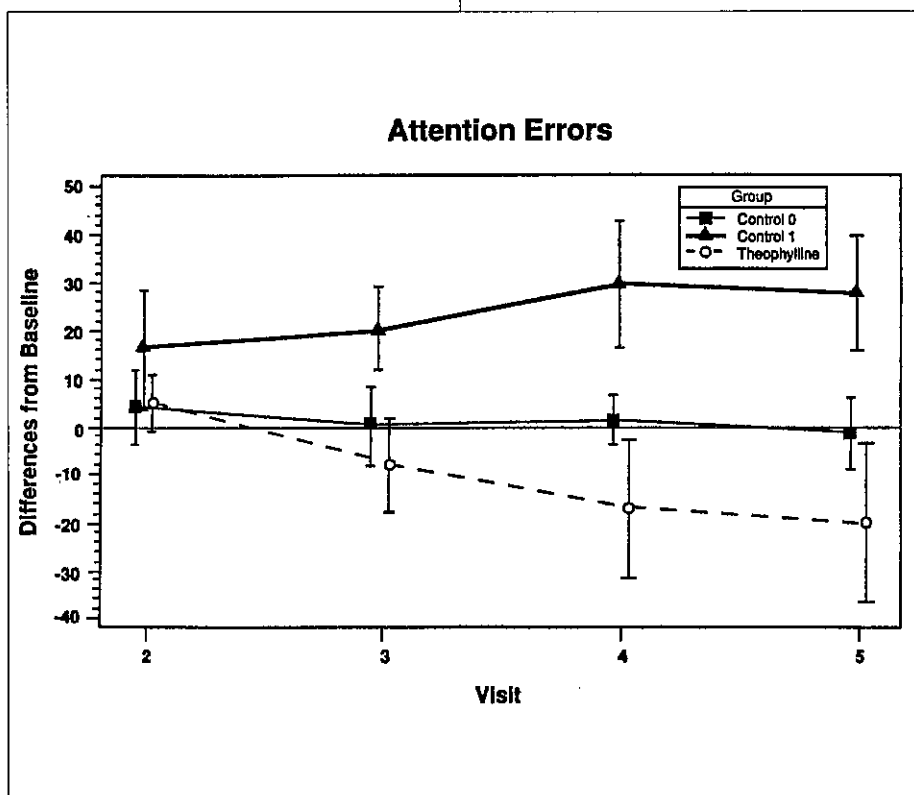
(Continued on page 4)

## National Jewish receives AIDS research grant

National Jewish has received a \$2.98-million National Institutes of Health (NIH) grant to help fund a unique AIDS research program that will pool the skills of the institution's leading immunologists, cell biologists and biochemists. National Jewish is no stranger to AIDS research. The Center is internationally known for its work in the field of immune system biology, focusing on T cells and B cells and how they recognize and repel pathogens in the body. National Jewish researchers also were among the first to report that AIDS could occur in hemophiliacs and that HIV could be transmitted in blood products.

Eleven National Jewish investigators will attempt to determine exactly how HIV disables the immune system. The NIH-funded project will look at how HIV undermines the function of T cells, as well as the actions of another set of immune system scavenger cells called macrophages that consume foreign matter in the body. Researchers also will try to pin down how HIV short-circuits T cell development in the fetuses of infected mothers.

"The vast majority of AIDS patients die of secondary infections which they contract because their immune systems do not properly function," said John Cambier, Ph.D., the project's principal investigator. "The proposed studies will hopefully lead to strategies for reversing this HIV-induced immune suppression."



*The theophylline group consistently demonstrated fewer errors in attention over six months compared to baseline scores, while the non-asthma (Control 0) and asthma-without-theophylline (Control 1) groups remained constant or showed increased attention deficits.*

## Theophylline...

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theophylline demonstrated improved word recall and memory, while the asthma and non-asthma control groups showed no significant change.

While improved attention and memory in the theophylline group may seem a surprise, two other studies have reported similar results in children and adults.<sup>1,2</sup>

On the test for Fine Motor Control, however, the theophylline group exhibited decreased motor control after one month compared to the two control groups. These results persisted over six months.

We believe these results may be understood in the following way: Research has shown that caffeine, a xanthine compound closely related to theophylline, can result in improved attention, as well as nervous, jittery and disruptive behavior. It is likely that the stimulant properties of theophylline also can produce both desirable and undesirable side effects, improving alertness,

## Workshop on adverse drug reactions and allergies

A National Jewish CME workshop on adverse drug reactions and allergies will be held Thursday, June 21, at the Denver Hilton South.

Presenters will discuss:

- penicillin and B lactam hypersensitivity,
- allergies to local anesthetics, dyes, preservatives and radiocontrast media reactions, and
- aspirin/sulfite sensitivity.

Workshop attendees can receive three credit hours in ACCME Category 1 or 3.25 AAFP elective hours. For information or registration, contact Adele Gelfand, Manager of Professional Education, (303) 398-1359.

*"The theophylline group exhibited decreased motor control."*

but causing some difficulty curtailing physical movement.

### Summary

For both desired and undesired theophylline side effects, average changes were small. This suggests that either theophylline side effects are mild and, in general, do not warrant considerable concern or that a relatively few asthmatic children experience strong side effects. We suspect the latter is the case and are continuing to attempt to identify a high-risk subgroup of asthmatic children prone to theophylline side effects. The simple conclusion that theophylline causes significant behavioral disruption in many of the asthmatic children who receive it is, as yet, unwarranted. □

### References

1. Rappaport L, Coffman H, Guare R, Fenton T, DeGraw C, Twarog F: "Effects of theophylline on behavior and learning in children with asthma." *Am J Dis Child* 1989; 143:368-372.
2. Joad J, Ahrens R, Lindgren S, et al: "Extrapulmonary effects of maintenance therapy with theophylline and inhaled albuterol in patients with chronic asthma." *J Allergy Clin Immunol* 1986; 78:1147-1153.

This report is based on a study by Bruce G. Bender, Ph.D., Stanley J. Szeffler, M.D., Joey Lerner, M.D., and David Ikle, Ph.D.

Dr. Bender is a pediatric psychologist on staff at the National Jewish Center for Immunology and Respiratory Medicine. Dr. Szeffler is director of clinical pharmacology at National Jewish.

## Leung new head of pediatric allergy

Donald Leung, M.D., Ph.D., has joined National Jewish as head of the Division of Pediatric Allergy/Immunology.

Previously, Dr. Leung was director of the allergy program at Children's Hospital in Boston and associate professor of pediatrics at Harvard Medical School.

He attended Johns Hopkins University as an undergraduate and received his Ph.D. and M.D. degrees from the University of Chicago. He did his internship and residency training at Children's Hospital in Boston and was a clinical fellow in pediatrics at Harvard Medical School and a fellow in allergy/immunology at Children's.

## Howell becomes medical director for May Unit

Janice Hopkins Howell, M.D., has been named medical director for the May unit at National Jewish, the Center's 24-bed treatment section for children with respiratory/immunologic diseases complicated by psychosocial problems.

Bruce Miller, M.D., continues as psychiatric director of the unit.

Dr. Howell previously was a member of the pediatric department at Montreal Children's Hospital and taught for several years at the McGill University School of Medicine.

She also had appointments with the Regional Medical Center in Chibougamau, Quebec; the Area Health Education Program in Asheville, N.C.; and Forsyth Hospital in Winston-Salem, N.C., among others.

Dr. Howell received degrees in physical and occupational therapy before attending the Medical College of Pennsylvania. She was a pediatric resident at Montreal Children's Hospital and a clinical and research fellow at McGill University.

# Clinical Criteria for Referral to National Jewish

While most asthma and chronic respiratory disease patients can be managed successfully in private practice, some particularly difficult-to-treat cases can place extreme demands on your time and can strain the resources of your practice.

That's when National Jewish can be a uniquely valuable ally. Our physicians and allied health professionals specialize in treating patients who have not responded well to conventional treatment.

In most of these cases, besides unsatisfactory clinical progress, patients experience a severely impaired quality of life and a dramatic decline in work or school productivity. Unrealistic patient expectations, limited patient understanding of their disease and non-compliance with physician recommendations also frequently lead to deterioration of the doctor-patient relationship.

Our role is to work with you in diagnosis, treatment and education, returning to your care healthier, more knowledgeable, more manageable patients.

Following are some key clinical features of many people who are referred to National Jewish for specialized intervention. More detailed, specific criteria are available at your request.

## Outpatients

### *High steroid needs/adverse side effects*

- Patients with high steroid requirements (10 to 20 milligrams or more of prednisone per day for six months)
- Patients with significant side effects from medication, including 20 percent weight increase, elevated blood pressure and glucose (diabetes), osteoporosis, cataracts and psychological problems

### *Frequent absenteeism*

- Patients who lose significant time (10 percent or more) from

work or school due to their illness

### *Frequent health care use*

- Patients with frequent emergency room visits (more than two per year), hospitalizations (more than one per year) and emergency extended physician office visits for stabilization

## Inpatients

People who are appropriate inpatients exhibit the above characteristics, usually at an increased or aggravated level, as well as:

- a history of respiratory failure or sudden near-death cyanotic episodes
- persistent poor medical compliance and self care
- significant emotional or behavioral disorders that interfere with medical compliance
- significant unrelieved impairment in breathing
- ventilator dependency
- severe malnutrition
- need for continuous IV
- persistent conditions (atopic dermatitis, infections or morbid obesity) unresponsive to outpatient therapy.

Additional criteria may include factors such as a severely dysfunctional family or drug/alcohol abuse.

The bottom line for all of these patients is that they have not responded well to "regular" or conventional therapy. They go for months or even years without substantial improvement before they are referred to National Jewish.

Five-year National Jewish outcomes studies indicate that National Jewish patients can achieve significant gains in clinical function and quality of life, resulting in dramatically reduced health care resource consumption and costs.

Utilization review is conducted by National Jewish nurses and physicians before admission and continually during the patient's stay to assess appropriateness of hospitalization and diagnostic

and treatment planning. The estimated date of discharge form must be completed by the attending physician every three days.

*FOR MORE INFORMATION ON REFERRAL CRITERIA OR ADMITTING PROCEDURES, CALL NATIONAL JEWISH ADMISSIONS AT 1-800-222-5864, EXT. 1571 OR 1-303-398-1571.*

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## **Three pediatric pulmonologists join medical staff**

Three pediatric pulmonologists have joined the National Jewish medical staff, significantly expanding the Center's service in this area.

Leland Fan, M.D., Derek Uchida, M.D., and Carl White, M.D., previously were staff members at Children's Hospital in Denver.

Pediatric airway and breathing problems requiring bronchoscopy, plus chronic pulmonary disease of unknown etiology, are the types of complicated cases the new pulmonologists specialize in handling.

Dr. Fan was chief of the Division of Pulmonary Medicine at Children's and is associate professor of pediatrics at the University of Colorado School of Medicine. He graduated from Baylor College of Medicine and also studied at the University of Colorado and the University of California.

Dr. White is an assistant professor of pediatrics at the University of Colorado School of Medicine. He graduated from Baylor College of Medicine and has done postgraduate work at Baylor and the University of Colorado.

Dr. Uchida also is an assistant professor of pediatrics at the University of Colorado School of Medicine. He graduated from Stanford University Medical School and later studied at the University of Colorado.

## **CME Calendar**

The following weekly conferences are conducted at National Jewish. Unless otherwise noted, each is held in Heitler Hall in the Goodman Building. All physicians in the community, as well as those traveling through Denver, are welcome to attend.

### **Immunology Course/ Immunocorrelates—**

Monday, 8 a.m.

### **Research in Progress—**

Tuesday, noon

### **Denver Allergy Rounds—**

Wednesday, 8 a.m.

### **Pulmonary Medicine Grand Rounds—**

Thursday, 7:30 a.m.

(Location varies; call for details.)

### **Pediatric Grand Rounds—**

Thursday, 8 a.m.;

8:30 a.m. on second Thursday

### **Medicine and Pediatrics, Immunology Research in Progress—**

Thursday, 4 p.m.

### **Topics in Pulmonary Biology, Physiology and Pathology—**

Friday, 7 a.m.

### **Pulmonary Research Conference—**

Friday, 8 a.m.

### **Medicine Second Opinion Conference—**

Friday, 11:30 a.m.

*Medical/Scientific Update* is a monthly publication of the National Jewish Center for Immunology and Respiratory Medicine designed to inform professional colleagues about our clinical programs and research activities. We welcome your comments.

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### **An Educational Ally**

LUNG LINE<sup>®</sup>, a free informational service, can save you time and act as an educational resource by helping teach patients about respiratory, allergic and immunologic diseases. Highly trained registered nurses are available to answer your patients' questions at 1-800-222-LUNG. In Denver, callers should dial 355-LUNG. LUNG LINE<sup>®</sup> nurses always encourage callers to discuss information with their physicians.

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