

Clinical aspects of allergic disease

Theophylline's effect on neutrophil function and the late asthmatic response

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Background: *The decrement in lung function associated with the late asthmatic response after allergen challenge is believed to be mediated by an inflammatory response in the airways. Theophylline has been shown to inhibit the late asthmatic response, but the mechanisms are not clear.*

Objective: *The study was designed to determine whether theophylline would inhibit the late asthmatic response by reducing neutrophil activation and subsequent superoxide production.*

Methods: *Twelve subjects with asthma underwent treatment in this double-blind, randomized, crossover study. Each subject received theophylline and placebo in random order in two treatment periods of 3 weeks each. Each treatment period was followed by an allergen challenge and blood neutrophil function analysis.*

Results: *At therapeutic levels theophylline increased FEV₁ at baseline and during the allergen challenge and increased the percentage suppression of neutrophil superoxide production by adenosine.*

Conclusion: *Theophylline improved pulmonary function at baseline and during an allergen challenge, in part perhaps, by increasing the neutrophil's response to feedback inhibition by adenosine. However, theophylline did not decrease the severity and duration of the late asthmatic response. (J Allergy Clin Immunol 1996;98:251-7.)*

Key words: *Asthma, theophylline, late asthmatic response, adenosine*

The late asthmatic response (LAR) is characterized by a slowly developing, poorly reversible airway obstruction and an inflammatory reaction in the airways in response to inhalation of an allergen.¹ This inflammation is characterized by an influx of eosinophils or neutrophils, depending on the stimulus causing the reaction and the time of analysis.^{2,3}

Several studies in human beings⁴⁻⁸ and animals⁹ have shown that theophylline inhibits the LAR. Many mechanisms have been postulated including bronchodilatation,¹⁰ reduction in capillary permeability,¹¹ and inhibition of neutrophil activation.¹² The effect of theophylline on the neutrophil is in-

Abbreviations used

IAR:	Immediate asthmatic response
LAR:	Late asthmatic response
PMNs:	Polymorphonuclear leukocytes

triguing and has been supported by animal studies, which reveal that pretreatment of guinea pigs with theophylline significantly reduces the influx of neutrophils in the airway.⁷ In addition, neutrophils from patients with asthma have been shown not to respond to regulatory signals provided by adenosine, but this characteristic was reversed with theophylline, resulting in decreased superoxide ion production.¹⁰ Given these data on the effect of theophylline on the neutrophil in both animals and human beings, we hypothesized that theophylline would inhibit the LAR and act in part by decreasing neutrophil activation.

METHODS

Subjects

Twelve subjects with asthma as defined by the American Thoracic Society,¹³ six men and six women between the

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TABLE I. Subject characteristics

Subject	Age (yr)	FEV ₁ (% pred)	Allergen used
M	41	106	Timothy grass
M	41	102	Timothy grass
F	51	105	Cat
M	42	92	Cat
F	46	79	Horse
F	34	90	Timothy grass
F	47	75	Cat
M	30	79	Timothy grass
F	33	101	<i>Pteronyssinus</i> mite
M	24	61	Common sagebrush
M	34	78	Cat
F	28	81	Cat
Mean $\pm$ SEM 37.6 $\pm$ 2.4 89.4 $\pm$ 4.1			

ages of 24 and 51 years (37.6 ± 2.4 years), were recruited from the greater Denver community. Subject characteristics are shown in Table I. In addition, the subjects' asthma symptoms had not changed in severity or required inhaled or oral corticosteroids for at least 6 weeks before study. They did not use medications known to interact with theophylline (e.g., macrolides, quinolones, cimetidine). Finally, no medical problems other than asthma were present. All subjects gave consent to this protocol, which was approved by the Institutional Review Board.

Study design

Allergen challenge. All subjects underwent a baseline/screening allergen challenge to document the presence of an LAR before the study began. The antigen used for the challenge was chosen by symptom history, positive skin prick test results, and/or history of a known late response after challenge with the antigen (Table I). An immediate asthmatic response (IAR) was defined as a decrease in FEV₁ of 20% or greater within 5 to 10 minutes of an allergen administration. An LAR was defined as a second decrement in lung function of 15% or greater of at least 1 hour's duration from baseline, usually occurring 4 to 6 hours after an allergen challenge. All challenges began at 7:00 AM.

The diluent used for preparation of the allergen for inhalation was 0.9% sodium chloride (NaCl) with 0.4% phenol. By serial dilution, solutions of 1:10, 1:100, 1:1000, 1:10,000, 1:100,000, and 1:1,000,000 wt/vol were made. The same DeVilbiss 646 nebulizer (DeVilbiss Health Care, Inc., Somerset, Pa.) with the components in the same spatial orientation was used for each subject during the different challenge days. A French Rosenthal dosimeter (Baltimore, Md.) was used, and the initial volume of solution in the nebulizer was kept constant at 1.5 ml.

After two measurements of FEV₁ within 10% of each

other, each subject inhaled diluent (5 inhalations at 20 psi for 0.6 seconds), and FEV₁ was measured 10 minutes later (again, two measurements within 10%). If there was no change in FEV₁ after inhalation of the diluent, the first dose of allergen at a concentration of 1:1,000,000 was given. Spirometry was performed 10 minutes after delivery of the allergen. If FEV₁ fell by less than 15% from baseline, the next dilution of allergen was given. If FEV₁ fell between 15% and 19%, another FEV₁ measurement was obtained after 10 additional minutes. If the change in FEV₁ was still between 15% and 19%, the same concentration of allergen was administered again, with spirometry repeated 10 minutes after administration.

Once an IAR had occurred, FEV₁ was measured every 15 minutes until it returned to baseline or until a plateau was reached. The FEV₁ measurements were then repeated every hour until the termination of the LAR or until 12 hours after the challenge if an LAR did not develop.

Once the subjects demonstrated both the IAR and LAR, they received a once-daily theophylline preparation (Uniphyll), and doses were titrated until the serum theophylline concentration ranged from 14 to 20 μ g/ml. Blood levels were measured 12 hours after administration to reflect a peak level at approximately 7:00 AM. After the appropriate theophylline dose was established, each patient underwent a 1-week washout period and then entered the double-blind crossover portion of the study. Patients received theophylline and placebo in random order during two treatment periods of 3 weeks each. The serum theophylline level was checked after approximately 1 and 1/2 weeks, or halfway through the treatment period. The treatment periods were separated by a 1-week washout period. At the end of each period, subjects underwent repeat allergen challenge with the same allergen as given previously during the baseline screening. In addition, blood was drawn before and 4 hours after challenge for analysis of neutrophil respiratory burst (superoxide production) and percent suppression of superoxide production by adenosine.

Peripheral blood neutrophil studies. Neutrophils (>97% pure) were isolated as previously described¹² from heparinized whole blood through the sequential application of Ficoll-Hypaque (Pharmacia, Uppsala, Sweden) centrifugation and 3% dextran sedimentation. Contaminating erythrocytes were lysed by exposure to hypotonic saline solution. Polymorphonuclear leukocytes (PMNs) were washed and resuspended in phosphate-buffered saline at a concentration of 10^7 cells/ml. Respiratory burst activity was measured as the generation of reduced cytochrome. Quadruplicate samples of PMNs (5×10^5) in flat-bottom, 96-well microtiter plates (Immulon II; Dynatech, Chantilly, Va.) were left in a resting state, treated with 10^{-6} mol/L formyl-methionyl-leucyl-phenylalanine (Sigma Chemical Co., St. Louis, Mo.) or treated with 10^{-5} mol/L 2-chloroadenosine (Sigma Chemical Co.) and 10^{-6} mol/L formyl-methio-

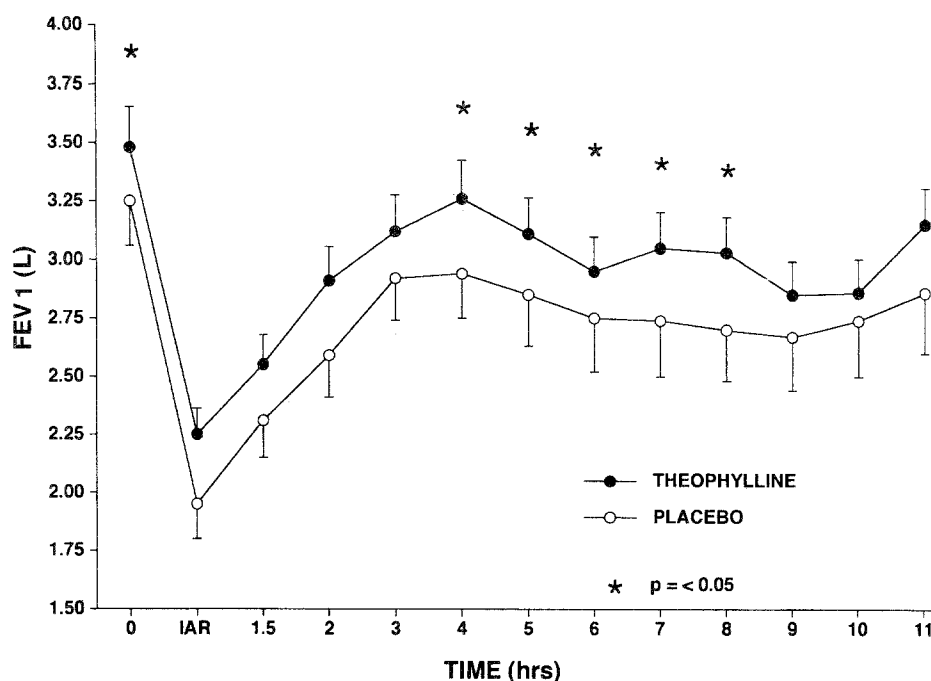


FIG. 1. Mean absolute FEV₁ values for each time point are plotted over time during allergen challenges while subjects were receiving placebo and theophylline. White circles represent mean FEV₁ values during placebo administration and dark circles represent FEV₁ values during theophylline administration.

nyl-leucyl-phenylalanine. After a 15-minute incubation at 37°C, the absorption at 550 nm was measured on a Dynatech ELISA reader. Superoxide (O₂⁻) production is reported as nanomoles of O₂⁻ per 5 × 10⁵ PMNs per minute with the formula:

$$\text{nmol O}_2^- \text{ produced} = 100 \times (\text{OD}/6.3)$$

where OD is optical density. Suppression of superoxide production was calculated as a suppression index according to the formula:

% Suppression =

$$\left(1 - \frac{\text{Superoxide in the presence of ligand}}{\text{Superoxide in the absence of ligand}} \right) \times 100$$

Statistical analysis

The outcome physiologic variables were severity, duration, and time to onset of the LAR and severity and duration of the IAR. Outcome variables for neutrophil function were the percent suppression of superoxide production by adenosine measured before and after allergen challenge. The sample size reflects an 80% power to detect a difference in FEV₁ of 250 ml with a type I error of 5%.¹⁴ Analysis was performed with a two-period crossover analysis of variance model.¹⁵ Group 1 was defined as the subjects who received theophylline first followed by placebo, and group 2 was defined as those who received placebo followed by

theophylline. Carryover effects were tested for significance at the 10% alpha level, and period-treatment effects were tested for significance at the 5% alpha level. Finally, the areas under the percent baseline FEV₁-time curves for the immediate response (hours 0 to 3) and the late response (hours 4 to 10) while subjects were receiving placebo and theophylline were calculated with the trapezoidal rule.¹⁶ Areas were compared by using Student's paired *t* test. Significance was tested at the 5% alpha level.

RESULTS

Spirometry

IAR. The mean serum theophylline level at the time of the allergen challenge was 16.4 ± 0.69 µg/ml during the theophylline treatment period. All 12 subjects demonstrated an IAR with both theophylline and placebo with the same allergen that was used for each subject during the baseline/screening challenge. The concentration of allergen required to produce the IAR was similar for theophylline and placebo (geometric means 1:50 and 1:63, respectively). The mean baseline FEV₁ during theophylline administration was significantly higher than that during placebo administration (3.48 ± 0.22 L and 3.25 ± 0.19 L, respectively, *p* = 0.02) (Fig. 1). However, this increase in

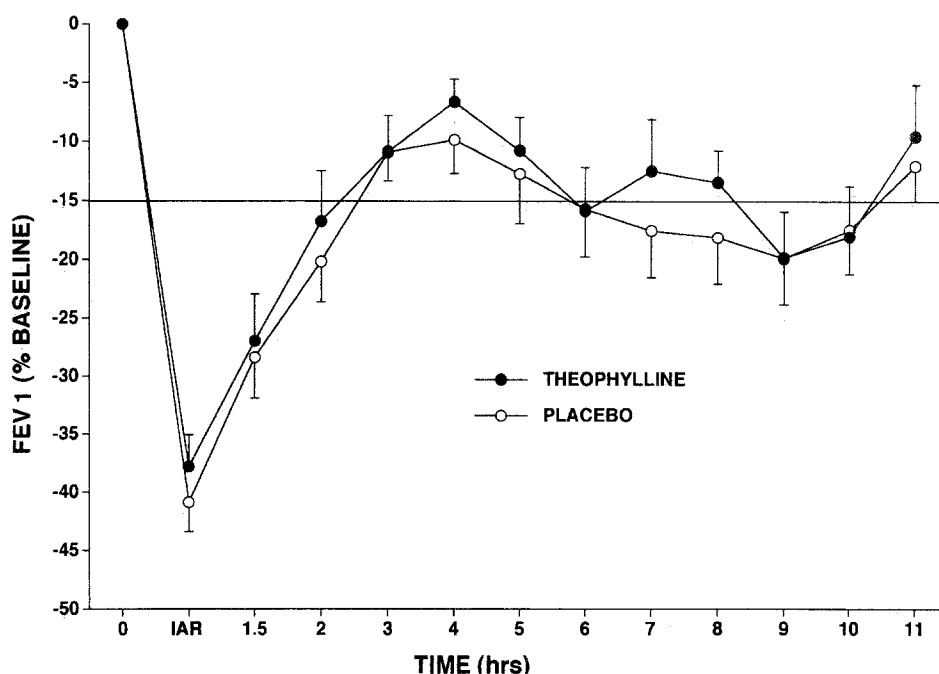


FIG. 2. Mean percentage changes in FEV₁ from the baseline value before the study are plotted over time during allergen challenges while subjects were receiving placebo and theophylline. White circles represent percent change in FEV₁ during placebo administration, and black circles represent percent change in FEV₁ during theophylline administration.

baseline FEV₁ did not alter the severity and duration of the immediate response in the theophylline group because the areas under the percent baseline FEV₁-time curves were not significantly different between theophylline and placebo (94.89% vs 86.98%, respectively, $p = 0.18$) (Fig. 2).

LAR. Eleven of 12 subjects demonstrated an LAR while receiving theophylline, and 11 of 12 demonstrated an LAR while receiving placebo. Subject 2 did not have an LAR after the challenge while receiving theophylline, and subject 4 did not have an LAR after the challenge while receiving placebo. As with the baseline, the absolute FEV₁ was higher at several points throughout the challenge during theophylline administration ($p \leq 0.05$, Fig. 1). In addition, the area under the absolute FEV₁-time curve is greater for the theophylline curve as compared with placebo (297.0 vs 267.8, respectively, $p = 0.007$, Fig. 1), suggesting that overall pulmonary function at baseline and during the LAR is improved with theophylline treatment. However, when the curves showing percentage change in FEV₁ from baseline over time are compared (Fig. 2), the area under the curve is not significantly different for the theophylline and placebo groups (233.4 vs 257.2, respectively, $p = 0.51$), suggesting that the severity and duration of the LAR are not decreased with theophylline treatment. The time to onset of the LAR was no different

between the two groups (2.92 ± 0.78 hours vs 2.96 ± 0.69 hours for placebo and theophylline, respectively, $p = 0.81$).

Blood neutrophil analysis

The subjects exhibited a decreased response to suppression of the neutrophil respiratory burst by adenosine as shown in a previous study by Sustiel et al.¹² but there was no difference before allergen challenge between the placebo and theophylline treatment periods ($23.10\% \pm 8.91\%$ and $29.61\% \pm 8.91\%$ for placebo and theophylline treatment periods, respectively, $p = 0.62$). However, the percent suppression of the neutrophil respiratory burst by adenosine during the placebo period decreased from $23.10\% \pm 5.33\%$ before challenge to $9.49\% \pm 4.81\%$ after challenge, which trended toward significance ($p = 0.09$). This reduction in the percentage suppression by adenosine after challenge was not seen in the theophylline group ($29.61\% \pm 8.91\%$ and $30.33\% \pm 8.06\%$ before and after challenge, respectively, $p = 0.095$). Therefore the percent suppression of the neutrophil respiratory burst by adenosine was significantly greater in the theophylline group after the allergen challenge ($9.49\% \pm 4.81\%$ vs. $30.33\% \pm 8.06\%$ in placebo and theophylline groups, respectively, $p = 0.05$) (Fig. 3).

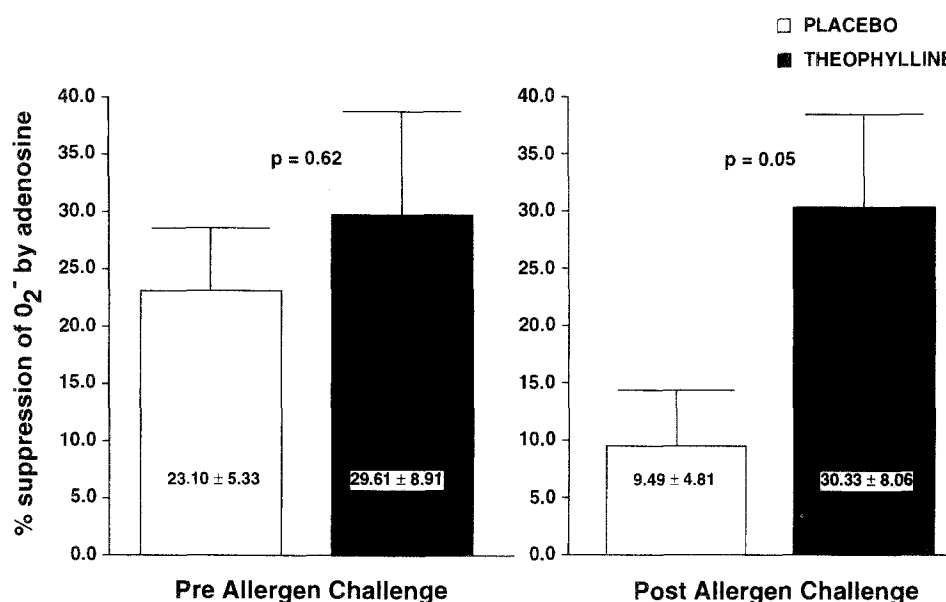


FIG. 3. Adenosine-induced percentage suppression of neutrophil superoxide production in the theophylline and placebo groups from blood analyzed before and 4 hours after allergen challenge. *White bars* represent the placebo group, and *black bars* represent the theophylline group.

DISCUSSION

These results show that theophylline produced a significant improvement in baseline FEV₁ and improved pulmonary function throughout the IAR and LAR. However, the severity and duration of the IAR and LAR were not altered. Our results were different from other studies,^{4,6} which demonstrated that theophylline decreased both the severity and duration of the LAR. Our study design differed from these studies in that we used a once-daily theophylline preparation administered at 7:00 PM, with resulting serum levels in the therapeutic range at the start of the challenge. However, we did not measure levels at the time of the LAR 6 to 8 hours later, when levels were probably lower. Studies by Hendeles et al.⁷ and Crescioli et al.⁸ showed that once-daily theophylline preparations modestly attenuated the LAR. In both studies theophylline was administered in the morning, before challenge, as compared with our evening administration, which may explain why we were unable to show an attenuation of the LAR. Although Ward et al.⁶ showed that relatively low serum theophylline levels resulted in attenuation of the LAR, perhaps a more constant daytime level is required both at the time of challenge and during the LAR to result in protective effects. Alternatively, it is possible that theophylline does not significantly attenuate the LAR. Cockcroft et al.¹⁷ evaluated the effect of a twice-daily theophyl-

line preparation on the LAR in a group of patients with atopic asthma. They were unable to demonstrate that theophylline resulted in a significant reduction in the LAR or in allergen-induced airway responsiveness to methacholine.

Neutrophils from patients with asthma have been shown to generate more superoxide in response to stimulation from formyl-methionyl-leucyl-phenylalanine than neutrophils from nonasthmatic subjects.¹⁸ Thus neutrophils from patients with asthma are "primed" in that they are capable of responding more vigorously to a submaximal stimulus.¹² Furthermore, neutrophils from patients with asthma do not respond to feedback signals from adenosine, which binds to neutrophils and reduces superoxide production through adenylyl cyclase at the A₁ and A₂ receptors.^{12,19} Methylxanthines, such as theophylline, compete directly with adenosine, bind to adenosine receptors on the neutrophil, and have been shown to also reduce superoxide production through 3'/5' cyclic adenosine monophosphate, although this is somewhat controversial.²⁰⁻²² Adenosine is a physiologically relevant mediator to study because increased concentrations of circulating adenosine have been shown to occur after bronchoprovocation with either inhaled allergen or methacholine, suggesting that this purine nucleoside is released during an asthmatic response.²³ In addition, inhaled adenosine causes bronchoconstriction in patients with asthma, and this is almost completely reversed by theophyl-

line.²⁴ Although adenosine may potentiate asthma when given exogenously, it appears to modulate superoxide production by granulocytes through endogenous action on the A₂ receptor. In our study theophylline did not decrease overall superoxide production significantly but did increase adenosine's ability to suppress superoxide production. In addition, we also noted an improvement in adenosine's ability to reduce neutrophil superoxide production, which correlated with the severity of the LAR during theophylline administration. After an allergen challenge, neutrophils are activated and are less receptive to feedback inhibition by adenosine.²⁴ This phenomenon was demonstrated by the neutrophils from our subjects while receiving placebo, when percent suppression decreased from 23.10% $\pm$ 5.33% to 9.49% $\pm$ 4.81% before and after challenge, whereas the percent suppression during theophylline administration remained constant (29.61% $\pm$ 8.91% and 30.33% $\pm$ 8.06% before and after challenge, respectively).

Theophylline has been shown to exhibit many antiinflammatory effects, including mitigation of the neutrophil respiratory burst, a reduction in leukotriene production, and a reduction in capillary permeability.^{10, 18} In an animal model, therapeutic serum concentrations of theophylline are associated with a diminished leukocyte influx into a bacteria-challenged lung and with diminished bactericidal activity.²⁵ Furthermore Ward et al.⁶ demonstrated that theophylline resulted in a reduction in the peripheral blood CD8⁺ T lymphocytes after allergen challenge. In this study we have evaluated one of many possible mechanisms of theophylline's actions. However, our results do support work from in vitro studies by Joseph et al.,²⁰ which also demonstrated that theophylline increases the feedback inhibition of the neutrophil respiratory burst by adenosine. We did not demonstrate a diminished respiratory burst by PMNs derived from subjects receiving theophylline in vitro. However, in the milieu of the asthmatic lungs, where adenosine is an active mediator,²³ the presence of theophylline would lead to diminished granulocyte function. Although we limited our studies to PMNs, it is also plausible that similar modulation of proinflammatory processes is present in eosinophils. Clearly, further study of the antiinflammatory mechanisms of theophylline is warranted to determine which mechanism is of greatest clinical importance.

In conclusion, our study demonstrates that theophylline improves pulmonary function at baseline, resulting in improved pulmonary function during the IAR and LAR. However, the severity and duration

of the immediate and late responses are unchanged by theophylline. Perhaps the improved baseline pulmonary function is due in part to an antiinflammatory effect on the neutrophil by adenosine.

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A shadow in the mist (Bill Pierson)

Sometimes I awaken to confusion.
Where in the museum of dream was I?
I can see him there before me,
His face afire with a job well done.
There had been many quorums before,
Forty-seven in all, but this was his zenith.
He accepted my hand and congratulations,
Deferring to those around him, it was over.
A few days of rest, recharge the batteries,
Then back to the land of great mist,
Where children and ideas were given life.
The owl had not yet called his name.
Had he known the price, one might suspect,
He would have chosen another path.
But this was no sensible universe,
And he was not consoled by such reflection.
Consumed by a dream he reached for,
Blind to connections with lesser things,
Birthing rage of those who criticized.
Mutterings from the shadows that can hide men.
This doer of deeds could not have done better.
Asthma is awful; let me introduce my son.
Persuader of the purse, he argued from strength,
But money changers answered, diminishing us all.

Bill knew his work was somehow sacred,
A trust earned by a few, delegated to no one,
A voluntary indenturing of self to others,
Worth a terrible toll—one Bill Pierson was ready to pay.
The thief of life was cruel in his half-measure.
Even Stritch could not undo the harm,
Leaving a hole in our soul that will not heal,
With weeks that seem like months, months like years.
Bill knew this world was not about grapes and honors.
It's about suffering, sleepless nights, the excruciation of failure,
The joy in a new mother's eyes, sadness as we bury our dead,
The exhilaration of knowledge, the ragged edge of grief.
A tortured soul cries out to be freed,
Perhaps held hostage by our pride and ignorance.
To be ransomed by healing ourselves and our profession,
Refusing as Bill would, to surrender principle to the heretics.

John C. Selner, MD
1/8/75063