Measurement of clinical change in progressive systemic sclerosis: a 1 year double-blind placebo-controlled trial of N-acetylcysteine

D. E. FURST, P. J. CLEMENTS, R. HARRIS, M. ROSS, J. LEVY,
AND H. E. PAULUS

From the Department of Medicine, UCLA School of Medicine, Los Angeles, California, USA

SUMMARY N-acetylcysteine was employed as a therapeutic agent in a 1-year, parallel, double-blind placebo-controlled, prospective study of 22 patients with progressive systemic sclerosis (PSS). Patients were closely followed-up and were extensively evaluated at baseline, 6, and 12 months. Most parameters remained unchanged during 1 year of study in both the NAC and placebo groups, which showed the need for prolonged studies of drugs in PSS if definitive results are to be obtained. Over the year of the study the diffusing capacity decreased in both groups, while several other parameters measured both increased and decreased. Several simple measures of function and skin distensibility were tested and two (oral aperture and handspread) were reproducible and sensitive enough to measure moderate changes of disease activity. They may be useful in future trials of drug effect in PSS.

Scleroderma is a disease of unknown aetiology characterised by increased collagen deposition in the skin and fibrosis involving numerous organs (D'Angelo *et al.*, 1969). There is also a vascular component to this disease and the immune system may be involved in the pathogenesis of some aspects of progressive systemic sclerosis (PSS) (Norton and Nardo, 1970; Johnson and Ziff, 1976; Salem and Morse, 1976; Kondo *et al.*, 1976).

N-acetylcysteine (NAC), as a thiol compound, is thought to act by reducing disulphide bonds of susceptible proteins to sulphhydryl groups (SH). SH groups have been shown to be important in various biological phenomena, including membrane transport, preservation of the activity of enzyme systems, and cell division (Lorber *et al.*, 1970a). Varying degrees of SH deficiency have been reported by Lorber *et al.* in connective tissue diseases, including scleroderma (Lorber *et al.*, 1970a). The same report documents changes in serum SH concentration which correlate with disease activity in rheumatoid arthritis (RA). This group also showed in vitro that elevation of serum thiols results in depression of

rheumatoid factor. NAC has been shown to increase the SH content in soluble protein in animals and man and has been used in RA with some possible benefit (Lorber *et al.*, 1970b; Barley and Vanal, 1970; Bailey and Sheffner, 1976). Further, acetylcysteine has been shown to decrease dermal inflammation when given subcutaneously or orally to animals for several doses before an inflammatory agent (Bailey and Sheffner, 1976). Finally, NAC inhibits migration inhibition factor (MIF) in vitro, possibly by cleaving polypeptide bonds of the MIF after the MIF is produced, and NAC given intraperitoneally or orally in large doses to rats causes suppression of in vivo, in-vitro mixed lymphocyte reactions (Bartfeld and Ataynata, 1971).

Patients and methods

PSS was classified as either scleroderma or CREST (subcutaneous calcinosis, Raynaud's phenomenon, oesophageal dysmobility, sclerodactyly, telangiectasis), the diagnosis being based on criteria described previously (Clements *et al.*, 1978). The definition of scleroderma required taut or hidebound skin beyond the face and hands, while CREST restricted taut or hidebound skin to hands and face. The degree of

visceral involvement was ascertained by means of a 7–10 day evaluation in hospital. Visceral involvement was defined as present in the lungs, gastrointestinal tract, cardiovascular system, and muscular system by rigorous criteria which have been outlined previously (Clements *et al.*, 1978). Renal involvement was defined as a serum creatinine greater than 1.5.

Twenty-two PSS patients agreed to participate in the study and voluntarily gave fully informed consents (Table 1). Patients with malignant hypertension and acute renal failure were excluded from the study. Patients taking immunosuppressive drugs or prednisone (in a dose greater than 10 mg daily) were excluded. All patients entered the study between August 1973 and August 1974. After initial evaluation to assess the extent of their disease patients were randomly assigned to NAC or placebo treated groups.

MEDICATION

Identically appearing 500 mg capsules of NAC (supplied by Mead-Johnson, Inc.) or placebo were dispensed. Randomisation according to a random numbers table was monitored by the UCLA pharmacy. Therapy was begun with 2–4 capsules daily and increased to a maximum of 20 capsules daily given in equally divided doses over a 2-month period. If the full dose was not tolerated, the highest tolerated dose was used.

ASSESSMENTS

On entering the study and at 6 months and 12 months (± 2 months) the patients entered the UCLA Clinical Research Center for careful standard evaluations to document the degree of cutaneous and visceral involvement.

Included in the evaluation were: chest, hand, and feet radiographs, cine oesophograms, upper gastrointestinal series with small-bowel follow-through, barium enema, oesophageal manometrics, electrocardiogram, treadmill evaluations, pulmonary function tests, arterial blood gases, electromyograms

(EMG), 72-hour stool collections for faecal fat determinations, creatinine and protein determinations on a 24-hour urine collection, complete blood count (CBC) with differential and platelet count, erythrocyte sedimentation rate, quantitative immunoglobulins, serum protein electrophoresis (SPEP), anti-DNA, ANA, latex fixation, total haemolytic complement, third component of complement, aldolase, creatine phosphokinase, SMA-12 (bilirubin, alkaline phosphatase, SGOT, SGPT, total protein, calcium, phosphorus, cholesterol, glucose, BUN, uric acid, lactic dehydrogenase, serum creatinine), thyroxine, tri-iodothyronine, serum carotene. These tests were performed by standard methods by the UCLA Hospital Clinical Laboratory.

During hospitalisation and monthly thereafter the patients underwent a history and physical examination as well as a number of measures of function and skin distensibility.

Oral aperture was measured as millimeters to the outer vermilion borders of the lips when the mouth was maximally opened. The area was calculated as maximum vertical semiaxis times maximal horizontal semiaxis times π (area of an ellipse).

Handspread was measured as the maximum distance in millimeters from tip of thumb to most protruding portion of the fifth digit (usually the tip of the finger) when the patient spread her hand, palm down, on the table (no downward pressure was to be applied—only lateral stretch).

The distance between the tip of the third finger and the most distal observable flexor wrist crease was measured in millimeters as the patient tried to touch her wrist with her third finger.

Grip strength was the highest pressure achieved on a sphygmomanometer for a sustained period on the second or third of 3 attempts with each hand, as outlined by Lee *et al.* (1974). The sphygmomanometer was used wrapped in a standard manner and was used only for this purpose. Baseline pressure was 40 mmHg. The patient was asked to hold her arm unsupported and palm up. If this was not possible, then the same position was used at each visit.

Ring size of the proximal interphalangeal of the third finger of each hand was measured with jeweller's rings.

Joint count was the sum of tender joints as assessed by firm palpation of 29 joints or groups of joints as previously published (Furst *et al.*, 1977).

Statistical analysis was by Student's paired and unpaired *t* tests.

Results

From Tables 1 and 2, it can be seen that these patients were comparable at the initiation of the study. Of the

Table 1 General patient characteristics (mean $\pm$ SEM)

	NAC	Placebo
Weight (kg)	55.1 $\pm$ 3.7	60.1 $\pm$ 4.3
Age (yr)	45.8 $\pm$ 3.6	43.8 $\pm$ 4.5
Sex	10 F/1 M	9 F/2 M
Duration of disease (yr)	9 $\pm$ 2.9	13.5 $\pm$ 4.1
Diffuse skin involvement	9/11 (82%)	8/11 (73%)
CREST	2/11 (18%)	3/11 (27%)
Cardiac involvement	6/11 (55%)	4/11 (36%)
Lung involvement	10/11 (91%)	9/11 (82%)
Renal involvement	0/12 (0%)	1/11 (9%)
Gastrointestinal involvement	10/11 (91%)	9/11 (82%)

Table 2 Baseline values and changes over 1 year (mean $\pm$ SEM)

	NAC		Placebo	
	Beginning of trial	End of trial	Beginning of trial	End of trial
Cardiovascular				
Examination	3	4 (33) ¹	3	3 (0)
Arrhythmias on ECG or treadmill	0	0 (0)	1 ²	0 (100)
Chest film ³	2	3 (50)	3	4 (33)
Pulmonary				
Interstitial fibrosis (x-ray)	5	11 (220)	0	3 (300)
Po ₂ (mm/Hg)	84 $\pm$ 1.8	88 $\pm$ 2.5 (4.6)	86 $\pm$ 2.3	92 $\pm$ 3.7 (6.3)
Vital capacity (ml)	2659 $\pm$ 260	2605 $\pm$ 309 (2.0)	2702 $\pm$ 243	2692 $\pm$ 205 (0.3)
Forced expiratory volume in one second (ml)	2246 $\pm$ 249	2129 $\pm$ 286 (5.5)	2327 $\pm$ 209	2223 $\pm$ 189 (4.7)
FEF 25–75% (l/s) ⁴	2.57 $\pm$ 0.54	2.49 $\pm$ 0.4 (3.2)	3.12 $\pm$ (0.25)	2.73 $\pm$ 0.36 (14)
Total lung capacity (ml)	4605 $\pm$ 272	4675 $\pm$ 313 (1.5)	4170 $\pm$ 356	4098 $\pm$ 317 (1.7)
Residual volume (ml)	1600 $\pm$ 117	1761 $\pm$ 84* (9.2)	1455 $\pm$ 108	1387 $\pm$ 117 (4.9)
Diffusing capacity (ml/min/mmHg)	16.1 $\pm$ 1.9	12.0 $\pm$ 1.2* (36)	2.05 $\pm$ 1.4	15.5 $\pm$ 1.26* (32)
Gastrointestinal				
Oesophageal (see text)	—	—	—	—
Duodenal diameter (cm)	2.8 $\pm$ 0.5	2.8 $\pm$ 0.26 (0)	2.2 $\pm$ 1.8	2.1 $\pm$ 1.7 (4.7)
Faecal fat (g/72 hours)	7.6 $\pm$ 1.8	6.8 $\pm$ 0.95 (1.2)	10.1 $\pm$ 3.3	10.3 $\pm$ 4.6 (1.1)
Renal				
Serum creatinine (mg %)	0.7 $\pm$.05	0.7 $\pm$.03 (0)	0.8 $\pm$.08	0.9 $\pm$ 0.09 (12)
Creatinine clearance (ml/min)	70 $\pm$ 5	77 $\pm$ 7 (10)	74 $\pm$ 10	71 $\pm$ 11 (4)
Proteinuria (mg/l)	93 $\pm$ 14	151 $\pm$ 48 (62)	81 $\pm$ 25	91 $\pm$ 12 (12)
Skin and joints				
X-rays hands and feet ⁵	8	10	7	9
Joint count (tenderness)	11.1 $\pm$ 2.6	10.2 $\pm$ 2.4 (9)	5 $\pm$ 2.4	7.2 $\pm$ 2.3 (44)
Handspread (R) (mm)	169 $\pm$ 9.1	164 $\pm$ 9.6 (3)	156 $\pm$ 9.7	169 $\pm$ 9.1 (3.5)
3rd finger to wrist (R) (mm)	39.5 $\pm$ 5	33 $\pm$ 2.3 (20)	68 $\pm$ 15.2	69 $\pm$ 17† (0.2)
Oral aperture (see text)	1977 $\pm$ 126	2256 $\pm$ 88* (12.3)	1997 $\pm$ 180	2283 $\pm$ 189 (13)
Grip strength (R) (mm/Hg)	125 $\pm$ 8	123 $\pm$ 10 (2)	127 $\pm$ 8	147 $\pm$ 17 (13)
Jeweller's ring ⁶ size (R)	9.1 $\pm$ 0.5	8.5 $\pm$ 0.5 (7)	9 $\pm$ 0.73	8.9 $\pm$ 0.74 (1)
Immunology				
IgA (mg/100 ml)	296 $\pm$ 56	316 $\pm$ 49 (6.7)	364 $\pm$ 74	309 $\pm$ 66 (18)
IgA (mg/100 ml)	1340 $\pm$ 152	1325 $\pm$ 251 (1.1)	1394 $\pm$ 131	1250 $\pm$ 96 (12)
IgM (mg/100 ml)	166 $\pm$ 24	143 $\pm$ 21 (16)	288 $\pm$ 59	197 $\pm$ 33 (16)
Latex (tube dilution)	2.8 $\pm$ 0.6	2.0 $\pm$ 0.2* (39)	2.3 $\pm$ 0.6	2.4 $\pm$ 0.4 (4.2)
ANA (tube dilution)	1.7 $\pm$ 0.4	1.1 $\pm$ 0.7 (17)	1.3 $\pm$ 0.15	2.6 $\pm$ 0.92 (100)
Third component of complement (mg/100 ml)	133 $\pm$ 7.2	132 $\pm$ 6.7 (0.7)	128 $\pm$ 10.3	128 $\pm$ 10.5 (1.6)
Total haemolytic complement (haemolytic units)	56 $\pm$ 10.6	45 $\pm$ 6.3 (24)	42 $\pm$ 7.2	42 $\pm$ 4.6 (0)
Anti-DNA (% binding)	18.5 $\pm$ 1.9	17.1 $\pm$ 5.4 (8)	21.4 $\pm$ 1.2	17.8 $\pm$ 2.3 (20)
Weight (kg)	55.1 $\pm$ 3.7	53.7 $\pm$ 1.5 (2.6)	60.1 $\pm$ 4.3	57.5 $\pm$ 3.3 (5.4)
Haematocrit (vol. %)	40 $\pm$ 1.2	37 $\pm$ 2.0 (9)	40 $\pm$ 0.8	37 $\pm$ 2.0 (8)
Westergren erythrocyte sedimentation rate (mm/h)	24 $\pm$ 2.8	30 $\pm$ 5.1 (20)	29 $\pm$ 4.5	29 $\pm$ 5.2 (0)
Creatin phosphokinase (% of upper limits of normal)	88 $\pm$ 30	93 $\pm$ 43 (5.2)	56 $\pm$ 8.7	112 $\pm$ 41 (50)

¹Percentage change between beginning and end. ²Recurrent paroxysmal atrial tachycardia (PAT). ³Cardiac enlargement or pulmonary artery prominence. ⁴Forced expiratory flow 25 to 75%. ⁵Tuft resorption and/or subcutaneous calcinosis. ⁶Measured over 3rd PIP. *Within group statistical difference $P < 0.05$. †Between group statistical difference $P < 0.05$.

11 patients who started on NAC 4 discontinued medication: 2 secondary to gastrointestinal distress, 1 secondary to a rash, and 1 because of deterioration in disease. The average daily dose of drug for the 7 who completed the 1-year study was 9.4 ± 0.4 g (SEM). Four of the 11 placebo treated patients discontinued medication: 2 because their disease deteriorated, 1 secondary to gastrointestinal distress, and 1 because she did not wish to continue to take so many capsules. Average daily dose for the placebo-treated group was 9.7 ± 0.2 g. Thus the comparison at 1 year was actually between 7 NAC-treated patients and 7 placebo-treated patients.

The results in each area of interest are included in Table 2. There were no significant changes when comparing the 2 groups over the year of study except in testing the distance from the tip of the 3rd finger to the wrist crease. This difference is related to the large (although not statistically significant) difference between the 2 groups at baseline. Each group had significant ($P < 0.02$) deterioration in diffusing capacity in 1 year. In the NAC-treated group residual volume increased significantly ($P < 0.05$). Oral aperture increased significantly in the NAC-treated group ($P < 0.01$) and latex titres decreased statistically significantly ($P < 0.05$).

The muscle testing parameters employed (CPK, aldolase, biopsy, EMG) were those which have been published previously (Clements *et al.*, 1978). They did not change significantly in either group over the year of study.

Oesophageal manometrics and cine oesophograms were also analysed separately, and they too remained unchanged during the study for both the placebo and NAC-treated groups.

Complete blood count, platelet count, differential, SMA-12, thyroxine, tri-iodothyronine, arterial P_{CO_2} , and base excess as well as some of the remaining pulmonary function tests were not included in Table 2 as they did not change and added nothing to the information presented in the Table.

Oral aperture was evaluated as a measure of skin distensibility. The area measured was calculated as an ellipse, as the open mouth is more ellipsoid than circular. In 10 normal volunteers this area was 3076 ± 167 (SEM) mm^2 . Mean intraobserver differences, measured in 10 PSS patients by the same observer at approximately the same time of day for 3 consecutive days, was 4%. Interobserver differences were 19% and diurnal variation was 15% (see Table 3). The coefficient of variation (CV), defined as the mean divided by the standard deviation, averaged 0.24. This is a measure of relative variability and gives an idea of the precision of the measurement. A low CV (e.g., 0.05) indicates that the measurements are very reproducible, while a high CV (e.g., 0.50) shows that there is much variation about the mean. A CV of 0.27 indicates moderate relative variability and indicates that a moderate change in disease state must occur before the measurement in question can reliably detect it.

Handspread measures were surprisingly consistent between observers (differences were 1 to 5%), but

diurnal variation was large (about 16%) (Table 3). Coefficients of variation averaged 0.25.

The most inconsistent measures were those relating to the distance from the tip of the third finger to the most distal wrist crease. Here coefficients of variation averaged 0.52. It appeared as if evening measurements were slightly more consistent than morning ones, perhaps a sign of less gel phenomenon in the hands by evening time (Table 3). The timing of measurements was as for oral aperture.

As can be seen in Table 2, changes in both groups were generally in the same direction over the year of study. For the NAC-treated group the greatest percentage changes occurred in the diffusing capacity (Dco), latex titre, and proteinuria. The change in Dco, along with increased residual volume, indicated statistical worsening of disease but may not be clinically significant during the period of the study. Oral aperture increased significantly. Latex titre decreased statistically, although not clinically, significantly. This latter change would be expected on the basis of previous reports using NAC (Lorber *et al.*, 1970b).

There were no significant changes in any of the parameters examined in the placebo-treated group, except for Dco, where significant deterioration was noted.

Discussion

This 1-year double-blind randomised placebo-controlled study of NAC in the treatment of PSS was discontinued after 22 patients had been entered into the trial because additional supplies of NAC and its matched placebo were no longer available.

When the data was analysed after all entered patients had continued medication for a year (or had

Table 3 Variation in measures of skin distensibility

	N	Oral aperture (mm^2)	Handspread (mm)		Tips of third finger to wrist crease (mm)	
			R	L	R	L
Measured by D.E.F. in a.m.						
1st	10	1938 $\pm$ 441* (0.23)†	156 $\pm$ 37 (0.23)	162 $\pm$ 46 (0.28)	35 $\pm$ 25 (0.71)	29 $\pm$ 14 (0.48)
2nd	10	1997 $\pm$ 634 (0.32)	163 $\pm$ 40 (0.24)	168 $\pm$ 47 (0.28)	34 $\pm$ 30 (0.88)	40 $\pm$ 17 (0.43)
3rd	10	2014 $\pm$ 570 (0.28)	166 $\pm$ 42 (0.25)	170 $\pm$ 46 (0.27)	36 $\pm$ 26 (0.72)	38 $\pm$ 16 (0.42)
Maximum difference in measures made by D.E.F. in a.m.	10	76 (4%)§	13 (8%)	8 (5%)	2 (6%)	11 (28%)
Measures by D.E.F. in p.m.	6	2430 $\pm$ 636 (0.26)	181 $\pm$ 37 (0.20)	193 $\pm$ 25 (0.13)	37 $\pm$ 10 (0.27)	35 $\pm$ 17 (0.49)
Maximum difference for D.E.F. a.m. vs. p.m.	10	291 (15%)	25 (15%)	31 (17%)	3 (8%)	6 (17%)
Measured by P.J.C. in p.m.	6	2013 $\pm$ 536 (0.27)	179 $\pm$ 30 (0.17)	183 $\pm$ 30 (0.16)	29 $\pm$ 9 (0.31)	27 $\pm$ 12 (0.44)
Differences between D.E.F. and P.J.C. in p.m.	10	417 (19%)	2 (1%)	10 (5%)	8 (24%)	8 (29%)

*Standard deviation. †Coefficient of variation. §Percentage difference. D.E.F. and P.J.C. are the investigators' initials. R=right; L=left. a.m.=between 7 a.m. and 10 a.m.; p.m.=between 4 p.m. and 7 p.m.

discontinued medication early), we became aware of several facts. We had initiated the study for the dual purpose of evaluating NAC as a treatment modality in PSS and in order to study intensively the natural history of cutaneous and visceral involvement in PSS. We confirmed the high frequency of abnormal Dco in PSS lung disease, as had been noted previously by Guttadauria *et al.* (1977). We also noted decreased total lung capacities and FEF 25–75%. We found, however, that Dco changed more than the other pulmonary function tests and may therefore be a more sensitive measure of pulmonary function change in our group of patients, as has been suggested previously (Wilson *et al.*, 1964).

The degree of muscle involvement was surprising (90%) and is detailed in another publication. Further, the recurrent evaluations initiated with this study have pointed out some of the spontaneous serological and serum changes that occur in PSS. ANA was positive (>1:10) in 6 (27%) patients at initial evaluation. Over the year of study 1 further patient became positive, while most of the other 6 who were originally positive had significant titre changes (Table 4). Latex was positive in 5 (23%) initially, and became positive in 1 more, while 4 patients had significant drops in these latex titres (Table 4). CPK, too, changed by large amounts (Table 4).

Methods to evaluate skin distensibility and tethering have been examined in the past: for example, that published by Grahame and Harvey (1975). The manoeuvres tend to be rather cumbersome and difficult to use, however. We therefore tested several simplified measures of skin distensibility, although it is realised that those which we used are to some extent a combined measure of joint, muscle, and skin function. In order to evaluate the variability of these measurements 10 patients were examined on 3 successive days while in hospital for evaluation.

For oral aperture there was no correlation of the area of the oral aperture with temperomandibular pain or joint count. As can be seen in Table 3, there was little variation in measurement of mean oral aperture when 1 observer did all the measurements

at approximately the same time of day, while diurnal variation and interobserver errors both contributed significantly to variability. The coefficient of variation of about 0.27 indicates that the test is only moderately sensitive as an indicator of disease change.

The degree of contracture of the fingers, pain due to ulceration, or joint pathology and bone resorption would all be expected to affect the measurement of hand spread. However, within a given individual these changes would be minimised over a short period and the reproducibility of the measurement could be assessed. The mean intraobserver error and interobserver differences were both approximately 5%. Like oral aperture, the CV was about 0.25. Since the maximum mean differences are relatively small, and are consistent from morning to evening, this measurement may be useful as a measure of moderate changes in this disease.

The distance from the tip of the third finger to the most distal wrist creases was occasionally impossible to ascertain because no wrist crease could be found. Unlike the oral aperture, it appeared to be greatly influenced by joint stiffness, effort, ulcers, occasional difficulty in finding the wrist crease, etc. It was a much less consistent measure than the others, as is shown by the large CV for this measure (average: 0.52) (Table 3) and probably is not a very useful measure.

Unfortunately there is no accepted effective therapy in PSS, so that it is impossible to demonstrate the sensitivity of these techniques as measures of drug effect. At present they should be viewed as simple, rapid methods to measure the presence of changes in skin, joint, and muscle in PSS. Oral aperture may be a more 'pure' measure of skin distensibility than the other tests as it appears to be least affected by alterations in the joint. It may nevertheless reflect muscular or tendinous as well as skin changes.

Of central interest to this report is the finding that there was *no significant change* in most of the parameters measured in the placebo group over the year of study. This emphasises the fact that PSS is in general a disease in which measurable changes occur over long periods of time. The lack of change in our placebo group is in part secondary to the lack of sensitivity of the measurements available to ascertain change in PSS and in part because the disease often does change slowly. Our patients, although having extensive visceral involvement, had had their disease for long periods and were not changing rapidly. Further, the drug we used was known to be benign and without serious toxicity. This perhaps introduced a patient-selection bias towards patients without severe, rapidly progressive disease. Finally, a major pathological feature of PSS is fibrosis, which may be

Table 4 Changes in parameters over 1 year

	6 months		12 months	
	Rises	Declines	Rises	Declines
Dco†	—	10 (45%)	1 (4.5%)	14 (67%)
ANA*	2 (9%)	—	3 (14%)	4 (18%)
Latex*	—	3 (14%)	2 (9%)	4 (18%)
CPK†	1 (4.5%)	3 (14%)	4 (19%)	4 (19%)

Number in parentheses is the percentage of patients who changed.

†Change of 4 ml/min/mmHg defined as a real change.

*Change of 2 tube dilutions defined as a real change.

†Change of 50% from beginning of study defined as a real change.

irreversible. We might therefore have expected our patients to stabilise with effective therapy rather than to show significant improvement. For all the above reasons we feel that it is generally necessary to continue studies of PSS for longer than 1 year unless a group of patients with rapidly progressive disease is chosen for the study.

Since the above factors are operative in many of the reported studies (Jansen *et al.*, 1968; Silver and Gitlin, 1973; D'Alacron-Sergovia *et al.*, 1974; Steigerwald, 1974; Binnick *et al.*, 1977), we feel that other published studies of 1 year's duration or less, even if controlled, may not have been conclusive on the basis of the length of the study alone.

One year of NAC therapy produced no significant improvement in the disease. Unfortunately, because we were not able to continue the drug for more than 1 year and there was no significant deterioration in the placebo-treated patients we cannot determine whether NAC prevented progression of the disease.

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