Final Report

RELATIONSHIP BETWEEN AIR QUALITY AND THE RESPIRATORY STATUS OF ASTHMATICS IN AN AREA OF HIGH OXIDANT POLLUTION IN LOS ANGELES COUNTY

Contract Numbers A1-151-33 and A4-135-33

(July 1, 1982 - April 7, 1986)

Prepared for the California Air Resources Board.

From the UCLA Schools of Medicine and Public Health, UCLA, Los Angeles, CA 90024.

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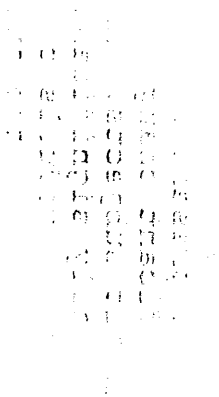
Submitted by: Henry Gong, Jr., M.D. (Principal Investigator)
Associate Professor of Medicine
Associate Chief
Pulmonary Division
Department of Medicine
School of Medicine
University of California at Los Angeles (UCLA)
Los Angeles, California 90024
Telephone: (213) 825-9235

Co-Investigators: Michael S. Simmons and Donald P. Tashkin, M.D., UCLA School of Medicine
Virginia A. Clark, Ph.D., Anne H. Coulson, and Gary H. Spivey, M.D., UCLA School of Public Health



ABSTRACT

Relationship Between Oxidant Air Pollution and the Respiratory Status of Asthmatics in an Area of High Oxidant Pollution in Los Angeles County. H. Gong, Jr., M.S. Simmons, V.A. Clark, D.P. Tashkin, A.H. Coulson, and G.H. Spivey.

A 230-day study of 83 asthmatics residing in an area of high oxidant air pollution was performed to evaluate: 1) the potential effects of ambient ozone on daily respiratory symptoms, medication use and peak expiratory flow rates; and 2) the characteristics of ozone-sensitive subjects. After completing a detailed questionnaire and pulmonary function and psychological tests, each subject kept a daily record of symptoms, medication use, and peak expiratory flow rates (PEFR). The subjects consisted of 43 males and 40 females with an average age of 33 years (range 7-70) and mild-to-severe asthma treated with inhaled bronchodilators and other anti-asthma medications. A Nebulizer Chronolog was attached to each canister of inhaled bronchodilator to objectively monitor its use and to make possible comparisons with diary reports. Daily maximum hourly average ozone concentrations in the study area were less than 0.12 parts per million (ppm) for 102 days, 0.12-0.19 ppm (National Primary Standard) for 65 days, 0.20-0.34 ppm (first-stage alert) for 60 days, and 0.35-0.38 ppm (second stage alert) for 3 days.

Data were analyzed by several statistical methods, including multiple linear regression for each subject across time. Resulting regression coefficients were weighted inversely to their variance and averaged over subjects to derive an overall relation between ozone and the dependent variables. Analyses showed no significant overall effect of ozone on group respiratory status. However, consistent and statistically significant relationships were found in a subset of 63 subjects (75.9%). Two subgroups of "extreme" and "moderate" responders to ozone (based on their regression coefficients for ozone) were identified but they were neither statistically nor clinically different from the other subjects except in several categories of the Asthma Symptom Checklist. The responses in symptom scores, day PEFR, and night PEFR, as predicted by slope coefficients for ozone, were clinically significant for eight subjects (9.6%) during the study, according to operational criteria. We conclude that the ambient ozone concentrations present during the study were associated with statistically significant changes in the respiratory status of the majority of asthmatic subjects. Although only a small subset of subjects had clinically significant responses to ozone, we speculate that more individuals could have had clinically relevant effects if their asthma and the oxidant air pollution were more severe than present in this study.

ACKNOWLEDGMENTS

The efforts and advice of the following co-investigators are gratefully acknowledged: Virginia A. Clark, Ph.D., Donald P. Tashkin, M.D., Anne H. Coulson, and Gary Spivey, M.D. The following individuals were essential to the conduct of the study: John Dermand and Nancy Moore for supervising subject recruitment and the Glendora laboratory and for performing the daily procedures; Michael S. Simmons for database management, data analysis, and his thoughtful suggestions; Parivash Nourjah for data programming; Michael Crist and Gina Aharonoff for data editing; Gerald J. Cookson for aeroallergen analyses; James W. Sayre, Ph.D., for meteorological information; Deborah Cresswell, Ph.D., for assistance in interpreting the psychological test results; Nancy Marshello for typing the manuscript; and John Jung, California Air Resources Board, El Monte, CA, for use of a hygrothermograph. Roger Detels, M.D., and Stanley Rokaw, M.D. (deceased), provided consultative advice and assistance in subject recruitment. The contract officers of the California Air Resources Board, Dane Westerdahl, Ph.D., and John K. Moore, Ph.D., provided important advice and support throughout the study. We are also very appreciative to the subjects for their continued and interested participation in the study.

This report was submitted by the UCLA Schools of Medicine and Public Health in fulfillment of Contracts A1-151-33 ("Relationship Between Air Quality and the Respiratory Status of Asthmatics in an Area of High Oxidant Pollution in Los Angeles County") and A4-135-33 ("Evaluation of the Health Effects of Air Pollution in Asthmatics by a Novel Application of Analysis Methods") awarded by the California Air Resources Board. Work was completed as of January 30, 1986.

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SUMMARY AND CONCLUSIONS

Study Design

We conducted an 11-month population study of asthmatics residing in an ozone-impacted area of Los Angeles County to evaluate: 1) the potential effects of oxidant air pollution on daily respiratory symptoms, medication use, and day and night peak expiratory flow rate (PEFR); and 2) the characteristics of ozone (O_3)-responsive subjects. The community of Glendora, California, was selected as the study site since it had historically been exposed to frequent and high concentrations of oxidant air pollution and the local air quality could be measured by two monitoring stations (one in nearby Azusa and one in Glendora).

The study sample consisted of local residents who had a history consistent with the diagnosis of bronchial asthma and who used a bronchodilator in the form of a metered-dose inhaler (MDI). Subjects were not excluded on the basis of age (except those less than seven years of age), sex, race, severity of asthma, or quantity of anti-asthma medications.

Subjects were recruited by identifying and contacting asthmatics from two previous epidemiological studies in the same area and later from local advertisements. Subjects then were interviewed at the Glendora laboratory and each subject completed a detailed questionnaire regarding medical history, occupational and residential exposures, commuting patterns, time spent outdoors, and socioeconomic status. The subjects underwent spirometry before and after inhaled bronchodilator (isoproterenol). Some subjects also had methacholine bronchoprovocation. Further documentation of asthma was obtained in some subjects by requesting medical records from their physicians.

Each subject was instructed in the use of a daily diary (for self-reporting of symptom scores and medication use) and a personal mini-Wright peak flow meter (to be used and recorded three times in the morning and evening). A Nebulizer Chronolog (NC) was attached to each subject's MDI to objectively record each actuation according to clock time and date.

Each subject also completed a battery of psychological tests (i.e., Asthma Symptom Checklist, Panic-Fear Symptom Scale, and State-Trait Anxiety Inventory) to characterize individual acute and chronic psychological status. This testing was performed twice during the study, i.e., once during good air quality (test 1) and once during a smoggy period (test 2).

During the study each subject visited the laboratory at least every two weeks to deliver the completed diary, to be issued a new diary form, and to have the NC interpreted and reset. Comparisons with the laboratory-based spirometer and standard Wright peak flow meter were routinely performed to assess the accuracy of each

subject's mini-Wright peak flow meter. The best (highest) morning and evening PEFR values were used in subsequent analyses. The daily medication use was standardized into an asthma medication index (AMI) which weighted and combined all anti-asthma medications used and emergency visits to a physician or emergency room for acute asthma. During each visit the subject also completed a questionnaire regarding symptoms consistent with a cold, hospitalizations, travel outside the study area, and the time spent outdoors (between 12 noon and 6 P.M.) since the previous visit. A participation fee was paid at the end of the study.

Possible confounding factors were monitored during the study. Values for daily temperature and relative humidity were obtained from the nearby Ontario Airport. Barometric pressure and counts of atmospheric pollen, spores and other potential aeroallergens were monitored daily at the study site.

The data were analyzed with several graphic and statistical techniques. Time plots were made of the levels of air pollutants, temperature, humidity, aeroallergens, etc., for the period of study to graphically examine trends in the data across time. Average values of symptom scores and day and night PEFR across subjects were also plotted over the same time period to determine if the subjects had worsening respiratory variables during poor air quality. Standard univariate analyses were calculated to obtain the mean, standard deviation, median, and distribution of continuous variables such as the baseline demographic and pulmonary function characteristics of the subjects, psychological tests, symptom scores, AMI, PEFR, air pollutants, meteorological indices, and aeroallergens. Factor analysis were performed on the results of the symptom scores in the daily diary and Asthma Symptom Checklist and the different aeroallergens monitored during the study to determine appropriate relationships and categorizations. Regressions and correlations were performed on the symptom scores, AMI, day PEFR, and night PEFR across subjects, as well as with ozone concentrations, to find possible relationships. Correlations among the various air pollutants, temperature, and relative humidity were obtained to determine their relationships and internal consistency. Mean values of symptom scores, AMI, and day and night PEFR on days when ozone concentrations were low (<0.12 ppm), moderate (0.12-0.19 ppm), and high (≥ 0.20 ppm) were compared using analysis of variance (ANOVA) across ozone concentrations and subjects.

The major method of statistical analysis was the computation of separate multiple linear regressions for each individual and weighted averaging of the individual coefficients. The regressions examined the relationships between independent variables (e.g., aeroallergens, temperature, relative humidity, and combinations of ambient air pollutants) on various days (t, t-1, t-2, and t-3) and dependent variables (symptom scores, asthma medication index, day PEFR, and night PEFR). Further statistical investigation of relationships between ambient ozone and respiratory status consisted of multiple linear regressions for each individual of the four previously stated dependent variables,

with each regression having the following form:

$$\text{Day PEFR}_t = A + B\ (\text{Day PEFR}_{t-1}) + C\ (\text{ozone}_t)$$

where A, B, and C are regression coefficients for each individual and t denotes the current day and t-1 the previous day. A weighted average of the C's was obtained across subjects where the weights were the inverse of the variance of each value of C. If the regression coefficient C (which was multiplied by the daily maximum hourly average concentration of ozone) was significantly different from zero in either a large negative or positive direction, a significant ozone effect was considered to be present.

The values of the regression coefficients C obtained for each individual also helped identify a group of subjects who appeared sensitive to ozone. The ozone coefficients from each of the individual regressions were ranked and the average rank was computed for each subject. Subjects with the highest average ranks were considered to be "responders" to ozone.

The responders were then classified into two groups depending upon whether their individual average slope coefficients for ozone were greater than 0.674 standard deviations from zero in an adverse direction for symptom score, day PEFR, and/or night PEFR. Subjects in the appropriate extreme quartile in at least one of these three outcome variables were designated as "responders-1" (equivalent to "moderate" and "extreme" responders of the entire study population). Similarly, subjects in the appropriate quartile in at least two of these variables were designated as "responders-2" (equivalent to "extreme" responders). These two groups of responders were compared to the respective "less responsive" subjects according to baseline and other characteristics.

The clinical significance of the respiratory responses predicted by the individuals' regression equations for ozone was determined by evaluating their predicted responses to 0.35 ppm ozone. We considered clinically significant adverse responses to 0.35 ppm ozone to be: 1) an average increase of >1 unit in symptom score (on a 1 to 7 scale) or 2) an average decrease in the subject's day or night PEFR of >5% of the subject's respective averages during the study period.

Results from the Asthma Symptom Checklist (ASC) were analyzed to determine if subjects with high, moderate, or low symptom category scores had the same average slope coefficients for ozone from the multiple regression equations using the respiratory outcome variables as the dependent variables. In addition, psychological characteristics in the responders-1 and responders-2 were compared to the respective remainders of the group.

Major Results

1. A total of 109 subjects were initially recruited; 91 subjects completed the 11-month study (February-December, 1983). Eight of the 91 subjects were subsequently excluded from analysis due to lack of varying asthma during the study period. Thus, 83 subjects constituted the final study population for analysis. The baseline demographic, clinical, and socioeconomic characteristics of the 83 subjects did not significantly differ from those of the 26 excluded subjects.

2. Although only 25 subjects showed a $\geq$10% increase in the forced expired volume in one second (FEV_1) following bronchodilator inhalation during baseline testing, five subjects had positive methacholine bronchoprovocation and another eight subjects had medical records confirming asthma. Bronchodilator administration to document airway reactivity could not be performed in 18 subjects because of their refusal or medical contraindications. However, all subjects had histories consistent with asthma and were using inhaled bronchodilators as well as other prescribed anti-asthma medication throughout the study.

3. The data analysis was limited to a 230-day period (April 15 - November 30) because of the different times the subjects entered the study and the high frequency of missing or incomplete data encountered during the early part of the study. Exclusion of data from analysis was made for colds, travel, and hospitalizations. Although 2,837 subject-days were ultimately excluded, 16,151 analyzable subject-days were available for final analysis.

4. Air quality data revealed the following number of days with the indicated daily maximum hourly average ozone values: 0.01 - 0.11 parts per million (ppm) O_3 = 102 days; 0.12 - 0.19 ppm O_3 (National Primary Standard) = 65 days; 0.20 - 0.34 ppm O_3 (SCAQMD first stage alert) = 60 days; and 0.35 - 0.38 ppm O_3 (SCAQMD second stage alert) = 3 days.

The daily maxima recorded for sulfur dioxide, oxides of nitrogen, carbon monoxide, nitrogen dioxide, and total hydrocarbons did not exceed state or national air quality criteria during the study. Sulfates exceeded the California Air Quality Standard (25 ug/m^3) on four days. However, total suspended particulates frequently (on 78% of days with available data) exceeded 100 ug/m^3, which was the California Air Quality Standard until 1983.

Daily values for temperature, relative humidity, and barometric pressure were consistent with the climate and altitude of the Glendora area. The data appeared internally consistent in that temperature was higher and relative humidity was lower at 1 P.M. than at 1 A.M. In addition, temperature was significantly correlated (P=0.0001) with ozone concentrations but not with other pollutants.

Numerous potential aeroallergens were recorded daily but all spores, pollens, grasses, molds, and miscellaneous debris collected by the Roto-Rod sampler were generally low in median counts. The single exception was a group of common molds (Basidiomycetes, e.g., rusts, smuts, mushrooms) which were frequently counted in the thousands per square centimeter (daily mean $\pm$ SD: 1843 $\pm$ 2116).

5. In general, the symptom scores and AMI (including MDI usage) were relatively low or unchanged during most of the study period, suggesting that the majority of subjects had mild or stable asthma. In addition, the majority (77%) of subjects had average PEFR values during the study which were within the normal predicted range or mildly decreased.

6. Although several Nebulizer Chronologs had technical problems during the study, the majority of the Nebulizer Chronologs reliably functioned for 16,269 subject-days (86% of total possible), with 47 subjects having >90% useful days. Fifty of the 83 subjects had almost perfect agreement between the NC and diary reportings of MDI usage during the study period. The average daily NC-diary differences in MDI recordings per subject were relatively small, indicating fairly reliable diary reporting. Twenty-three subjects showed wide differences between the NC and diary results for MDI use. At least 66 subjects had fewer uses than with a normal maintenance regimen on most days, suggesting that they predominantly used their MDI on an as-needed basis. This type of medication use supports the impression that these subjects had relatively mild, stable asthma.

7. Regression and correlation between ozone and average symptom scores over subjects, AMI, and day and night PEFR showed weak, nonsignificant relationships. Similarly, these daily outcome variables were compared for days with maximum ozone in three ranges (i.e., <0.12 ppm; 0.12-0.19 ppm; ≥ 0.20 ppm) but no statistical or clinical significance was detected. These findings were not related to the time spent outdoors on "clean" or "smoggy" weekdays or weekends.

8. The multiple regression analyses also supported the lack of an overall significant relationship between ozone (and other independent variables) and respiratory status, despite the use of lagged variables and inclusion of other pollutants, meterological variables, aeroallergens, and AMI. Specifically, the multiple regression analyses for the 83 subjects showed only a few significant relationships between respiratory status and the measured concentrations of outdoor air pollutants (including ozone), whether tested individually or in combinations. Total suspended particulates directly affected the PEFR but this relationship was neither logical nor consistent in the analyses. Carbon monoxide had a direct but inconsistent effect on medication use. Ozone concentrations on day t, t-1, t-2, and t-3 did not have a statistically significant effect on any respiratory variable, even when adjusting for medication use, symptoms, and

PEFR on day t-1. Symptoms and the other respiratory variables on day t-1 significantly influenced the same variables on day t and were more contributory to changes in the variables than ozone. Respiratory symptoms were directly affected by medication use on days t, t-1, t-2, and to a lesser extent, t-3. Aeroallergens from the groups mold 1 (Basidiomycetes) and trees 1 (Aceraceae, Fagaceae, and Ulmaceae) showed statistically significant negative relationships to respiratory variables, although only the effect of trees 1 was considered clinically relevant. Temperature and humidity (regardless of time of measurement) did not significantly influence the respiratory variables.

9. The potential respiratory effects of ambient ozone in subsets of the study population were evaluated in several ways. An initial multiple regression analysis was performed on those subjects whose ozone coefficients on days t, t-1, t-2, and t-3 were in the top quartile for the dependent variable (i.e., symptom score, AMI, night PEFR, and day PEFR). This analysis revealed statistically significant and consistent effects of ozone on day t and day t-1.

We also assessed the potential size of the subgroups of "ozone responsive" subjects by performing multiple regression analyses on the data of increasingly larger numbers of subjects, based on their average ozone coefficients for symptom score, AMI, day PEFR, and night PEFR and adjusting for the previous day's value of the dependent variable. Medication use was not significantly related to ozone even in the 20 subjects with the highest ozone coefficients with the AMI as the dependent variable. On the other hand, respiratory symptoms and day and night PEFR were significantly and consistently influenced by ozone on day t and the dependent variable on day t-1 for as many as 63 subjects. This finding contrasts with the lack of a statistically significant overall effect of ozone for the entire sample of 83 subjects.

Twelve responders-2 (i.e., "extreme responders") and 27 responders-1 to ozone were also identified according to their ozone coefficients for each outcome variable. Multiple regression analyses of these two subsets of ozone responders (adjusting for the value of the dependent variable on day t-1) showed highly significant and consistent ozone effects on symptoms, night PEFR, and day PEFR. The effect of the dependent variable on day t-1 was also significant in both groups of designated responders. Ozone did not affect medication use in either group. These two groups were separately compared to the respective remainders of the study population but there were no significant differences in demographic, clinical or physiological characteristics between the groups of subjects. The responders also did not significantly differ from the other subjects in their symptom scores, AMI, PEFRs, and the time spent outdoors during the study.

10. The clinical significance of the responses in symptom score, day PEFR, and night PEFR, as predicted by the individual

regression equations for ozone, was evaluated. The results indicated that the majority of subjects had no clinically significant responses to ozone exposure during the study period, according to operational criteria. Specifically, no subject had evidence of significant worsening of symptoms attributable to ozone during the study. Seventy-five subjects (90.4%) did not have clinically significant worsening of their day or night PEFR during the study. However, eight subjects (9.6%) showed clinically relevant average decreases in either their day and/or night PEFR. Five of these subjects had >5% average decreases in both day and night PEFR and the other three subjects had >5% average decreases in their night PEFR only. Six of these individuals were using either inhaled and/or oral corticosteroids, suggesting that their asthma was moderate to severe.

11. The psychological results indicated that the majority of subjects had "moderate" scores in all tests. Test scores were similar for each subject during the two testing periods. Significant effects were found when the 71 adults' scores in the Asthma Symptom Checklist (ASC) were classified as high (upper 25% of group scores), moderate (middle 50%), and low (lower 25%) and related to the subjects' slope coefficients for ozone from multiple regressions using respiratory variables as the dependent variable. There was a significant and consistent tendency for the subjects with high scores on fatigue, hyperventilation, dyspnea, congestion, and rapid breathing to have more negative slope coefficients than the other subjects. In other words, subjects with selected, high ASC category scores had day and/or night PEFR more affected by ozone than subjects with low or moderate scores.

Although the above responders to ozone did not differ from other subjects in most of the psychological items measured, there were significant differences in several symptom categories of the Asthma Symptom Checklist, with the responders scoring consistently higher than the other subjects in the factors representing fatigue, hyperventilation, and rapid breathing. However, the higher scores of these responders were not associated with ambient ozone concentrations since the test scores were similar during relatively low (test 1) and high (test 2) ozone days. The significance of the psychological results is yet to be determined.

Conclusions

1. The results indicate that the respiratory status of the study population (i.e., subjects with asthma) as a whole was neither clinically nor statistically related to the presence of maximum hourly average concentrations of ozone ranging from <0.12 to 0.38 ppm. Numerous analyses supported this overall conclusion. Graphically, the periods of high ozone concentrations did not coincide with periods of low average PEFR. The analysis of mean PEFR during periods of low, moderate, and high ozone time periods also showed no consistent or significant differences. The more complex individual multiple regression analyses showed no overall effect of ozone. Numerous subsidiary analyses were performed to

determine that the lack of a relationship between respiratory status and ozone was not due to confounding factors.

Although there was no significant overall effect of ozone on respiratory variables in the 83 asthmatic subjects, multiple regression analysis of subjects whose ozone coefficients on various days were in the top quartile for dependent variables (respiratory measures) showed significant and consistent effects of ozone on day t and the previous day (t-1). Multiple regression testing of subsets as large as 63 subjects involved regressions of today's symptom score or day PEFR or night PEFR on today's ozone and yesterday's value of the same responses. The analyses showed highly significant ozone coefficients in the regressions of symptom score and day and night PEFR. Thus, consistent and statistically significant relationships exist between ambient ozone concentrations and adverse asthmatic response in a substantial proportion of a population of predominantly mild asthmatics residing in a high-ozone area. Although the analogous results for the whole sample are not significant, the finding of statistically significant adverse relationships for a large subset is notable because of the well-known difficulty of characterizing asthmatics and the large temporal variability in their respiratory responses.

2. The clinical significance of the respiratory responses, as predicted by the individual's regression equations for ozone, was considered to be absent for respiratory symptoms (symptom scores) during the study period. However, an average decrease in the day or night PEFR of >5% of the subject's respective averages during the study period was observed in eight subjects, most of whom had moderate-to-severe asthma. The remaining 75 subjects did not have significant clinical worsening of their day or night PEFR.

3. It does not appear possible to distinguish on clinical grounds which asthmatic individual will adversely respond to increased ambient ozone levels, according to the results of this study. Although 69 (83%) of the subjects perceived that their asthma was worsened by poor air quality, the subsets of "moderate" and "extreme" responders to ozone (according to statistical criteria) could not be significantly differentiated from the respective remainders of the group by demographic, clinical, or physiological variables. The only significantly different variables were in several symptom categories of the Asthma Symptom Checklist. The significance of this finding is unclear at this time.

4. The inability to demonstrate a significant overall clinical relationship between the respiratory status of a free-living population of asthmatics and ambient ozone concentrations does not mean that this association does not exist. Factors which may have influenced the study results are discussed and include the lack of a threshold level of ozone sufficient to worsen asthma, mild nature of the subjects' asthma, behavioral or physiological "adaptation", and out-migration of a more sensitive subset of the general asthmatic population.

5. The multiple linear regression analysis used in this study appears to be an accurate, sensitive, and powerful statistical technique for assessing the potential immediate and delayed effects of ozone (or other air pollutant) on outcome variables in each individual across time. This statistical method is applicable to data analysis in other epidemiologic studies. The software for the statistical program and other information may be obtained from the project staff (Michael Simmons, Pulmonary Division, Department of Medicine, UCLA Medical Center, Los Angeles, CA 90024).

6. Psychological characterization of asthmatic subjects may be an important and revealing variable in epidemiologic studies, as well as clinically, since asthma can be significantly influenced by emotional factors. Although this study did not demonstrate that air pollution can affect the overall psychological state of asthmatics, the responders to ozone scored significantly higher than other subjects in several categories of the Asthma Symptom Checklist.

7. The Nebulizer Chronolog (NC) may have a beneficial role in epidemiological studies which require accurate monitoring and assessment of the use of metered-dose inhalers (MDIs). The NC can objectively measure MDI usage alone and validate individual diary reporting as well as drug compliance in general.

RECOMMENDATIONS

As a result of this study the investigators recommend the following for future studies:

1. Future studies of populations at risk for health effects from air pollution should characterize the study population as well as possible. For example, asthmatics should have a consistent clinical history, physician verification, and physiological evidence of increased airway reactivity. The latter may be either in the form of significant bronchodilation and/or bronchoconstriction following appropriate pharmacologic (or other) challenge during pulmonary function testing. However, practical difficulties will occur in any large population study, e.g. from refusal to testing by the subjects, medical contraindications, and necessity for uninterrupted medication use.

2. It is possible that a similar study involving only subjects with clinically moderate-to-severe asthma may result in more revealing relationships between respiratory status and ambient ozone. Although these subjects are more medicated than mild asthmatics, they may, nonetheless, be more susceptible to ozone and demonstrate more measurable changes in respiratory status over time.

3. The study area must include a sufficient number of days with both low and high air pollution. Areas with very frequent and high air pollution (e.g., Stage 2 ozone alert levels) would be ideal to best detect positive relationships. However, the presence of this type of environment is impossible to control even in historically impacted areas, due to meterological conditions and ongoing regulatory efforts.

4. The Nebulizer Chronolog (NC) is a helpful, objective monitor of the true frequency of use of metered-dose inhalers (MDIs) in asthmatics. Depending on the population and goal of the study, it may be very helpful to document and/or confirm MDI usage as recorded in daily diaries with the NC. The NC offers reasonable utility and reliability in epidemiological studies despite some technical limitations. The NC will not replace daily diaries if the subjects are also using oral medications and total medication use is an outcome variable.

5. Confounding factors and nonrelevant data must be carefully reviewed and adjusted for. Concurrent monitoring of meterological conditions and spore-pollen counts is necessary when investigating the respiratory effects of air pollution. Exclusion of data for nonexposure to the local air quality and other causes for respiratory exacerbation (e.g., viral infections) in asthmatics must

be made.

6. The multiple linear regression technique used in this study appeared to be a powerful and sensitive statistical model for epidemiological studies and should be considered when applicable.

7. Subsets of responders to ozone or other air pollutants should be selected (according to clinical and/or statistical methods), characterized, and compared to "less responsive" subjects. This process may help differentiate individuals at greater risk of developing health effects from air pollution.

8. Indoor or personal monitors of air pollution would be ideal to accurately determine individual total exposure and dose-effects. Unfortunately, their cost in a large population is prohibitive and the technology is inadequate at this time, thus limiting the practicality of this approach. Perhaps selected individuals (e.g., the most sensitive subjects) could be monitored indoors in future studies.

9. Future studies of responders to ozone (identified through epidemiologic evaluation) might include controlled exposures to ozone in environmental chambers to directly document their symptomatic and physiological responses to this air pollutant. "Adaptation" could also be similarly investigated in the "nonresponders."

10. A study (including controlled environmental exposures) of a population which has moved out of an impacted area for health reasons would be important in order to understand the motives for out-migration. This type of study, however, would be very difficult and complex.

11. Behavioral studies in relation to air pollution are needed since staying indoors during smoggy days may be a common preventive practice by many individuals. Surveys of outdoor-indoor patterns and motives for staying indoors or curtailing outdoor activities on smoggy days may be of value. Psychological testing may also provide more information about the subjects, particularly if emotional status is suspected to influence the medical disorder (e.g., asthma) or is affected by air pollution. More investigation in this area is necessary to assess the role of psychological factors in behavioral and/or physiological responses to air pollution.

REPORT

INTRODUCTION

Photochemical (oxidant) air pollution has been implicated as a cause of adverse health effects in humans (1). Individuals with bronchial asthma may represent a sentinel "at risk" population for poor air quality due to the presence of hyperreactive airways and increased susceptibility to irritating gases, particulates, and other asthmogenic stimuli. These stimuli may produce clinical and/or physiological changes which may be more amplified or readily demonstrable in asthmatics than in other patient groups. Thus, this patient population is considered epidemiologically relevant for research aimed at establishing and/or revising ambient air quality standards for the protection of sensitive individuals.

However, epidemiological studies of asthmatics have not provided a clear consensus about 1) the incidence and magnitude of increased respiratory sensitivity to oxidant air pollution in a large, well-defined group of exposed asthmatic individuals, and 2) the effect of long-term exposure to alternating low and high air pollution concentrations. The lack of reproducible results has usually been attributed to complex issues involving study design, statistical analysis, the heterogeneous nature of the asthmatic population, and numerous confounding variables that may modify responses to outdoor air pollutant exposure (e.g., aeroallergens, occupation, indoor pollution, cigarette smoking). The validity and reliability of routine measures of respiratory health (i.e., self-reported symptoms, medication usage, and lung function) have only been partially characterized.

Epidemiological studies using one or more groups or panels of subjects have both advantages and disadvantages. Panel studies are frequently difficult to design and implement and have been criticized because of possible subject-selection bias, different exposure doses, and the complex physicochemical nature of community air. Nevertheless, a panel of asthmatics who reside in the same community is concurrently exposed to generally similar types and concentrations of atmospheric pollutants, and each participant may act as his or her own control. A carefully planned, prospective panel study is probably the most practical and relevant epidemiological tool available to provide specific information about health changes in large populations in their natural environment, assuming that methodology, measurements, and statistical analysis are appropriate and their limitations are recognized.

The UCLA Schools of Medicine (Pulmonary Division) and Public Health (Epidemiology Division) completed a year-long study of the relationship between ambient oxidant (ozone) air pollution and the respiratory status of a large group of asthmatic subjects residing in Los Angeles County. The goals of the study were to 1) determine the longitudinal relationship between ambient ozone

concentrations and daily respiratory measures (symptoms, medication use, and peak expiratory flow rates) in asthmatics, and 2) identify and characterize asthmatics who are most sensitive to changes in ambient ozone concentrations. Unlike previous epidemiological studies, this investigation utilized several novel modalities, i.e., Nebulizer Chronologs, psychological testing, and a different statistical approach, to characterize the panelists and their behavior. These and other techniques in the design and conduct of the study may serve as a useful model for epidemiological investigations.

MATERIALS AND METHODS

Page No.

MATERIALS AND METHODS

A. Study Site

The South Coast Air Basin has a seasonal air pollution period with frequent first- and second-stage alerts for ozone occurring primarily between July and October. Scattered, transient episodes may also occur at other times of the year, such as in the spring and early summer. Therefore, we conducted the panel study from January to December, 1983, to obtain a sufficient number of both "clean" and "polluted" days for comparative purposes as well as to maximize the potential for observing distinct health effects by including as many "alert" days as possible.

The community of Glendora, California, was selected as the focus of this study. Glendora is situated approximately 800 feet above sea level and is located in the eastern San Gabriel Valley, east of downtown Los Angeles and abutting the foothills of the San Gabriel Mountain Range. This area has historically been exposed to levels of oxidant air pollution of greater concentrations, frequency, and duration than monitored in other areas of the South Coast Air Basin (2). However, Glendora may occasionally have concomitantly increased concentrations of sulfates which may modify the effects of oxidants.

The Glendora-UCLA Pulmonary Research Laboratory was established at a convenient location (535 Forestdale Avenue, Glendora), which was within several blocks of a community hospital. The laboratory was staffed by two full-time technicians (one of whom lived in Glendora) and was open, for the most part, Tuesdays through Saturdays to accommodate screening and biweekly visits.

The laboratory was located nearly equidistant between two air quality monitoring stations: 1) two miles east (usually downwind) of the monitoring station #70-060 (803 North Loren Avenue, Azusa) which was supervised by the South Coast Air Quality Management District (SCAQMD); and 2) approximately two miles southwest (usually upwind) of the monitoring station #70-591 (840 Laurel Avenue, Glendora) which was supervised by the California Air Resources Board (CARB). The stations measured ambient concentrations of ozone (O_3), sulfur dioxide (SO_2), oxides of nitrogen (NO_x), nitrogen dioxide (NO_2), and carbon monoxide (CO) on an hourly basis and total suspended particulates (TSP), sulfates, nitrates, and hydrocarbons (HC) on a daily basis. Air quality data from both stations were obtained for review. Previous studies (3,4) have demonstrated that the SCAQMD station in Azusa temporally and quantitatively reports data that are representative for oxidants and other air pollutants 5 to 10 miles downwind (east), e.g., including the Glendora area.

B. Subjects

An initial sample size of at least 100 asthmatic subjects was selected as the most reasonable and practical number. This number

of panelists would hopefully allow for subsequent attrition, missing data, and a proportion of subjects who would not show significant changes in their asthma during the study period, while still providing sufficient data for valid conclusions. Each subject received a participation fee and bonus payment for completing the study.

C. Screening Criteria

Screening criteria for entry into the study were as follows:

1) presence of asthma, according to the clinical criteria of the American Thoracic Society (5), for at least the previous two years;

2) willingness to reside in the Glendora area during the study period, excluding vacations or infrequent trips out of the area; and

3) regular or as-needed use of a bronchodilator in the form of a metered-dose inhaler (MDI).

Potential subjects were not excluded on the basis of age, (except those less than seven years of age), sex, race, severity of asthma, or the quantity of anti-asthma medications being used. Although lung development continues until the age of 25 years, it was decided to recruit children and adolescents (ages 7-18 yrs) with asthma since each subject was his/her own control and young individuals with asthma might constitute an important sensitive subgroup. Volunteers who had serious or unstable concomitant medical disorders or who planned to be outside the Glendora area for much of 1983 were excluded.

D. Recruitment

Recruitment of subjects began by identifying asthmatic individuals who had recently participated in two UCLA-affiliated epidemiological studies involving the general population (6) and asthmatics (7). The first study (6) involved a survey of residents in two census tracts (4009 and 4010.02) in Glendora, whereas the second study (7) had recruited subjects living in the Glendora area by advertisements in community newspapers and contacts via the local lung association. It was anticipated that most of the sample would originate from the first source (6). However, it became apparent that recruitment from both of these sources would be inadequate and it was decided to also seek potential subjects by advertising in local newspapers and doctors' offices and by word-of-mouth.

Asthmatic subjects who participated in previous epidemiological studies (6,7) were initially contacted by a letter from the respective principal investigator, who explained the new study, encouraged subject participation, and announced that the individual would be called within several weeks regarding the new

study (see Appendix A). During the telephone call, the study was explained more fully, questions answered, eligibility criteria ascertained, and verbal agreement to participate and visit the field laboratory was obtained. Volunteers acquired by local advertisements called in and were screened accordingly.

E. Screening Procedures

Interested individuals who appeared to be qualified for the study were invited to the Glendora laboratory for further screening, briefing, and confirmation of asthma. Following written informed consent, each subject completed a detailed baseline questionnaire (Appendix B) which included information about their general medical history, medications, smoking habits, occupational and residential exposures, commuting patterns, time spent outdoors, prior residences, and socioeconomic status, as well as specific inquiries about their asthma and other atopic disorders, i.e., age of onset, current symptoms and severity, precipitating causes, emergency room visits and hospitalizations, and family history.

Following measurements of height and weight, each subject underwent spirometry (8), before and (usually) after inhalation of aerosolized isoproterenol (0.15 mg), on a computerized spirometer (SRL Sentry System 80, Gould Medical Products, Dayton, Ohio) under the supervision of a trained technician. Spirometry included the measurements of forced vital capacity (FVC), forced expired volume in one second (FEV_1), and forced midexpiratory flow ($FEF_{25-75\%}$). Predicted values for these spirometric indices were derived from Morris (9) for adults and from Polgar and Promadhat (10) for children. Subjects who showed a 15% or greater improvement from baseline FEV_1 following isoproterenol inhalation were considered asthmatic according to physiologic criteria. Subjects who showed less than 15% improvement in FEV_1 after bronchodilator administration were considered asthmatic if they had one or more of the following results: 1) $\geq$15% increase in FEV_1 following bronchodilator inhalation on a subsequent screening visit; 2) a positive methacholine bronchoprovocation test (11), i.e., 15% or greater decrement from control FEV_1; or 3) medical records confirming the clinical diagnosis of asthma and the beneficial use of anti-asthma medication(s). However, the spirometric, bronchodilator, and bronchoprovocation data were not used as absolute criteria for the presence of asthma in this study, which primarily relied on clinical history (5).

F. Respiratory Measures

1. General

The primary daily measures of respiratory status (dependent variables) consisted of three distinct but related types of indices:

1) Subjective - self-reported ratings of day and night symptoms in a diary. Each subject also recorded total medication use in his/her daily diary.

2) Physiological - self-administered morning and evening measurements (three times each) of peak expiratory flow rate (PEFR) with a personal mini-Wright peak flow meter (PF-239, Armstrong Industries, Northbrook, IL).

3) Behavioral - independent monitoring of each use (actuation) of a metered-dose inhaler attached to a Nebulizer Chronolog (see below). Each subject also recorded daily MDI usage in his/her diary.

2. Symptoms and Peak Expiratory Flow Rate

The daily diary and PEFR measurements were completed by each subject at set times in the morning (7 or 8 A.M.) and evening (7 or 8 P.M.). A parent assisted in these measurements for some of the young subjects. Individual day and night symptoms (wheezing, shortness of breath, chest tightness, cough, sputum production, tension or anxiety, other) and an overall rating of the subject's asthma for the previous 12-hour period were rated according to a 7-point scale (i.e., 1 = no symptoms; 2 = very mild discomfort; 3 = mild discomfort; 4 = moderate discomfort; 5 = moderately severe discomfort; 6 = severe discomfort; 7 = very severe or incapacitating discomfort). Subjects also recorded the number of asthma attacks and their duration during 12-hour periods. The highest (best) morning and evening values of PEFR were used in subsequent analyses.

3. Medications

The subjects recorded in the diary the types and doses of all medications used each day. All anti-asthma medications were subsequently coded, weighted, and combined into a single daily medication score called the asthma medication index (12) which excluded nonasthmatic medications. The asthma medication index (AMI) summarizes the therapeutic potency and efficacy of anti-asthma drugs (theophyllines, oral and inhaled beta-agonists, and corticosteroids) into a single standardized score which can be used for comparison of medication requirements in the same individual or between individuals over time (12). Oral alternate-day corticosteroid usage was scored by averaging the dosage over the adjacent "on" and "off" or tapering days so that the potentially large fluctuations in daily medication scores would be avoided or minimized. Three realistic examples are presented to demonstrate the calculation of the daily AMI:

	Daily AMI
1) Patient with mild asthma:	
Albuterol MDI, 2 puffs 4 times a day	
or 0.5 units/puff x 2 puffs x 4	= 4.0 units

2) Patient with moderate asthma:
Albuterol MDI, 2 puffs 4 times a day
or 0.5 units/puff x 2 puffs x 4 = 4.0
Theodur, 200 mg 3 times orally a day
or 2.1 units/tablet x 1 tablet x 3 = 6.3
Total = 10.3 units

3) Patient with severe asthma:
Albuterol MDI, 2 puffs 4 times a day
or 0.5 units/puff x 2 puffs x 4 = 4.0
Theodur, 300 mg 3 times orally a day
or 3.2 units/tablet x 1 tablet x 3 = 9.6
Vanceril MDI, 2 puffs 4 times a day
or 1.2 units/puff x 2 puffs x 4 = 9.6
Prednisone, 10 mg orally a day
or 10 units/tablet x 1 tablet x 1 10.0
Total = 33.2 units

The daily AMI for oral prednisone (10 mg a day) in the third example is also equivalent to an alternating dose of 20 mg on one day and 0 mg on the next day. These examples pertain to prescribed drug use only and do not include additional (as-needed) MDI or other anti-asthma drug use in the event of acute treatment for worsening asthma. Any as-needed medication usage or emergency visits to a physician or emergency room for acute asthma would be scored accordingly and added to the daily AMI.

4. Nebulizer Chronolog

The Nebulizer Chronolog (NC) was another means to monitor anti-asthma drug use and to verify diary recordings. The NC (Model NC-100, Advanced Technology Products, Denver, CO) independently and automatically records the time and date of each actuation of the attached MDI (13,14). This device is a small holder that attaches to most commercially available canisters used to deliver an aerosolized bronchodilator (e.g., Medihaler, Bronkometer, Alupent, Ventolin) and consists of a battery-operated, crystal-controlled time piece capable of logging and storing 256 nebulizer actuations, with resolution of four minutes and an accuracy of $\pm$1 minute/month. The stored information is later interpreted (during each visit to the laboratory) on a microcomputer and printed out to display the clock time and date of each MDI use.

The use of the NC represents a behavioral measurement which may provide insights into appropriate or arbitrary over- or underusage of the MDI as compared to recordings in the daily diary. Assuming that the MDI is the only nebulizer used by the subject and is the most frequently used as-needed anti-asthma medication, the NC data indicate the daily pattern and amount of use of aerosolized bronchodilator. Thus, these results may reflect the acute respiratory health of the user, his/her compliance, and, to some extent, psychological responses to his/her respiratory status.

G. Psychological Testing

All subjects completed a battery of psychological tests (Appendix B) at the end of the first four weeks of participation and again during September or October. All adults and children greater than 13 years of age rated their perceptions of asthma attacks in the Asthma Symptom Checklist (ASC) (15) and Panic-Fear Symptom Scale (16,17) and their acute and general anxiety in the State-Trait Anxiety Inventory (STAI) (18). Similarly, children between 7 and 13 years of age completed the ASC and the State-Trait Anxiety Inventory for Children (STAIC) (19) with the assistance of a parent. Each test instrument was administered and scored according to published procedures (15-19).

The psychological tests were administered to evaluate the subjects' psychological characteristics in relation to asthma and in general. Psychological research (13-17) indicates that asthmatics may be grouped according to behavioral symptom clusters and that these patterns may explain or relate to responses during asthmatic attacks, e.g., coping styles, use of as-needed medications, frequency of emergency treatment and hospitalization. Therefore, the psychological components of asthma and related medication use may be important confounding factors in evaluating individuals' responses to potential asthmogenic stimuli, including oxidant air pollution.

H. Conduct of Study

Each subject and, if applicable, a subject's parent were fully informed about the study requirements and trained to use the daily diary, mini-Wright peak flow meter, and the Nebulizer Chronolog. Unknown to the subjects, the recorded data for each subject's first two or four weeks in the study were not used in data analysis since this initial period was designated as pre-study training to correct errors and technical problems and to answer questions. The training period, as well as the screening procedures and participation fee, also facilitated the collection of as reliable and complete data as possible.

During the study each subject visited the laboratory in Glendora at least every two weeks to deliver the completed daily diary, to be issued a new diary form, and to have the NC interpreted and reset for subsequent use. Spirometry with the laboratory-based computerized spirometer and a calibrated standard Wright peak flow meter (PF-286, Armstrong Industries) were also routinely performed to check the accuracy of each subject's mini-Wright peak flow meter (20). Each subject also completed a biweekly questionnaire (Appendix B) regarding symptoms consistent with a viral respiratory infection, hospitalizations, travel outside the study area, and time spent outdoors (between 12 noon and 6 P.M.) since the previous visit.

I. Confounding Factors

Daily temperature and relative humidity were continuously monitored by a hygrothermograph (Instruments Corporation, Baltimore, MD) at the laboratory. However, the instrument malfunctioned for two months during the summer and it was decided to use only the daily meteorological information from the Ontario Airport throughout the study period. The airport is 17 miles east (usually downwind) of the study site. Results were obtained from measurements at both 1 A.M. and 1 P.M. for use in the analyses.

Barometric pressure was monitored daily (8 A.M.) with a mercurial barometer (Curtin Matheson Scientific, La Brea, CA), which was located in the laboratory.

Outdoor pollen, spores, and other potential aeroallergens were monitored daily with a rotating arm impactor (Roto-Rod sampler, Ted Brown and Associates, Los Altos Hills, CA), which was installed 6 feet above ground in a nearby residential area of Glendora. The sampling device was set to run continuously at 2400 rpm for 100 seconds per 10-minute cycle. The adhesive-coated lucite sampling rods were replaced every morning and mailed to a contracted laboratory technologist each week for microscopic analysis (21). Results were reported as the count (number of spores, pollen, etc.) per square centimeter for each type of potential allergen on each day (Appendix C).

Questions about symptoms (i.e., fever or sore throat) consistent with a viral respiratory infection or cold, travel outside the Glendora area (for greater than 12 hours), time spent outdoors (between noon and 6 P.M.), and hospitalizations since the previous visit were asked by the technician during each subject's biweekly appointment at laboratory. Although information about the subjects' time spent outdoors, occupational exposure, household heating, cooking fuel, etc., was obtained, we did not directly monitor individual exposure to indoor pollution. Personal indoor monitoring of air quality was not implemented in this study.

J. Data Cleaning

Careful, thorough review and cleaning of the collected data were essential procedures prior to statistical analysis. The very large number of variables and the even larger number of observations for each subject over time resulted in a time-consuming effort. Each data point was related to many others around it, either on the same day or on days before or after it. The analysis took advantage of this inter-dependence but was also sensitive to outliers. Taking advantage of this dependence made it possible to catch outliers by looking for temporal irregularities in the data, in addition to the usual range checks, etc. Also, the physiological inter-dependencies between symptoms and PEFR and between the different spirometric indices, were

exploited. The larger data sets were cleaned with special attention to the following:

1) Medication recordings. We checked for invalid medication codes and doses and for each large change in the use of any medication on consecutive days. While most of these fluctuations were due to "as-needed" use of anti-asthma medications caused by changes in the subject's asthmatic status, keypunch and coding errors were discovered using this as a data-cleaning method.

2) Symptom recordings. In addition to checking for invalid symptom scores, several variables were checked for internal inconsistencies. For instance, a respiratory symptom score of "6" or "7" (severe) would be inconsistent with a low overall rating. Also, if asthma attacks were indicated on the diary, there should have been reasonable values recorded in the diary for the average durations of the attacks. The peak flow measurements were checked for large differences between each of the three recorded efforts as well as for extreme values. All night values were compared with day values to check for unexpected daily fluctuations.

3) Pulmonary function tests. There are many relationships between the different spirometric indices that can be exploited in searching for outliers. For instance, the FEV_1/FVC ratio should not be greater than 100%, and the peak expiratory flow rate should not be greater than the $FEF_{25-75\%}$. The measurements from the Wright and Mini-Wright peak flow meters were compared with each other and with the peak flow rate measured with the Gould computerized spirometer.

4) Bi-weekly questionnaires. The cleaning of data from the bi-weekly questionnaires was more conventional than with the other data sets. Each section was checked for internal inconsistencies and compared to the previous bi-weekly questionnaire, where appropriate. However, all of these variables were screened very carefully because of their importance. Since data were excluded when the subject had a cold or the flu and when the subject was out of the study area, no errors could be tolerated in these sections of the questionnaire. Errors would not only cause data to be excluded unnecessarily, but might also cause data to be included inappropriately in the analysis.

5) Data from the two local air quality monitoring stations were cleaned, edited, and provided by the respective agencies.

K. Computer Facilities and Programs

Data cleaning and analysis were performed with the IBM 3081 computer, located in Hospital Computing Services, UCLA Center for the Health Sciences. Statistical Analysis System (SAS), a comprehensive data base management and statistical application system (22), was extensively used to maintain, edit, and merge files, plot data, calculate descriptive statistics, and drive the Biomedical Programs (BMDP) (23) which were used for more complex

analyses. The fairly complete, structured programming language of SAS enabled us to write very complex programs for data cleaning and analysis, taking advantage of the powerful features of SAS, such as automatic Julian date conversions and calculations and BY-group processing. The applications of the specialized SAS procedures are presented subsequently. Details regarding its operation and limitations may be obtained from the project staff (Michael Simmons, Pulmonary Division, Department of Medicine, UCLA Medical Center, Los Angeles, CA 90024).

The IBM 3033 computer at the Office of Academic Computing (OAC) at UCLA was also used for some of the analyses involving a customized SAS procedures with subroutines from the International Mathematical Subroutine Laboratory (IMSL) (24) which were not available at the hospital facility. The Versatec plotter at the OAC was used for plots of environmental and outcome variables over time.

L. Statistical Analysis

1. General Analyses

The data were analyzed with several graphic and statistical techniques. Time plots were made of the levels of air pollutants, temperature, humidity, etc., for the period of the study to graphically examine trends in the data across time. Average values of symptoms scores and day and night PEFR across subjects were also plotted for the same time periods to determine if the subjects reported worsening respiratory variables during poor air quality. Standard univariate analysis were calculated to obtain the mean, standard deviation, median, and distribution of continuous variables such as the baseline demographic and pulmonary function characteristics of the subjects, psychological results, symptoms scores, AMI, PEFR, air pollutants, meterological indices, and aeroallergens. Factor analyses were performed on the results of the symptom scores in the daily diary and Asthma Symptom Checklist and the aeroallergens monitored during the study to determine appropriate relationships and categorizations.

The existence of possible relationships in the data for all subjects was investigated by correlations between several measures of asthmatic response (i.e., symptom scores, asthma medication index, day PEFR, and night PEFR) and by regressions on ozone concentrations. Correlations among the various air pollutants, temperature, and relative humidity were performed to determine their relationships and internal consistency. Mean values of symptom scores, AMI, and day and night PEFR on days when the daily maximum hourly concentrations of ozone were low (<0.12 ppm), moderate (0.12-0.19 ppm), and high (≥ 0.20 ppm) were compared using analysis of variance (ANOVA) across ozone concentrations and subjects.

2. Multiple Regression Analyses

The major form of statistical analysis for studying the longitudinal effects of ambient ozone was based on a modification of the statistical approach reported by Korn and Whittemore (25,26). Although we originally planned to use this logistic technique, subsequent discussions (27) and review of the type of data collected in our study directed our analysis to a related but different approach (see Discussion).

In this study multiple linear regressions for each individual across time were calculated and the individual coefficients underwent weighted averaging. In multiple linear regressions, the outcome variable was respiratory status (e.g., day PEFR) on day t and the predictor variables were respiratory status on the previous day (t-1) and the concentration of ozone on day t. The values of t ranges from day 2 to the end of the study period for each individual. Hence, days in the study were equivalent to each sample size for each subject. The resulting equation for each subject (using day PEFR as an example of an outcome variable) was as follows:

$$\text{Day PEFR}_t = A + B\ (\text{PEFR}_{t-1}) + C\ (\text{Ozone}_t)$$

where A, B, and C are regression coefficients for each individual and t denotes the current day and t-1 the previous day. The term PEFR_{t-1} minimizes or removes the related effect of the PEFR level from the previous day so that any ozone effect on day t can be better isolated. The final analyses used equations equivalent to the above model. A weighted average of the C's were obtained across subjects where the weights were the inverse of the variance of each value of C. The weights, Wi, were equal to the inverse of the Ci for the ith person. Adjusted weights, wi, were computed as follows:

$$wi = \frac{nWi}{\sum^{n} Wi}$$

where n is the sample size (n=83). The new weights have the property that $\sum wi=n$. The weighted average of the Ci was computed as follows:

$$\bar{C} = \frac{\sum^{n} wiCi}{n}$$

Weighting by inverse variances minimizes the variance of the weighted average of the Ci. If a coefficient C was significantly different from zero in the direction of an adverse response (i.e., increase in symptom score or decrease in PEFR), a statistically significant adverse effect of ozone was considered to be present.

Numerous regression equations were calculated to determine possible response-stimulus relationships between respiratory status (symptom score, asthma medication index, night PEFR, and

day PEFR) and aeroallergens, temperature, humidity, and air pollutants (CO, NO_x, NO_2, SO_2, sulfates, TSP, hydrocarbons, and ozone), both alone and in various combinations. The effects of ozone (daily maximum hourly concentration) and the average ozone concentration on days t, t-1, t-2, and t-3, both alone and in combinations, were also evaluated in the regression models. The effect of ozone was further evaluated by accounting for the previous day's medication use, symptom score, night PEFR, and day PEFR. This approach not only allowed assessment of the effect of ozone on individual outcome variables but also the detection of possible "delayed" asthmatic exacerbations occurring one or more days after exposure to increased ozone concentration, i.e., the term t-1 can be replaced by t-2 or other appropriate lag times. This statistical method is also minimally affected by missing data which may occur due to subjects having colds or temporarily leaving the Glendora area, e.g., on vacation.

The values of the regression coefficients C obtained for each individual (from the above model equation for day PEFR) also helped identify a group of individuals who appeared sensitive to ozone. Individuals with significant coefficients C can be considered "responders" to ozone, compared to the remaining individuals whose coefficients C were not significant.

Specifically, regression coefficients for ozone were obtained for each subject from four separate multiple regression equations using symptom score, asthma medication index, and day and night PEFR as the outcome variables (from the above model equation for day PEFR). The ozone coefficients for each of the equations were ranked, and the average rank was computed for each subject. Subjects with the highest average ranks were considered to be possible subsets of subjects with outcome variables correlated to ozone, i.e., responders to ozone.

We then classified the subjects into two groups of responders (equivalent to "moderate" and "extreme" responders) on the basis of the value of the individual coefficients (C) described above. Individual slope coefficients for ozone which were greater than 0.674 standard deviations from zero (equivalent to the top or bottom quartile of the sample) in an adverse direction were determined separately for symptom score, day PEFR, and night PEFR. The asthma medication index was excluded from this analysis since the AMI did not appear to be related to ozone even in the most responsive subjects using the above multiple regression equation and initial ranking of ozone coefficients.

Subjects in the extreme quartile for at least one of the three variables (i.e., symptom score and day and night PEFR) were considered in the group designated as responders-1 ("moderate" and "extreme" responders together). Similarly, subjects in the extreme quartile in at least two of the three variables were designated responders-2 (i.e., "extreme" responders only). The two groups of responders were compared separately to the respective remaining "less responsive" subjects according to their

baseline and other characteristics by ANOVA and other statistical tests.

The clinical significance of the respiratory responses predicted by the individuals' regression equations for ozone was determined by evaluating their predicted responses to 0.35 ppm ozone. This ozone concentration was the approximate range over which ozone concentrations generally varied during the study. We considered clinically significant adverse responses to 0.35 ppm ozone to be: 1) an average increase of >1 unit in symptom score (on a 1 to 7 scale) or 2) an average decrease in the subject's day or night PEFR of >5% of the subject's respective averages over the study period. If a subject's coefficient for ozone, multiplied by 0.35 ppm, was greater than one (i.e., one unit on the symptom scale), then a clinically significant (adverse) effect of ozone on symptoms was considered to have occurred during the study. Similarly, the threshold level for clinically significant changes in day or night PEFR during this study was:

$$\frac{-1(0.05X \text{ subject's average day or night PEFR during study})}{0.35}$$

with lower (more negative) coefficients indicating an adverse effect. We considered these operational criteria to be reasonable since the known fluctuations of respiratory status in asthmatics and the presence of possible measurements errors should be balanced and adjusted for by the long duration of the study and numerous longitudinal measurements.

The psychological results from the Asthma Symptom Checklist (ASC) were further evaluated. Two-way ANOVA (across sex and symptom category score) was performed on the average slope coefficients for ozone to determine if subjects who had low (lower 25% of group scores), moderate (middle 50%), or high (upper 25%0 scores had the same average slope coefficients from the multiple regression equations using the respiratory outcome variables as the dependent variable. Symptom category scores of the responders-1 and responders-2 were also compared to the results of the respective remainders of the group.

RESULTS

RESULTS

A. Baseline Studies

1. Initial Study Population

The panel study began on February 1, 1983, due to slow recruitment and problems with the battery component of the Nebulizer Chronolog, and concluded by December 15, 1983. A total of 109 subjects had been enrolled in the study by April, and they included 56 males and 53 females with 76 subjects greater than 17 years of age. Fifty-one subjects (46.8%) began the study in February, 57 (52.3%) in March, and one subject (0.9%) in early April. Approximately 50% of the subjects were recruited by local advertisements and the remaining 50% from prior epidemiological studies (6,7).

Eighteen subjects withdrew or were dropped early in the study due to noncompliance to the study protocol, recurrent colds or insufficient exposure to the study environment (greater than four weeks' absence from the study area). The baseline characteristics of the 18 excluded subjects are summarized in Table 1. Six (33.3%) of the 18 subjects were between 11 and 18 years of age. These 18 subjects participated in the study for an average $\pm$ standard deviation (SD) of 67 $\pm$ 38.8 days (range = 13-117 days), with 10 subjects beginning the study in February and eight in March.

Ninety-one subjects (91/109 = 83%) completed the study and consisted of 48 males and 43 females (82 White, 8 Hispanic, 1 Black) with an average age of 34 years (SD = 17.4; median 30; range 7-70 years), duration of asthma of 18 years (SD = 14.2; median 13; range 1-50 years), and a nonsmoking history in 84 subjects. Forty-one subjects began the study in February, 49 in March, and one in early April.

Eight (9%) of the 91 subjects were ultimately excluded from analysis because they showed no evidence of varying asthma over time, i.e., they had consistently low symptom scores and minimal or absent use of their MDI or other anti-asthma medications during the study period. Their baseline characteristics are summarized in Table I. These eight subjects participated for an average of 297 days (SD = 16.2 days; range = 258-308 days) and all but one subject began the study in February. Thus, 26 (24%) of the original 109 subjects were excluded from the final analyses.

2. Final Study Population

The baseline demographic and clinical characteristics of the 83 final subjects are summarized in Table 2. Twenty-six subjects (31%) were between 7 and 18 years of age, whereas four subjects (5%) were between 60 and 70 years. Differences between males and females were minimal except for the males' younger age (27.4 $\pm$ 15.9 SD vs. 37.9 $\pm$ 16.6 years) and greater work-travel mileage

(14.5 ± 12.5 SD vs. 11.1 ± 2.5 miles, one-way). Thirty-four (41%) of the 83 subjects were recruited from epidemiological sources (6,7) while the remaining 49 subjects (59%) were recruited by local advertisements. All subjects lived within a four-mile radius of one of the air quality monitoring stations, i.e., in the adjacent communities of Glendora, Azusa, or Covina. None of the subjects reported a change in residence during the study. Sixty-nine (83%) of the 83 subjects reported that smog worsened their asthma. The 83 subjects participated for an average of 282 days (SD = 20.3; range 203-315 days), with 34 subjects (41%) beginning in February, 48 (57.8%) in March, and a single subject in early April. All subjects continued in the study until mid-December, except for two individuals who finished on September 27 and November 30.

Twenty-four subjects noted worsening of asthmatic symptoms while at work. However, only six subjects had occupations which appeared to have possible asthmogenic conditions; these subjects worked as a beautician, brewer, chemical worker, and as construction workers (three subjects in the latter category). One fireman did not complain of increased respiratory symptoms during his work activities. Other socioeconomic information (Table 3) indicated that the majority of subjects were in households with middle-class incomes and had a high school education.

3. Pulmonary Function

The baseline pulmonary function data for the 83 subjects are summarized in Table 4. As expected, a large range of values for the percent of predicted FEV_1 (the primary index of large airway obstruction such as present in active asthma) was present. Although 42 (51.8%) of the 83 subjects had a normal FEV_1 ($\geq$80% of predicted FEV_1), this finding was consistent with the diagnosis of mild asthma since this disorder characteristically fluctuates in intensity. On the other hand, 22 subjects (26.5%) showed mild-to-moderate airways obstruction (60-79% of predicted FEV_1) and 18 subjects (21.7%) had severe airways obstruction (<59% of predicted FEV_1). Sixty subjects (72.3%) also had less than 80% of their predicted $FEF_{25-75\%}$, suggesting the presence of small airways disease or dysfunction.

4. Airways Reactivity

An attempt was made to document increased airway reactivity (a physiological hallmark of asthma) by routine administration of an inhaled bronchodilator (isoproterenol). This was possible in 65 subjects (78.3%) and this group showed a mean increase in FEV_1 of 8.4% from baseline FEV_1 (Table 4). Only 10 subjects demonstrated a significant post-bronchodilator response of $\geq$15% increase in FEV_1. The remaining 55 subjects did not significantly increase their post-bronchodilator FEV_1. Isoproterenol inhalation was either refused or judged medically inappropriate in 18 subjects, most of whom were children who had a parent who refused this aspect of the protocol.

Further documentation of hyperreactive airways was attempted in the subjects who did not significantly bronchodilate (despite a second trial) or who did not receive the bronchodilator. Medical records confirmed the diagnosis of asthma and the benefit of bronchodilator medications in eight subjects (five of whom did not receive isoproterenol testing). A modified methacholine bronchoprovocation test (11) was positive ($\geq$15% decrease in FEV_1 from control value) in 5/5 patients (two of whom did not receive isoproterenol testing). Thus, a total of 23 subjects (27.7%) showed physiologic (spirometric) or physician-recorded evidence (medical records) of active airways reactivity or asthma (Table 5).

5. Anti-Asthma Medications

Another indication of the diagnosis of asthma and its severity may be observed in the subjects' reported medication regimens. Although individual medication use was recorded daily and checked routinely by the study staff, we also specifically determined the anti-asthma medications used during the initial part of the study (i.e., on April 15) and the conclusion of the study (i.e., November 30). This separate analysis provided information about the types and quantity of anti-asthma medications used on these two days and, thus, an approximation of the stability or change in the medication regimens (Table 6). Only subjects using an MDI to deliver an adrenergic bronchodilator aerosol were included in the study. Six subjects eventually discontinued MDI usage before the end of the study, but all except one subject still continued using oral anti-asthma medication(s). Subjects using a MDI alone may be considered to have mild asthma while the use of a MDI and other anti-asthma medication (especially oral corticosteroids) suggest the presence of moderate-to-severe asthma. Except for MDI usage in six subjects, the subjects' drug regimens of theophylline compounds, oral adrenergic agents, and/or corticosteroids did not change significantly (i.e., remained stable) based on the two times of evaluation. For example, 23 subjects used either inhaled and/or oral corticosteroids on the initial evaluation day and 22 of these subjects continued their use by the end of the study. A hand-held nebulizer (with an air compressor) was also used to deliver inhaled bronchodilators by six subjects during the initial part of the study and by four subjects at the completion of the study.

6. Excluded Subjects

The 26 subjects ultimately excluded from the study and the final 83 subjects did not significantly differ in most of their demographic, clinical, and pulmonary function results (Tables 1-4). Socioeconomic data were not obtained for the 18 initially excluded subjects, but the other eight subsequently excluded individuals had similar distributions of household income and highest education level attained, compared to the 83 subjects. The excluded subjects had a higher frequency of coexisting atopy (primarily hay fever). Although the percent of predicted forced

vital capacity (FVC), FEV_1, and $FEF_{25-75\%}$ and the post-bronchodilator change in FEV_1 were somewhat lower in the 83 final subjects, the differences were not significantly different due to the wide range of overlapping values.

7. Psychological Results

The battery of psychological tests was completed twice by the 83 subjects during the study period. No subject's results differed significantly between the two tests, indicating good reliability and reproducibility of the instruments. These results also indicated that the group's general (chronic) psychological status was stable and not necessarily related to ongoing changes in air quality since the tests were administered during periods of good and then poor air quality. Only the first set of psychological test results was used for the purpose of analysis. Summaries of the psychological results for the adults (i.e., age 13 and above) and children (i.e., age 7-12) are presented in Tables 7 and 8, respectively.

The Asthma Symptom Checklist (ASC) described the patient's subjective responses during asthmatic attacks and provided a measure of illness (asthma) - specific anxiety (15). The results of the 71 adults' experiences with 50 ASC symptoms were evaluated by factor analysis, which generated eight independent symptom categories of related complaints (Table 7). Although the resulting symptom categories differed from the data of the original investigators (15) in the number (8 vs 10) and the types of individual symptoms within each category, the differences were minimal. Ten symptoms did not significantly fall into any category in our factor analysis. Only the mean scores are presented since future analysis will deal with the more complex issue of standardization and comparison to the results of other studies (15). Categorization of the subject's scores in each symptom category was operationally defined as high (i.e., greater than one standard deviation above the mean) and low (i.e., greater than one standard deviation below the mean). Scores between those extremes would be in a moderate range. On the basis of this scheme, the number of subjects with high scores in the eight symptom categories ranged from 7 to 16. The number of subjects with low scores in the same symptom categories ranged from 11 to 15.

The Panic-Fear Symptom Scale consists of 15 items from the Minnesota Multiphasic Personality Inventory (MMPI) and measures characterological anxiety in relation to fear and emotional stability (16,17). Scale scores can be related to the intensity of panic-fear, i.e., scores of 2 or less relate to the low panic-fear group, 3 to 8 to the moderate panic-fear group, and 9 or greater to the high panic-fear group. Using these cut-points, 50 (70%) of the 71 adults were in the moderate panic-fear group. Ten subjects were in the low panic-fear group (scores ≤ 2), whereas 11 subjects were in the high panic-fear group (scores ≥ 9).

The State-Trait Anxiety Inventory (STAI) measures acute or transitory anxiety (state) and chronic or characteristic anxiety (trait) (18). The score on either form can range from 20 to 80; the higher the score, the greater the level of anxiety. Average STAI scores in the 71 subjects were similar in both state (average score 35.5) and trait anxiety (37.8) (Table 7). Normative reference data for the STAI are not available for large samples of asthmatic patients. For the purpose of this report, the highest range of scores (i.e., 50-59) was considered to represent high anxiety. Therefore, seven subjects indicated extreme state anxiety and six subjects indicated extreme trait anxiety.

We also evaluated whether or not the subjects' perception of poor air quality ("smog") as a precipitant of asthmatic attacks influenced their psychological test results. Fifty-nine (83%) of 71 subjects indicated in their baseline questionnaire that smog worsened their asthmatic condition, whereas 12 subjects did not perceive such a relationship. However, comparison of the two groups did not show significant differences in their scores from the eight symptom categories of the ASC, the Panic-Fear Symptom Scale, or the STAI ($p=0.11$ to 0.96; t-tests).

The ASC results for the 12 children in the study (Table 8) were not factored due to the small number of subjects. For this report their results are presented in two ways: 1) according to the results of the factor analysis of symptom categories for the 71 adult subjects (using mean scores), and 2) according to the solution presented by Kinsman and coworkers (15) (using their standard scoring method). The validity of these approaches in children remains problematic and requires further analysis. Nevertheless, the number of subjects with high (>55) and low (<45) standard scores was evenly distributed for Kinsman's C1, predominantly high for C4 and C8, intermediate for C2 and C6, and low in C3, C5, and C7.

Results of the State-Trait Inventory for Children (STAIC) indicated an average score of 29.0 for state anxiety and 38.4 for trait anxiety in children between 7 and 12 years of age (Table 8). Four children scored between 40 and 49 and one subject scored 50 out of a possible score of 60.

Results of the Asthma Symptom Checklist, Panic-Fear Symptom Score, STAI, and STAIC will be the subject of future analyses which will deal in more detail with the replication, standardization, and application of the different test instruments in this study sample.

B. Longitudinal Results

1. Exclusions

In addition to information in the baseline questionnaires, a tremendous amount of data was collected during the study. For example, the following data were accumulated for 109 subjects:

- 24,976 subject-days of symptoms (or 49,000 separate half-day records representing slightly over 1,000,000 measurements).
- 25,437 subject-days of medication use.
- 68,720 inhaler actuations recorded by Nebulizer Chronologs.
- 149,856 measurements of PEFRs.
- 1,590 bi-weekly questionnaires and pulmonary function tests performed at the Glendora laboratory.

This voluminous collection of raw data required intensive and careful cleaning, review, and decision making, the first of which was to limit the number of subjects to 83 (see previous section). The next step was to define and restrict the number of valid or usable study days for analysis.

The panel study encompassed 10-1/2 months (February 1 - December 15) and a total of 19,024 actual subject-days (72.3% of the possible total of 26,311 subject-days = 83 subjects x 317 days) which were initially available for analysis. However, it was decided to analyze data collected between April 15 and November 30 (a period of 230 days) for several reasons: 1) subjects entered and left the study at different times, and data from the first 2-4 weeks of participation (i.e., pre-study training period) for each subject were automatically deleted; 2) missing or incomplete data were more frequent during the early part of the study; and 3) the 230-day period still encompassed an adequate number of days with low and high ozone concentration (see air quality results). As a result, 18,988 subject-days or an average of 228.8 days/subject were available for analysis in the 83 subjects.

We then developed various data exclusion criteria for inadequate exposure to the study area's air quality (i.e., travel outside the Glendora area) and possible exacerbation of asthma due to stimuli other than air pollution (i.e., viral infections or colds). Data recorded during travel outside the Glendora area for greater than 12 hours were excluded from the final analysis. When the subject indicated absence from the area for most of the afternoon, the diary data for that day and night were excluded. Most of the travel for vacations or other reasons occurred between June and September, with an average of 3.3 days per subject per month for these four months and 1.4 days per subject per month for the other months. Thus, 1,662 days for travel were excluded, resulting in an average of 20 days/subject (SD = 17.9; range = 1-103 days). Fifty-two subjects (62.7%) had $\leq$20 days excluded due to significant travel. Only five subjects had 51 to 103 excluded days.

We also excluded data for individuals with probable viral upper respiratory tract infections or colds for a two-week period following its symptomatic onset. The subjects' self-reports of a

"cold or flu" were verified by the presence of specific symptoms (i.e., associated fever or sore throat) in order to distinguish between infection and acute allergic flares. This rigorous rule was used to allow for adequate recovery time since respiratory infection per se may enhance airway reactivity (28,29) and worsen asthma, as well as increase sensitivity to potentially asthmogenic stimuli such as ozone. Fifty-four subjects (65.1%) had one to seven separate episodes of viral syndromes during the study period: 23 subjects (42.6%) had one episode, 18 had two episodes, eight had three, three had four, and one subject each had five and seven episodes. The total number of excluded days was 1,502 days, resulting in an average of 27.8 days/infected subjects. Seventeen children or minors (age 7 to 17) contributed 601 days (601/1,1502 = 40.0%) and had a higher average number of infection-excluded days/subject (35.4 days) and episodes/subject (2.4) than the adults (24.4 days/subject and 1.8 episodes/adult, respectively). The number of monthly episodes of infection for the group was evenly distributed (mean 14.1/month) except for four episodes in July and 20 in November.

Hospitalized days were also excluded for each subject since the patients were not actively exposed to outdoor air pollution during the hospitalization and were receiving intensive inpatient therapy for the indication of their hospitalization (exacerbation of asthma in all cases). Six subjects (all adults) were hospitalized one or three times during the study period; three patients were admitted in November, one subject in April, May, and June, and one subject twice in August. The eight hospitalizations resulted in the exclusion of 43 days for this group or an average of 5.4 days per hospitalization (range 1 to 15 days).

On the other hand, days with urgent visits to either an emergency room of physician were not excluded from analysis. Five subjects required emergency treatment during the study, two once, and the other three patients twice. These five patients spent a total of 71 days in this type of treatment (14 days/subject; range = 7 to 21 days). One subject apparently required a total of 100 days of "routine" office visits for treatment of her asthma. Both types of treatment were given relatively high scores for calculation of the asthma medication index.

Thus, 2,837 subject-days were ultimately excluded as a result of the above adjustments, leaving a total of 16,151 analyzable subject-days or an average of approximately 195 days/subject (SD = 29.2; range 89-230 days). The resulting data were then submitted to further univariate and multivariate analyses.

2. Air Quality and Meterological Data

Air quality data for ozone, sulfates, TSP, and hydrocarbons from the SCAQMD monitoring station in Azusa were used whenever available since the CARB station in Glendora did not have complete data during the study period. Data for SO_2, CO, NO_2, and NO_x were obtained from the Glendora station. Missing values from the

primary station were filled in by data (if available) from the other monitoring station. Any days without information from both the Glendora and Azusa stations on one or more air pollutants were noted. Substituted values were not used and days without specific air pollutant recordings were not subsequently analyzed for the missing air pollutant(s). The following air pollutants were expressed as daily maximum hourly average concentrations: in the analyses: O_3, SO_2, NO_x, NO_2, and CO. The following air pollutants were expressed as daily 24-hour average concentrations: sulfates, TSP, and total hydrocarbons.

The univariate statistics for the ambient concentrations of air pollutants during the study period are summarized in Table 9. Both monitoring stations indicated that ozone was frequently increased above California and other air quality standards. The number of study days falling within various ranges of daily maximum hourly concentrations of ozone was as follows: 0.01 - 0.11 parts per million (ppm) O_3 = 102 days (44.4% of study days); 0.12 - 0.19 ppm O_3 (National Primary Standard) = 65 days (28.2%); 0.20 - 0.34 ppm O_3 (SCAQMD first stage alert level) = 60 days (26.1%) and 0.35 - 0.49 ppm O_3 (SCAQMD second stage alert level) = 3 days (1.3%) (Figure 1 and Table 9). The California one-hour standard for ozone is 0.10 ppm.

Regression and correlation of 5,615 O_3 values from both monitoring stations showed a highly significant correlation ($r = 0.97$; $p < 0.001$), with a regression line of: $Y = 0.91X - 0.75$, with Y = Azusa ozone value and X = Glendora ozone value. The average difference ($\pm$ SD) between the Glendora and Azusa data for ozone was only 1.2 ± 1.4 parts per hundred million (pphm) (median = 1; range = -7 to 10). The Azusa data were used for analysis, and Glendora ozone values were used to fill in for missing Azusa data (following a minimal linear adjustment) since the Glendora data set had more missing ozone concentrations.

The daily maxima recorded for air pollutants other than ozone generally did not exceed ambient air quality standards (Figures 2-8; Table 9). Specifically, sulfur dioxide (Figure 2), oxides of nitrogen (Figure 3), nitrogen dioxide (Figure 4), carbon monoxide (Figure 5), and total hydrocarbons (Figure 8) did not exceed state or national air quality criteria in the study area. Sulfates (Figure 6) exceeded the California standard (daily 24-hour average concentration of 25 ug/m^3) on 4 days, of which 2 were in late May and one each in June and September. Total suspended particulates (Figure 7) were frequently (on 141 days or 141/181 = 78% of all days with available recordings) above the daily 24-hour average concentration of 100 ug/m^3 (the California Air Quality Standard in effect until 1983), although this pollutant did not exceed the national standard (260 ug/m^3).

The meterological results (Table 10 and Figures 9-12) were internally consistent, with higher temperatures and lower relative humidity at 1 P.M. than at 1 A.M. Overall, there was minimal fluctuation in barometric pressure, particularly in late summer

and early fall. The average barometric pressure was 742 millimeters of mercury (mm Hg), with 21 days (9.3%) between 735-739 mm Hg, 191 days (84.9%) between 740-744 mm Hg, and 13 days (5.8%) between 745-749 mm Hg. The 21 days with barometric pressures between 735 and 739 mm Hg occurred in April (2 days), May (9 days), June (6 days), and September (4 days). The observed barometric pressures were considered reliable, reasonable, and fairly accurate since the average elevation of Glendora is 800 feet above sea level which is equivalent to approximately 740 mm Hg (Glendora Chamber of Commerce. Personal communication).

The daily values for the air pollutants and meterological indices during the study period were also regressed and correlated with each other to determine their relationships and the internal consistency of the data (Table 11). Although the large number of analyses resulted in many significant relationships, the number and pattern of correlations of $r \geq 0.47$ ($p=0.0001$) strongly indicated that the data were reasonable, valid, and appropriately related. As anticipated, ozone correlated highly with concurrent NO_2, TSP, and temperature (at 1 P.M. and 1 A.M.). Nitrogen oxides (NO_x), NO_2, and CO were highly correlated with each other as were TSP and suspended sulfates. Total suspended particulates were highly correlated with all pollutants except SO_2 and hydrocarbons, both of which had relatively poor correlations with the other pollutants and meterological variables. Temperature was correlated significantly ($p = 0.0001$) only with ozone concentration, while humidity did not correlate significantly with the levels of ozone and other air pollutants.

3. Aeroallergen Data

The Roto-Rod sampler operated daily from January 26 to December 14, 1983 (323 days). Roto-Rod samples were analyzed and daily results were available for 282 days (87.3%). Roto-Rod results were reported for 200 days (87%) during the study period between April 15 and November 30 (230 days). Missing data resulted from either an inability to change the sampling rods on schedule at the Glendora laboratory (primarily on weekends) or the loss of samples. Results were unavailable for five days in August, six days in July, and eight days in September (including a single six-day period), as well as for four or fewer days in May, June, October, and November.

Twenty-three families of trees, shrubs, and grasses, six families of Gymnosperms, seven of Basidiomycetes (club fungi), two of Ascomycetes (sac fungi), and three of Deuteromycetes (fungi imperfecti, which included 14 genera) were evaluated with each sample. The large number of different types of spores and pollens and their highly variable daily counts necessitated a more manageable categorization scheme for analysis. Therefore, 10 groups of potential aeroallergens were established:

Trees 1 = Family Aceraceae (box elder, maples); Fagaceae (oak, beech); Ulmaceae (elm).
Trees 2 = All other trees.

Shrubs 1 = Family Compositae: generae Ambrosia (ragweed) and Artemesia (mugwort, sagebrush type).
Shrubs 2 = All other shrubs and weeds.
Grasses = Family Gramineae.
Gymnosperms (all families) = juniper-cypress, redwood, pine-spruce cedar, etc.
Molds 1 = Basidiomycetes (rusts, smuts, mushrooms).
Molds 2 = Ascomycetes (sac fungi).
Molds 3 = Deuteromycetes (Penicillium, Aspergillus, Alternaria, Helminthosporium, etc.)
Miscellaneous = algal cells, lichen, ferns, insect parts, etc.

Factor analysis of the 10 groups did not indicate any advantage of further combination (collapsing) of the current categories.

Univariate results of the daily collected concentrations of potential aeroallergens are presented in Table 12. Except for the Molds 1 group (rusts, smuts, mushrooms), the potential aeroallergens had generally low median values as compared to the higher average values. The daily counts of the spores, pollens, grasses, molds, and miscellaneous debris are also depicted as logarithmic values (i.e., logarithms to the base 10) over time in Figures 13-22 due to the great range of daily counts during the study period.

4. Symptom Scores

Self-reported scores were recorded twice daily (day and night) for individual symptoms and the overall asthma rating. The consistently low mean group values are summarized in Table 13. Theoretically, the overall asthma rating should reflect the other symptom scores (except possibly tension), making it possible to use the overall rating exclusively in analysis or to combine it with asthma symptoms to reduce the measurement variability. The relationship between the overall asthma rating and the individual symptom ratings was investigated by correlation and factor analyses, as well as plotting both the raw values and seven-day moving averages over time. As in almost all analyses, each program was run separately for each subject because of inherent differences between subjects. The calculated correlations were based on the averages of the individual correlations for the 83 subjects. Although day and night tension scores were significantly correlated ($r = 0.95$) to each other, they were less related ($r = 0.42$ to 0.52) to the day and night pulmonary symptoms and overall asthma ratings. Tension scores were not further analyzed for the purpose of this report. Factor analysis confirmed that all the respiratory symptoms (excluding tension) and overall asthma ratings (day and night) were highly related for all the individuals and could be collapsed into a single symptom score. Thus, the daily average of six day and six night symptom scores (i.e., wheezing, shortness of breath, chest tightness, coughing, sputum production) and overall asthma rating provided a single daily symptom score for each individual.

5. Asthma Medication Index and Nebulizer Chronolog Data

Approximately 95 different preparations and doses of anti-asthma medications and treatments in an emergency room or by a physician were combined into a daily asthma medication index (AMI) for each individual. Clinically, subjects with a daily AMI score $\leq$9.9 could be considered to have "mild" asthma. Subjects with a daily AMI between 10.0 and 29.9 could be considered to have "moderate" asthma, whereas individuals with AMI scores $\geq$30 should have "severe" asthma requiring multiple bronchodilators and corticosteroid therapy. The group data for the daily AMI during the study period are presented in Table 14. The average daily AMI was 9.8 units, suggesting that an aerosolized bronchodilator (delivered by MDI) and another agent such as an oral theophylline compound or beta-agonist were used on a daily basis (see examples of AMIs in Materials and Methods). However, the majority of subjects required much less medication and probably had relatively mild asthma during most of the study since the median value for the AMI scores was only 4.8 units. Approximately 65% of the daily AMI scores were <10 units, whereas only 9% were $\geq$30 units, which is indicative of severe asthma requiring multiple anti-asthma medications and possibly frequent visits to a physician.

The data collected from the Nebulizer Chronolog (NC) were informative for several reasons. Performance-wise, the NC malfunctioned for 1/2 month in 17 subjects, 1 month in 8 subjects, 1-1/2 months in 4, and for 2 or more months in 5 subjects, as well as for shorter time periods in other subjects. Some data were lost due to recurrent memory overflow in the NC or to the combination of NC malfunction and memory overflow (1/2 month in one subject and for 2 or more months in 4 subjects in both categories). Specifically, 2,578 subject-days (14%) out of the possible 18,847 subject-days during the 230-day study period were found to have malfunctioning NCs, resulting in 16,269 useful subject-days (group mean $\pm$ SD as percent: 86 $\pm$ 18.1%) for analysis. The group median value was 93.4% useful NC days, with 47 (53.6%) of the 83 subjects having >90% useful days and 26 subjects (31.3%) having 100% useful NC days (i.e., no days with malfunctioning NCs). Only five subjects had less than 50% useful NC data (range 14-47%).

We were particularly interested in the agreement between the MDI recordings in the daily diary and by the NC. Eight subjects had either obviously unreliable daily data in regard to MDI usage or had multiple, large periods of missing data in their diary and/or NC (due to malfunction and/or memory overflow). These eight subjects were excluded from subsequent analyses comparing the MDI recordings by NC and diary. Thus, the remaining 75 subjects had analyzable concurrent diary and NC recordings which resulted in 12,335 subject-days or an average $\pm$ standard error of the mean (SEM) of 164 $\pm$ 4.9 days/subject (range = 22-230 days). The results for group and individual MDI usage recorded by NC are presented in Table 15. Sixty-six subjects (66/75 = 88%) used their MDIs less than 8 times a day, on the average. Since the

usual daily MDI maintenance regimen with inhaled adrenergic agonists is 8 times a day (i.e., 2 puffs every 6 hours), this level of usage suggests that the subjects predominantly used their MDIs on an as-needed basis. Only six subjects consistently used their MDI much more frequently than the usual maintenance level.

Predominant daily patterns between the MDI recordings by NC and in the diary showed a wide range of differences in MDI usage if we operationally evaluate the results on an absolute basis (Table 16). Fifty subjects (67%) had perfect agreement between the two recording instruments more often than over- or under-recording, whereas 25 subjects had more frequent days with either relative under- or over-recording in their diaries. However, the average daily NC-diary differences in MDI recordings per subject were relatively small (-1.1 to +1.1) in 60 subjects (80%) over the study period (Table 16), indicating fairly reliable diary recordings in these subjects. The mean daily diary recordings were higher (-1.2 to -6.4) or lower (1.7 to 10.6) in 6 (8%) and 9 (12%) subjects, respectively; eight of these 15 subjects were judged "reliable" by the laboratory technicians who were not aware of the long-term relationships of the NC-diary results. "Reliability" was based upon the subjects' general compliance in regularly visiting the laboratory and completing all aspects of the daily dairy.

6. Peak Expiratory Flow Rates

The subjects' PEFR values from their mini-Wright peak flow meters were routinely checked during laboratory visits against the standard Wright peak flow meter (PF-286) and the computerized Gould spirometer, both of which were calibrated daily. For the purpose of this report, the PEFR values were compared to assess their accuracy on one day during two selected study periods: time 1 = the first set of concurrent daily readings on or just after July 15, and time 2 = the last set of concurrent daily values on or just before October 31, 1983. Regression analysis of values measured at time 1 showed that the values from the mini-Wright had significant ($p<0.001$) correlations to those from the standard Wright ($r=0.97$) and Gould spirometer ($r=0.87$). The correlation between the standard Wright and Gould spirometer was also high ($r=0.89$; $p<0.001$). Similarly, regression analysis of values measured at time 2 showed that the values from the mini-Wright were significantly ($p<0.001$) correlated to those from the standard Wright ($r=0.97$) and Gould spirometer ($r=0.86$). The results from the latter two instruments again showed significant correlations ($r=0.85$; $p<0.001$). These results indicate that the mini-Wright peak flow meters used by the subjects were capable of providing accurate and reliable data as compared to the standard Wright peak flow meter and the computerized spirometer.

Univariate results from the daily values of peak expiratory flow rate (PEFR) in the 83 asthmatic subjects are summarized in Table 17. In this table, the absolute (rather than the percent of predicted) PEFR values throughout the study period are presented.

The group mean and median values for PEFR in this study suggest that the majority of PEFR readings were relatively low, although there was large variation (SD = 131 liters/minute).

However, PEFR values vary greatly between subjects and are influenced by sex, age, height, and effort (30) as well as by recent bronchodilator use in asthmatics. Thus, a more meaningful method of analysis of the PEFR data is to standardize each individual's average day and night PEFR values over the 230-day study period as the percent predicted PEFR values (Table 18). We used the regression equations of Knudson and coworkers (31) which adjust for sex, age, and height. The results in Table 18 indicate that the average PEFR was approximately 87% of predicted during the day and night. This average group value is well within the normal range of 80-100% of predicted. Similarly, at least 54 subjects (65%) had normal average PEFR throughout the study period. Only 7 subjects (8.4%) had severely reduced average PEFR. These data indicate that the majority (at least 77% of the subjects) had relatively normal or mildly reduced average PEFR during the study.

C. Longitudinal Relationships

1. Dependent Variables and Ozone

The longitudinal relationships between symptoms, PEFR, and medication use (AMI) were evaluated since these outcome variables represent changes in asthmatic status and are related to each other in a complex manner. For example, a subject's symptoms may not necessarily increase during a period of high oxidant air pollution (or in the presence of other possible asthmogenic stimulus) due to an effective increase in medication usage during the early stages of worsening asthma. On the other hand, a stoic patient may have relatively stable medication use despite worsening of symptoms and PEFR.

The daily recordings by the 83 subjects of the number of asthma attacks and their duration were used to analyze their relationship to the AMI and, as a separate component, the MDI usage during the study period (Table 19). According to regression analysis, the correlations between day, night, and day and night (combined) were low (average $r=0.25$) for the AMI, although they were all statistically significant ($p<0.05$). The correlations between the number of asthma attacks and MDI usage were much higher during the day and night ($r=0.42$ and 0.44, respectively; $p<0.001$) although not when day and night are combined or between the duration of attacks and MDI usage.

The potential influence of delayed effects on the relationship of symptoms and medication use was also specifically evaluated. The correlation coefficients (r) between 1) AMI (dependent variable) and symptom score on day t-1, and 2) symptom score (dependent variable) and the AMI on day t-1 for each subject were calculated. A paired t-test between the correlation

coefficients of regressions 1) and 2) above showed a significant mean difference (0.076; p=0.0001) between the two dependent variables, indicating that symptoms on day t-1 and the AMI on day t correlated much more significantly than symptoms on day t and the AMI on day t-1. The above findings support the internal consistency and logical relationships of the symptom scores, AMI, and MDI usage.

The relationships between the daily maximum hourly average ozone concentration and the average of various outcome variables throughout the study were investigated by several standard methods. Regression and correlation between ozone concentration and average symptom score over subjects ($r = 0.002$; $p = 0.94$); AMI ($r = -0.04$; $p = 0.02$); day PEFR ($r = 0.02$; $p = 0.20$); and night PEFR ($r = 0.01$; $p = 0.67$) showed no statistically or clinically significant overall relationships. Similarly, the daily outcome variables were compared according to different ozone ranges (Table 20) by two-way ANOVA (across ozone and subject). No statistically significant differences were detected except for clinically nonsignificant higher day and night PEFRs during days with maximum hourly average ozone concentrations between 0.12 and 0.19 ppm ($p < 0.01$) compared to both higher and lower ozone concentration ranges.

Although the usage of the MDI was combined with that of other anti-asthma medications in the AMI, this component was also evaluated separately as an outcome variable since as-needed therapy may reflect acute changes in asthmatic status. Multiple regression testing of the maximum hourly average ozone concentration and MDI use on day t-1 (independent variables) and the MDI use on day t (dependent variables) showed that inhaler use on day t was significantly related ($p < 0.00001$) to MDI use on day t-1 but not to ozone ($p = 0.28$).

The amount of exposure to ambient oxidant pollution in all subjects was estimated by determining the time spent outdoors and as a function of the day of the week (weekday versus weekend). The biweekly questionnaires provided information for the periods between 12 noon and 6 P.M. (afternoon) when daily ozone concentrations are expected to be the highest. The average time spent outdoors on weekday afternoons during the study was 2.3 hours/subject (SD = 1.65; median = 2; range 0-6 hours), whereas the average time outdoors on weekend afternoons was 3.2 hours/subject (SD = 1.76; median = 3; range = 0-6 hours). The mean difference between the weekend and weekday afternoon hours spent outdoors was 0.98 hour (SD = 1.43; median = 0; range -4 to 6 hours) which is relatively minimal. The time spent outdoors was also not related to the presence or absence of a smog alert. Therefore, an adjustment for the time spent outdoors was not necessary.

2. Multiple Regression Analyses

The multiple regressions performed for all subjects in this

study are summarized in Table 21. The table is categorized according to 1) those analyses (A.-F.) aimed at detecting the effects of independent variables on the respiratory status of the entire group (83 subjects) and 2) those analyses (G.-I.) characterizing ozone responsiveness in subsets of subjects according to the ranking of their ozone coefficients for each of the dependent variables (latter discussed in next section). The outcome (i.e., dependent) variables (symptom score, asthma medication index, night and day PEFR) are listed first in Table 21. Next, the predictor (i.e., independent) variables are listed along with the lag time. For example, medication (t-1) signifies that medication use (AMI) on the previous day was used to predict today's symptoms in the second line of the table. In the third column of Table 21 the significance level is presented for the independent variables that are considered significant ($p < 0.05$).

The results of the multiple regression analyses (Table 21) for the 83 subjects can be summarized as follows. Respiratory symptoms were directly influenced by medication use on days t, t-1, t-2, and, to a lesser extent, t-3 (Table 21.A.). There were no significant correlations between the respiratory variables and all categories of aeroallergens, except for mold 1 and trees 1 (Table 21.B.). Although these two categories showed statistically significant negative relationships, only the effect of trees 1 was considered clinically relevant. Temperature and humidity (regardless of time) did not significantly affect the respiratory variables during the study (Table 21.B.). The measured concentrations of air pollutants (including ozone) were tested in combination and separately (Tables 21.C. and 21.D.), resulting in only a few significantly positive relationships. Total suspended particulates (TSP) directly affected the PEFR although this relationship was neither logical nor consistently present in the various permutations (Table 21.C.). Carbon monoxide (CO) directly affected medication use but this finding was also inconsistent. Ozone concentrations on day t, t-1, t-2, and t-3 (Table 21.D.) did not have a statistically significant effect on any respiratory variable. The lack of a statistically significant ozone effect persisted even when adjusting for medication use, symptoms and other respiratory variables on day t-1 (Tables 21.E. and 21.F.). As expected, symptoms and the other respiratory variables on day t-1 significantly influenced the same variables on day t, and thus, were more contributory to changes in respiratory variables than ozone. In summary, the multiple regression results indicated that ozone (and other air pollutants and environmental factors) did not significantly affect the respiratory variables of the 83 subjects as a whole.

3. Responders to Ozone

Subsets of the 83 subjects who were potentially responsive to ozone were identified using several approaches. An initial multiple regression analysis was performed on those subjects whose ozone coefficients on day t, t-1, t-2, and t-3 were in the top quartile for the dependent variable (i.e., symptom scores, AMI,

night PEFR, or day PEFR) (Table 21.G.). This analysis revealed significant and consistent effects of ozone on day t and t-1. This finding was not unexpected since the subjects were selected on the basis of their large regression coefficients for ozone. Although ozone on day t-2 was statistically significant for medication use and PEFR, its effects were not clinically consistent, e.g., a high ozone concentration on day t-2 was associated with high PEFR.

We then examined the effect of ozone in increasingly larger subgroups of individuals, based on their average coefficients for symptom score, AMI, day PEFR, and night PEFR, and adjusting for the previous day's value of the dependent variables (Table 21.H.). Thus, the 20 subjects with the highest average ozone coefficients were initially evaluated, then the 25 highest, 30, 35, etc., until 63 subjects were encompassed. This process was used to determine the potential size of the subgroups of subjects who had statistically significant ozone responsiveness. This analysis revealed that medication use (AMI) was not statistically related to ozone, even in the 20 subjects with the highest ozone coefficient with AMI as the dependent variable. On the other hand, respiratory symptoms and day and night PEFR were significantly and consistently influenced by ozone on day t and the dependent variable on day t-1 for as many as 63 subjects. This finding contrasts with the lack of a statistically significant overall effect of ozone for the entire sample of 83 subjects (Table 21.D.).

Twenty-seven subjects with one criterion (responders-1) and 12 subjects ("extreme" responders) with at least two criteria (responders-2) were ultimately selected as "responders" to ozone. As stated previously (Methods, Statistical Analysis), the two responder groups were defined by the presence of individual average slope coefficients for ozone greater than 0.674 standard deviations from zero in an adverse direction for symptom score, day PEFR, and/or night PEFR. The AMI was not used in defining these responders since medication use was not significantly related to ozone even in responders with the highest ozone coefficients (Table 21.H.). Subjects in the extreme quartile in at least one of these three outcome variables were designated as responders-1 (equivalent to "moderate" and "extreme" responders of the study population). Similarly, subjects with at least two variables were designated as responders-2 (equivalent to "extreme" responders). Multiple regression analysis of these two subsets of ozone responders was performed, adjusting for the value of the dependent variable on day t-1 (Table 21.I.). Both responders-1 and responders-2 showed highly significant and consistent ozone effects on symptoms, night PEFR, and day PEFR. The effect of the dependent variables on day t-1 was also significant in both groups of responders. Ozone did not affect medication use in either group.

These two groups of responders were also compared to the respective remainders of the 83 subjects to determine what factors

characterized the responders. Multiple characteristics from the baseline questionnaire and pulmonary function tests were compared by either nonparametric analysis (chi-square or Fisher's exact test) or one-way ANOVA with subsequent paired t-tests (Table 22). There were no significant differences in the subjects' demographic, clinical, or physiological data. The average values for symptom scores, day and night PEFR, and AMI during the study period also did not distinguish the responder group from the respective remainders of the study sample (Table 23), although the values for the mean symptom scores approached significance. The average AMI of the various groups during selected "smoggy days" (7/26/83-8/8/83 and 9/1/83-9/14/83) and "clean days" (4/15/83-4/28/83 and 11/16/83-11/30/83) also did not significantly differ. Responders also did not differ significantly from the other subjects in their time spent outdoors (12 noon to 6 P.M.) during both "smoggy" and "clean" weekdays and weekends (Table 24).

We also compared the same demographic, clinical, physiological, and psychological characteristics of the 20 "least responsive" subjects (with the smallest ozone coefficients) with those of the remaining 63 "more responsive" subjects (with larger ozone coefficients; see Table 21.H.). The variables listed in Tables 22-24 and 26 were similarly analyzed to determine if these 20 subjects were dramatically different from the other subjects in the study sample and to possibly account for the marked statistical differences between the 63 subjects (Table 21.H.) and the entire study sample (Table 21.D.). The results indicated no statistically significant differences for these variables except for two clinical features. Eighteen (90%) of the 20 "least responsive" subjects stated that their asthma was worsened by exercise, whereas 43 (68%) of the 63 remaining subjects had similar responses ($p = 0.046$, Fisher's exact test, 1-tail). On the other hand, only 13 (65%) of the 20 "least responsive" subjects stated that their asthma was worsened by "bad air," whereas 56 (86%) of the 63 remaining subjects had similar responses ($p = 0.013$, chi square).

As discussed in the Methods Section, the clinical significance of the respiratory responses, as predicted by the individual regression equations, was evaluated. Clinically significant adverse responses to 0.35 ppm ozone were considered to be: 1) an average increase of >1 unit in symptom score (on a 1 to 7 scale) or 2) an average decrease in the subject's day or night PEFR of >5% of the subject's respective averages over the study period. Based on these criteria, no clinically significant effect of ozone on symptoms during the study period was found from the individual regression equations. Similarly, no clinically significant effect of ozone on day or night PEFR was noted, except in eight subjects. Five of these subjects had >5% average decreases in both day and night PEFR. These individuals had relatively low average values for day (216 L/min; range 82 to 420 L/min) and night (219 L/min; range 84 to 414 L/min) PEFR and all but one subject were using either inhaled and/or oral corticosteroids on a daily basis. The three other subjects had

>5% average decreases in their night PEFR over the study period. Their average night PEFR was 208 L/min (range 81 to 288 L/min) and two of these subjects were using corticosteroids in addition to bronchodilators.

4. Psychological Associations

An indication of an association between ozone and psychological responses was demonstrated when the various symptom category scores in the Asthma Symptom Checklist (ASC) were related to the average slope coefficients for ozone from the multiple regression results using symptom score, day PEFR and night PEFR as the dependent variable (Table 25). The ASC scores of the 71 adults were classified as low (lower 25% of group scores), moderate (middle 50%), and high (upper 25%) and analyzed by two-way ANOVA (across symptom category and sex) of the slope coefficients for ozone. No significant effect of sex on the slope coefficients for ozone was found. However, subjects with high ASC scores for fatigue, hyperventilation, dyspnea, congestion, and rapid breathing (based on Kinsman's model) had a significant and consistent tendency to have low (i.e., more negative) slope coefficients for ozone (for day and/or night PEFR as the dependent variable) than the other subjects. In other words, subjects with selected high symptom category scores in the Asthma Symptom Checklist had their day and/or night PEFR more negatively affected (i.e., worsened) by ozone than subjects with low or moderate ASC scores.

Psychological test results for the 71 adult subjects were then analyzed by comparing the scores (t-tests) of the two responder groups and the remaining subjects (Table 26). The Asthma Symptom Checklist (ASC) was evaluated according to both this study's factor analysis and the model presented by Kinsman and coworkers (15). Significant differences ($p<0.05$) were observed for C2 (fatigue) in the responders-1 group and C7 (hyperventilation) in the responders-2 group according to this study's factor analysis of symptoms. Significant differences were observed for C3 (fatigue) and C10 (rapid breathing) in the responders-1 and for C10 (rapid breathing) in the responders-2 group according to Kinsman's model. The responders consistently had higher scores than the other subjects for these symptom categories. The responder groups did not significantly differ from the remaining subjects in their results from the Panic-Fear Symptom Scale and State-Trait Anxiety Inventory.

DISCUSSION

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DISCUSSION

The results of this longitudinal population study indicate that clinically relevant respiratory effects of ambient oxidant air pollution (with daily maximum hourly average concentrations <0.12 to 0.38 ppm ozone) were either 1) difficult to detect by the methodology of the study and/or 2) were relatively minimal in a large group of free-living asthmatics residing in an impacted area. However, analysis by multiple regression testing indicated that the majority of asthmatics was statistically (but not clinically) sensitive to fluctuations in ozone concentrations on the basis of symptom scores and PEFRs. These "responders" were similar to the other subjects of the group in most respects except for some psychological variables. The significance and limitations of our findings are now discussed.

A. Exposure to Ozone

The study area (Glendora, CA) appeared to provide a sufficient number of days with exposure to high (and low) ozone concentrations for analysis, with 128 days (55.6%) having $\geq$0.12 ppm O_3 and 63 days (27.4%) having $\geq$0.20 ppm O_3 (daily maximum hourly average concentration; Figure 1). Concurrent ozone data from the two local monitoring stations were highly correlated, supporting the validity and accuracy of the measurements. The 83 subjects lived within a four-mile radius of either monitoring station. Those subjects who traveled to work commuted approximately 5 miles each way (median value, Table 2). This relatively short distance (and travel time) from Glendora probably had minimal effect on the total ambient exposures to ozone since all commuting regularly occurred during morning (e.g., 7 to 8 A.M.) and evening (after 5 P.M.) hours and the community air quality within a 5-mile radius of Glendora is more or less equivalent. The average time spent outdoors by the subjects in the afternoon (the usual time for maximum ozone concentrations) was 2.3 hours/subject on weekdays and 3.2 hours/subject on weekends and was not statistically related to the presence or absence of a smog alert. However, these correlations were derived from biweekly (not daily) information and were retrospective in nature, suggesting the possibility of both under- and over-estimations. In addition, the exact nature of the outdoor activities was not determined.

Although the subjects were exposed to multiple air pollutants and potential aeroallergens in their daily outdoor activities, ozone was frequently increased above California and other air quality standards in the study area. Multiple regression testing with air pollutants other than ozone, aeroallergens, and other environmental factors as independent variables (Table 21) did not show statistically significant or clinically relevant effects on the respiratory status of the group.

B. Diagnosis of Asthma

Subjects with bronchial asthma were considered to be a desirable study population at risk for ozone-related respiratory effects. These individuals are assumed to have reversible or fluctuating bronchospasm and airways reactivity which would be apparent subjectively and objectively with concurrent variations in atmospheric ozone concentration. However, an acceptable definition of asthma is controversial and elusive at this time (32), which complicates the accurate diagnosis of this disorder in any study. The patient with a history consistent with asthma (i.e., episodic chest tightness, shortness of breath, cough, or wheezing) would generally be considered to have this disorder on clinical grounds (5). Physiological documentation of reactive airways (as observed in asthma) by either significant bronchodilation or bronchoconstriction (or both) following an inhaled beta-agonist or methacholine, respectively, would probably confirm the diagnosis of asthma. Subjects with chronic bronchitis and/or pulmonary emphysema would usually demonstrate minimal changes in airway reactivity with the pharmacologic techniques used in this study.

In this study the physiological confirmation of reactive airways was only partially successful. Forty-three (51.8%) of the 83 subjects had normal baseline FEV_1 ($\geq$80% of predicted FEV_1), and the remaining 40 subjects had mild-to-severe obstructive ventilatory defects on pulmonary function testing (Table 4). Only 10 of 65 subjects who received bronchodilator testing showed $\geq$15% increase in FEV_1 (Table 5). An additional 15 subjects increased their post-bronchodilator FEV_1 by 10-14%. Thus, the remaining 40 tested subjects responded with <10% increase in FEV_1 following bronchodilator inhalation, despite repeat testing during a subsequent visit to the laboratory.

The reason for the lack of a significant bronchodilator response in most of the tested study population is not clear but may relate to several possibilities. First, asthmatic subjects with a normal baseline FEV_1 (which may be present in asthma in remission) will generally increase their FEV_1 <10% following acute bronchodilator inhalation as compared to patients with more decreased baseline values of FEV_1 (33,34). Although the subjects were routinely asked to discontinue their anti-asthma medication and coffee use for at least 8 hours prior to baseline pulmonary function testing, it is problematic whether or not all the subjects did so. The presence of continued bronchodilator medications and xanthine-containing foods may blunt or decrease the effect of inhaled bronchodilators during pulmonary function testing. Serum theophylline measurements (in subjects taking theophylline compounds) and pre-screening monitoring with the Nebulizer Chronolog might have been helpful in this regard but were not used in this study. Finally, patients with active asthma may not bronchodilate acutely due to the presence of "fixed" air flow obstruction secondary to airway secretions, inflammation, and edema which are not directly affected by bronchodilators.

Neither the bronchodilation nor bronchoconstrictive procedures could be performed in 18 subjects who were judged medically inadvisable for either procedure or who refused (Table 5). Most of the refusals were from the parents of young subjects, despite the fact that the subjects were using MDIs on a maintenance or as-needed basis. The parents also refused to withdraw the anti-asthma medications prior to baseline pulmonary function testing.

Methacholine bronchoprovocation (11) was not performed in the large majority of subjects due to practical limitations, refusal by the subjects (or parent), and medical contraindications (e.g., baseline FEV_1 <70% of predicted). Of interest is that all subjects (five) who volunteered for the methacholine challenge showed positive results for airway reactivity (i.e., decreased FEV_1). Routine skin testing for acute hypersensitivity to allergens and measurement of serum immunoglobulin E were initially considered but not implemented since positive results do not necessarily correlate to the presence of asthma (35) and asthma in many patients is not allergically-mediated (36).

The final study population of 83 subjects was, therefore, primarily defined as "asthmatic" on the basis of a clinical history (or medical records) consistent with asthma, according to guidelines of the American Thoracic Society (5), and the reported use and benefit of anti-asthma medications. All subjects had a history consistent with active asthma (present for an average of 18 years), were told of the diagnosis of asthma by a physician, and were using at least a MDI for delivery of a bronchodilator. Sixty-six subjects (80%) had visited a physician for asthma on an average of 7.6 times in the previous year. The anti-asthma medications were generally prescribed except for 11 subjects who used an over-the-counter inhaler, Primatene Mist. In fact, 62 subjects (74.7%) were using prescribed anti-asthma medications (in addition to the MDI) during the early part of the study (Table 6). The pattern of medication use remained fairly constant (except in six subjects) when it was evaluated during the end of the study (Table 6). Eight of the 91 subjects who concluded the study (Table 1) were ultimately excluded from analysis because they showed no evidence of changing asthma (i.e., virtually no asthmatic symptoms and use of anti-asthma medications) during the study period. Thus, the final 83 panelists were considered to have asthma of varying severity according to historical and clinical indices.

Another indirect indication that the study population had asthma was observed in other physiologic data. A decreased $FEF_{25-75\%}$ (<80% of predicted) was observed in 60 subjects (72.3%) during baseline pulmonary function testing. Although this finding may be nonspecific, its presence is common in stable, asymptomatic asthmatics with normal FEV_1 and in the absence of other respiratory disorders and chronic smoking. Although cigarette smoking affects primarily small airways (resulting in decreased $FEF_{25-75\%}$) and promotes the development of chronic obstructive

pulmonary disease, it is unlikely that chronic bronchitis or pulmonary emphysema was present or frequent in the study sample since the average age of the subjects was 32 years (median, 30 years) and there were only seven current smokers. Two of the seven current smokers in the study population had normal $FEF_{25-75\%}$.

C. Possible Selection Biases

It is difficult to determine whether or not the study sample was significantly biased by the selection process or other factors such as the study location, duration of the individuals' participation, or participation fee. The residents of the Glendora area were primarily middle-class Caucasians, and the available demographic and socioeconomic data obtained from the subjects suggest that a fairly representative group of individuals was recruited.

Our study sample originated from two previous epidemiological studies (6,7) and local advertisements. The residents of the study area probably have greater interest or concern about their local air quality than citizens in communities with relatively low concentrations of air pollutants. This awareness is probably related to the occurrence of frequent episodes of poor air quality in the area and daily announcements regarding air quality from newspapers, radio, and television.

Despite the lengthy duration of the study a relatively large proportion (91 out of 109 subjects) persisted in this project due in part to the subjects' interest and the excellent rapport established between the panelists and the laboratory staff in Glendora. The participation fee was generally not provided until the subject completed his/her participation, although several subjects were given partial payments during the course of the study.

Finally, the 26 excluded subjects (Table 1) did not significantly differ from the final 83 subjects in demographic, clinical, and physiological data (Tables 1-4) except for a higher frequency of coexisting atopy in the excluded subjects. As discussed previously, the final 83 subjects appeared to satisfy appropriate clinical criteria for asthma, with a wide range of severity and medication use, which would be expected in a large free-living population of asthmatics. Thus, the study sample was, as well as could be determined, a representative group of asthmatic individuals residing in an ozone-impacted area.

D. Data Exclusions

The editing and exclusion of some data were considered necessary and did not appear to bias the results. In addition to limiting the data analysis to 230 days (April 15 to November 30), we further excluded data obtained during the study period for two reasons: 1) inadequate exposure to the study area's air quality

(i.e., travel outside the area for most of the afternoon or for greater than 12 hours and hospitalizations), and 2) possible exacerbation of asthma as a result of mechanisms unrelated to air quality (i.e., viral respiratory syndromes or colds, for two weeks following the onset of each episode).

The data exclusion process eliminated a significant number of subject-days from analysis to prevent or minimize possible influence by confounding variables. The inclusion of these data would possibly produce false-positive or -negative results regarding ozone-related effects on respiratory status and thus, make a firm, valid conclusion about cause-and-effect more tenuous. Although some appropriate data may have been excluded, the remaining 16,151 analyzable subject-days (or an average of 195 days per subjects) were considered to provide the most relevant and suitable data, as well as a quantitatively sufficient data base, for further analysis.

E. Medication Reporting and the Nebulizer Chronolog

The validity of symptom and medication reporting in personal diaries is a controversial issue and was evaluated in several ways in this study. For example, it was found that today's AMI and yesterday's symptoms significantly correlated (as expected) much more than today's symptoms and yesterday's AMI. The use of the MDI (according to diary recordings) also significantly correlated with the number of asthma attacks during the day and night (Table 19).

Whereas the validity of daily recordings for anti-asthma medication in tablet form remains problematic, the concurrent use of the Nebulizer Chronolog (NC) provided an objective, independent measure of MDI actuations and could be compared to and validate diary recordings of MDI usage. The MDI was considered an important form of medication administration in this group of patients since the MDI is the most frequently used as-needed medication for rapidly relieving acute asthmatic symptoms. In this study, at least 66 subjects predominantly used their MDI on an as-needed basis rather than as part of a daily maintenance regimen. Comparison of concurrent MDI data from the daily diary and NC (Table 16) indicated that the diary recordings agreed very well in at least 60 (80%) of the 75 subjects analyzed. The NC also indicated that 15 subjects largely under- or overused their MDI on most days as compared to concurrent diary recordings. The extent and frequency of agreement between the diary and MDI recordings were higher than expected and probably reflected the conscientiousness of most of the subjects in completing the diary. These findings generally support the internal consistency and logical relationships of the symptom scores, AMI, and, in particular, MDI usage and indicate that the NC can be a useful, objective monitor of MDI use and patient compliance (37).

F. Performance of the Nebulizer Chronolog

The utility of the NC in epidemiological studies must be tempered by the NC's technical performance in this lengthy study. Unfortunately, the NC malfunctioned at various times during the study for 1/2 to 2 or more months in at least 34 subjects. Technical malfunction were particularly troublesome since the turn-around time for repairs by the manufacturer was relatively slow (several weeks to over a month) and substitute NCs were not provided by the manufacturer. On the other hand, several subjects excessively used their MDI, resulting in memory overflow in the NC and lost data. This problem occurred even when these subjects returned to the laboratory (for resetting of the NC) within two-week intervals. As a result, data during approximately 2,578 subject-days (14%) out of a possible 18,847 subject-days were lost due to one or more of the above problems. Nevertheless, 73 subjects still had >90% useful NC days for analysis, indicating that major technical problems were related to specific NCs rather than to subject misuse or underuse.

The use of the NC in this study involved greater numbers of users and a longer duration of operation than previously reported (13,14,37). Although the NC was used in a smaller (41 subjects) and shorter (3 months) epidemiological study (13,14), the performance record or reliability of the device was not reported. Overall, the NC would appear to be useful in population studies requiring frequent, objective measurement of MDI usage. However, technical problems and other limitations (e.g., memory overflow) may occur and hopefully can be corrected by improved NC components or more frequent visits to the laboratory or office for resetting. The NC will not replace the daily diary when medications are taken by routes other than inhalation and need to be monitored.

G. Asthmatic Status During Study Period

The study population as a whole had relatively mild or stable asthma during most of the study period. This clinical impression is supported by the results of the overall daily symptom scores (Table 13), asthma medication index (AMI) (Table 14), and use of the MDI according to both diary reporting and the Nebulizer Chronolog (Tables 15 and 16). In addition, the majority (77%) of subjects had average PEFR values which were within the normal predicted range or mildly decreased (Table 18) during the study period. Day and night PEFRs were significantly higher when the daily maximum hourly average concentrations of ozone were 0.12 - 0.19 ppm but lower when ozone concentrations were <0.12 ppm (Table 20). This finding may be of statistical rather than of clinical significance since the PEFRs during low ozone concentrations (<0.12 ppm) were worse (more decreased) than during higher ozone concentrations (>0.20 ppm). There were also no statistically significant differences (by two-way ANOVA across ozone concentrations and subjects) in symptom scores and AMI by subject during low (<0.12 ppm), moderate (0.12-0.19 ppm), and high ($\geq$0.20 ppm) ranges of daily maximum hourly average concentrations of ozone (Table 20).

The lack of a significant overall group effect by ambient ozone on respiratory variables was also supported by multiple linear regressions across time (Table 21.D.-F.). Despite numerous permutations, including lagging of time and evaluation of numerous independent and consistent variables in addition to ozone, a statistically significant overall relationship between respiratory status and ozone was not found, despite the perception in 69 (83%) of the 83 subjects that smog worsened their asthma.

H. Multiple Regression Approach

We initially considered (and then rejected) using the logistic regression approach (25,26) as a primary method of evaluating ozone-related respiratory effects. This technique fits a logistic regression equation to each individual's daily measurements over time (25,26). The dependent variable may be the presence or absence of an asthmatic attack on day t, while the independent variables may include total suspended particulates, temperature, humidity, day of study, day of week on day t, and asthma status on day t-1. Weighted averages of the regression coefficients are then taken across all study subjects and tested to see if they are significantly different from zero.

However, the logistic regression method is restricted to a binary (yes or no) scale for the dependent variable (e.g., asthmatic attack, present or absent) and cannot adequately manage interval or continuous dependent data which are commonly measured in epidemiologic studies (27). The logistic method may lose significance if continuous data are forced into a binary system. For example, data for PEFR and symptom and medication scores (such as used in our study) consist of interval scales or continuous data. Although the symptom rating scales used in many studies are ordinal, it is, nonetheless, reasonable to treat the data as if they are interval values rather than arbitrarily collapsing them into simple yes-no consequences. Furthermore, the definition of an "asthmatic attack" is arbitrary and subjective since some asthmatics may have continuous "attacks" of asthma and cannot distinguish different levels of severity.

Thus, we ultimately considered it advantageous and possibly more sensitive and flexible to evaluate the outcome variables with a least squares regression model rather than with a logistic technique. The multiple regression technique as applied in this study was probably the most powerful statistical method of analysis currently available (27). This strategy has broad application to more data sets in epidemiological studies in which interval or continuous data are available and the difficult interpretation of an asthmatic "attack" can be avoided.

I. Subsets of Ozone Responders

Multiple regression analyses of different subsets of subjects revealed statistically significant relationships between ozone concentrations and adverse respiratory responses. Subjects whose

ozone coefficients on various days (t, t-1, t-2, and t-3) were in the top quartile for dependent variables (respiratory measures) showed statistically significant and consistent effects of ozone on day t and the previous day (t-1) (Table 21.G.). Subsamples as large as 63 subjects had highly significant ozone coefficients in the regressions of symptom score and day and night PEFR (Table 21.H.). This finding is noteworthy since there was no significant overall effect of ozone on the same respiratory variables in the entire sample of 83 subjects (Table 21.C.-F.). Thus, consistent and statistically significant relationships exist between ambient ozone concentrations and adverse asthmatic response in a substantial proportion of a population of predominantly mild asthmatics residing in a high-ozone area. The finding of statistically significant adverse relationships for a large subset of asthmatics is notable because of the well-known difficulty in characterizing asthmatics and the large temporal variability in their respiratory responses.

We also examined numerous demographic, clinical, physiological, and psychological characteristics of the remaining 20 "least responsive" subjects and could find no helpful or statistically differentiating features except for asthma worsened by exercise and air pollution. Although more of these subjects noted exercise-induced asthma, it is interesting that fewer of the 20 subjects (65%) had noted pollution-related asthma than the other 63 subjects (89%). Although one might infer that the "least responsive" subjects do not perceive a relationship between their asthma and air pollution, the clinical significance of this single finding remains uncertain in relation to the numerous negative or unremarkable results for the remaining analyzed variables.

The variable nature of asthma, the difficulty in defining asthma, and the contrasting regression results (Table 21.C.-F. and Table 21.H.) prompted an evaluation of the "most responsive" subjects. Multiple regression testing also enabled us to determine two subgroups of "responders" to ozone (responders-1 and responders-2, i.e., as defined by a slope coefficient for ozone of >0.674 standard deviations from zero, for at least one or at least two of the following outcome variables: symptom score and day and night PEFR). Regression analyses of these two groups (Table 21.I.) confirmed highly significant ozone coefficients for symptoms and day and night PEFR. These two groups were then compared to the remaining subjects according to demographic, clinical, physiological, and psychological characteristics (Tables 22-25). However, no significant differences were observed between the responder groups and the remaining subjects, i.e., one could not distinguish a responder (even an "extreme" responder) to ozone from the rest of the study group. Specifically, neither responder group (responders-1 and -2) was different from the "less responsive" subjects according to duration of residence in the Glendora area, age, baseline pulmonary function, AMI (including scores on clean and smoggy days), corticosteroid use, symptom score, PEFR, or time spent outdoors between 12 noon and 6 P.M.

The responses in symptom score, day PEFR, and night PEFR, as predicted by the individual regression equations of ozone, were evaluated for their clinical significance. The criteria for "clinical significance" were difficult to accurately define and required assumptions that took into account the high frequency of daily measurements over the 230-day study and known daily, weekly, and monthly fluctuations of respiratory symptoms and physiologic measures (i.e., PEFR) in asthmatic individuals. We considered either an average increase of >1 unit in symptom score (on a 1 to 7 scale) or an average decrease of >5% in a subject's day or night PEFR (compared to the subject's respective averages over the study period) to be clinically significant adverse effects. These respiratory changes were compared to a corresponding change of 0.35 ppm ozone which was in the approximate range over which ozone concentrations generally varied during the study. The results indicated that there were no significant effects of ozone on symptoms and, in general, on day or night PEFR during the study period, according to the above criteria. Specifically, no subject had evidence of clinical worsening of symptoms as related to the range of ozone levels present in the study. There were similar results with the day and night PEFR. However, eight subjects had small but clinically relevant coefficients for ozone in both day and night PEFR. Of interest is that six of eight affected subjects were using corticosteroids (as well as bronchodilators) on a daily basis and had relatively low average day and/or night PEFR during the study, indicating the presence of significant asthma. Thus, it appears that almost all of our subjects had clinically nonsignificant respiratory effects from the ambient ozone present in the study and that a small subset of subjects had clinically worsened PEFR during the study period.

J. Psychological Findings

We found significant relationships when the adult subjects were categorized according to low, moderate, and high scores on the Asthma Symptom Checklist (ASC) and two-way ANOVA was performed on the slope coefficients for ozone, across sex and the category scores (Table 25). There was a significant and consistent tendency for the subjects with high scores for fatigue, hyperventilation, dyspnea, congestion, and rapid breathing (as defined by Kinsman's model) to have low (i.e., more negative) slope coefficients for ozone (from multiple regressions using day and/or night PEFR as the dependent variable) than in subjects with low and moderate scores. In other words, ozone was associated with statistically significant worsening (i.e., decrease) in day and night PEFR in the subjects with several high ASC scores.

The battery of psychological tests (Table 26) was generally not helpful in distinguishing the responder groups from the "less responsive" subjects ($p > 0.05$, by t-tests). The exceptions were the ASC categories of fatigue ($p = 0.04$) and hyperventilation ($p = 0.01$) (according to this study's factor analysis) and fatigue ($p = 0.04$) and rapid breathing ($p = 0.02$ and 0.002) (according to Kinsman's model). However, the higher scores of the responders in

the respective ASC categories were not associated with ambient ozone since the test scores were similar during relatively low and high ozone days.

The significance of the psychological results in this study is not known as yet and will be the subject of subsequent, more detailed analyses. Oxidant air pollution was apparently not a significant determinant of the ASC or other psychological test results since the scores for each individual were similar when the battery of tests was administered during times of good and poor air quality. Results of similar psychological testing in asthmatics participating in other epidemiological studies dealing with air pollution (13,14) have not been reported to date. Experience with the ASC and Panic-Fear Symptom Scale has only been reported from one medical center and has been based on the perceptions of recovering asthmatic inpatients (14-17).

Although the testing techniques and scores of these psychological tests have not yet been reproduced or confirmed by other groups of investigators, we assumed that the symptoms perceived by the original group of patients (14-17) would be similar and applicable to stable, free-living or nonhospitalized individuals with asthma of varying severity. Indeed, the resulting ASC symptom categories in this study were very similar to those reported by Kinsman and coworkers (15). The psychological scores do not necessarily reflect cause-and-effect, but it has been appreciated for some time that there is a strong association between psychological characteristics and asthmatic status, from both clinical (14-17) and physiological (38,39) perspectives.

K. Other Possible Factors

The inability to demonstrate a positive clinical relationship between oxidant air pollution and the respiratory status in a group of asthmatics and to characterize the individuals with the highest ozone-related "sensitivity" does not necessarily mean that such relationships do not exist. As discussed previously, we do <u>not</u> believe that the following factors significantly contributed to the outcome of this study: a study cohort which was either too small in number, inappropriate for the purpose of investigation, or selected with obvious bias; inadequate air pollution or outdoor exposure (within the limits of this epidemiological study); excessive lost or excluded data; inaccurate diary reporting; consistently high medication use by most of the subjects which might offset any asthmogenic stimulus, including ozone exposure; inadequate adjustments for confounding variables; and weak statistical analysis. It remains possible, however, that future statistical methods may be developed which are more powerful and revealing that those currently available. The contributions of certain "asthmogenic" occupational and indoor (e.g., gas appliances) and personal (e.g., smoking) pollution were apparently small since either very few subjects or almost the entire group were associated with these factors. Temperature, humidity,

barometric pressure, and airborne pollens, spores, and other materials collected by the Roto-Rod sampler did not appear to influence asthmatic symptoms, medication use, or PEFR in this study (Table 21).

Thus, other factors which may have influenced our results should be considered. Asthma is a heterogeneous syndrome (32) and not all asthmatic individuals respond with bronchoconstriction to the same stimuli. As in any large population study, subsets of responders should be evaluated to determine the frequency or magnitude of their response to asthmogenic stimuli. Our analysis (excluding psychological markers) could not clinically differentiate the responders to ozone from the remaining subjects.

Although the baseline and other characteristics of the responder groups were not statistically different from the other asthmatics in the study, the great majority of the subjects appeared to have clinically mild or stable asthma, according to several analyses. The presence of such large numbers of mild or stable asthmatics may have minimized or precluded finding significant relationships between respiratory status and ozone. This is supported by our finding that 90% of our subjects had clinically nonsignificant respiratory effects from ambient ozone levels. We initially hypothesized that subjects with mild asthma (the majority in this study) might be less responsive to ozone as a group and that subjects with moderate-to-severe asthma (but also more medicated) might be more sensitive. Although, we did not exclude subjects with moderate-to-severe asthma in the study, we apparently enrolled primarily mild asthmatics as a result of our recruitment efforts. It is possible that a similar study in subjects with primarily moderate-to-severe asthma might result in more frequent clinically (as well as statistically) significant findings in relation to ozone levels.

Although the study period of 230 days had 60 days with stage 1 alert levels (SCAQMD), only three days were above 0.35 ppm O_3, suggesting that the subjects may not have been sufficiently exposed to an ambient ozone threshold level required to produce significant increases in symptoms and medication use and decreases in PEFR. The air quality present during the study was, of course, unpredictable and the product of both atmospheric conditions and ongoing local environmental regulations. However, this study, in the presence of more days with exposure to stage 2 levels of ozone, might have found a more positive clinical relationship between ozone and respiratory status. Along these lines, controlled environmental chamber studies (40,41) have exposed small numbers of medicated asthmatic volunteers to 0.2 ppm O_3 for two hours and have found no significant symptomatology or adverse changes in FEV_1 as compared to control exposures with filtered air. The volunteers had minimal to moderately severe asthma (40,41), suggesting that the number of subjects was inadequate to detect effects or that the subjects were not exposed to a sufficiently high dose of ozone to cause significant responses.

The subjects in this study may also have developed behavioral and/or physiological "adaptation" or "tolerance" to air pollution (42-45). Behaviorally, subjects may stay indoors and reduce their participation in outdoor activities on smoggy days, thus reducing their exposure and likelihood of ozone-related morbidity. We could not find significant differences in the time spent outdoors on weekdays and weekends or during clean air and smoggy conditions. This was also true when we examined the responder groups and the remaining subjects. On the other hand, symptomatic and physiological "adaptation" may occur in normal subjects (42,43) and in chronic bronchitics (44) repeatedly exposed to ozone in controlled chamber studies. Although tolerance to chronic exposures to air pollution in a large, free-living population is not documented, it is conceivable that the study population (or subsets) may have developed at least partial tolerance since the average residence time in Glendora was 8.5 years. Chamber studies using controlled ozone exposures in the responders and remaining subjects of this study might provide further insight into this possibility.

An important corollary of adaptation to oxidant air pollution is that not all individuals may develop such a "protective" mechanism (45), particularly in those who are most sensitive. Although this study was not designed to evaluate the effects of out-migration, it is possible that the most responsive asthmatics no longer lived in the study area and moved elsewhere prior to the initiation of the study. Out-migration would then possibly result in a selected local population which was able to somehow "tolerate" air pollution and exhibit few clinical problems related directly to oxidant exposure. This provocative speculation may be an important confounding factor in epidemiological studies of air pollution.

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Gong H Jr, Tashkin DP, Simmons MS, Coulson AH, Clark VA, Spivey GH, Sayre JW. Relationship between oxidant air pollution and respiratory status of asthmatics in Los Angeles County: methodology and study sample. Evaluation of the Scientific Basis for Ozone/Oxidants Studies. Lee SD (editor). Pittsburgh, PA: Air Pollution Control Association. 1985. pp. 226-237.

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GLOSSARY OF ABBREVIATIONS

AMI	asthma medication index
ANOVA	analysis of variance
ASC	asthma symptom checklist
CARB	California Air Resources Board
CO	carbon monoxide
$FEF_{25-75\%}$	forced midexpiratory flow
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
HC	hydrocarbons
MDI	metered-dose inhaler
NC	Nebulizer Chronolog
NO_x	oxides of nitrogen
NO_2	nitrogen dioxide
O_3	ozone
p	significance level
PEFR	peak expiratory flow rate
pphm	parts per hundred million
ppm	parts per million
r	correlation coefficient
SCAQMD	South Coast Air Quality Management District
SD	standard deviation
SEM	standard error of the mean
SO_2	sulfur dioxide
STAI	State Trait Anxiety Inventory
STAIC	State Trait Anxiety Inventory for Children
TSP	total suspended particulates
UCLA	University of California at Los Angeles

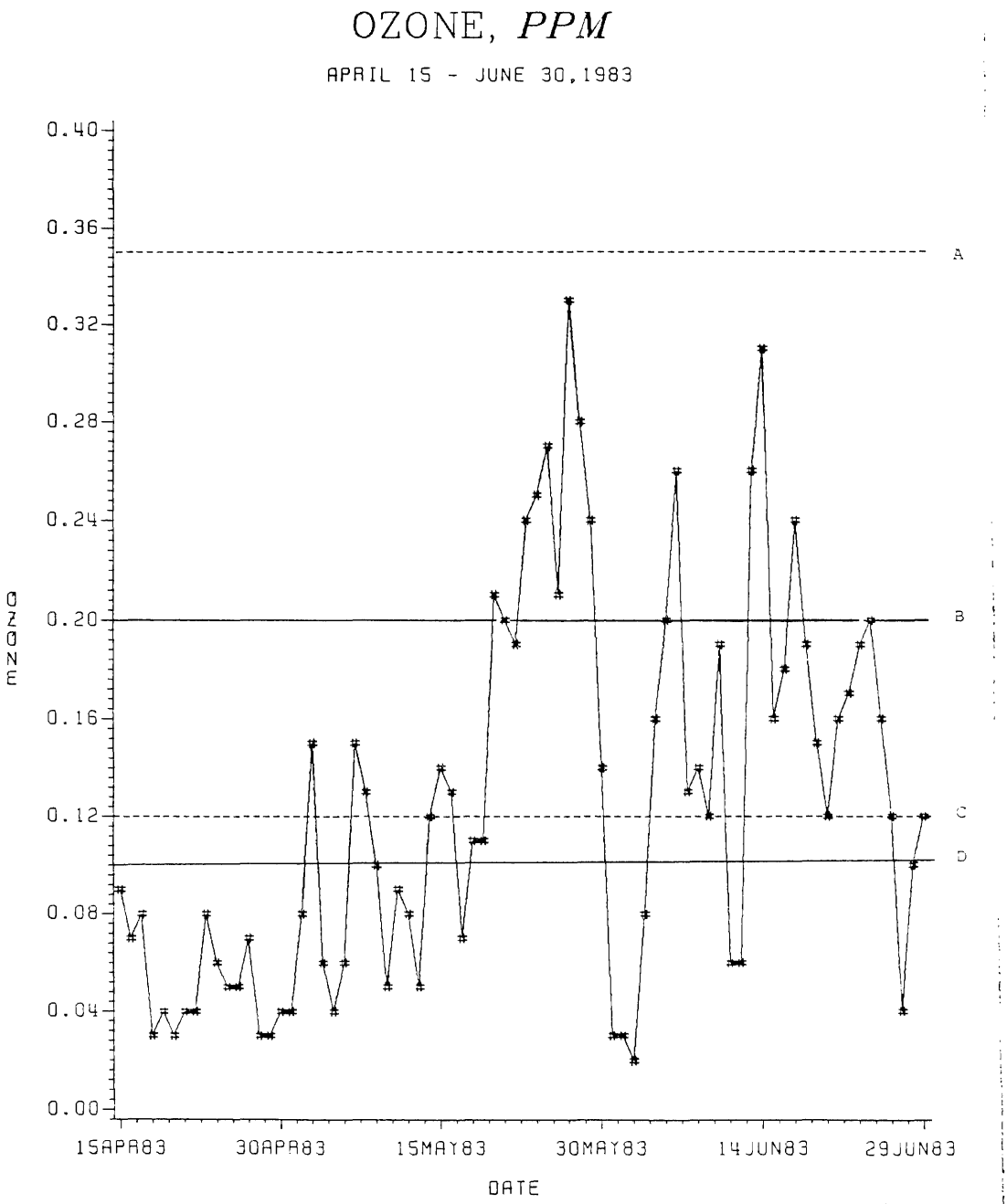


Figure 1A. Daily maximum hourly average concentrations of ozone (O_3) in parts per million (ppm) in Glendora area. Line A represents the SCAQMD Stage 2 Health Advisory; line B, the SCAQMD Stage 1 Health Advisory; line C, the National Primary Standard; and line D, the California Air Quality Standard.

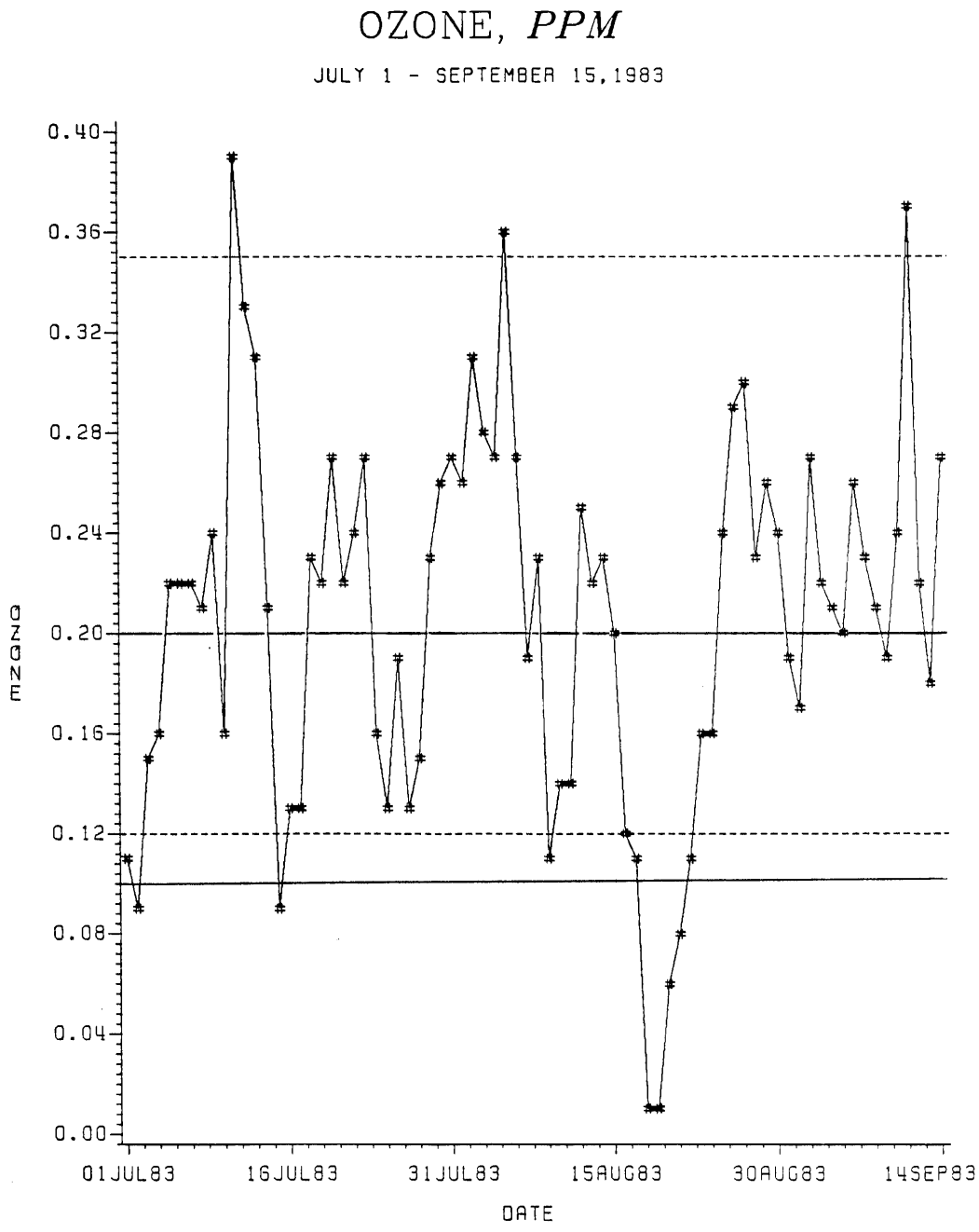
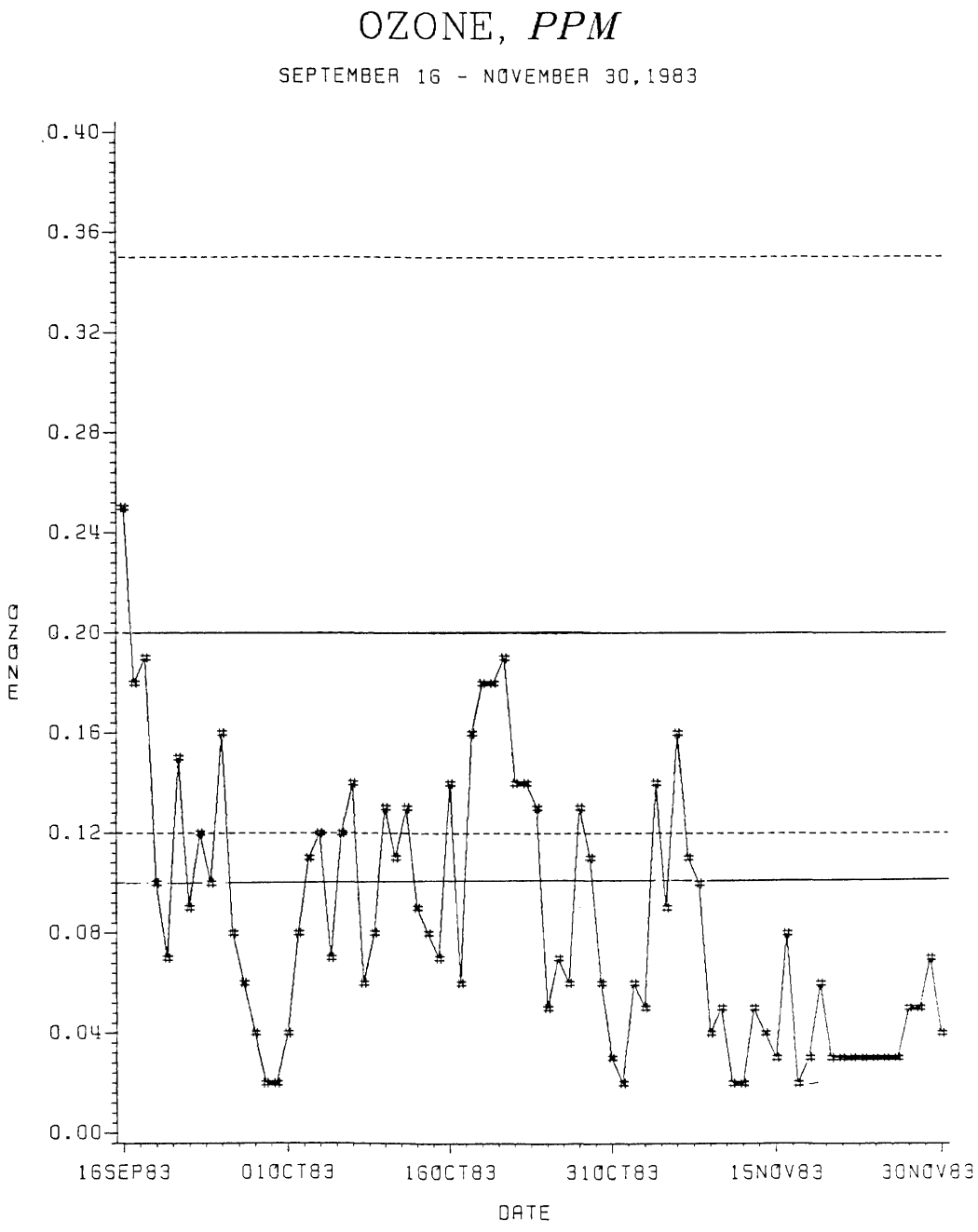

OZONE, PPM
JULY 1 - SEPTEMBER 15,1983
0.40
0.36
0.32
0.28
0.24
0.20
0.16
0.12
0.08
0.04
0.00
OZONE
01JUL83
16JUL83
31JUL83
15AUG83
30AUG83
14SEP83
DATE

Figure 1B.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0.12
0.08
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OZONE
16SEP83
01OCT83
16OCT83
31OCT83
15NOV83
30NOV83
DATE

Figure 1C.

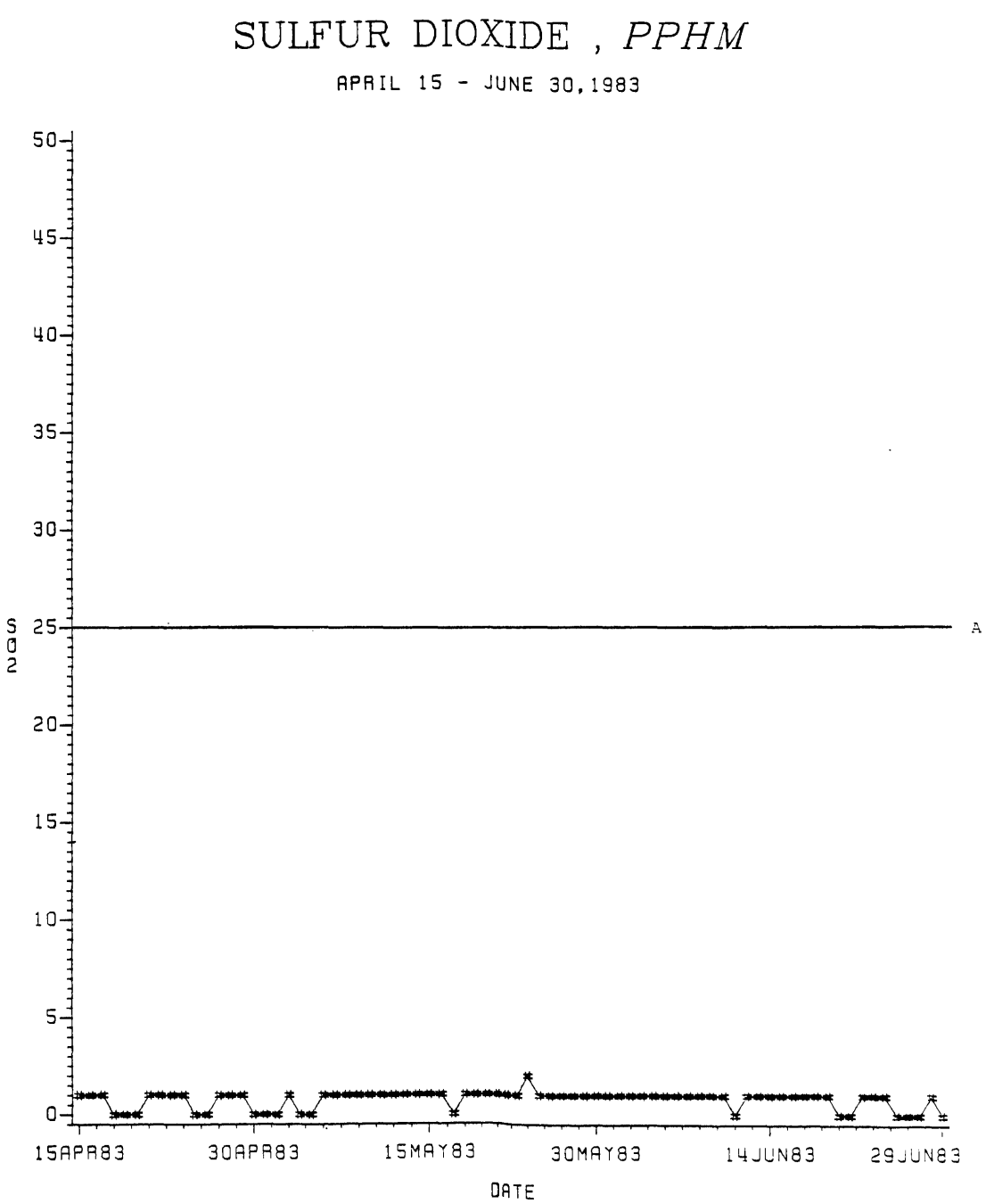
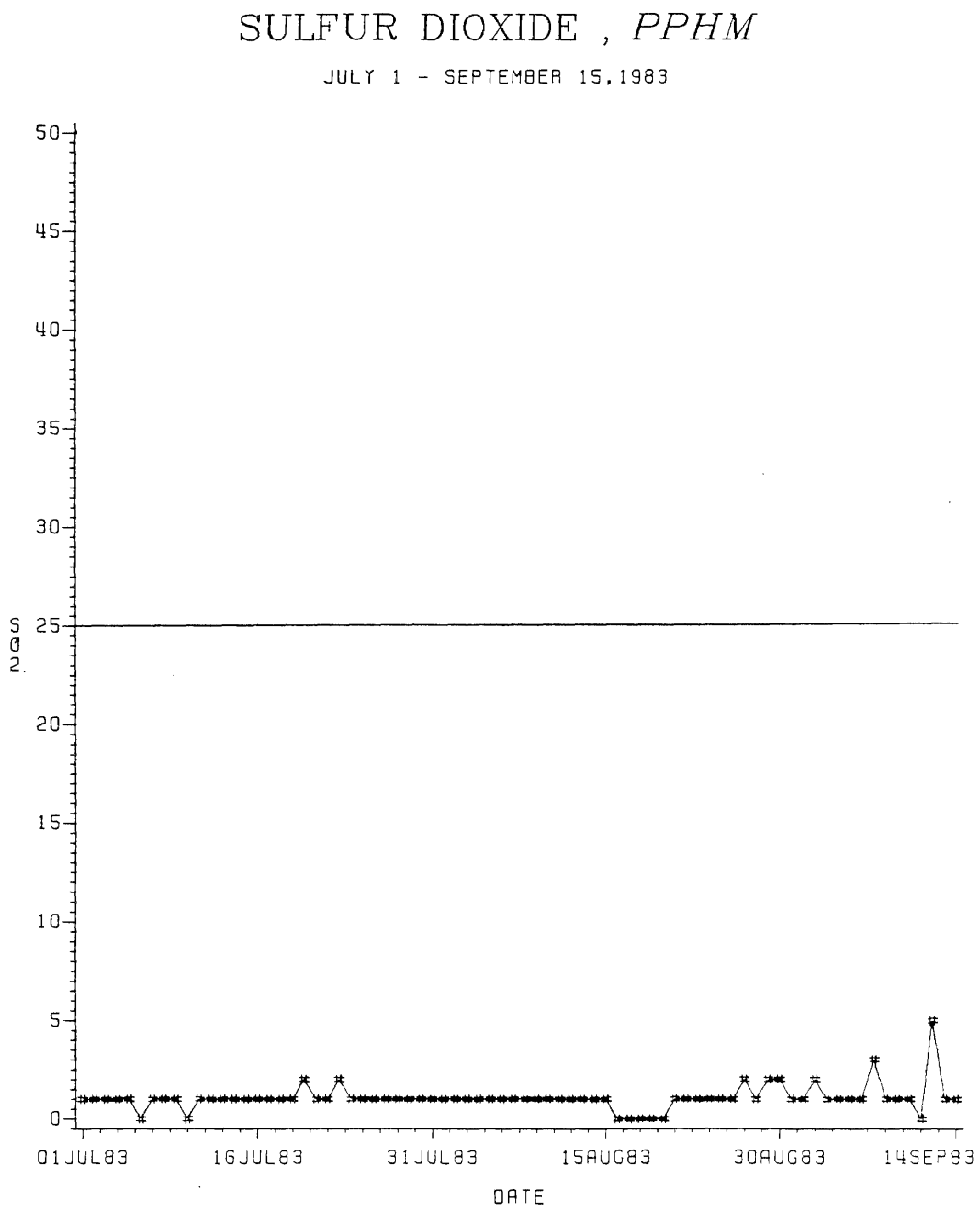


Figure 2A. Daily maximum hourly average concentrations of sulfur dioxide (SO_2) in parts per hundred million (pphm) in Glendora area. Line A represents the California Air Quality Standard.


SULFUR DIOXIDE , PPHM
JULY 1 - SEPTEMBER 15,1983
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45
40
35
30
25
20
15
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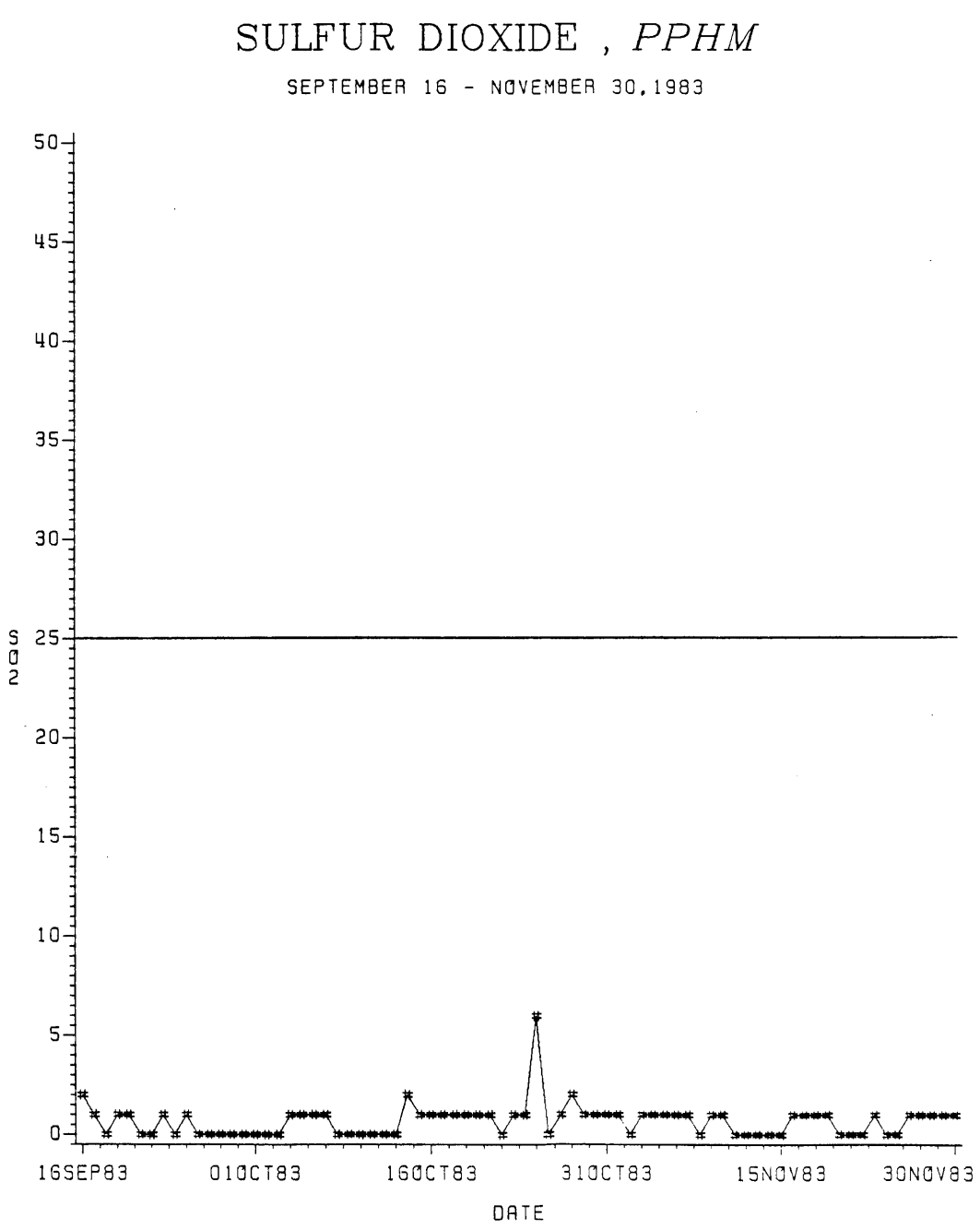
SO2
01JUL83
16JUL83
31JUL83
15AUG83
30AUG83
14SEP83
DATE

Figure 2B.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SEPTEMBER 16 - NOVEMBER 30,1983
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SO2
16SEP83
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DATE

Figure 2C.

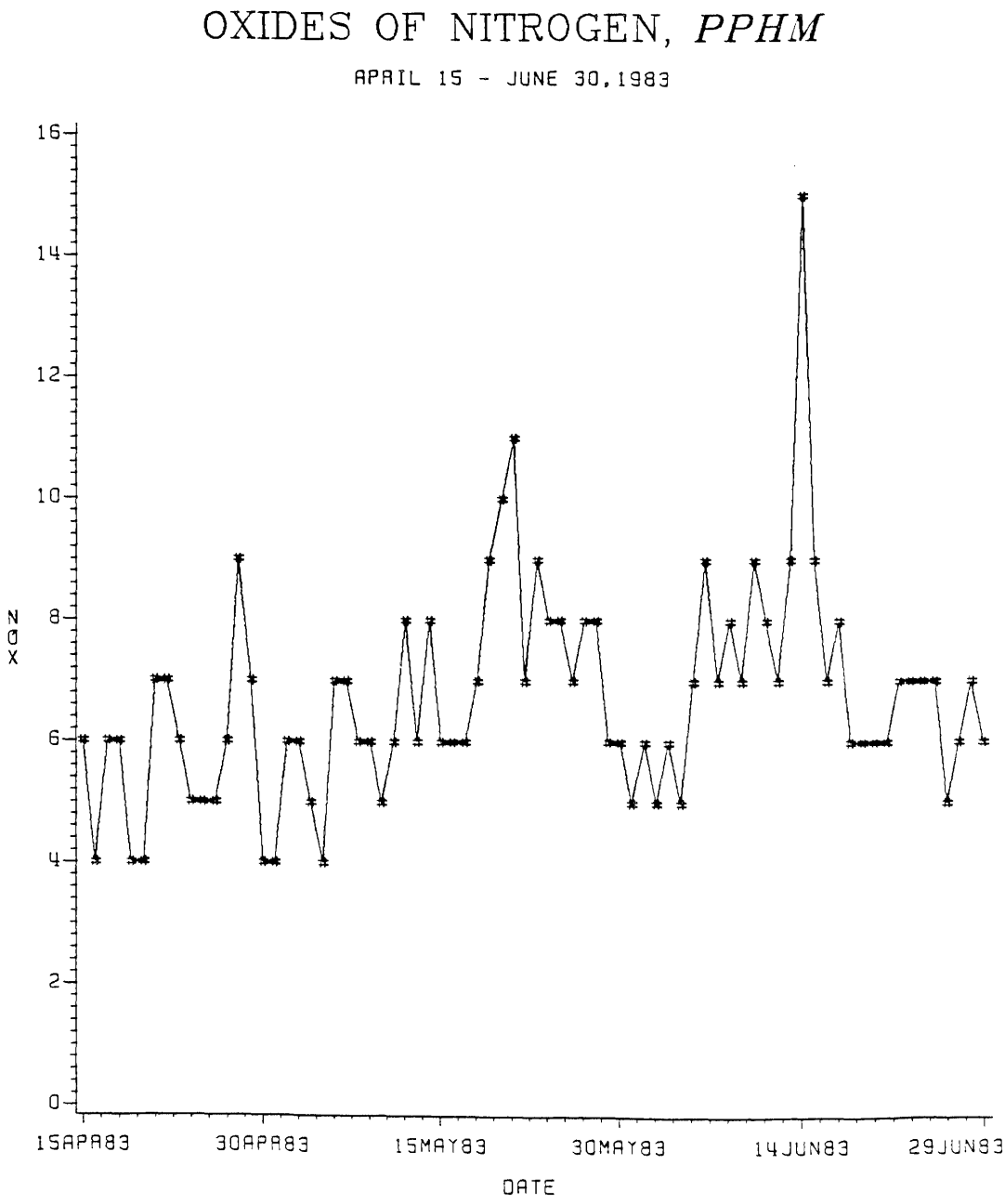
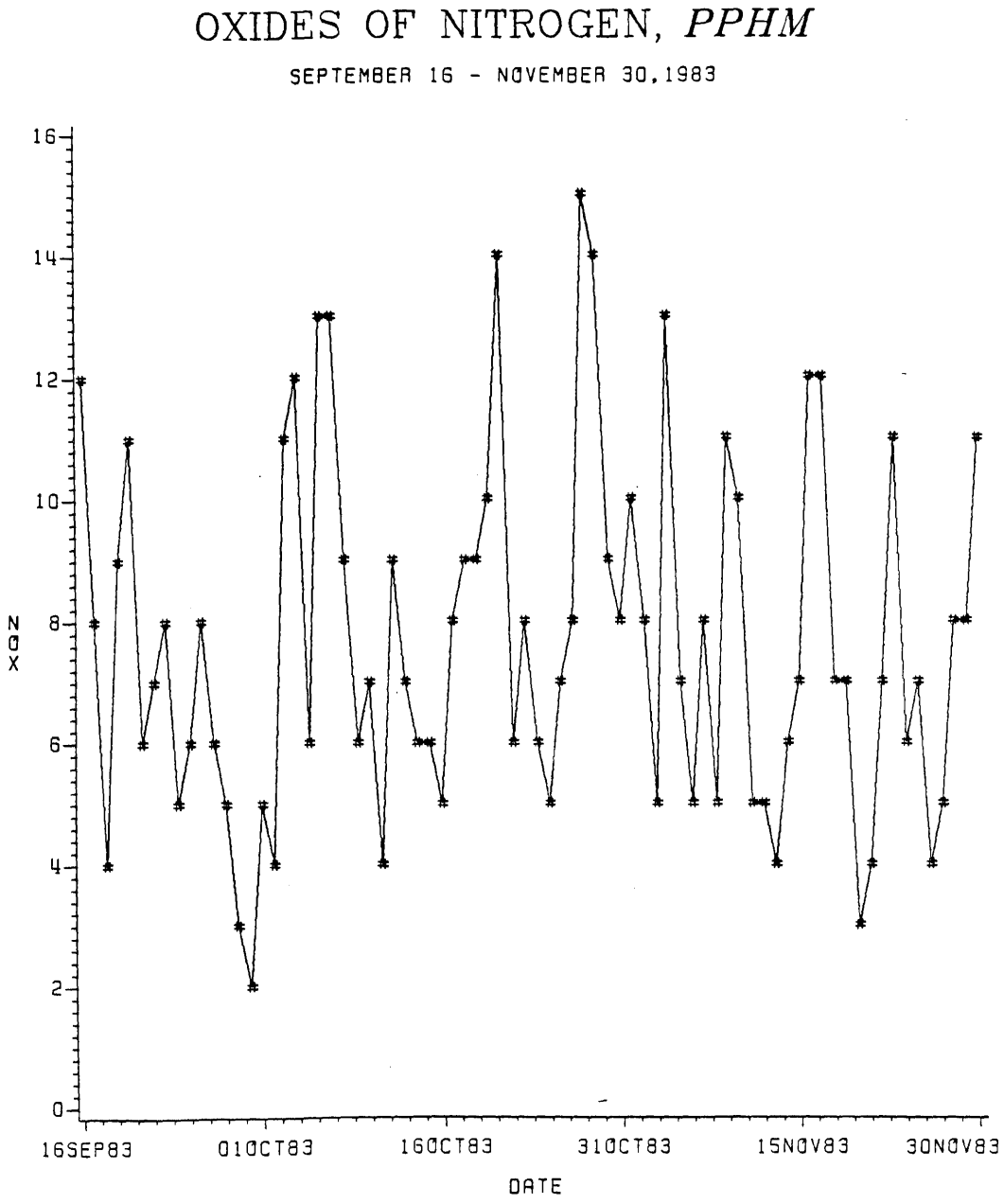


Figure 3A. Daily maximum hourly average concentrations of oxides of nitrogen (NO_x) in parts per hundred million (pphm) in Glendora area.


OXIDES OF NITROGEN, *PPHM*
SEPTEMBER 16 - NOVEMBER 30,1983
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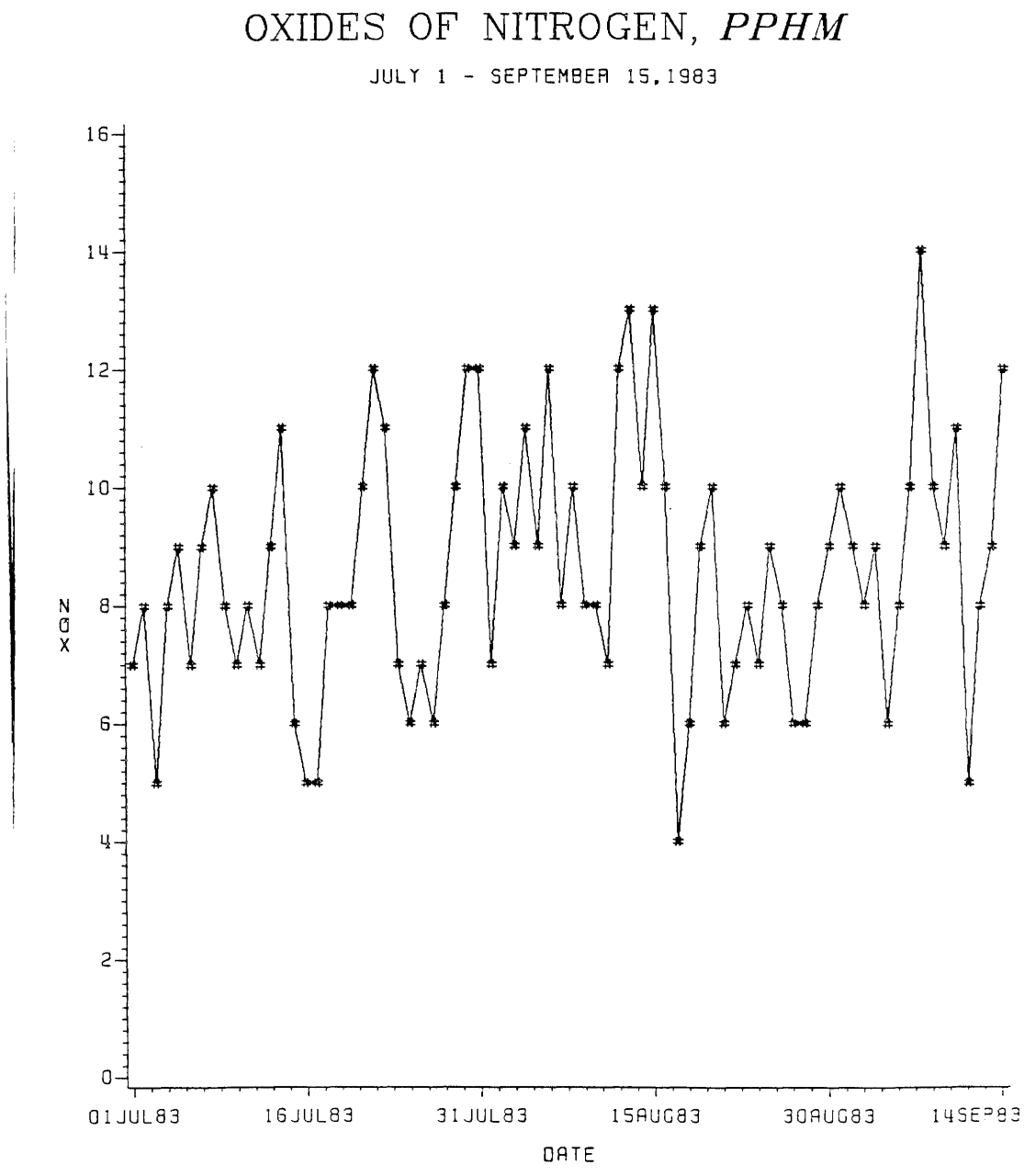
0
2
4
6
8
10
12
14
16
16SEP83
01OCT83
16OCT83
31OCT83
15NOV83
30NOV83
DATE

Figure 3B.


OXIDES OF NITROGEN, PPHM
JULY 1 - SEPTEMBER 15,1983
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16JUL83
31JUL83
15AUG83
30AUG83
14SEP83
DATE

Figure 3C.

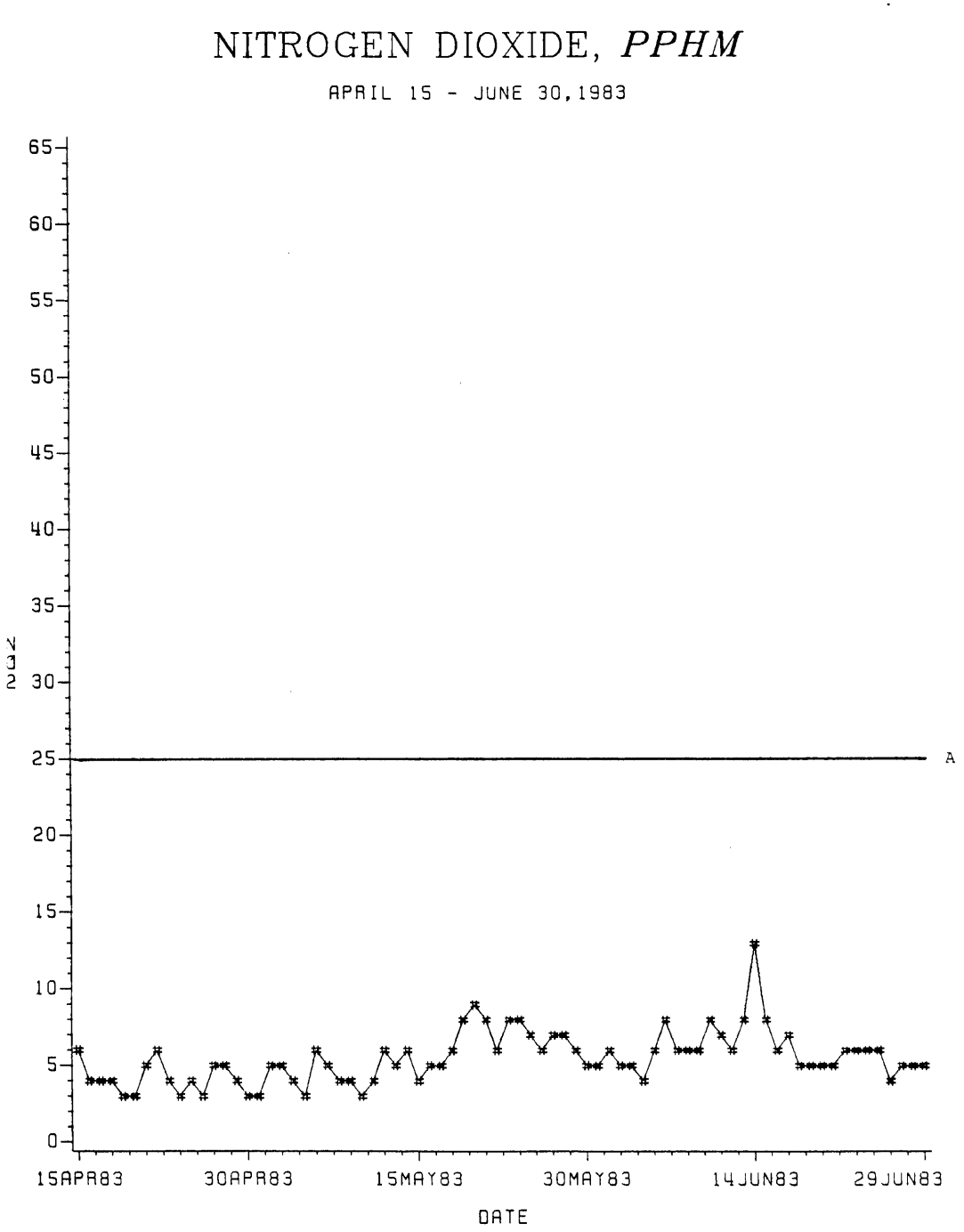
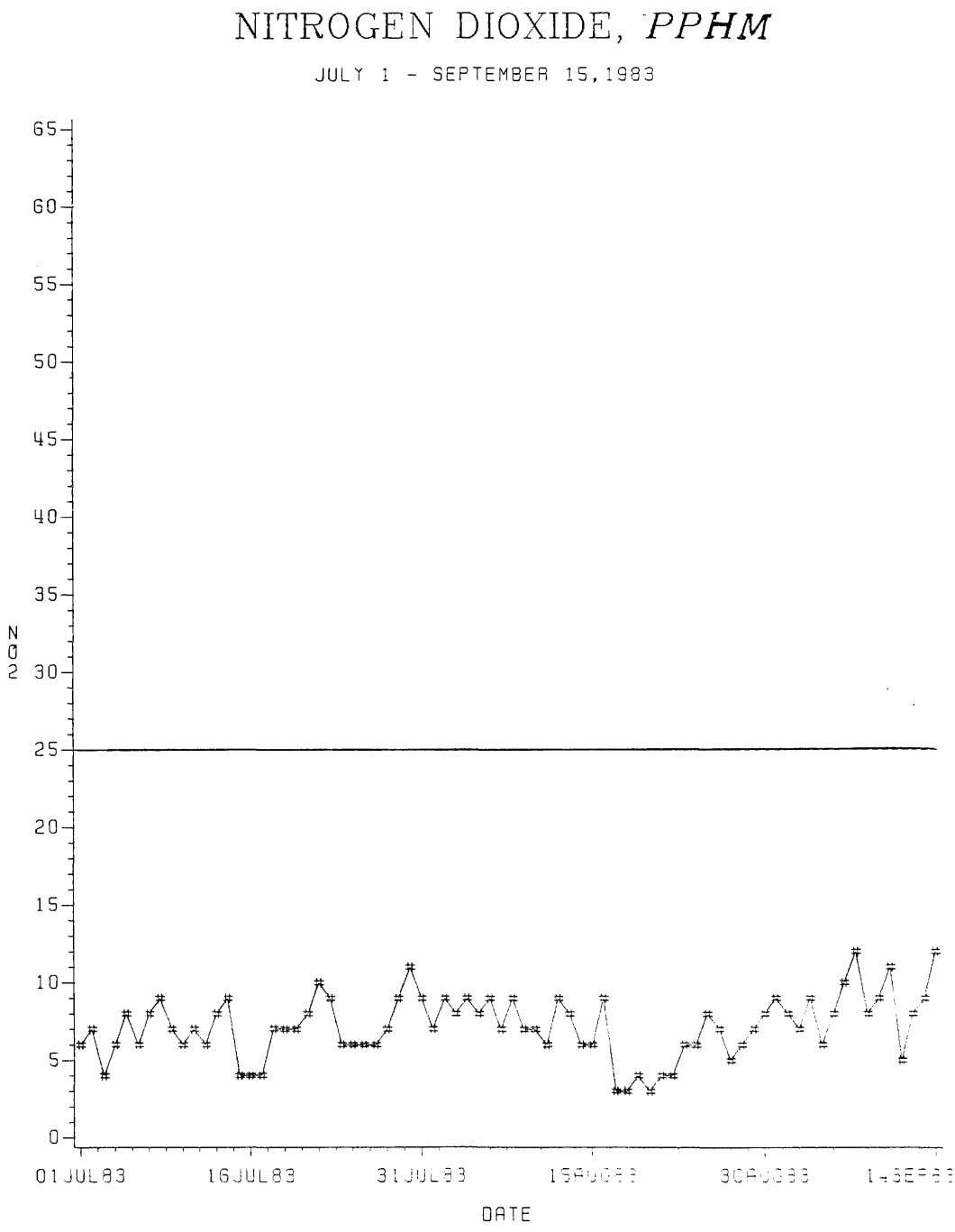


Figure 4A. Daily maximum hourly average concentrations of nitrogen dioxide (NO_2) in parts per hundred million (pphm) in Glendora area. Line A represents the California Air Quality Standard.


NITROGEN DIOXIDE, PPHM
JULY 1 - SEPTEMBER 15,1983
65
60
55
50
45
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35
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5
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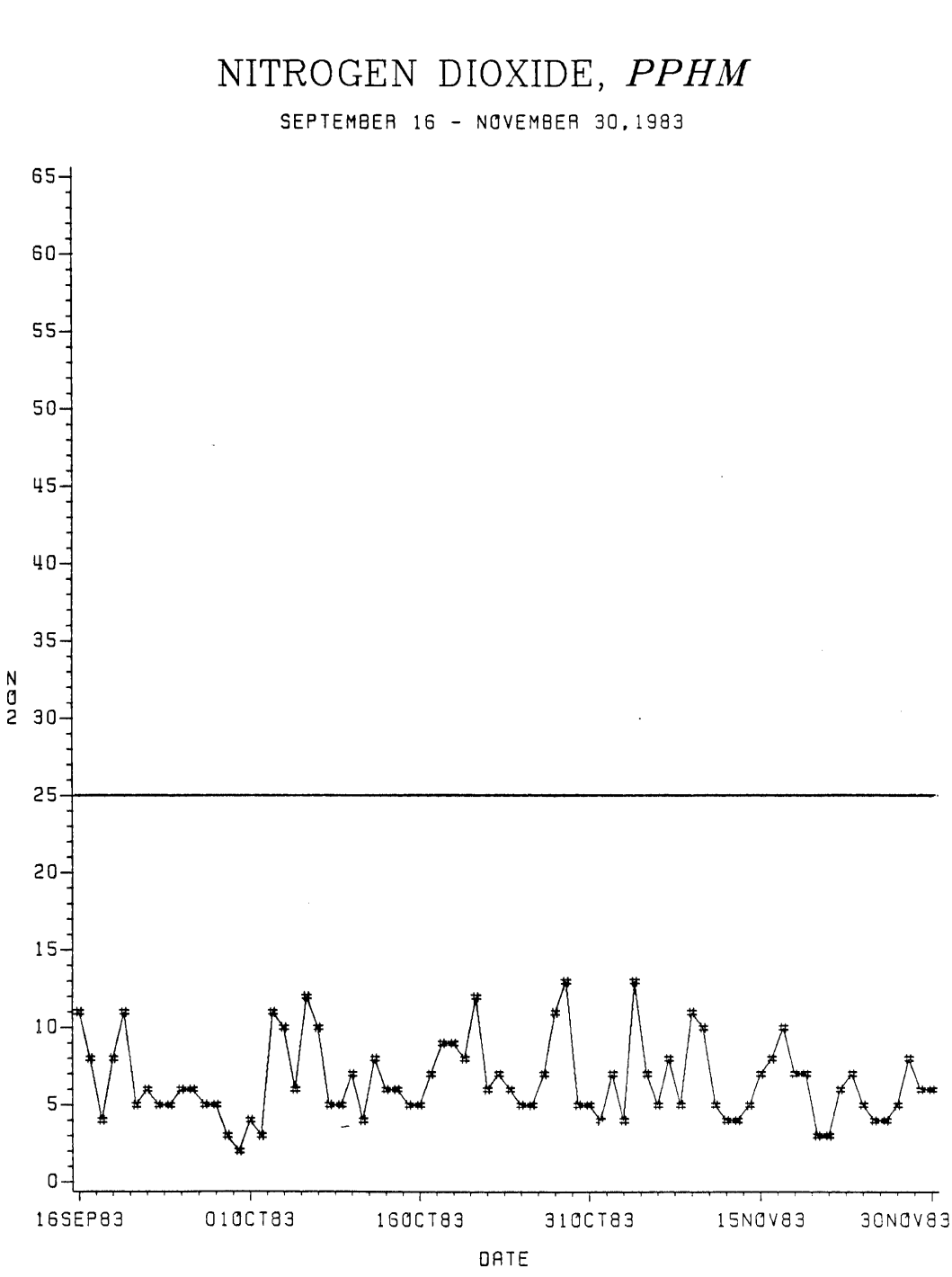
NO2
01JUL83
16JUL83
31JUL83
DATE

Figure 4B.


NITROGEN DIOXIDE, PPHM
SEPTEMBER 16 - NOVEMBER 30,1983
NO2
65
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45
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16SEP83
01OCT83
16OCT83
31OCT83
15NOV83
30NOV83
DATE

Figure 4C.

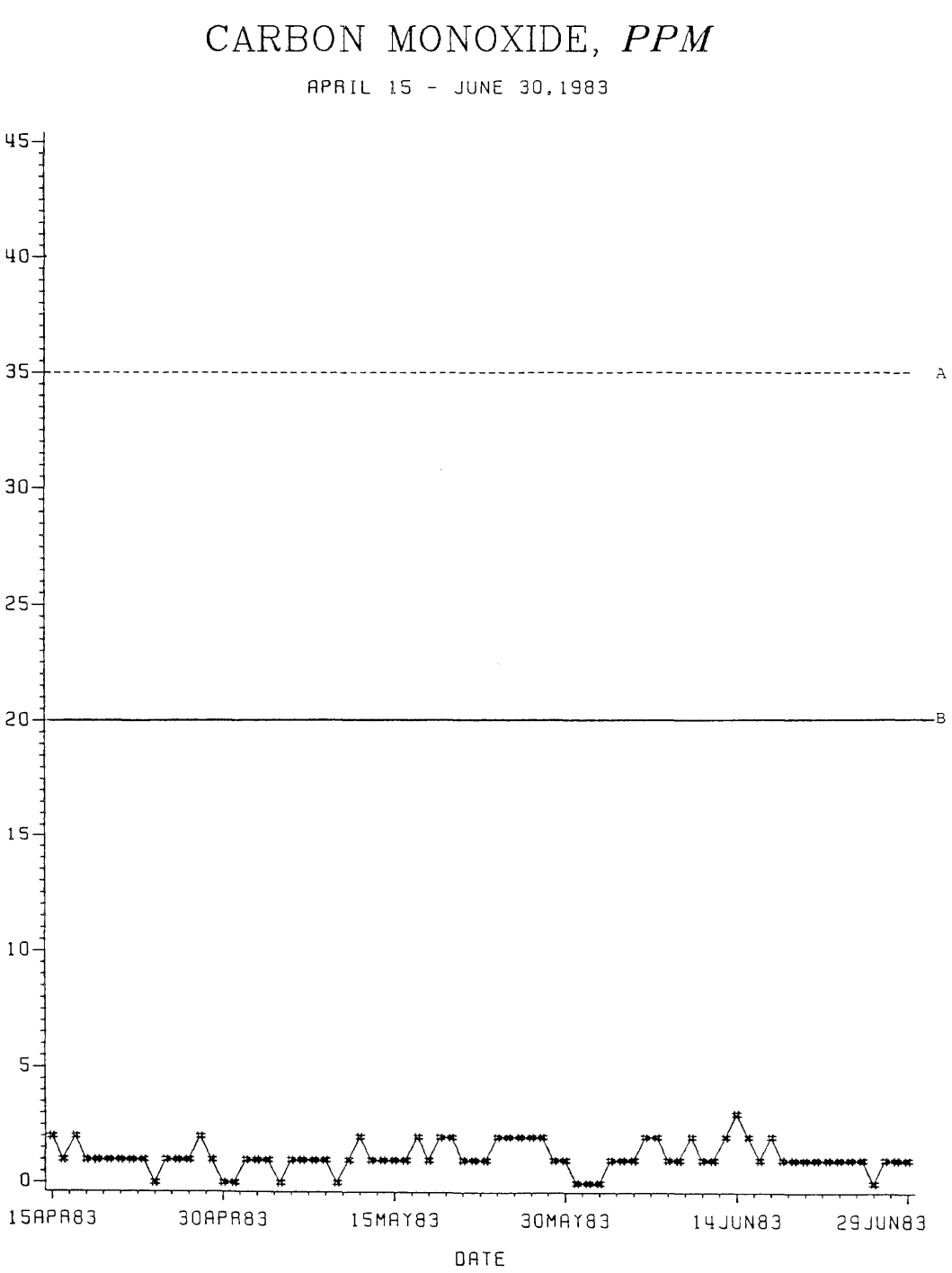

Figure 5A. Daily maximum hourly average concentrations of carbon monoxide in parts per million (ppm) in Glendora area. Line A represents the National Primary Standard. Line B represents the California Air Quality Standard.

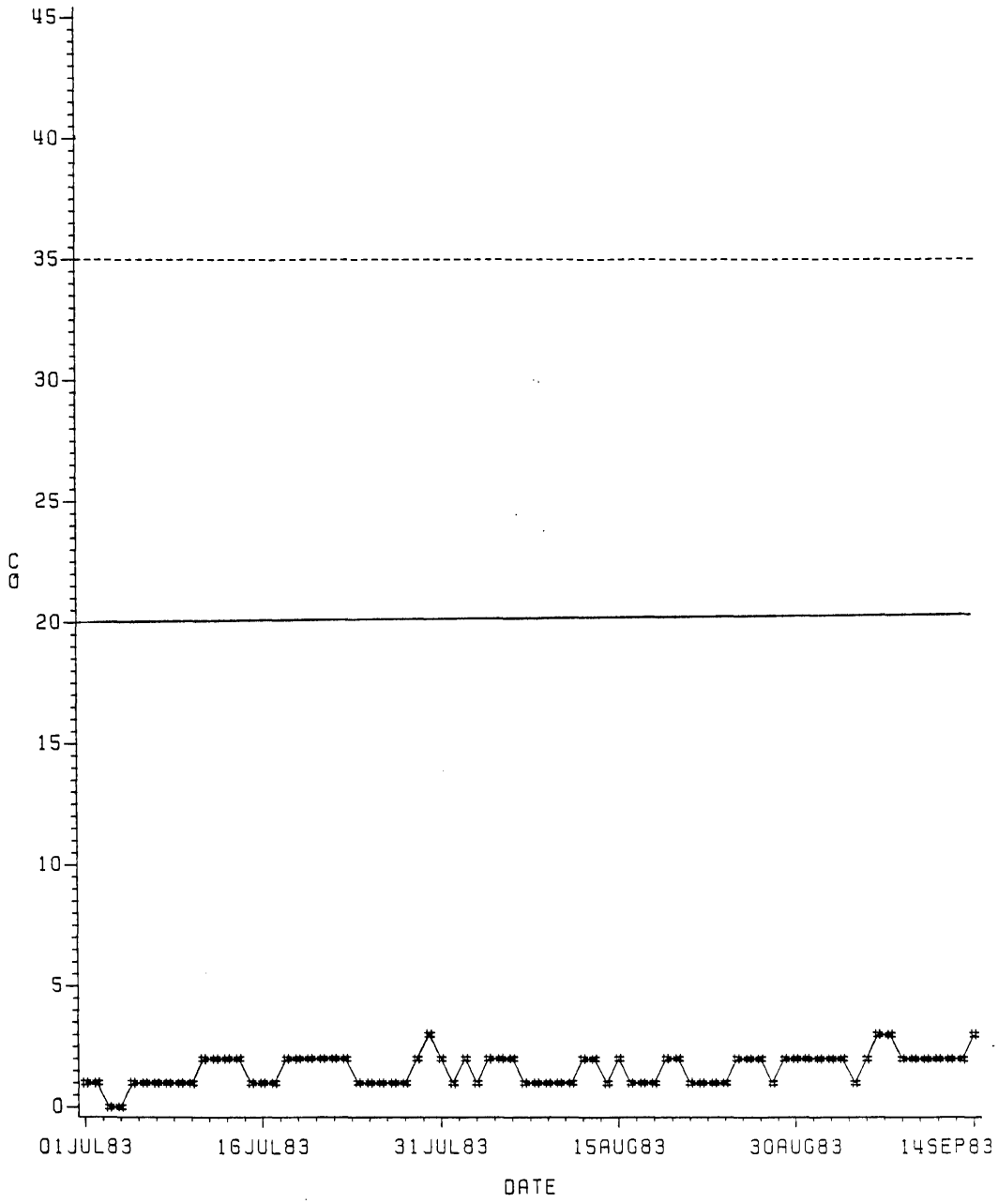
CARBON MONOXIDE, *PPM*
JULY 1 - SEPTEMBER 15,1983
45
40
35
30
25
20
15
10
5
0
CO
01JUL83
16JUL83
31JUL83
15AUG83
30AUG83
14SEP83
DATE

Figure 5B.

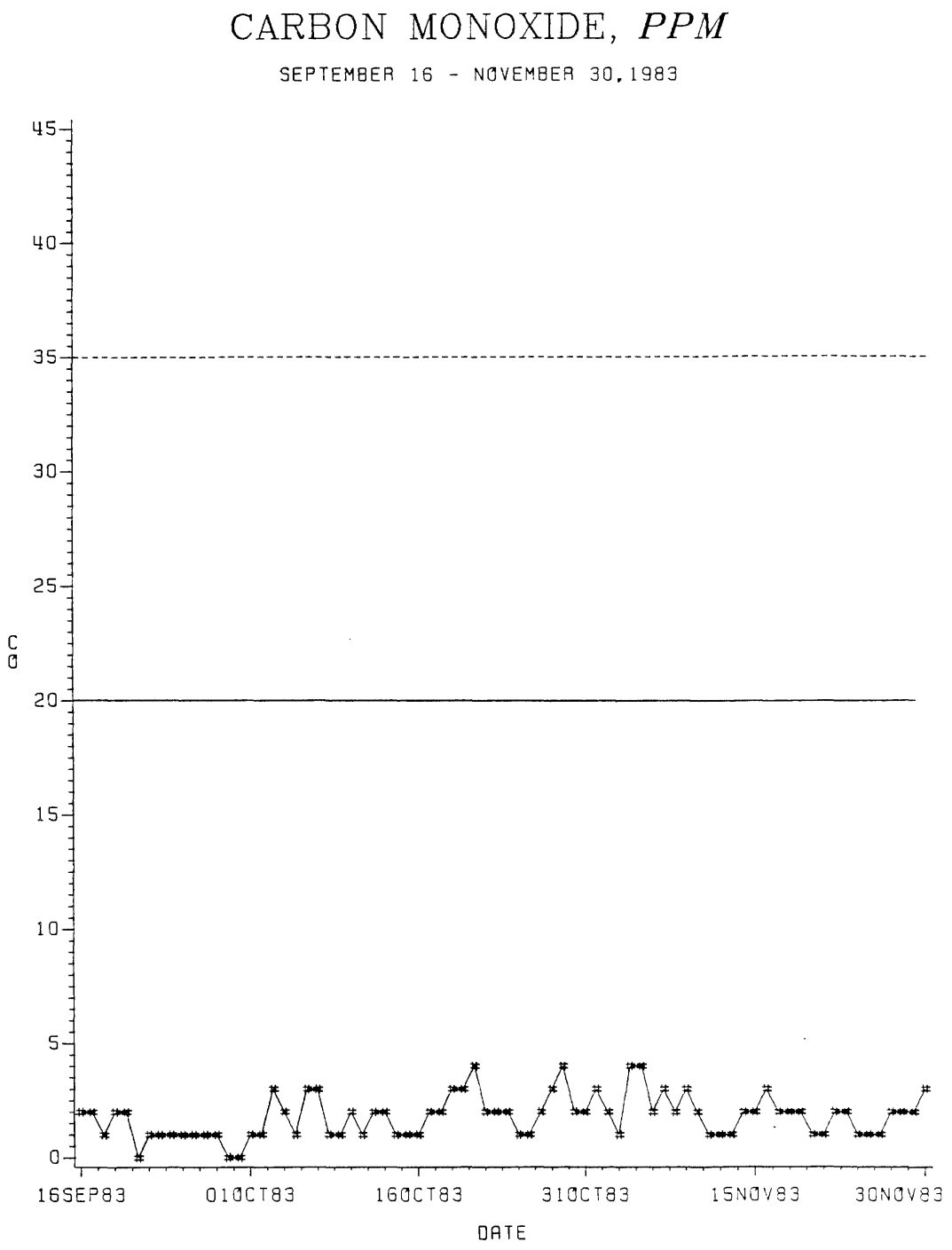
CARBON MONOXIDE, PPM
SEPTEMBER 16 - NOVEMBER 30,1983
45
40
35
30
25
20
15
10
5
0
CO
16SEP83
01OCT83
16OCT83
31OCT83
15NOV83
30NOV83
DATE

Figure 5C.

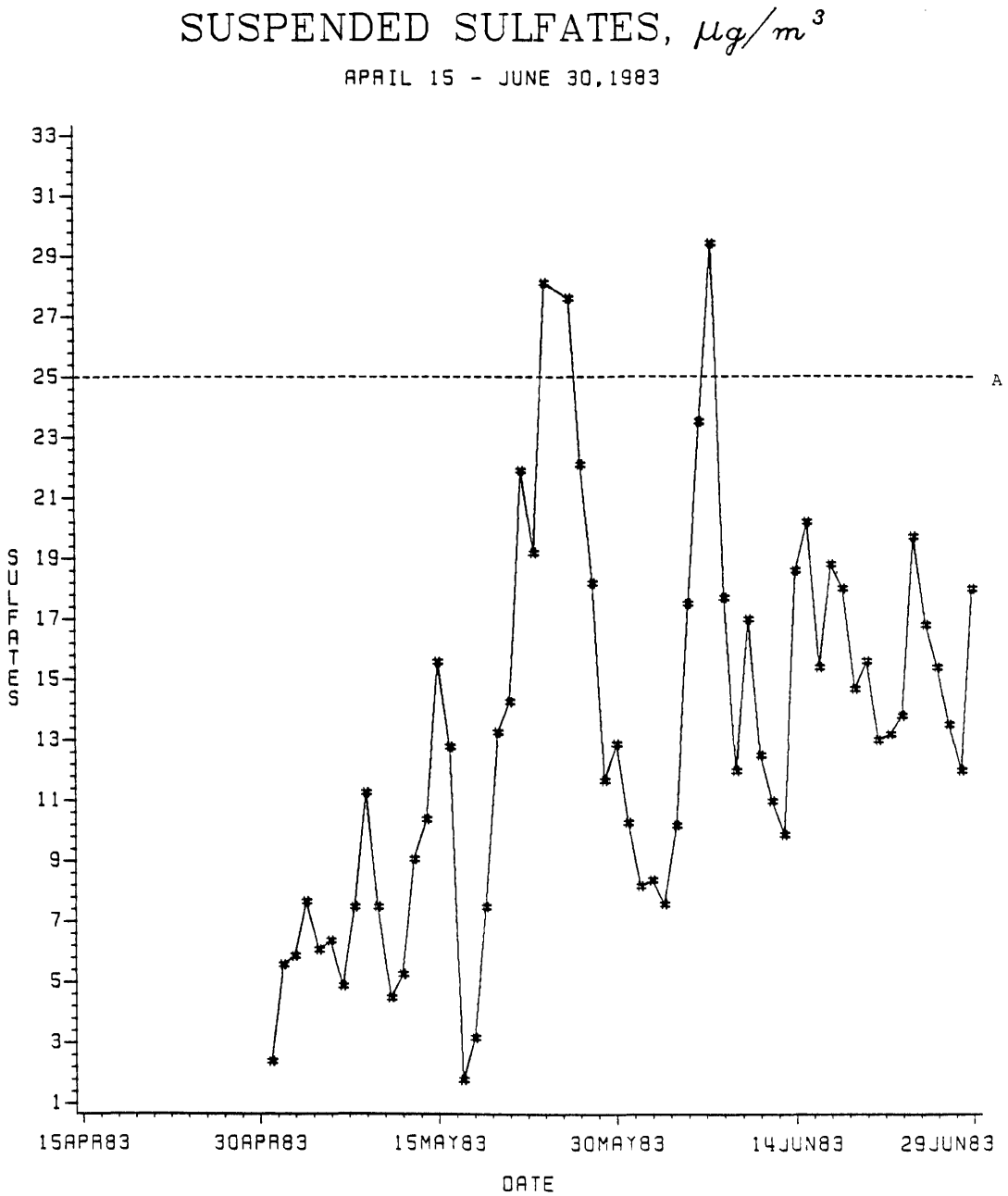

Figure 6A. Daily 24-hour average concentrations of suspended sulfates in micrograms per cubic meter ($\mu g/m^3$) in Glendora area. Line A represents the California Air Quality Standard.

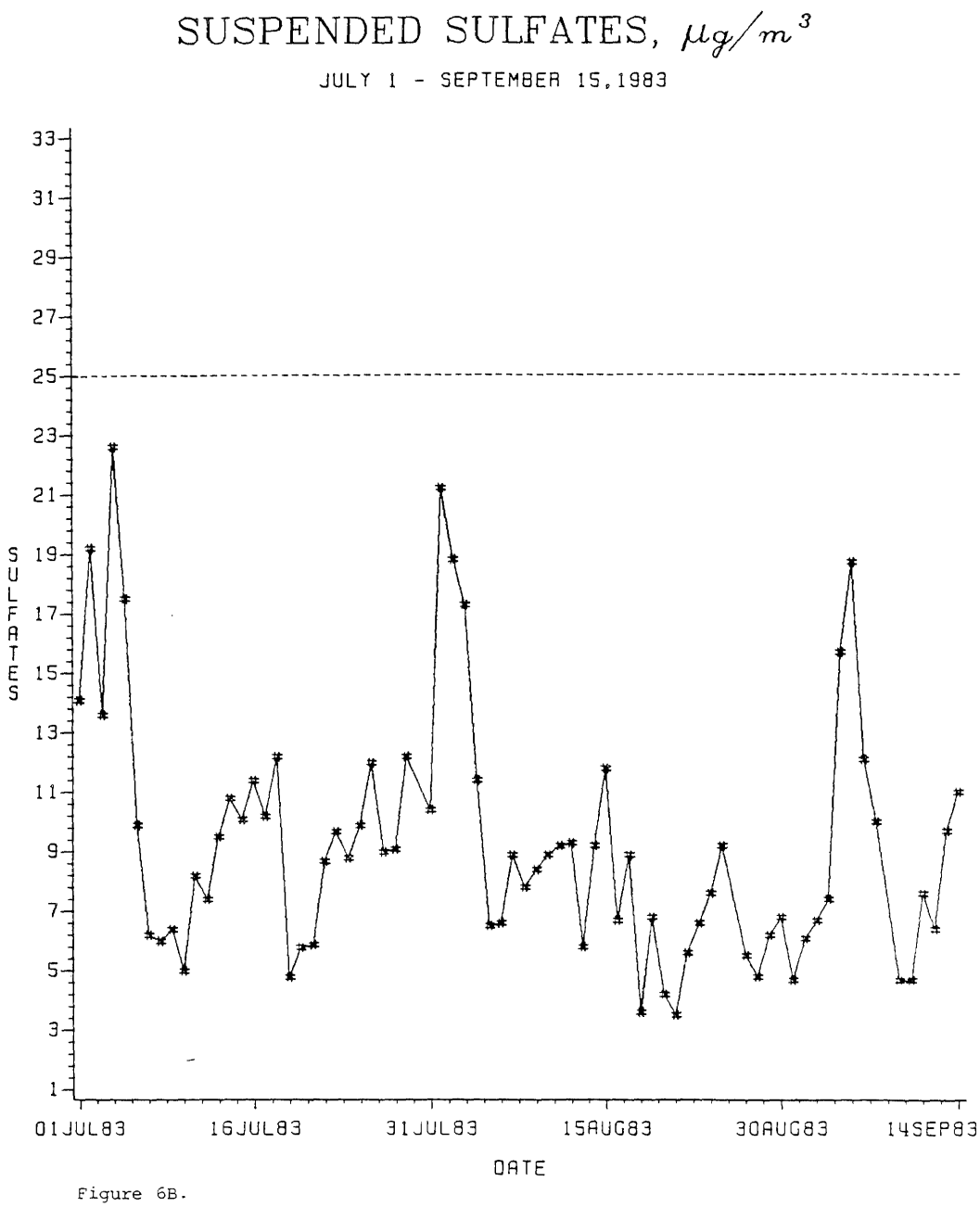
SUSPENDED SULFATES, μg/m³
JULY 1 - SEPTEMBER 15,1983
SULFATES
33
31
29
27
25
23
21
19
17
15
13
11
9
7
5
3
1
01JUL83
16JUL83
31JUL83
15AUG83
30AUG83
14SEP83
DATE

Figure 6B.

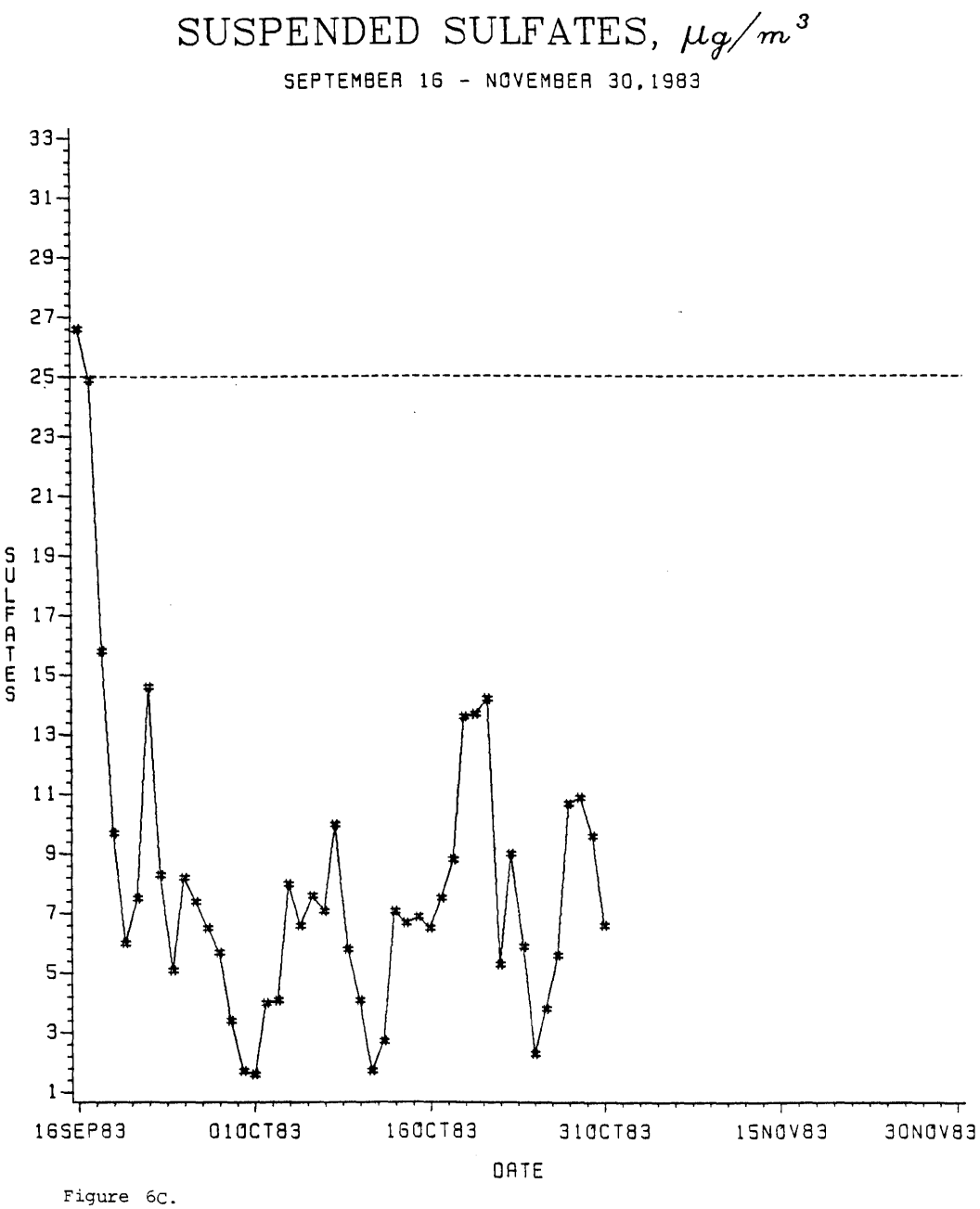
SUSPENDED SULFATES, μg/m³
SEPTEMBER 16 - NOVEMBER 30,1983
SULFATES
33
31
29
27
25
23
21
19
17
15
13
11
9
7
5
3
1
16SEP83
01OCT83
16OCT83
31OCT83
15NOV83
30NOV83
DATE

Figure 6c.

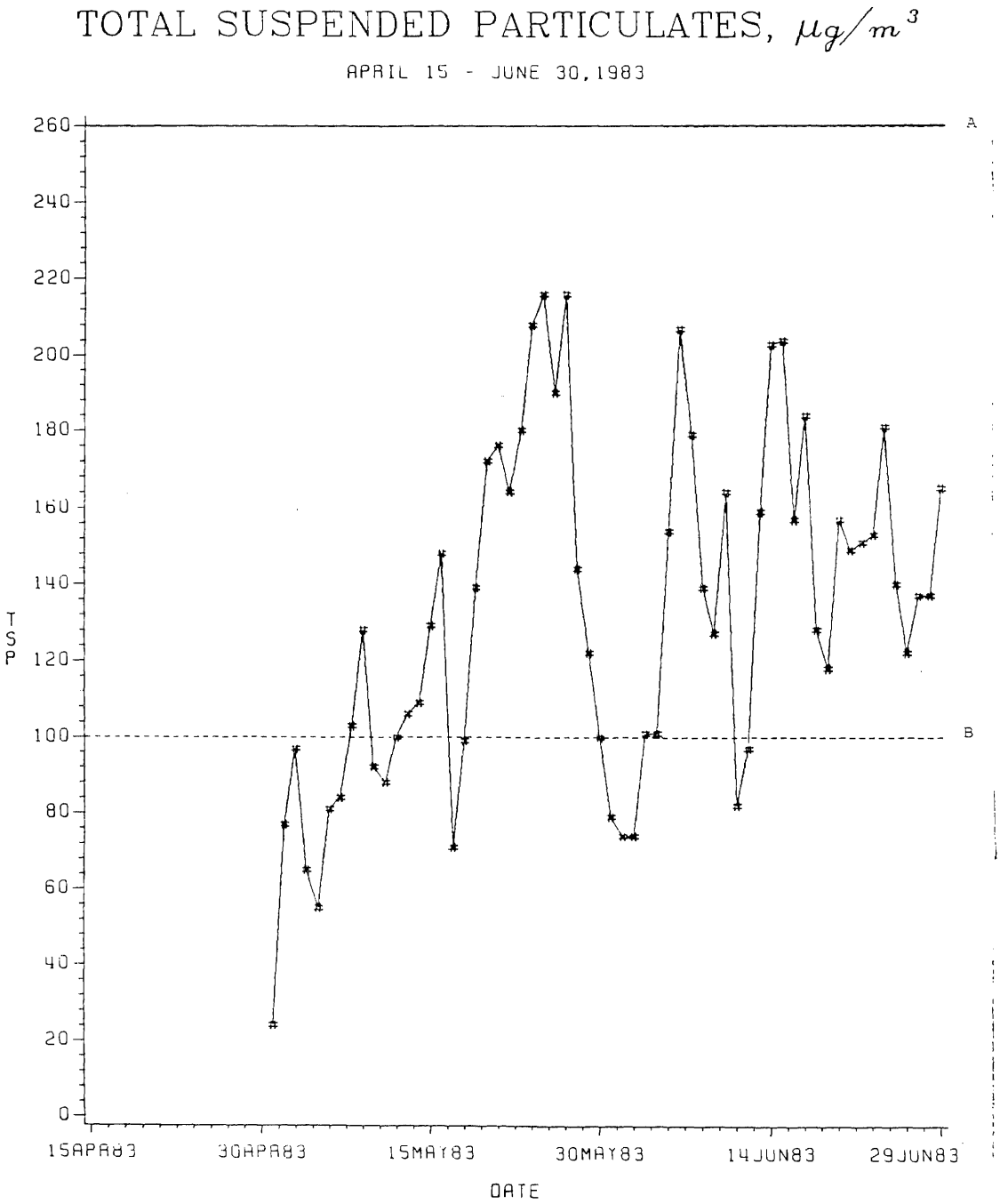

Figure 7A. Daily 24-hour average concentrations of total suspended particulates (TSP) in micrograms per cubic meter (ug/m^3) in Glendora area. Line A represents the National Primary Standard. Line B represents the California Air Quality Standard which was in effect until 1983.

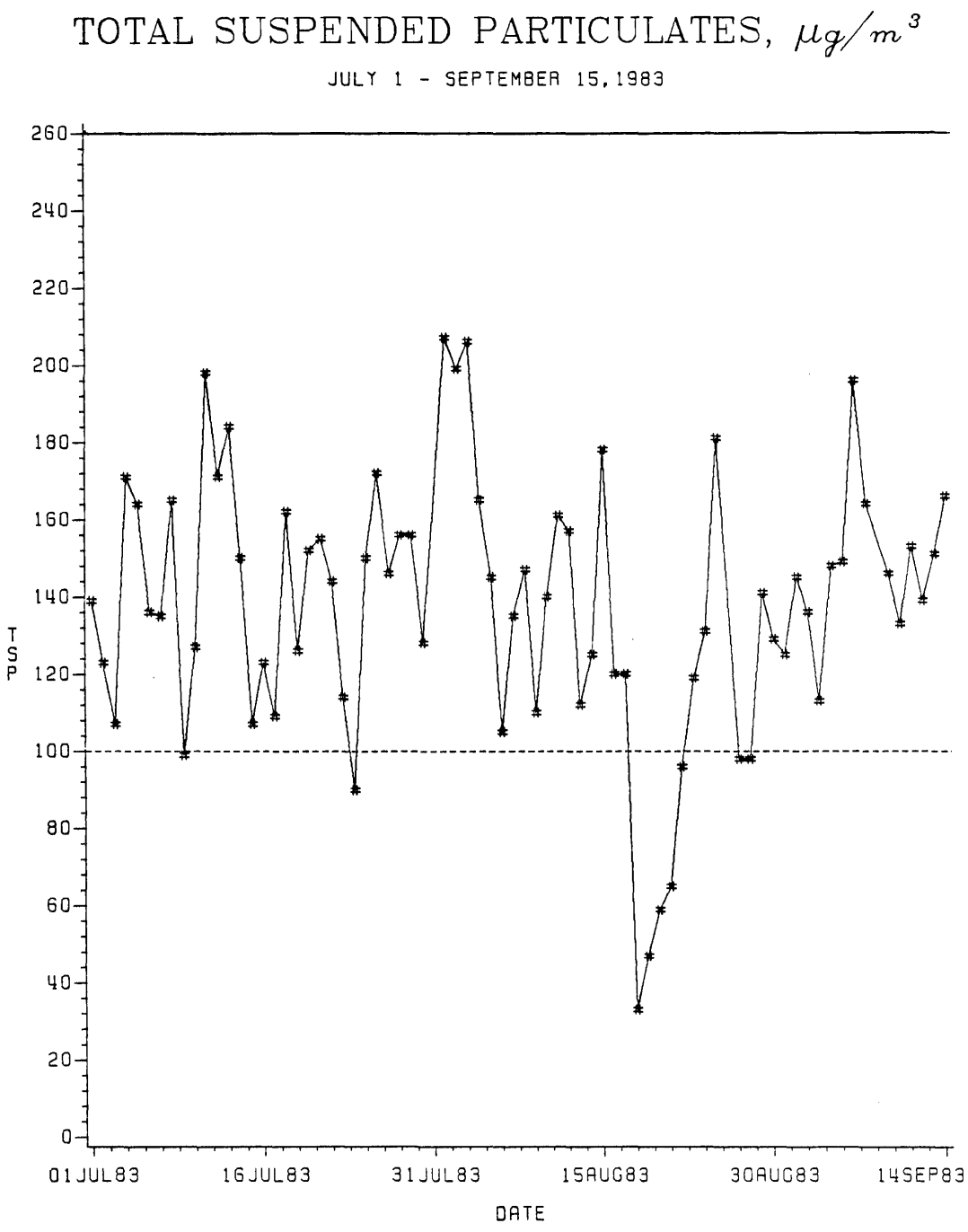
TOTAL SUSPENDED PARTICULATES, μg/m³
JULY 1 - SEPTEMBER 15,1983
TSP
260
240
220
200
180
160
140
120
100
80
60
40
20
0
01JUL83
16JUL83
31JUL83
15AUG83
30AUG83
14SEP83
DATE

Figure 7B.

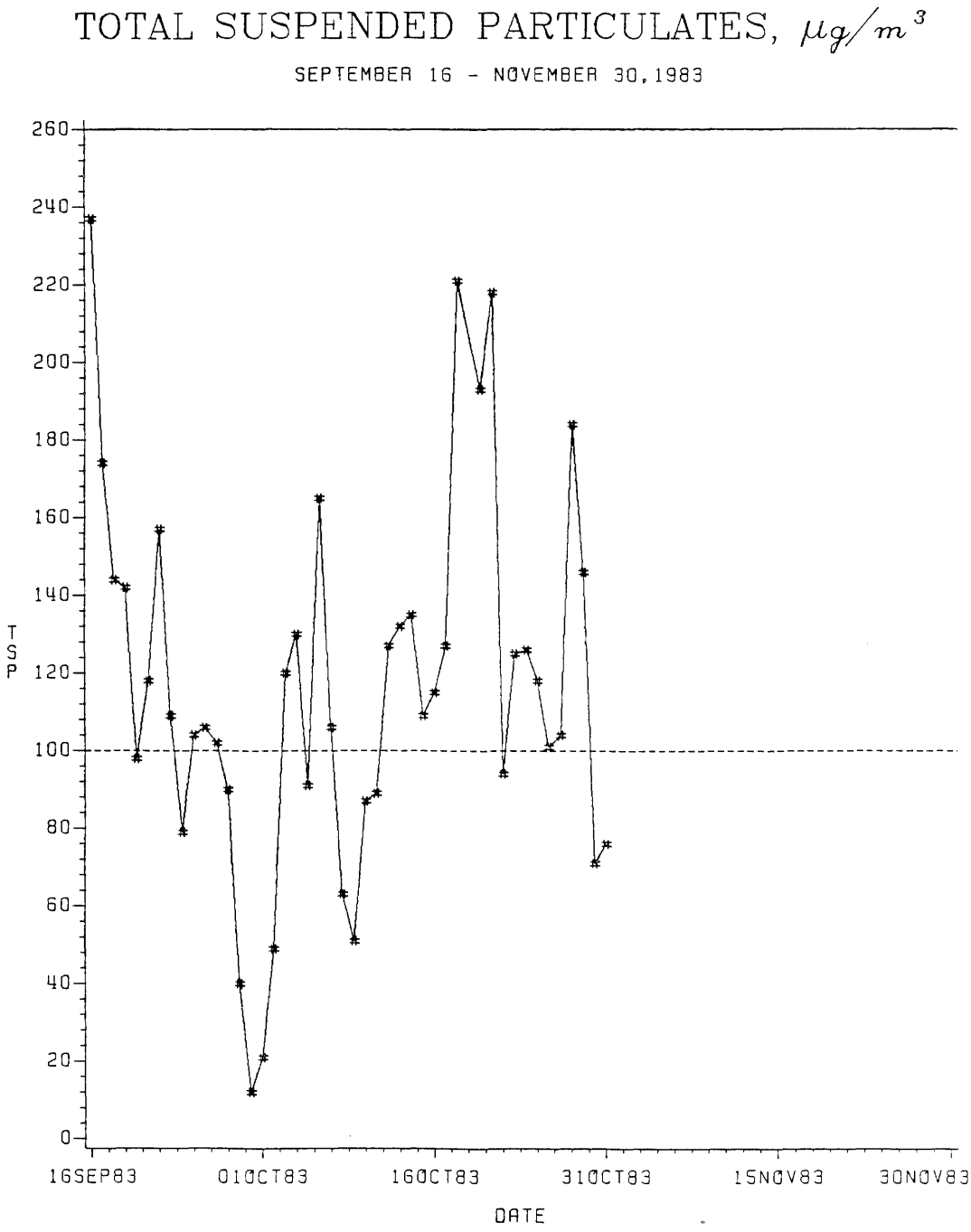
TOTAL SUSPENDED PARTICULATES, μg/m³
SEPTEMBER 16 - NOVEMBER 30, 1983
TSP
260
240
220
200
180
160
140
120
100
80
60
40
20
0
16SEP83
01OCT83
16OCT83
31OCT83
15NOV83
30NOV83
DATE

Figure 7C.

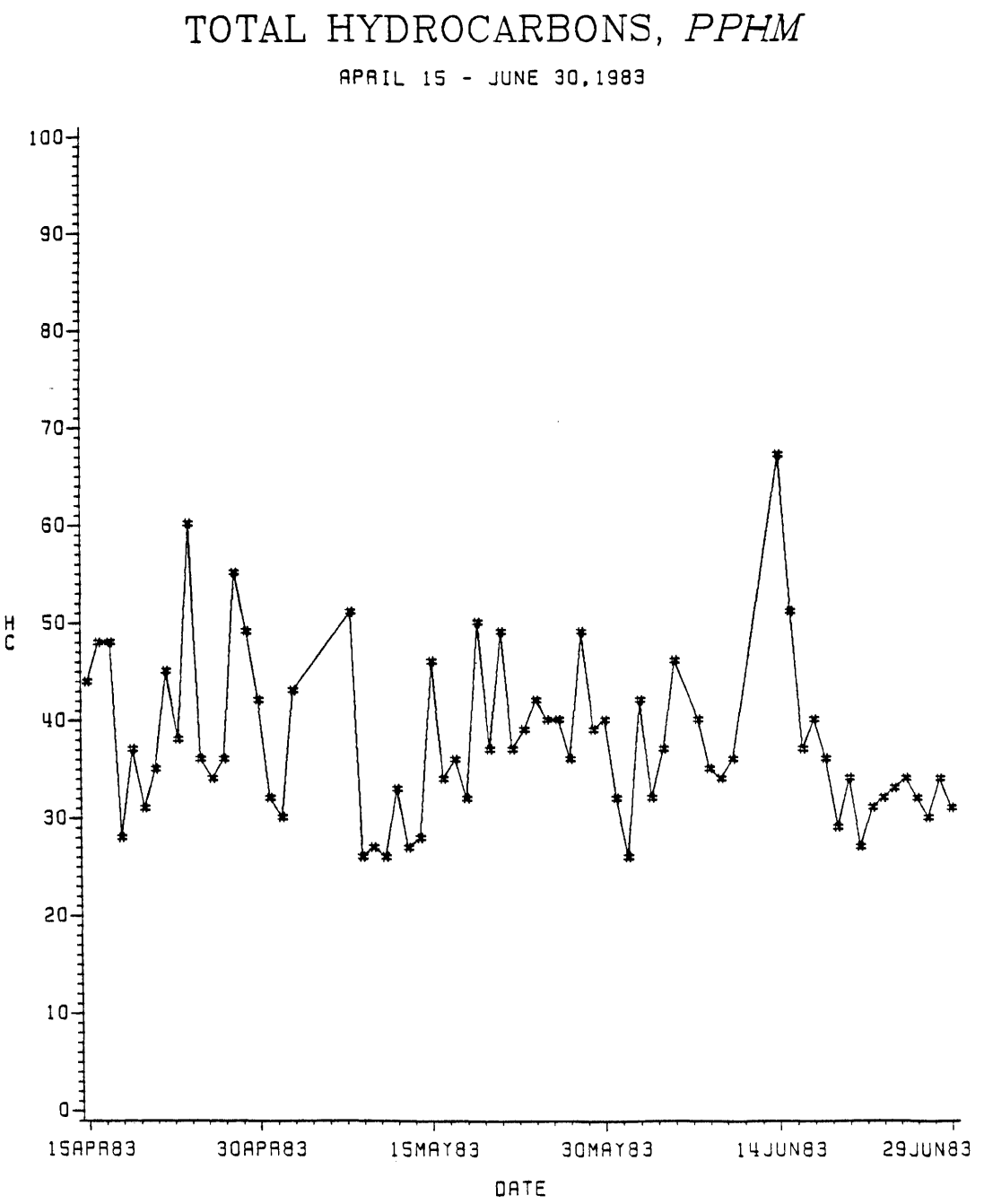

Figure 8A. Daily 24-hour average concentrations of total hydrocarbons (HC) in parts per hundred million (pphm) in Glendora area.

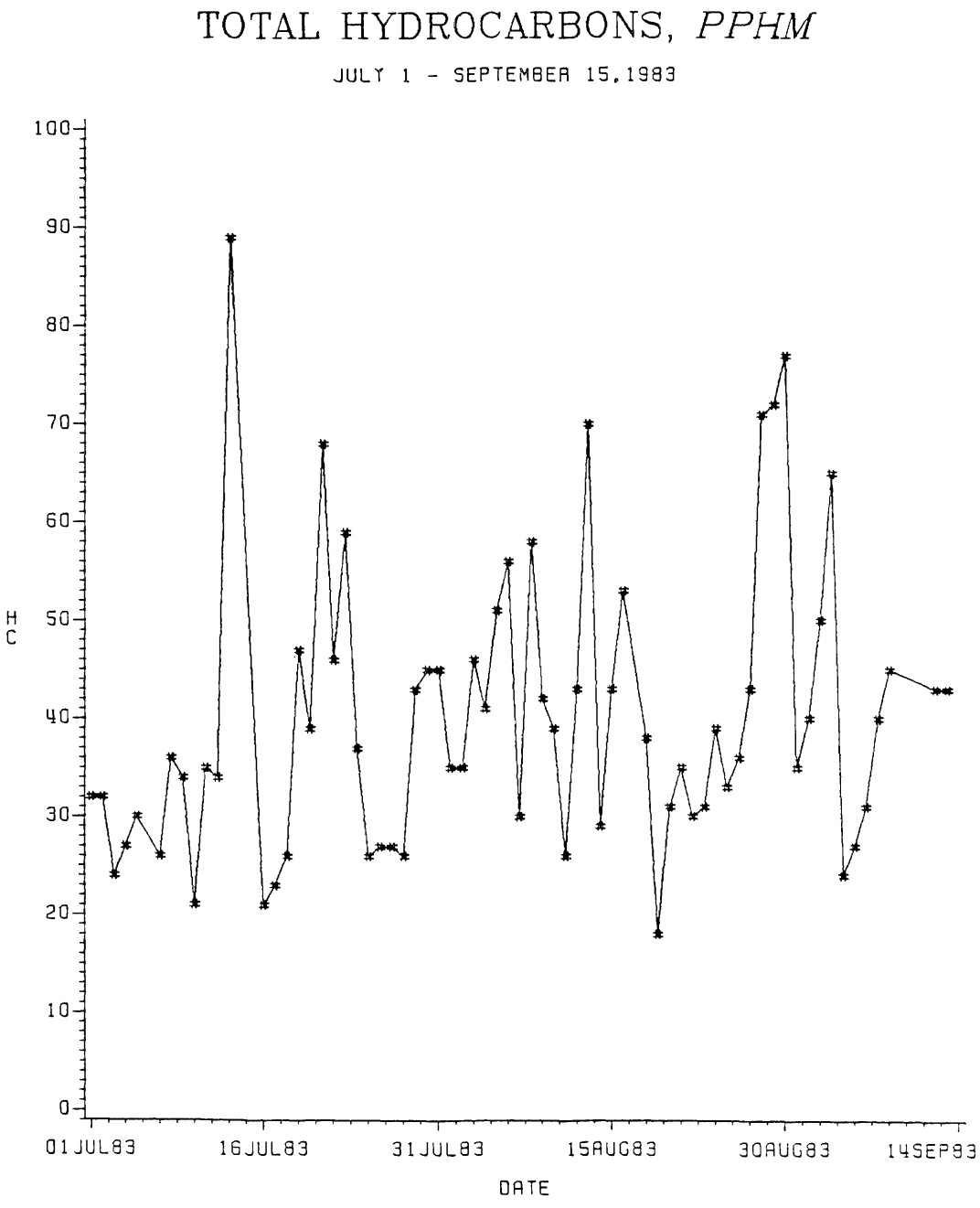
TOTAL HYDROCARBONS, PPHM
JULY 1 - SEPTEMBER 15,1983
HC
100
90
80
70
60
50
40
30
20
10
0
01JUL83
16JUL83
31JUL83
15AUG83
30AUG83
14SEP83
DATE

Figure 8B.

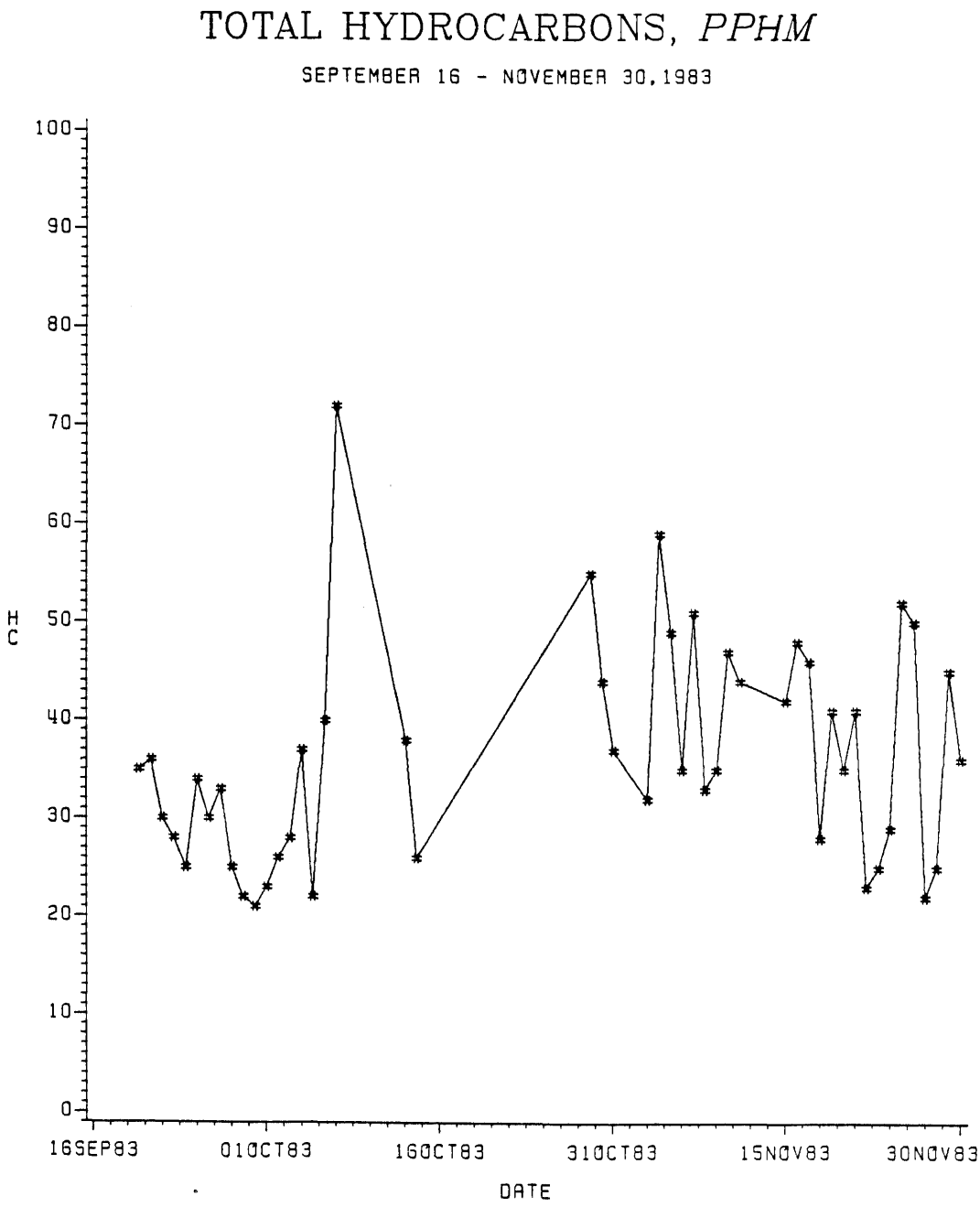
TOTAL HYDROCARBONS, PPHM
SEPTEMBER 16 - NOVEMBER 30,1983
HC
100
90
80
70
60
50
40
30
20
10
0
16SEP83
01OCT83
16OCT83
31OCT83
15NOV83
30NOV83
DATE

Figure 8C.

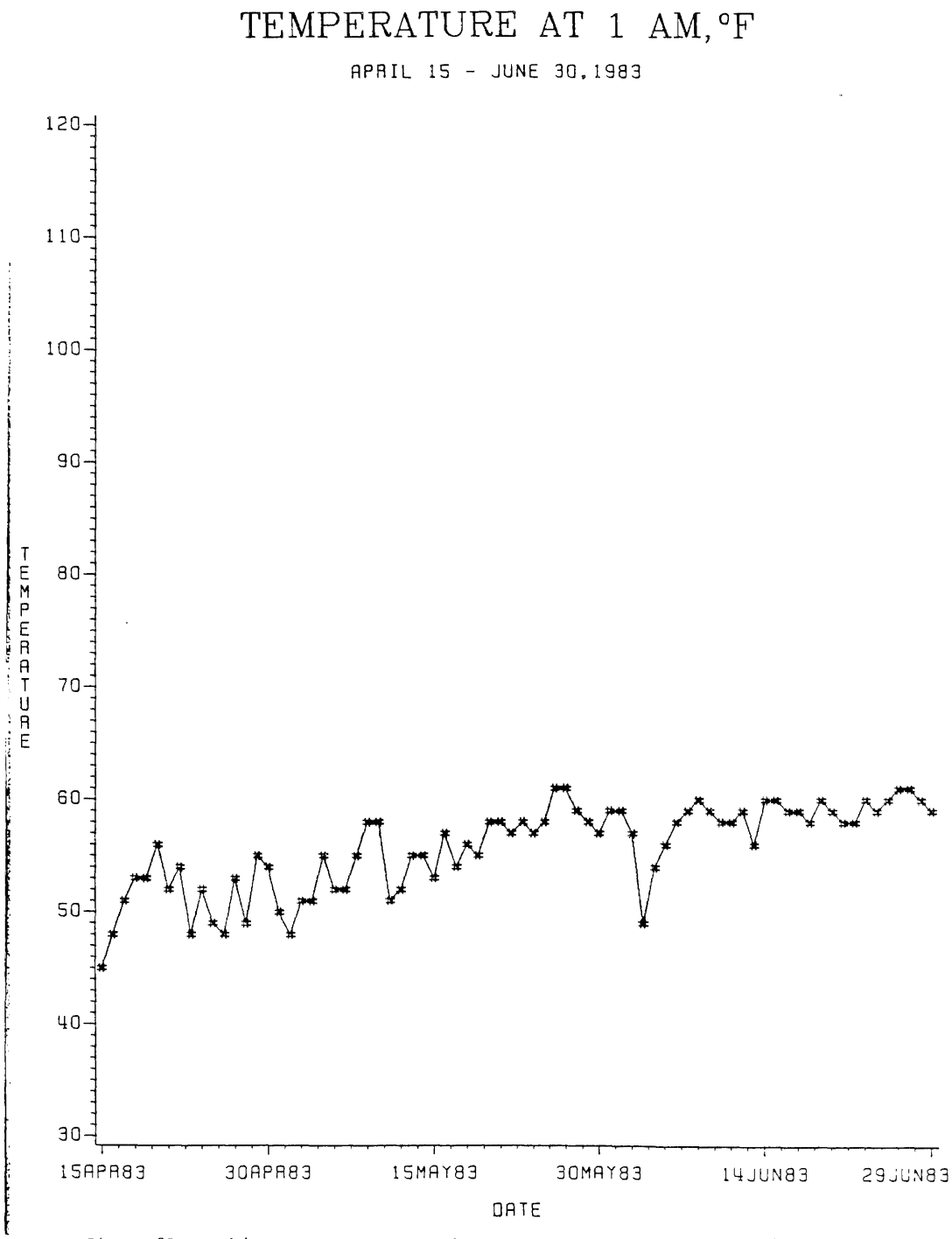

Figure 9A. Ambient temperature at 1 A.M. in degrees Fahrenheit (°F) in Glendora area.

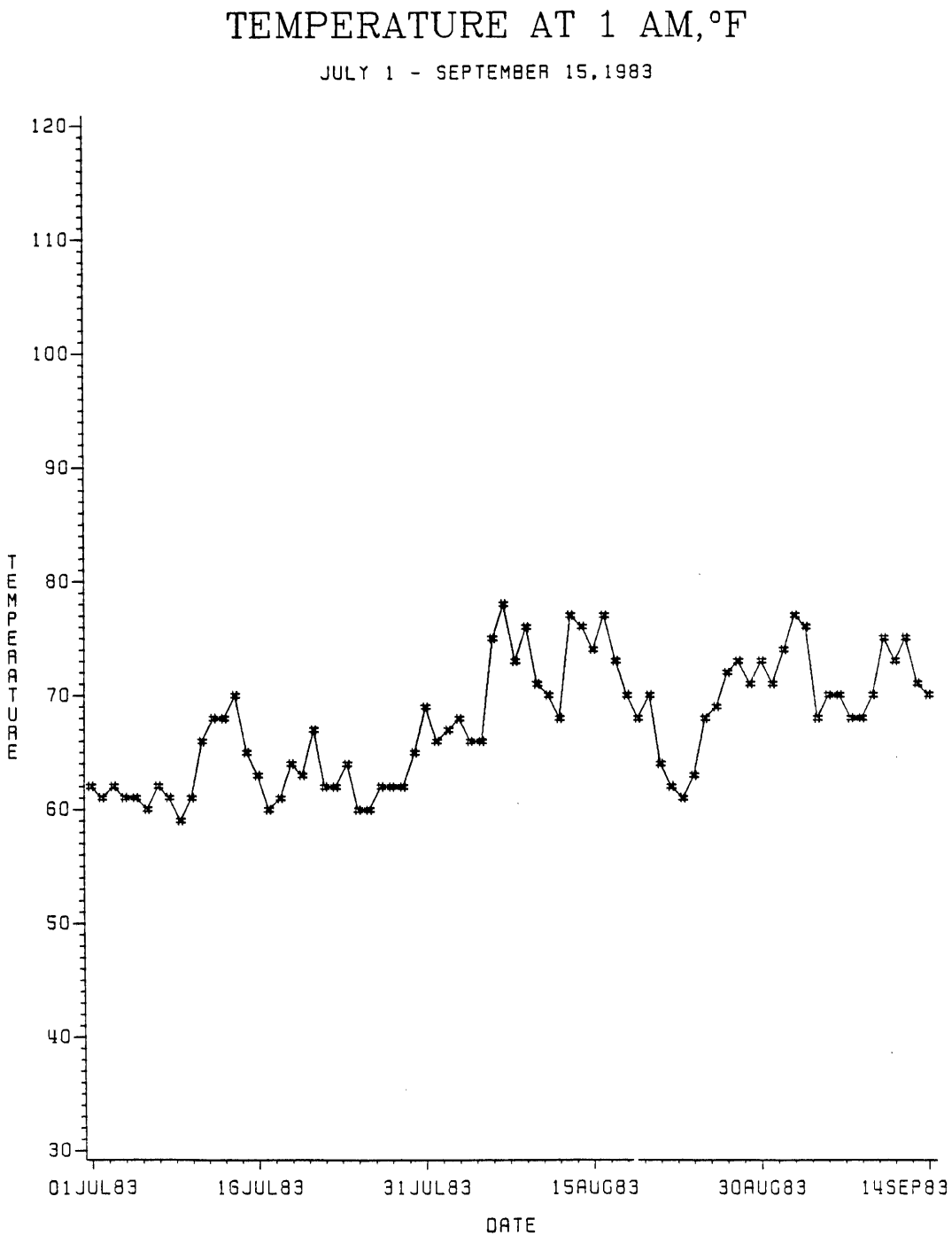
TEMPERATURE AT 1 AM,°F
JULY 1 - SEPTEMBER 15,1983
120
110
100
90
80
70
60
50
40
30
TEMPERATURE
01JUL83
16JUL83
31JUL83
15AUG83
30AUG83
14SEP83
DATE

Figure 9B.

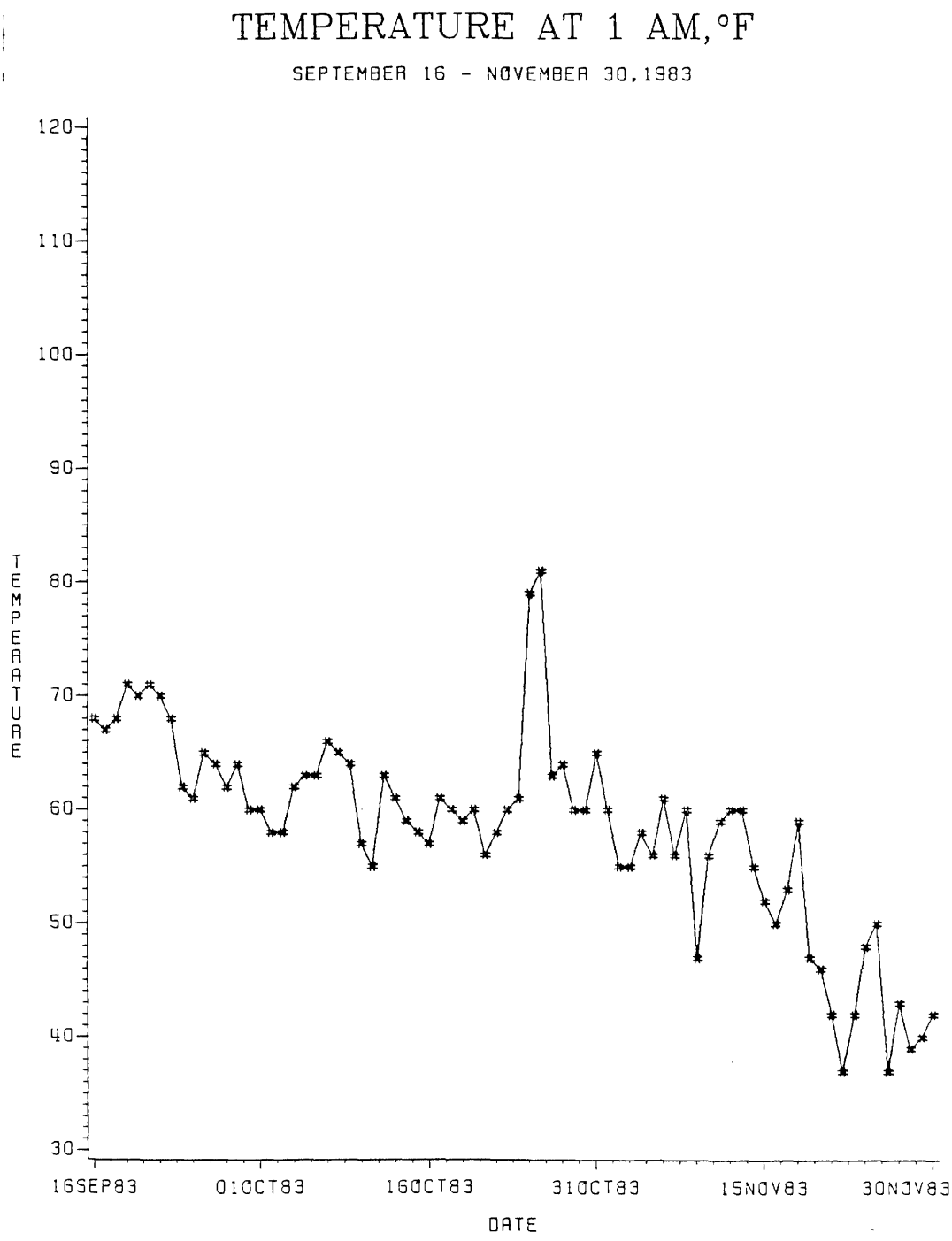
TEMPERATURE AT 1 AM,°F
SEPTEMBER 16 - NOVEMBER 30,1983
120
110
100
90
80
70
60
50
40
30
TEMPERATURE
16SEP83
01OCT83
16OCT83
31OCT83
15NOV83
30NOV83
DATE

Figure 9C.

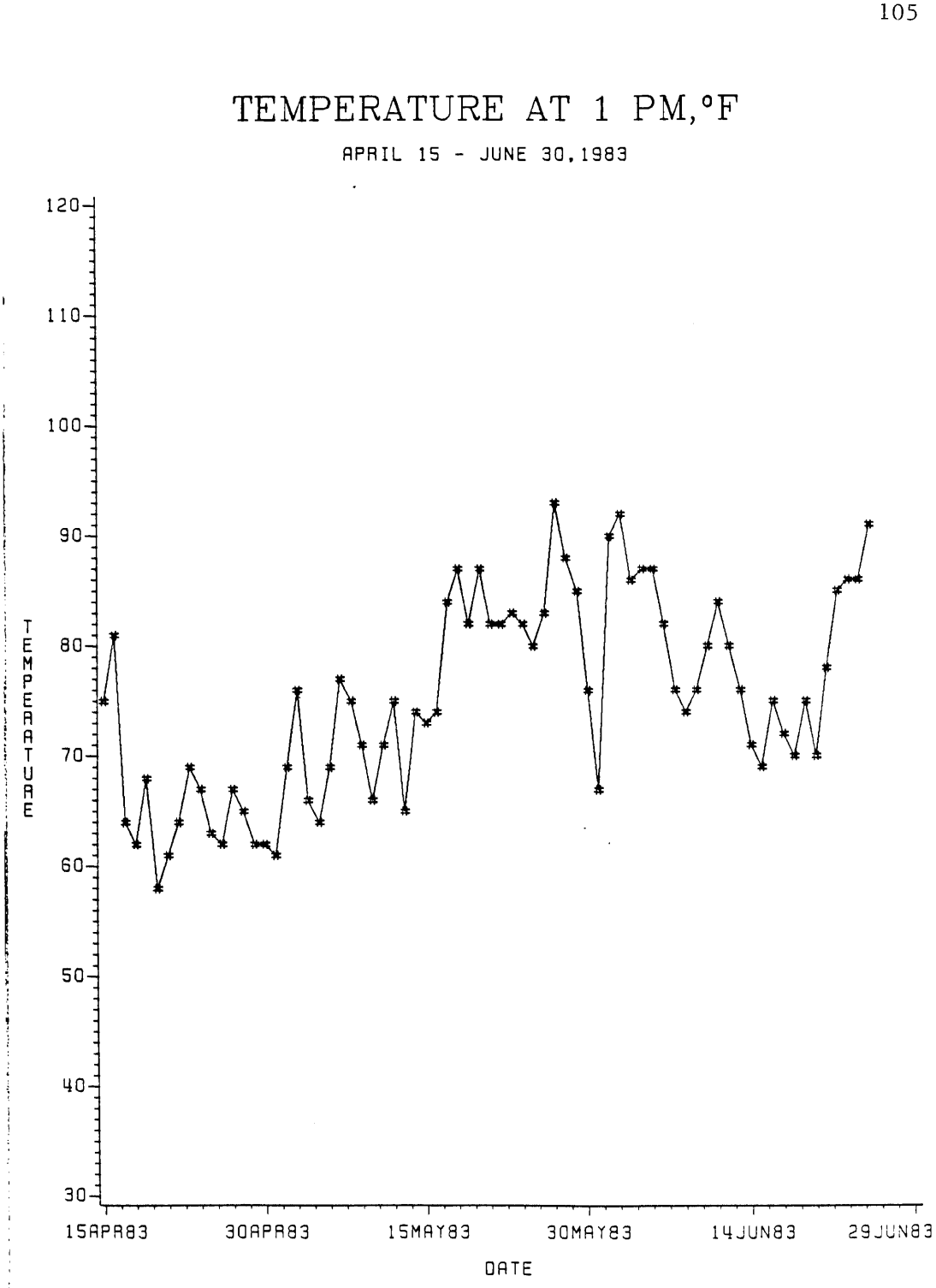

Figure 10A. Ambient temperature at 1 P.M. in degrees Fahrenheit (°F) in Glendora area.

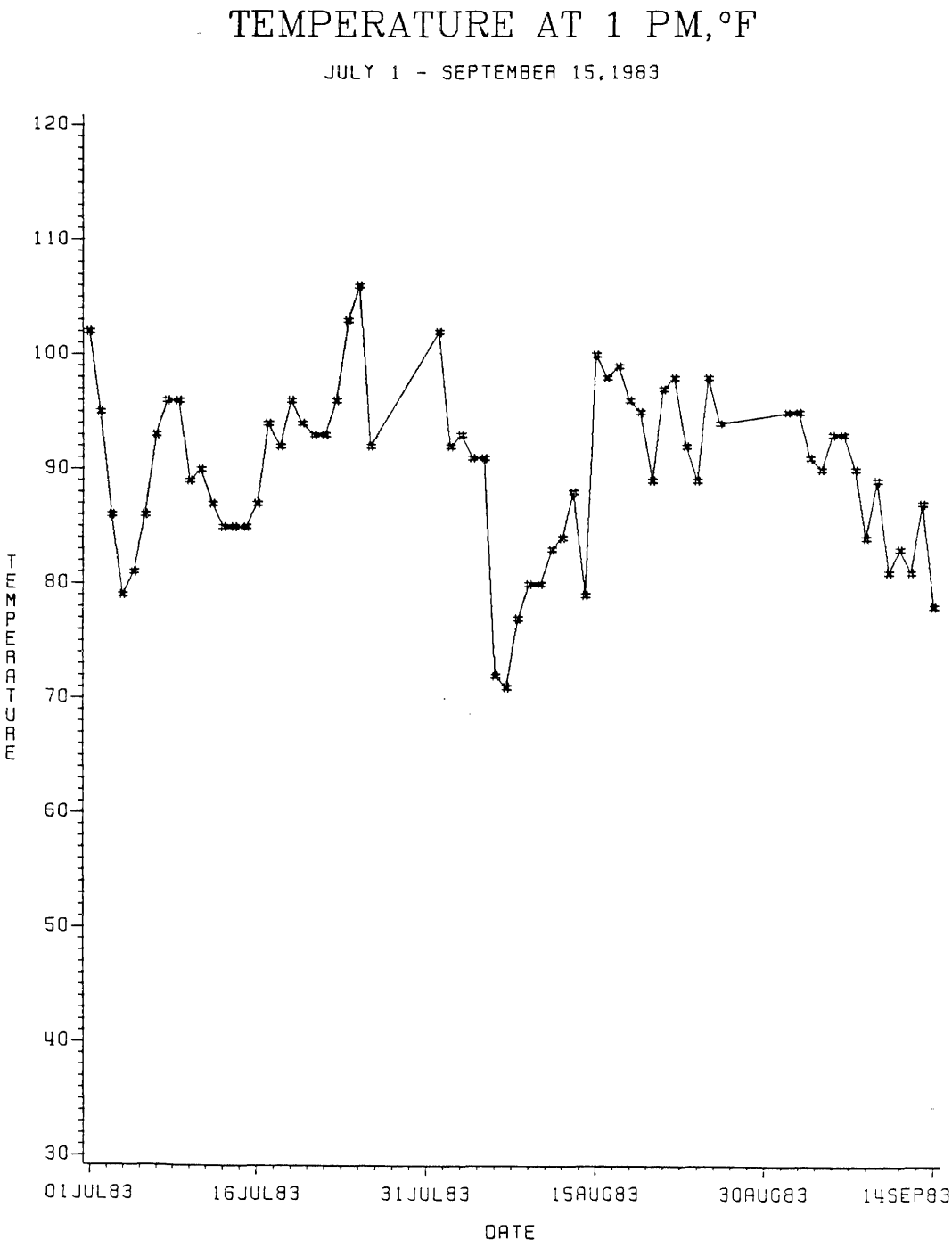
TEMPERATURE AT 1 PM,°F
JULY 1 - SEPTEMBER 15,1983
120
110
100
90
80
70
60
50
40
30
TEMPERATURE
01JUL83
16JUL83
31JUL83
15AUG83
30AUG83
14SEP83
DATE

Fig. 10B.

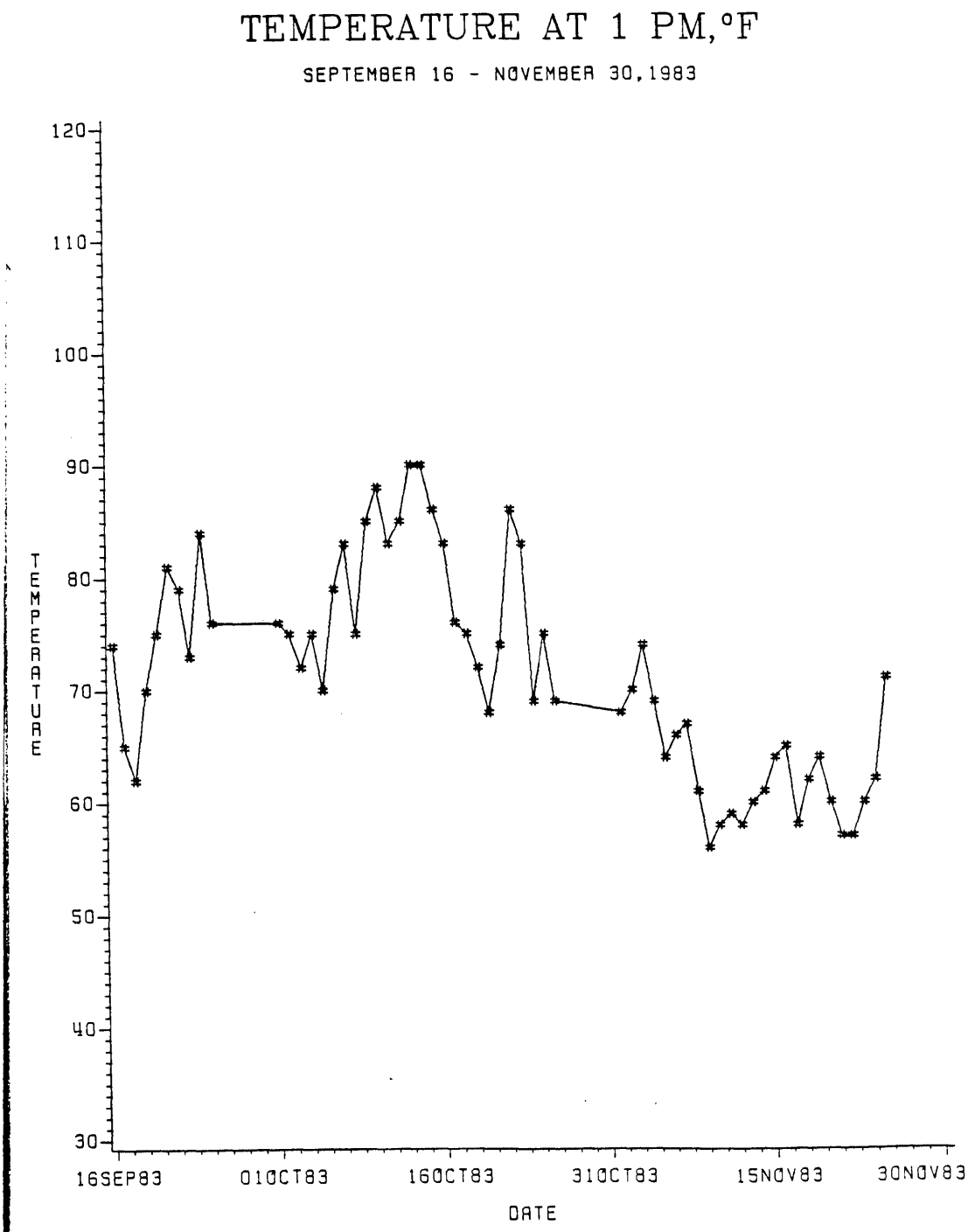
TEMPERATURE AT 1 PM,°F
SEPTEMBER 16 - NOVEMBER 30,1983
TEMPERATURE
120
110
100
90
80
70
60
50
40
30
16SEP83
01OCT83
16OCT83
31OCT83
15NOV83
30NOV83
DATE

Figure 10C.

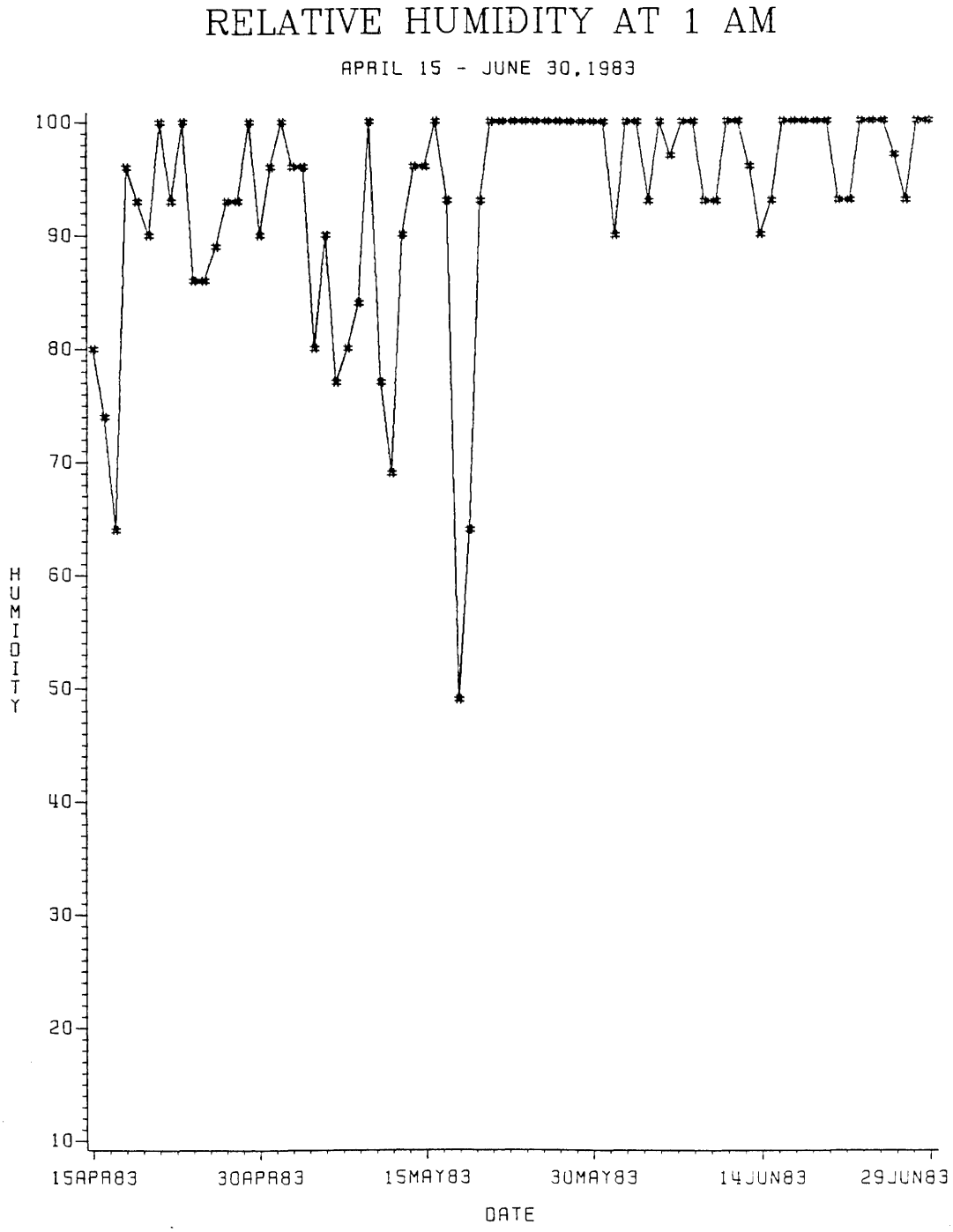

Figure 11A. Relative humidity at 1 A.M. in percent (%) in Glendora area.

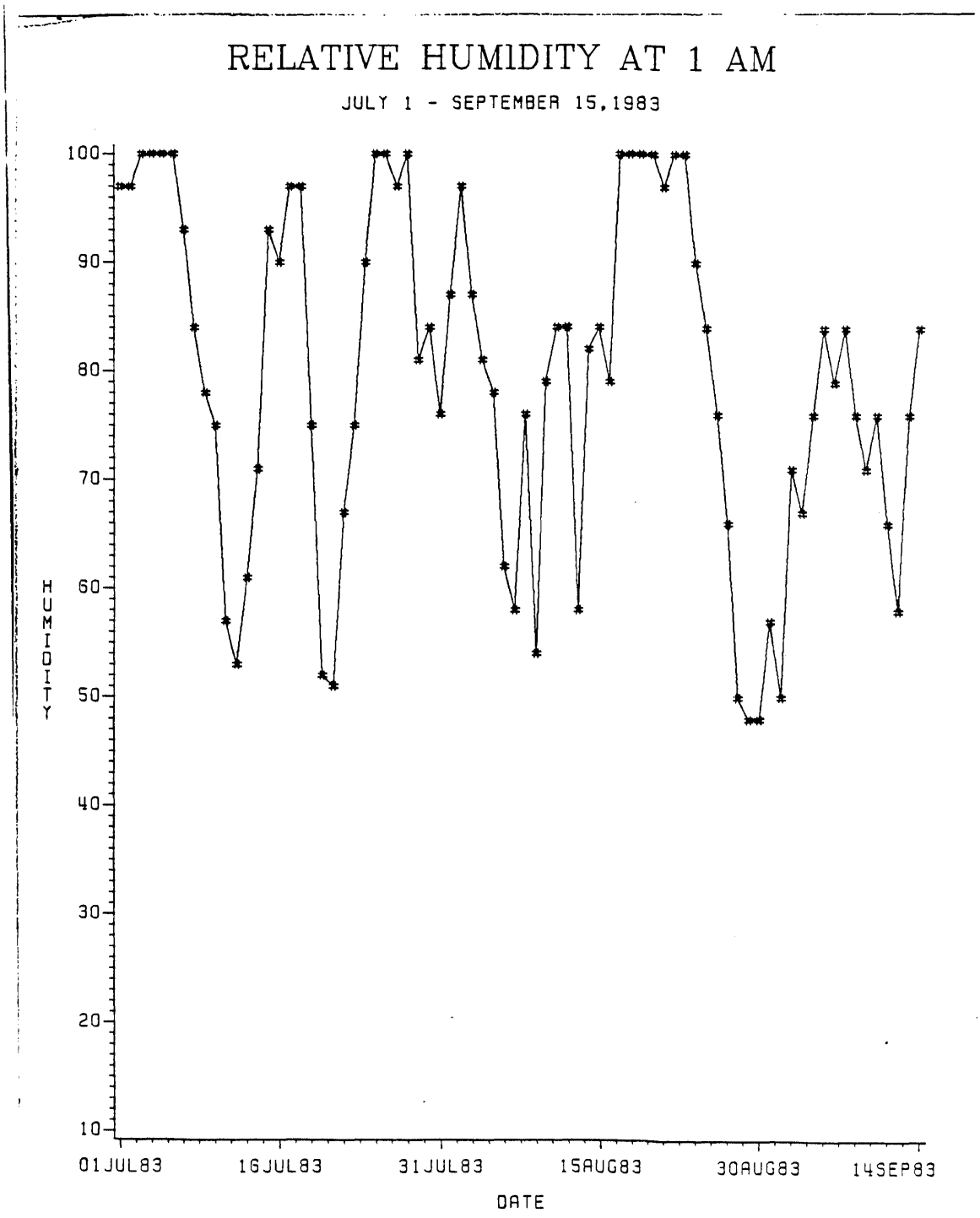
RELATIVE HUMIDITY AT 1 AM
JULY 1 - SEPTEMBER 15,1983
HUMIDITY
100
90
80
70
60
50
40
30
20
10
01JUL83
16JUL83
31JUL83
15AUG83
30AUG83
14SEP83
DATE

Figure 11B.

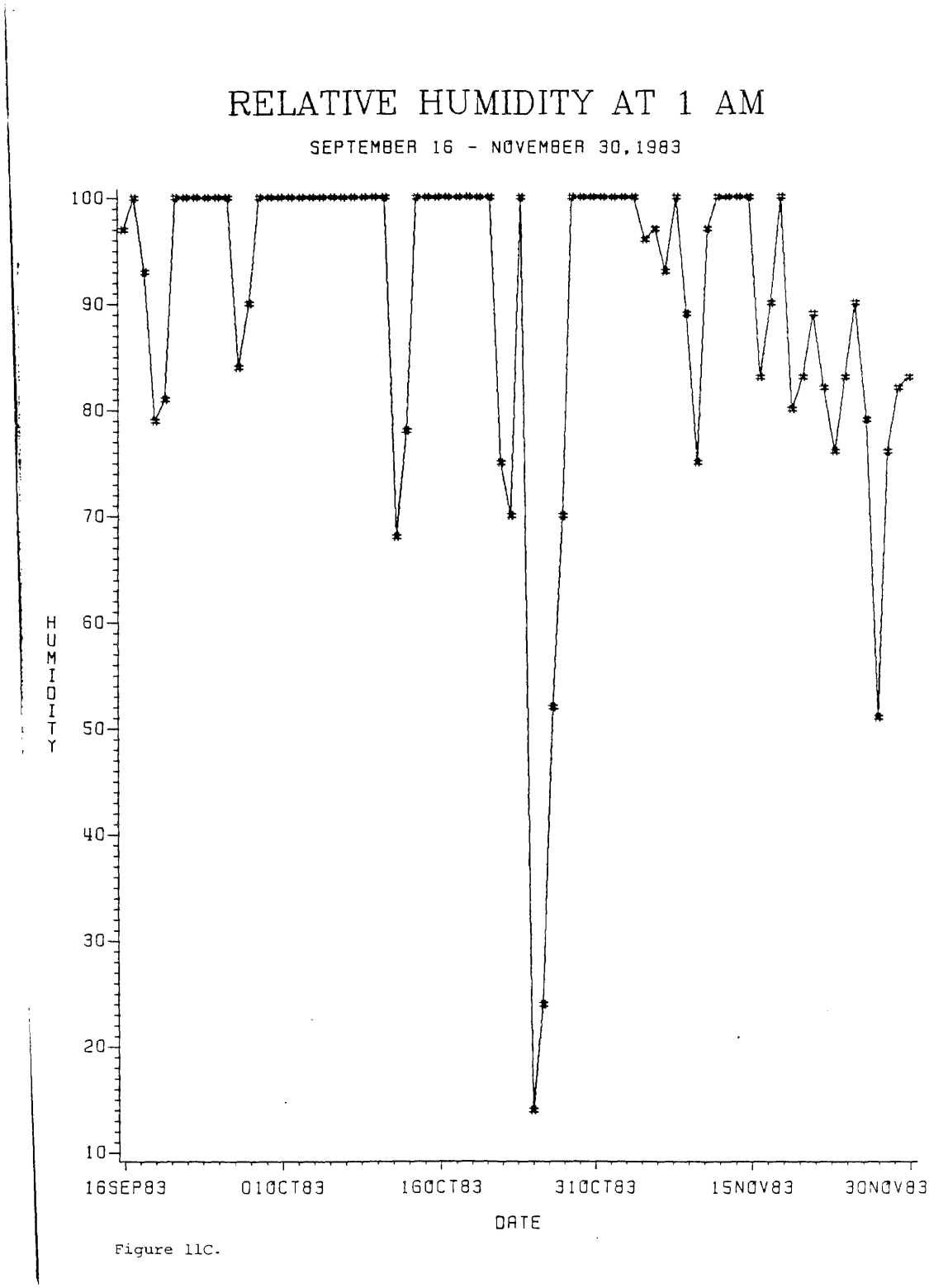
RELATIVE HUMIDITY AT 1 AM
SEPTEMBER 16 - NOVEMBER 30,1983
HUMIDITY
100
90
80
70
60
50
40
30
20
10
16SEP83
01OCT83
16OCT83
31OCT83
15NOV83
30NOV83
DATE

Figure 11C.

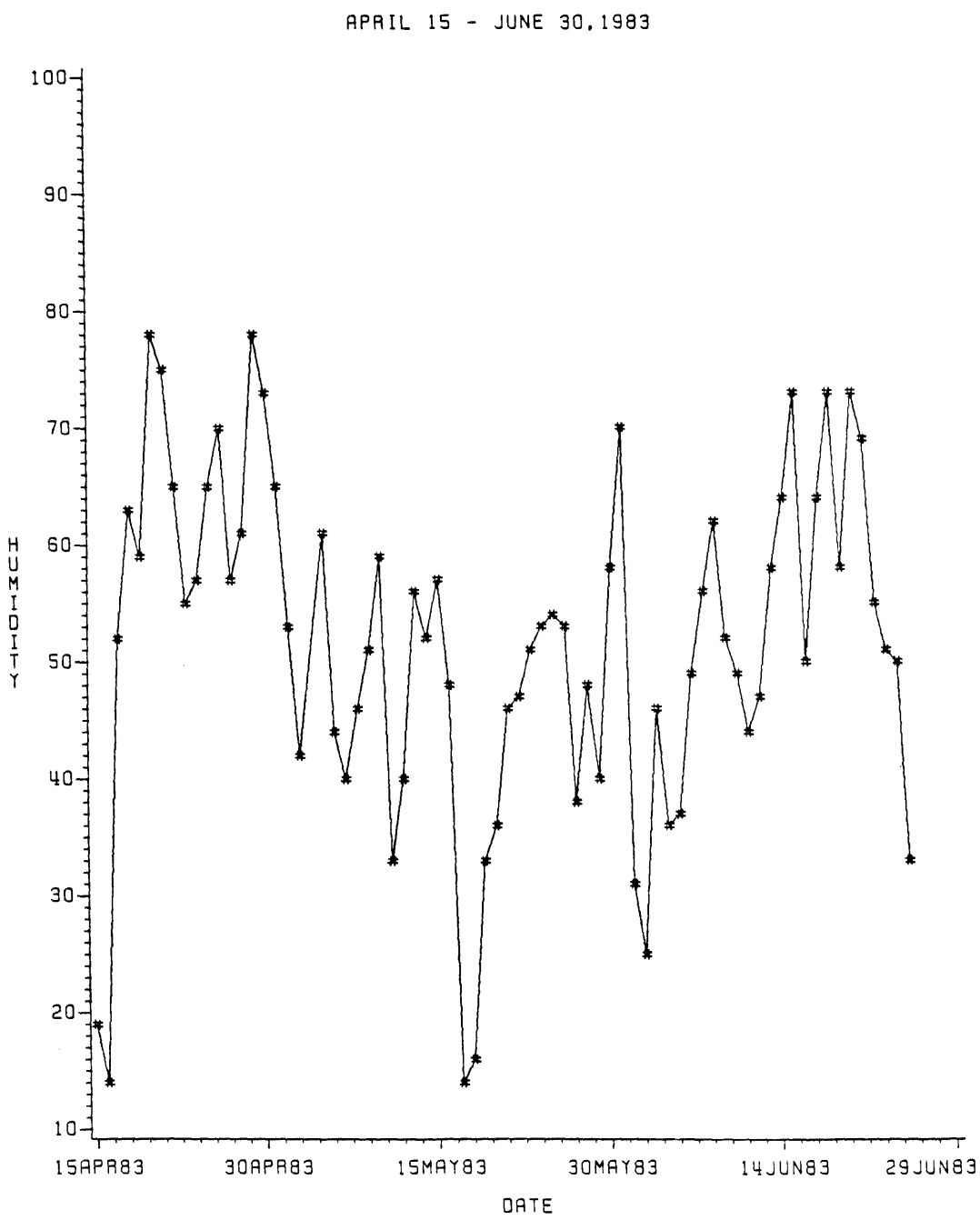

Figure 12A. Relative humidity at 1 P.M. in percent (%) in Glendora area.

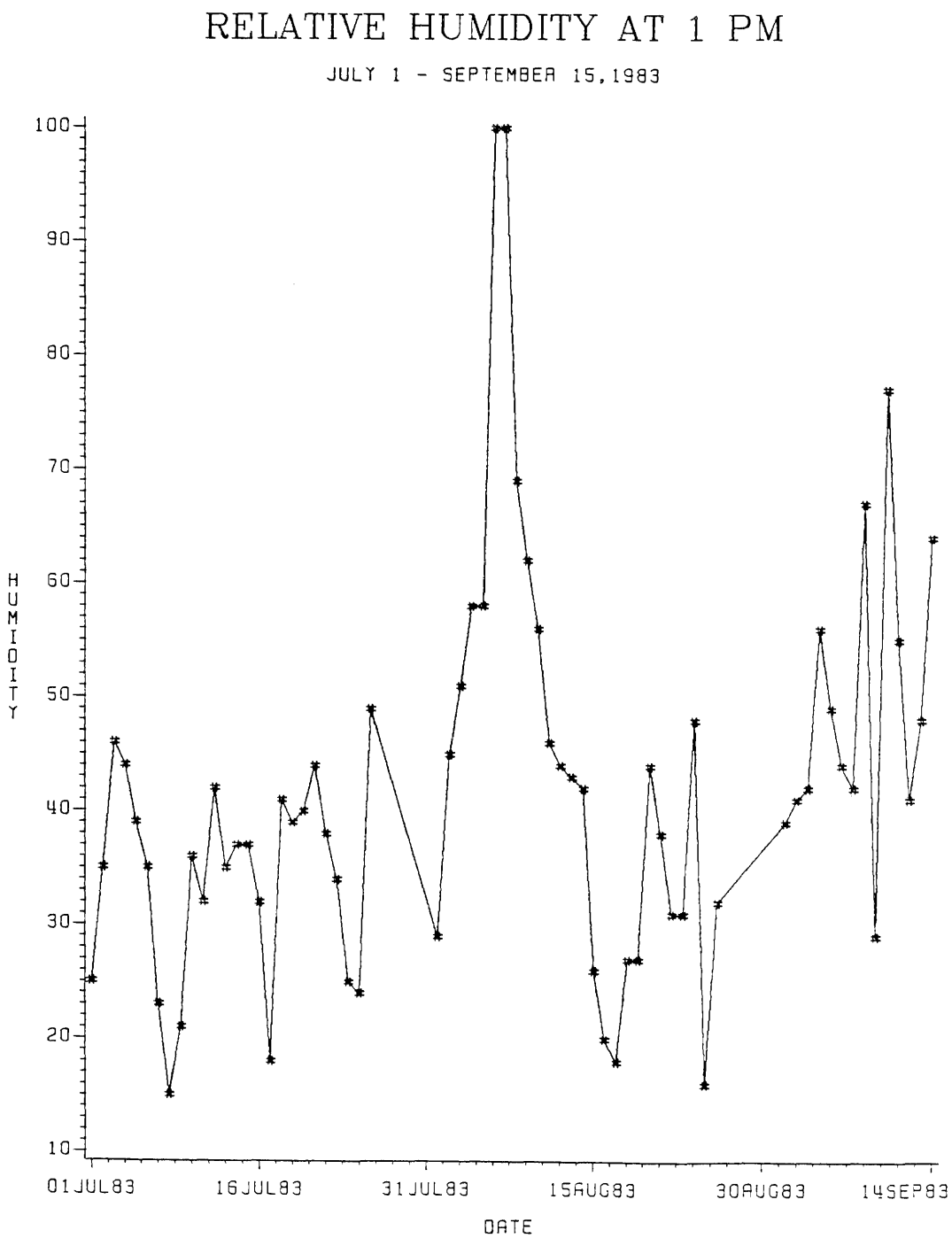
RELATIVE HUMIDITY AT 1 PM
JULY 1 - SEPTEMBER 15,1983
HUMIDITY
100
90
80
70
60
50
40
30
20
10
01JUL83
16JUL83
31JUL83
15AUG83
30AUG83
14SEP83
DATE

Figure 12B.

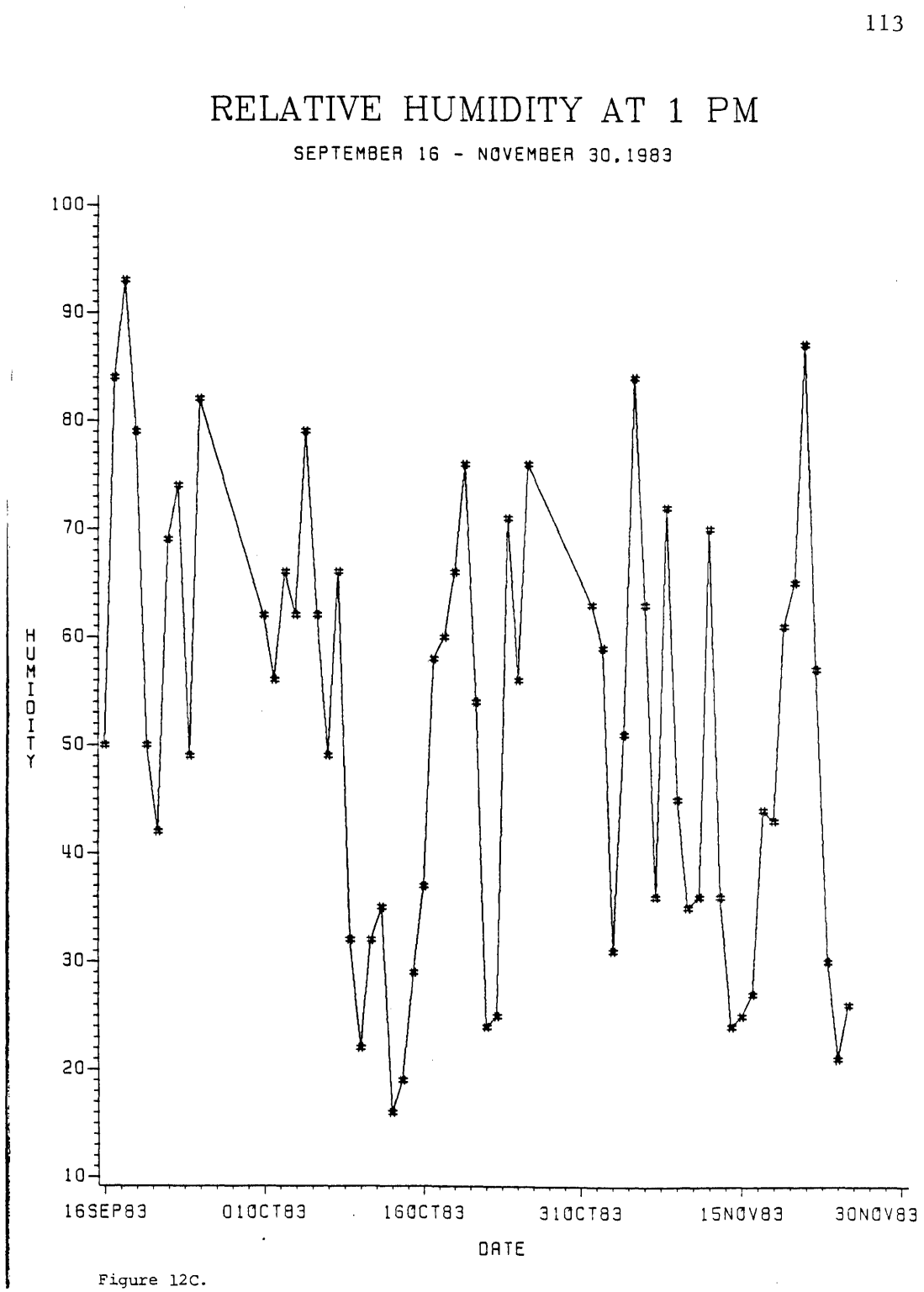
RELATIVE HUMIDITY AT 1 PM
SEPTEMBER 16 - NOVEMBER 30,1983
HUMIDITY
100
90
80
70
60
50
40
30
20
10
16SEP83
01OCT83
16OCT83
31OCT83
15NOV83
30NOV83
DATE

Figure 12C.

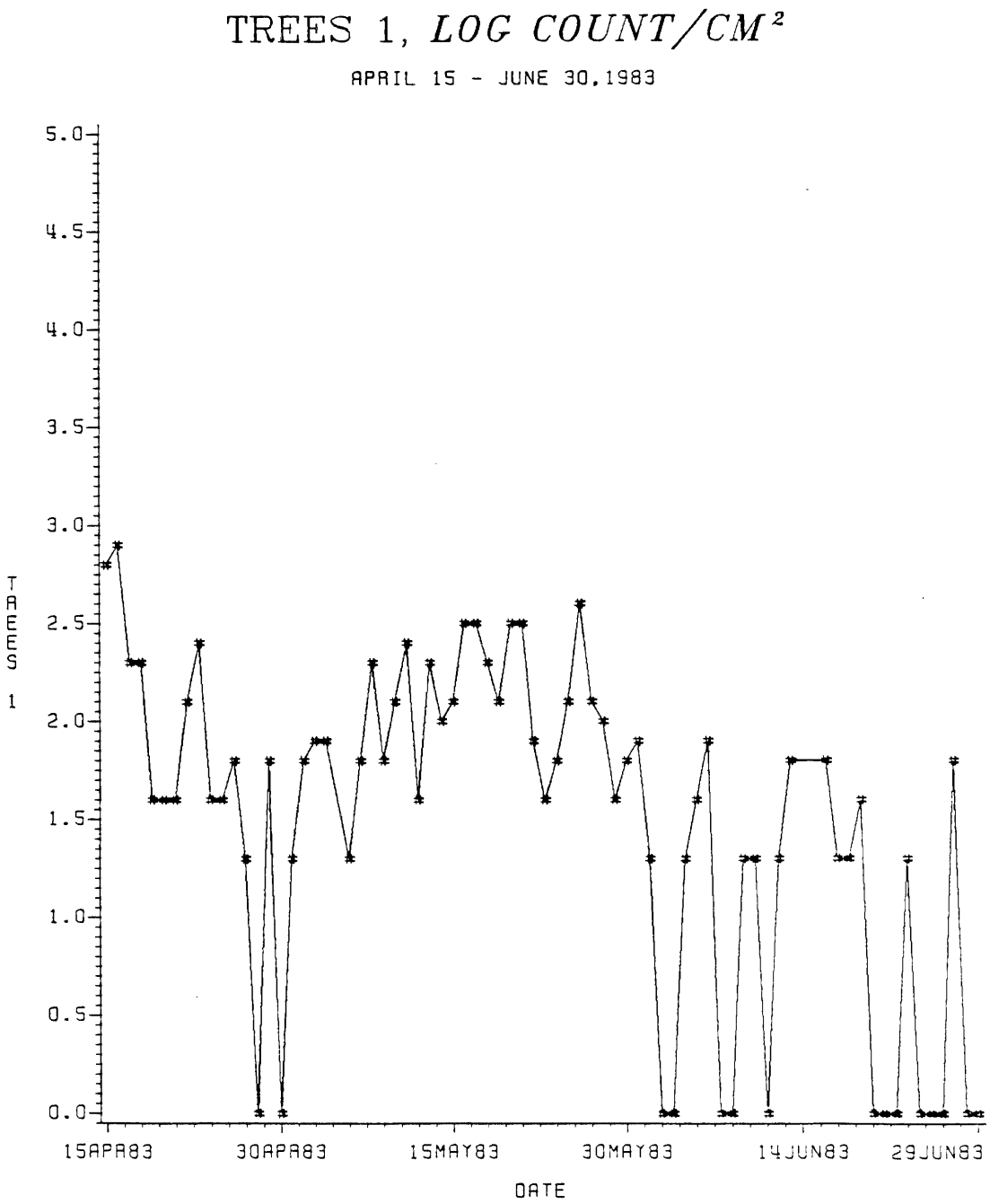

Figure 13A. Daily concentrations of atmospheric spores-pollen from Trees 1 as the logarithm (to the base 10) of the count per square centimeter (log count/cm^2) in Glendora area.

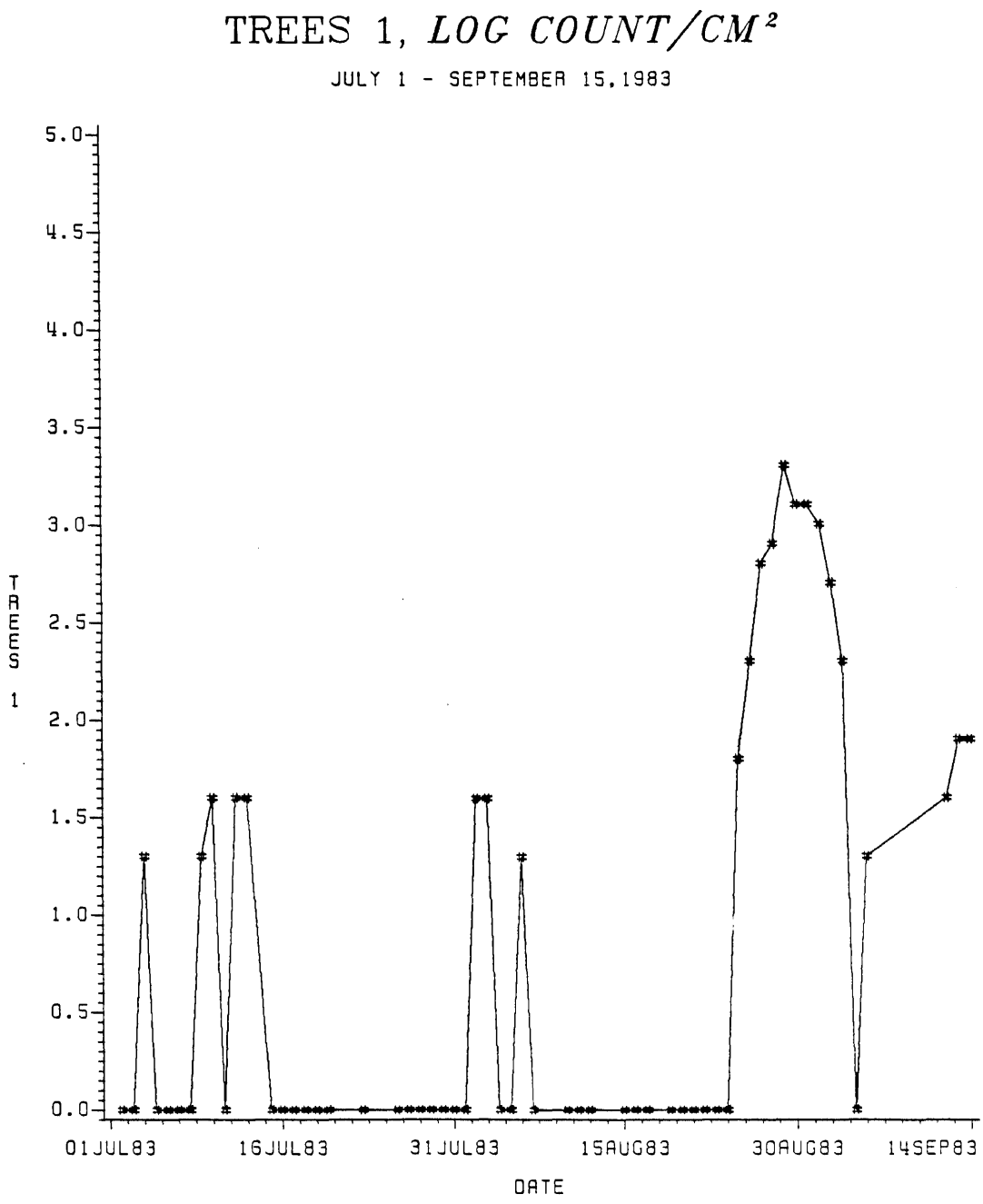
TREES 1, LOG COUNT/CM²
JULY 1 - SEPTEMBER 15,1983
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
TREES 1
01JUL83
16JUL83
31JUL83
15AUG83
30AUG83
14SEP83
DATE

Figure 13B.

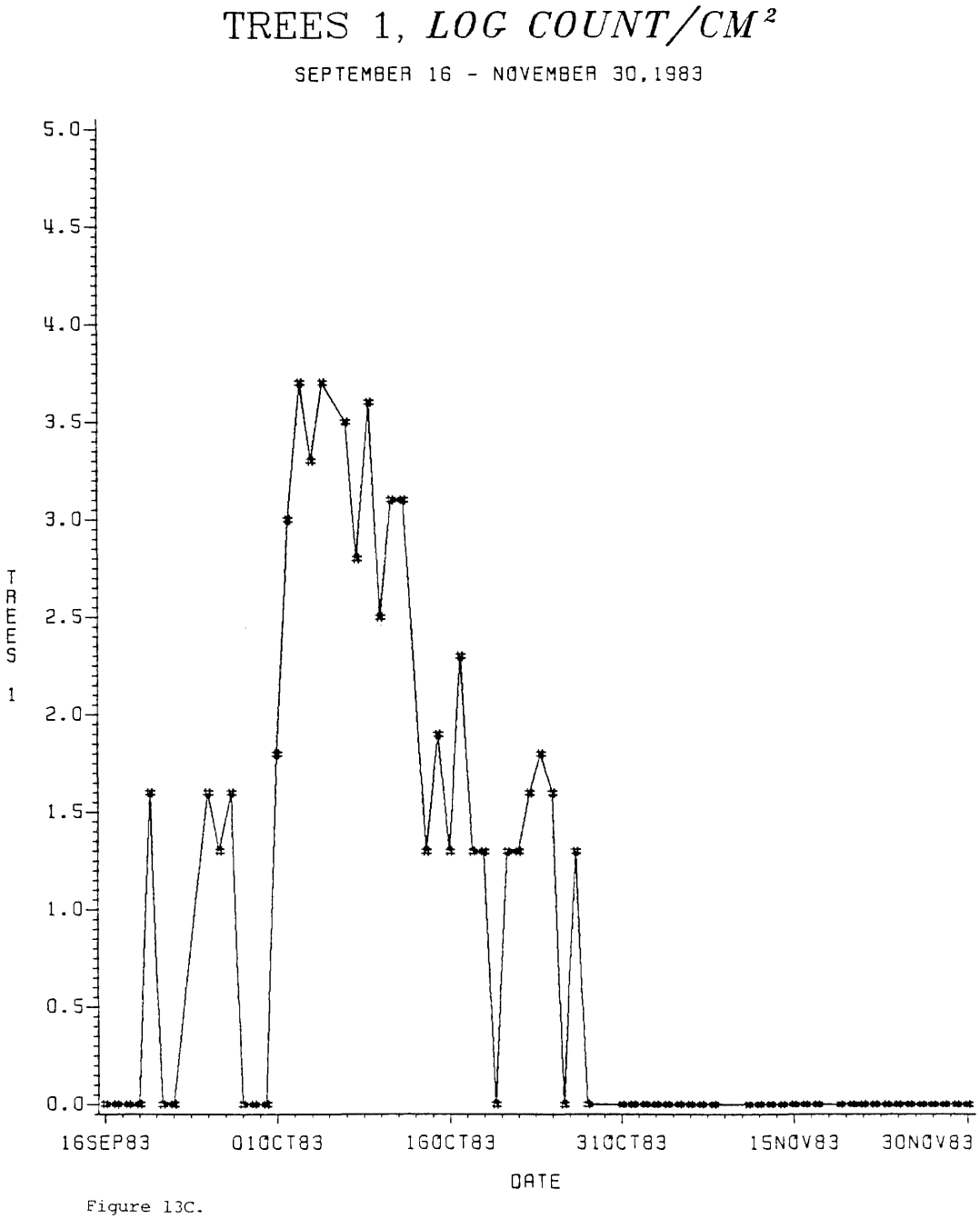
TREES 1, LOG COUNT/CM²
SEPTEMBER 16 - NOVEMBER 30,1983
TREES 1
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
16SEP83
01OCT83
16OCT83
31OCT83
15NOV83
30NOV83
DATE

Figure 13C.

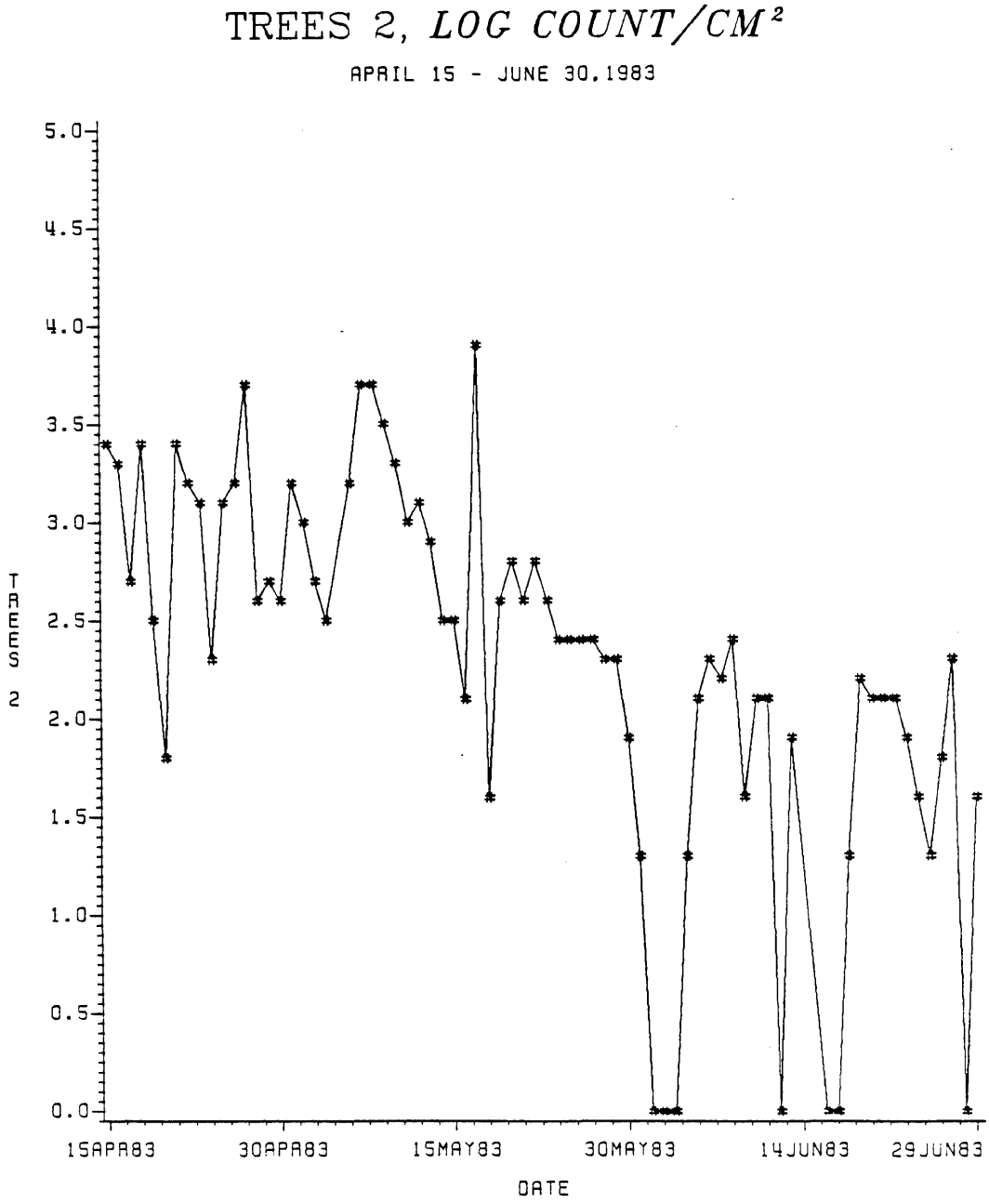

Figure 14A. Daily concentrations of atmospheric spores-pollen from Trees 2 as the logarithm (to the base 10) of the count per square centimeter (log count/cm^2) in Glendora area.

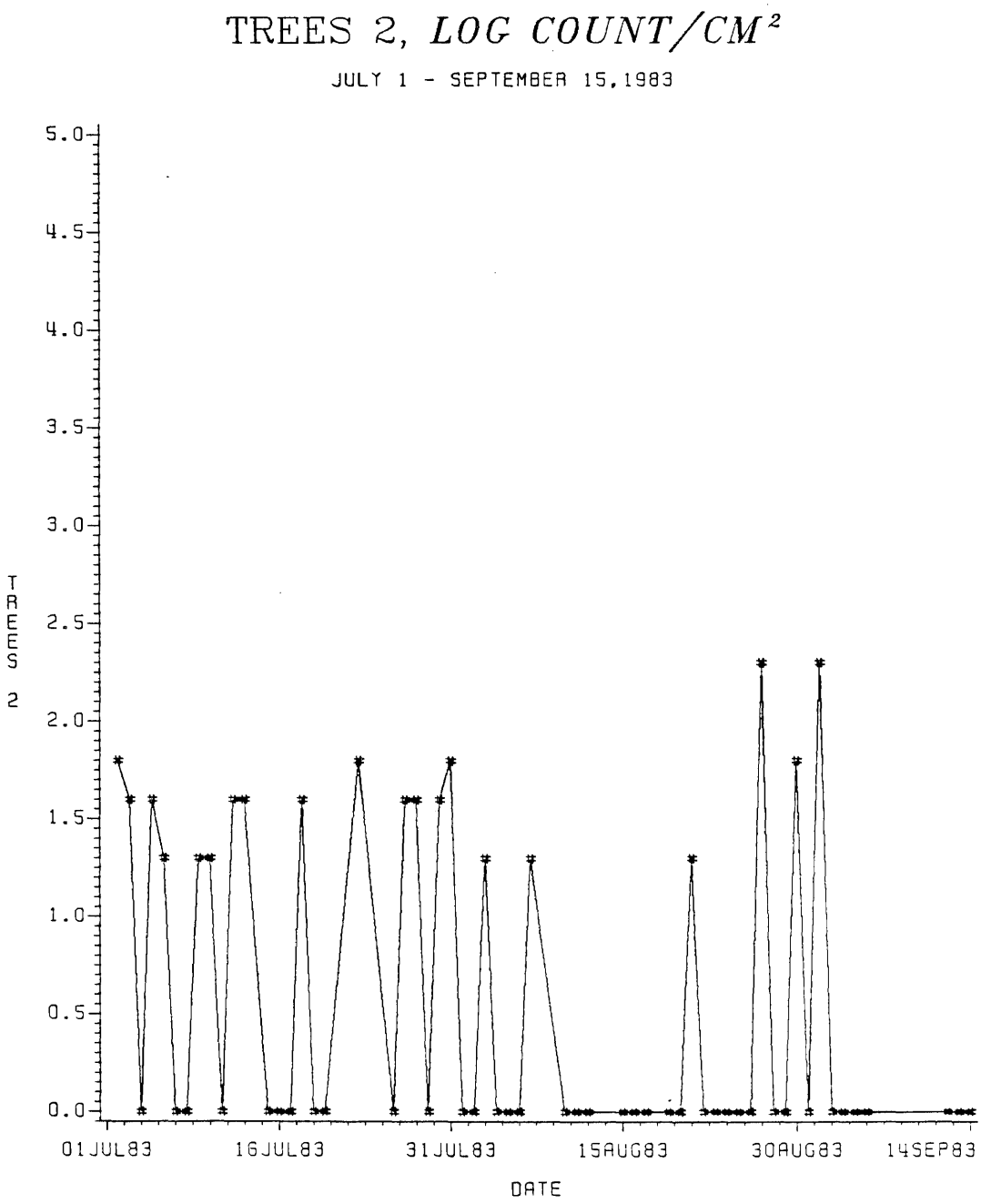
TREES 2, LOG COUNT/CM²
JULY 1 - SEPTEMBER 15,1983
TREES 2
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
01JUL83
16JUL83
31JUL83
15AUG83
30AUG83
14SEP83
DATE

Figure 14B.

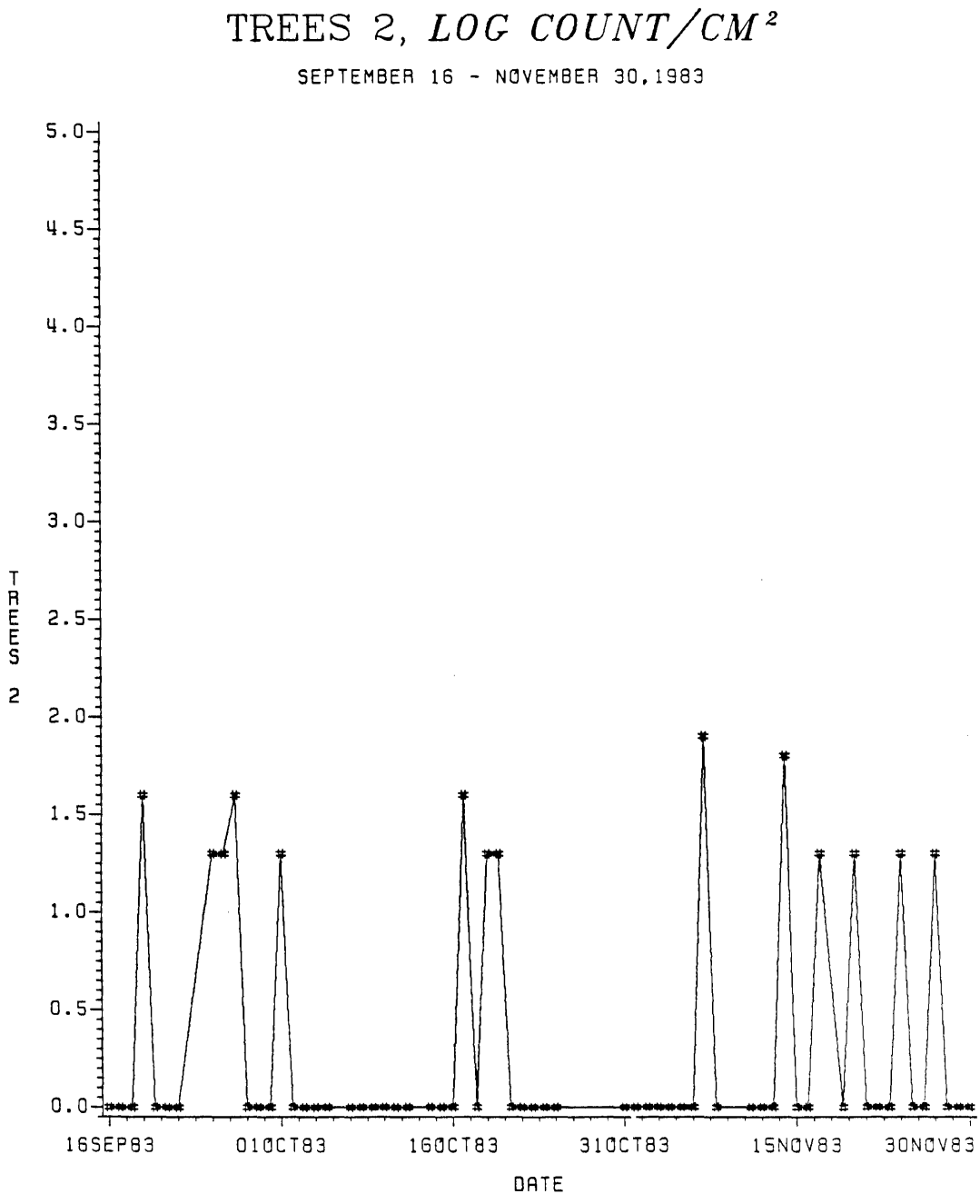
TREES 2, LOG COUNT/CM²
SEPTEMBER 16 - NOVEMBER 30,1983
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
TREES 2
16SEP83
01OCT83
16OCT83
31OCT83
15NOV83
30NOV83
DATE

Figure 14C.

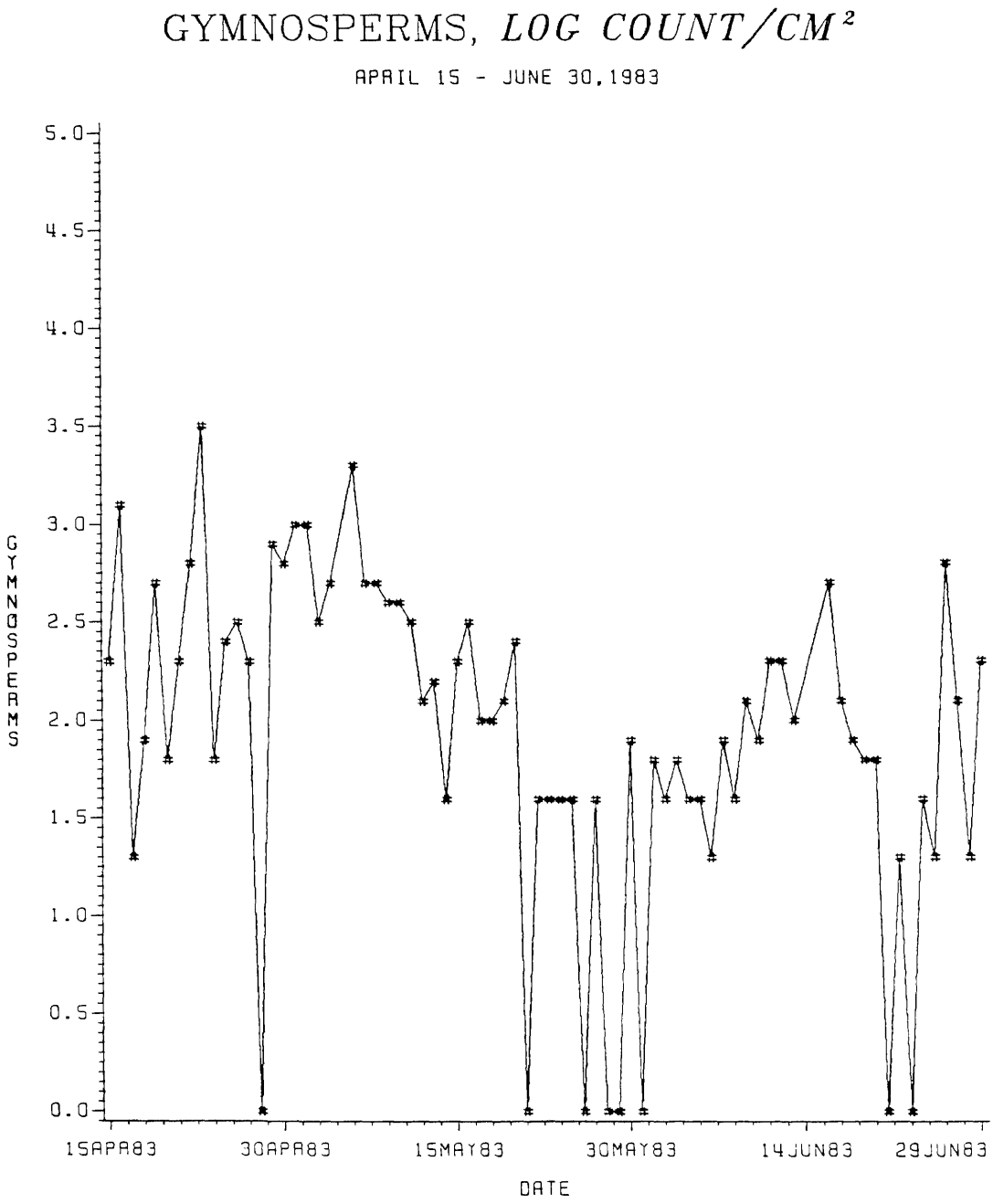

Figure 15A. Daily concentrations of atmospheric spores-pollen from Gymnosperms as the logarithm (to the base 10) of the count per square centimeter (log count/cm^2) in Glendora area.

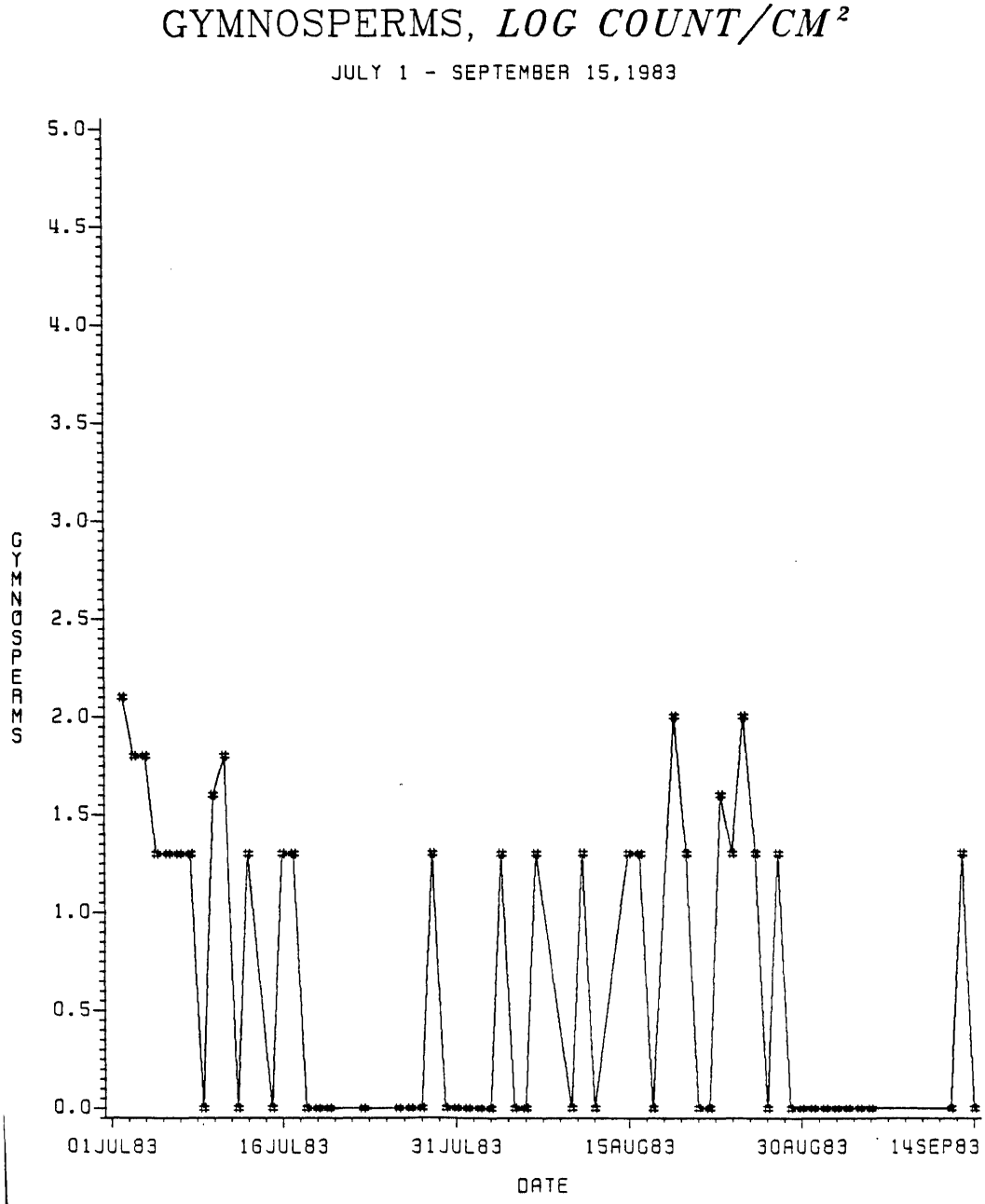
GYMNOSPERMS, LOG COUNT/CM²
JULY 1 - SEPTEMBER 15,1983
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
GYMNOSPERMS
01JUL83
16JUL83
31JUL83
15AUG83
30AUG83
14SEP83
DATE

Figure 15B.

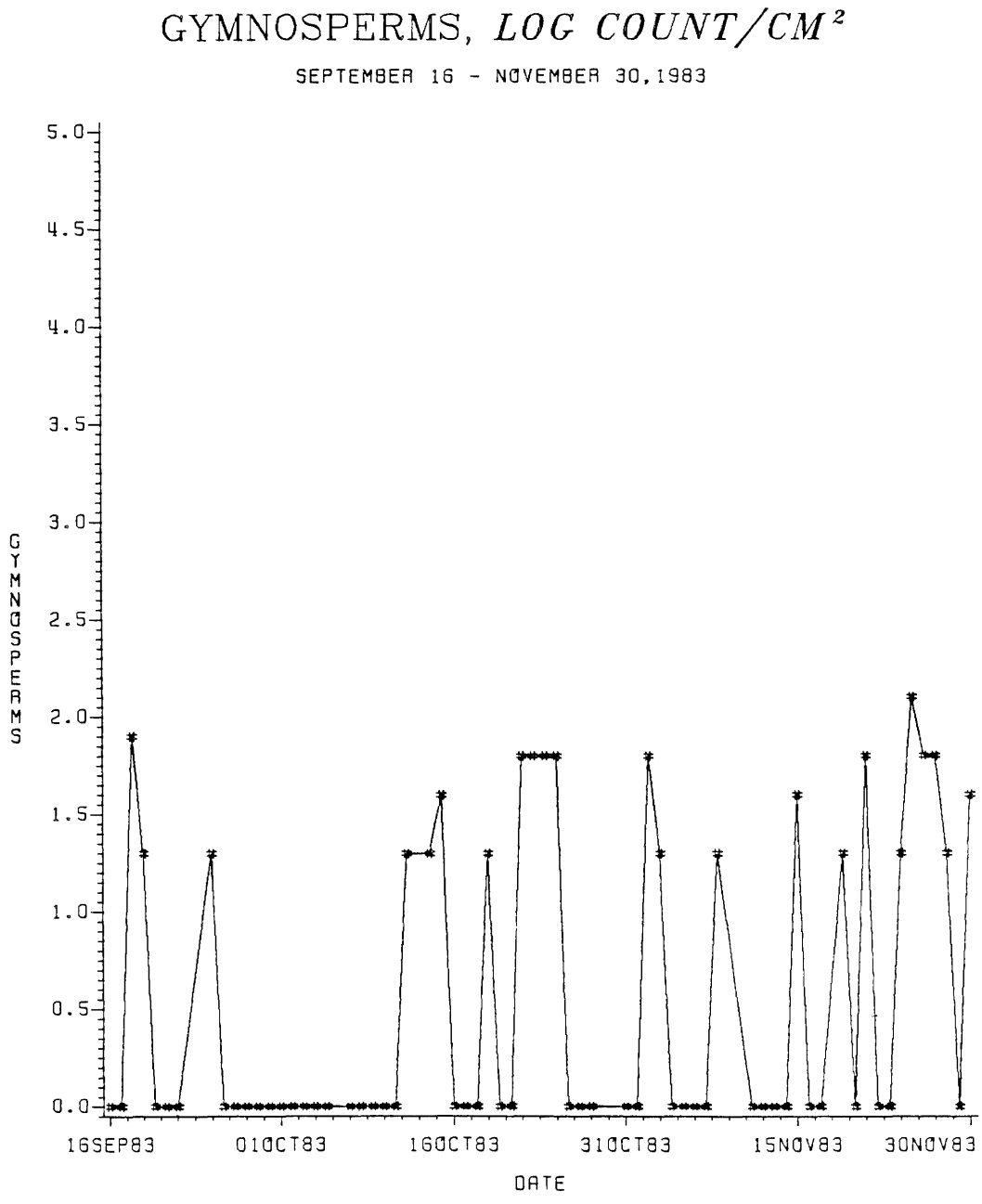
GYMNOSPERMS, LOG COUNT/CM²
SEPTEMBER 16 - NOVEMBER 30,1983
GYMNOSPERMS
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
16SEP83
01OCT83
16OCT83
31OCT83
15NOV83
30NOV83
DATE

Figure 15C.

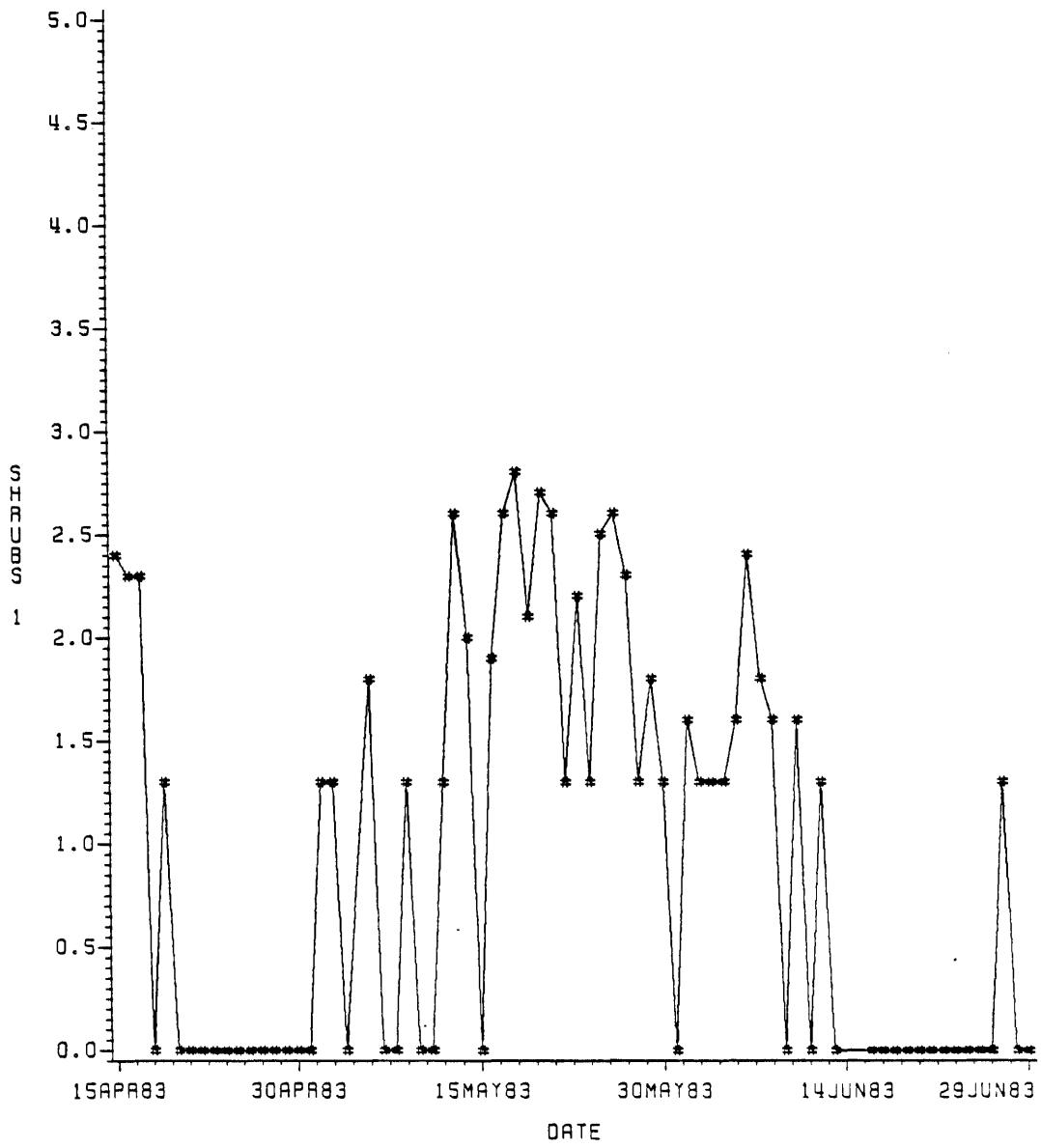

Figure 16A. Daily concentrations of atmospheric spores-pollen from Shrubs 1 as the logarithm (to the base 10) of the count per square centimeter (log count/cm^2) in Glendora area.

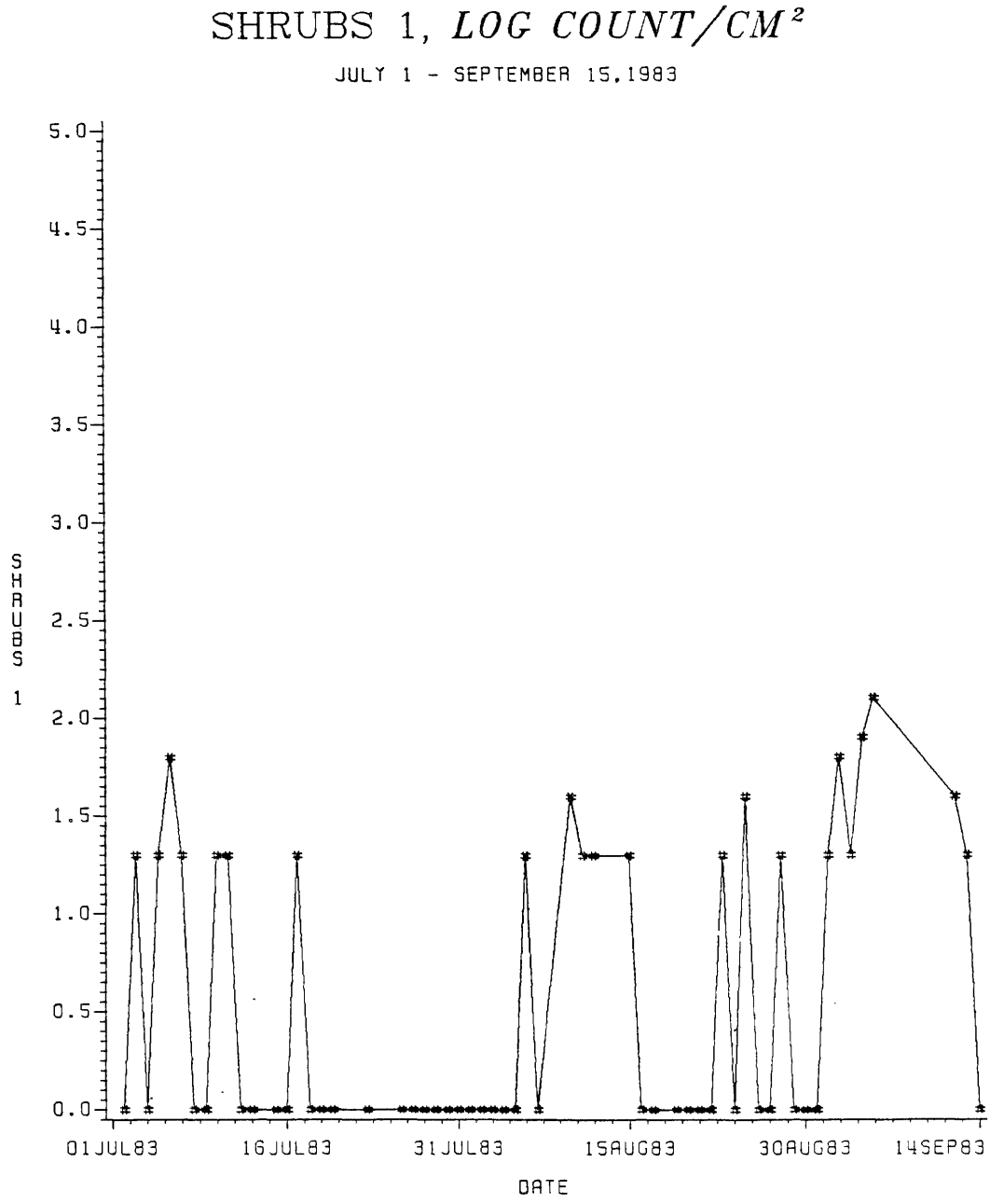
SHRUBS 1, LOG COUNT/CM²
JULY 1 - SEPTEMBER 15,1983
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
SHRUBS 1
01JUL83
16JUL83
31JUL83
15AUG83
30AUG83
14SEP83
DATE

Figure 16B.

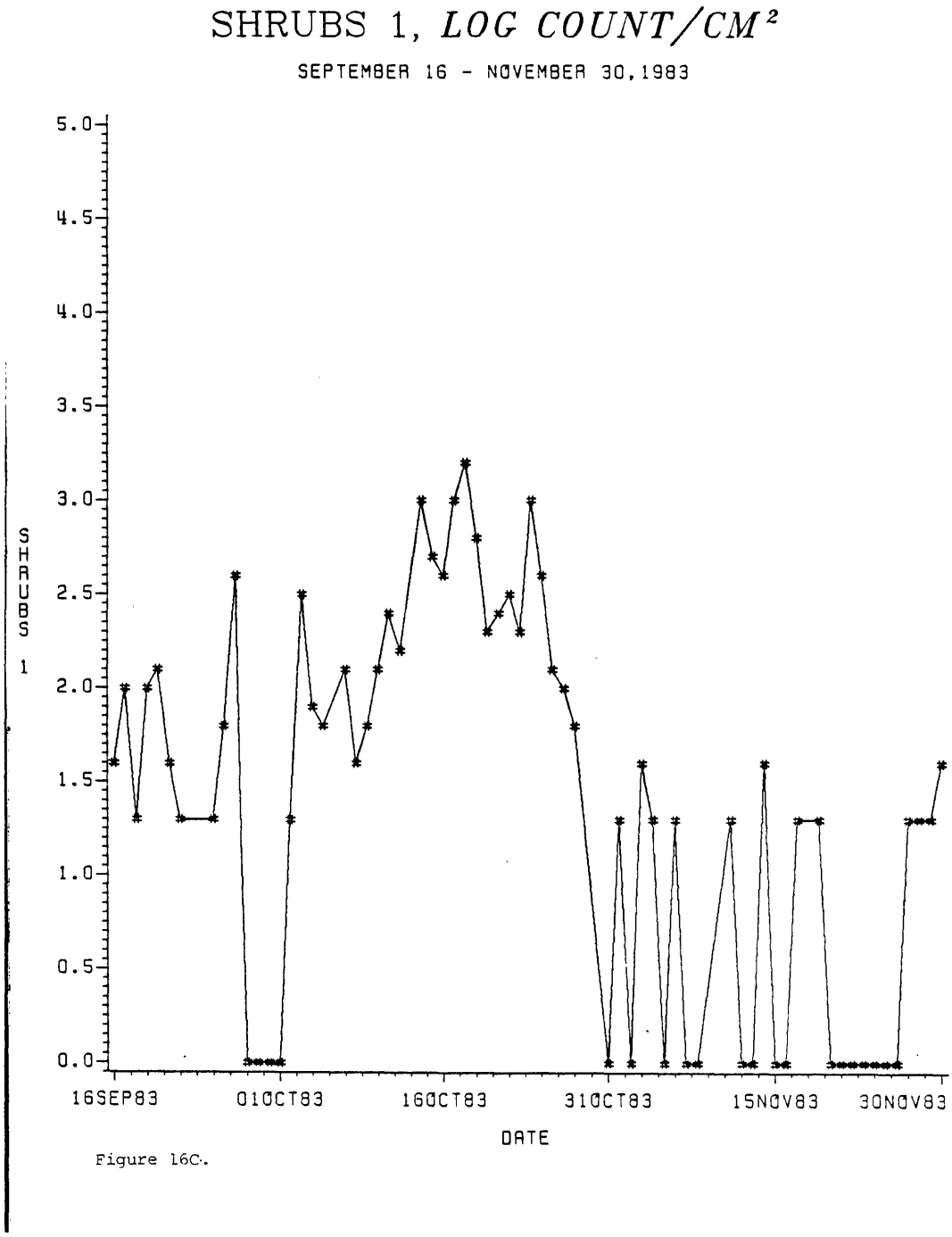
SHRUBS 1, LOG COUNT/CM²
SEPTEMBER 16 - NOVEMBER 30,1983
SHRUBS 1
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
16SEP83
01OCT83
16OCT83
31OCT83
15NOV83
30NOV83
DATE

Figure 16C.

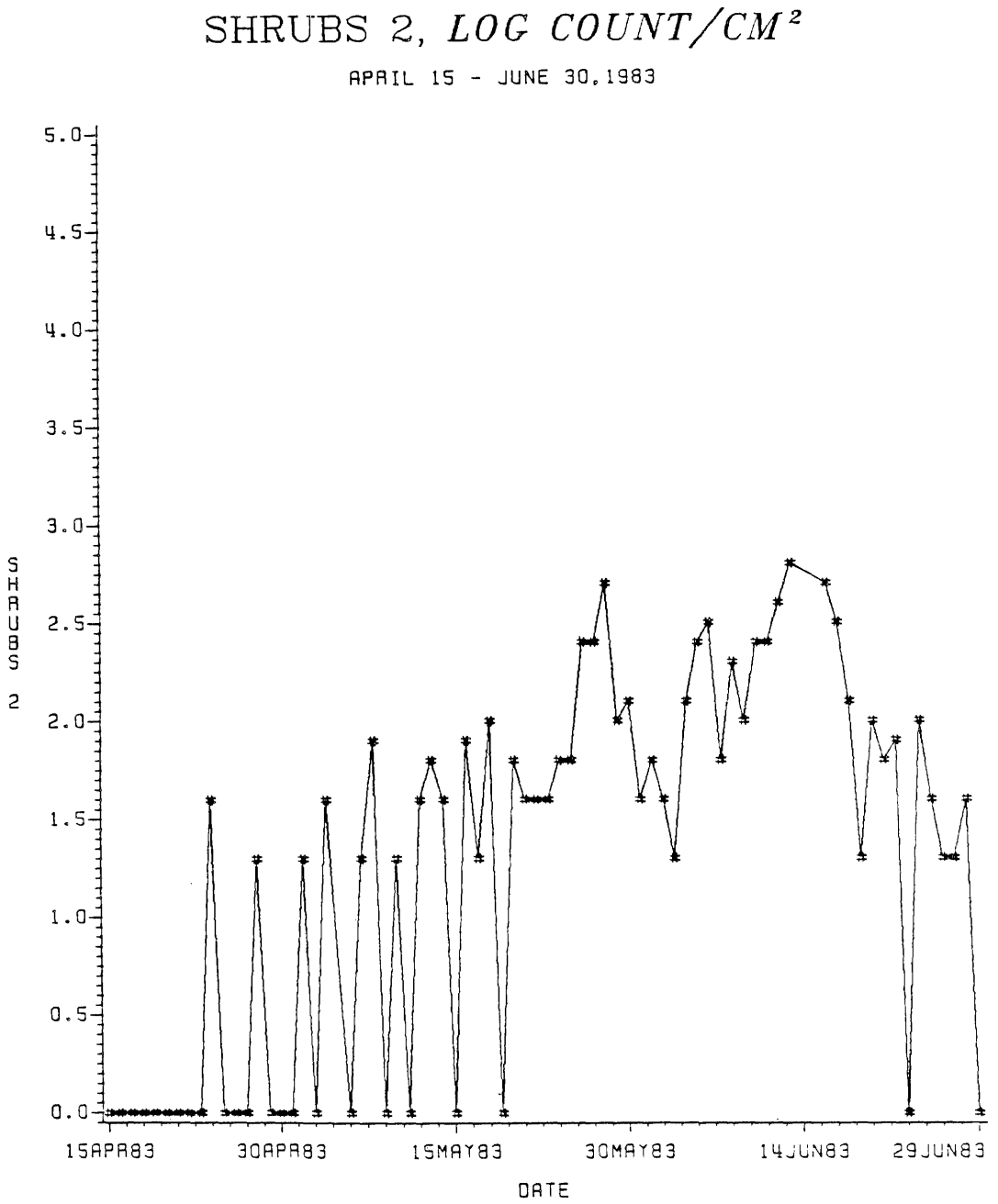

Figure 17A. Daily concentrations of atmospheric spores-pollen from Shrubs 2 as the logarithm (to the base 10) of the count per square centimeter (log count/cm^2) in Glendora area.

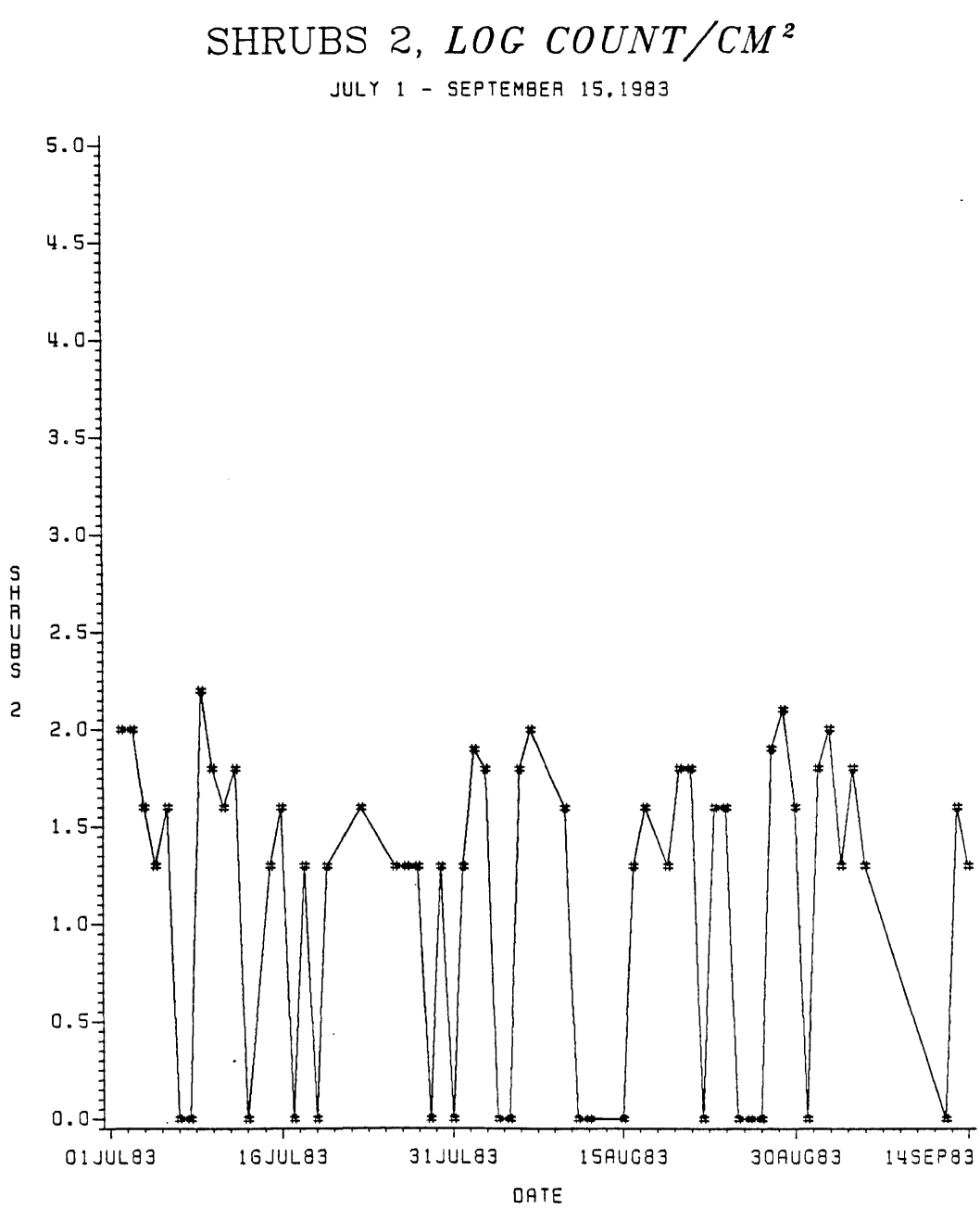
SHRUBS 2, LOG COUNT/CM²
JULY 1 - SEPTEMBER 15,1983
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
SHRUBS 2
01JUL83
16JUL83
31JUL83
15AUG83
30AUG83
14SEP83
DATE

Figure 17B.

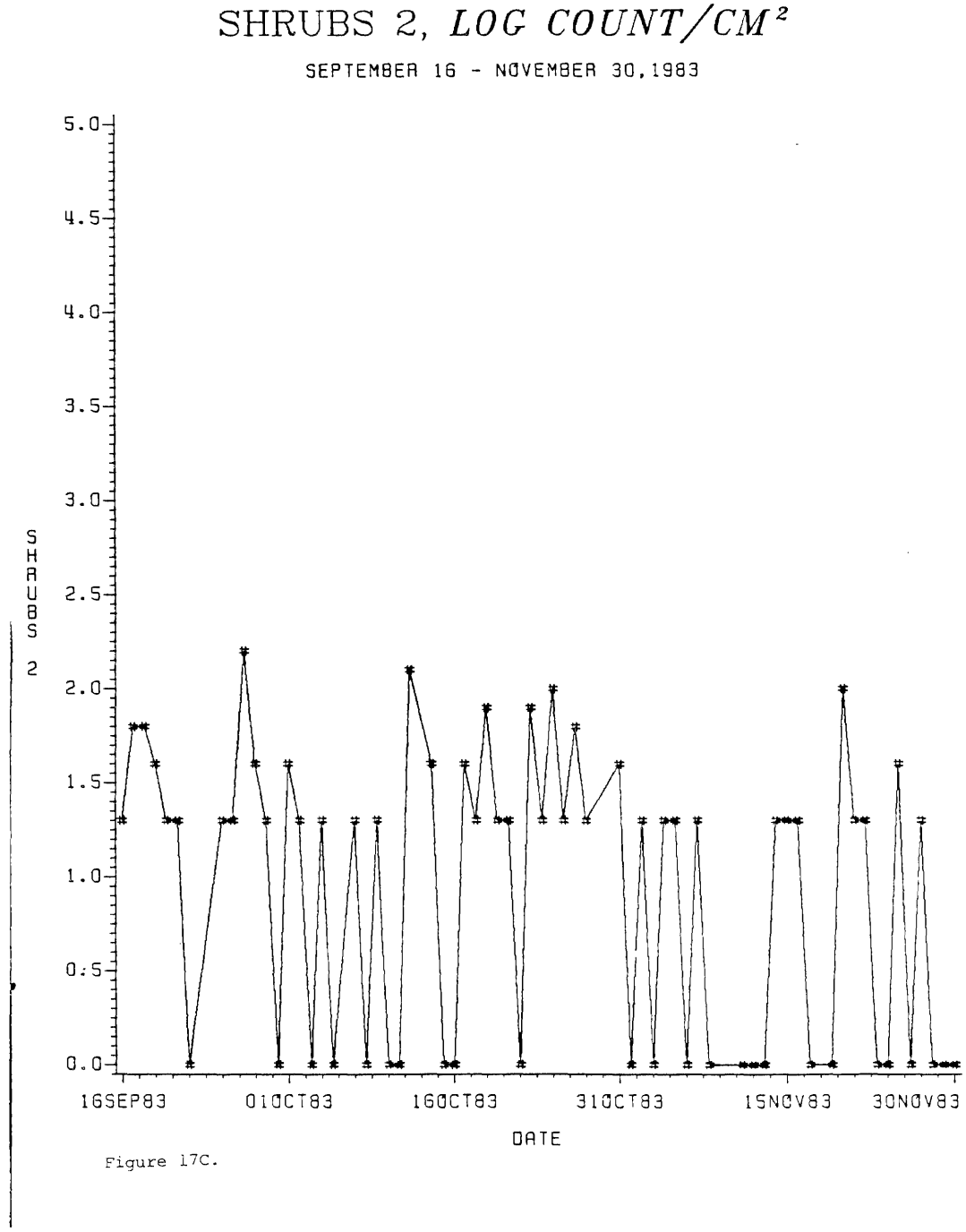
SHRUBS 2, LOG COUNT/CM²
SEPTEMBER 16 - NOVEMBER 30,1983
SHRUBS 2
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
16SEP83
01OCT83
16OCT83
31OCT83
15NOV83
30NOV83
DATE

Figure 17C.

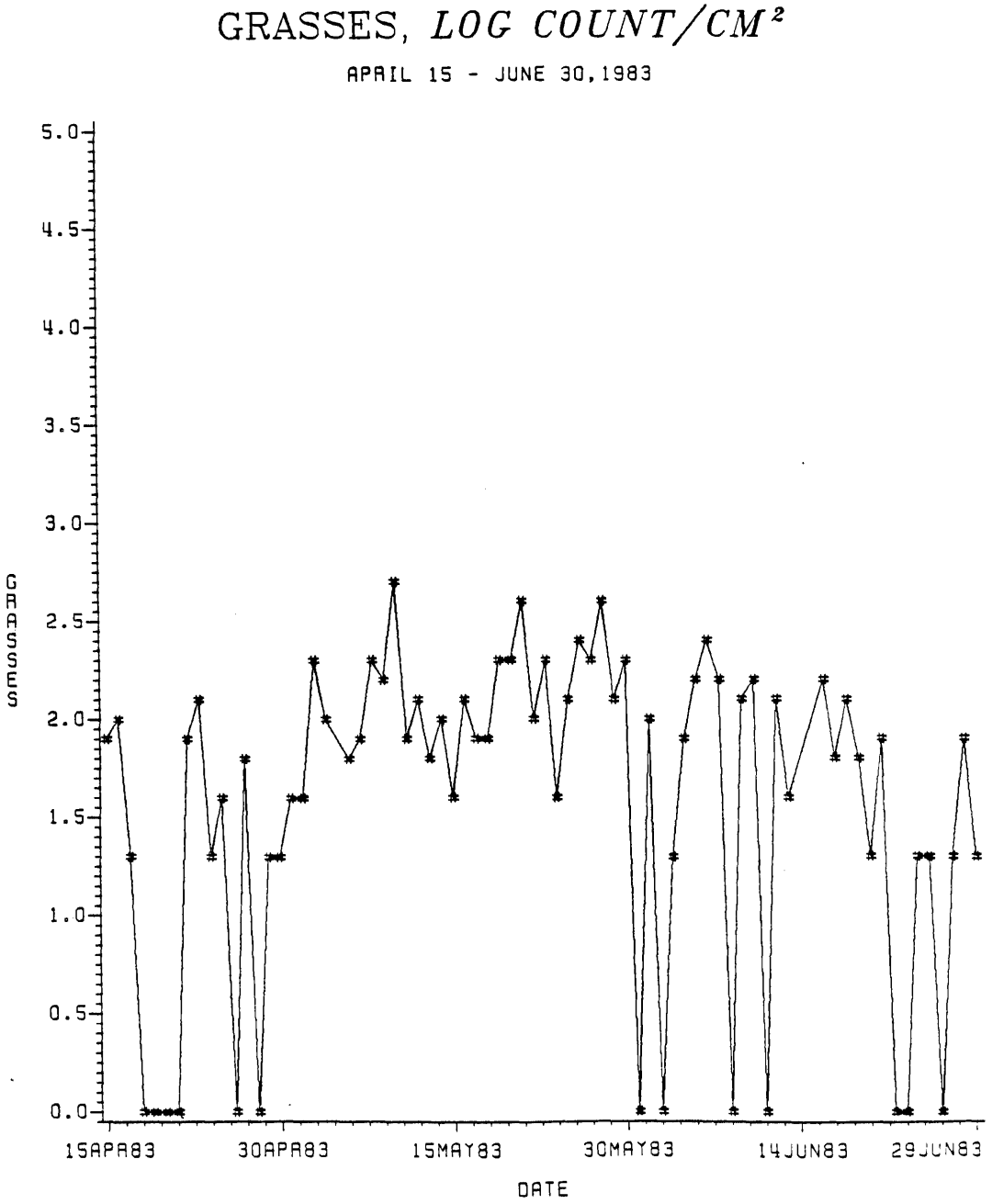

Figure 18A. Daily concentrations of atmospheric Grasses as the logarithm (to the base 10) of the count per square centimeter (log count/cm^2) in Glendora area.

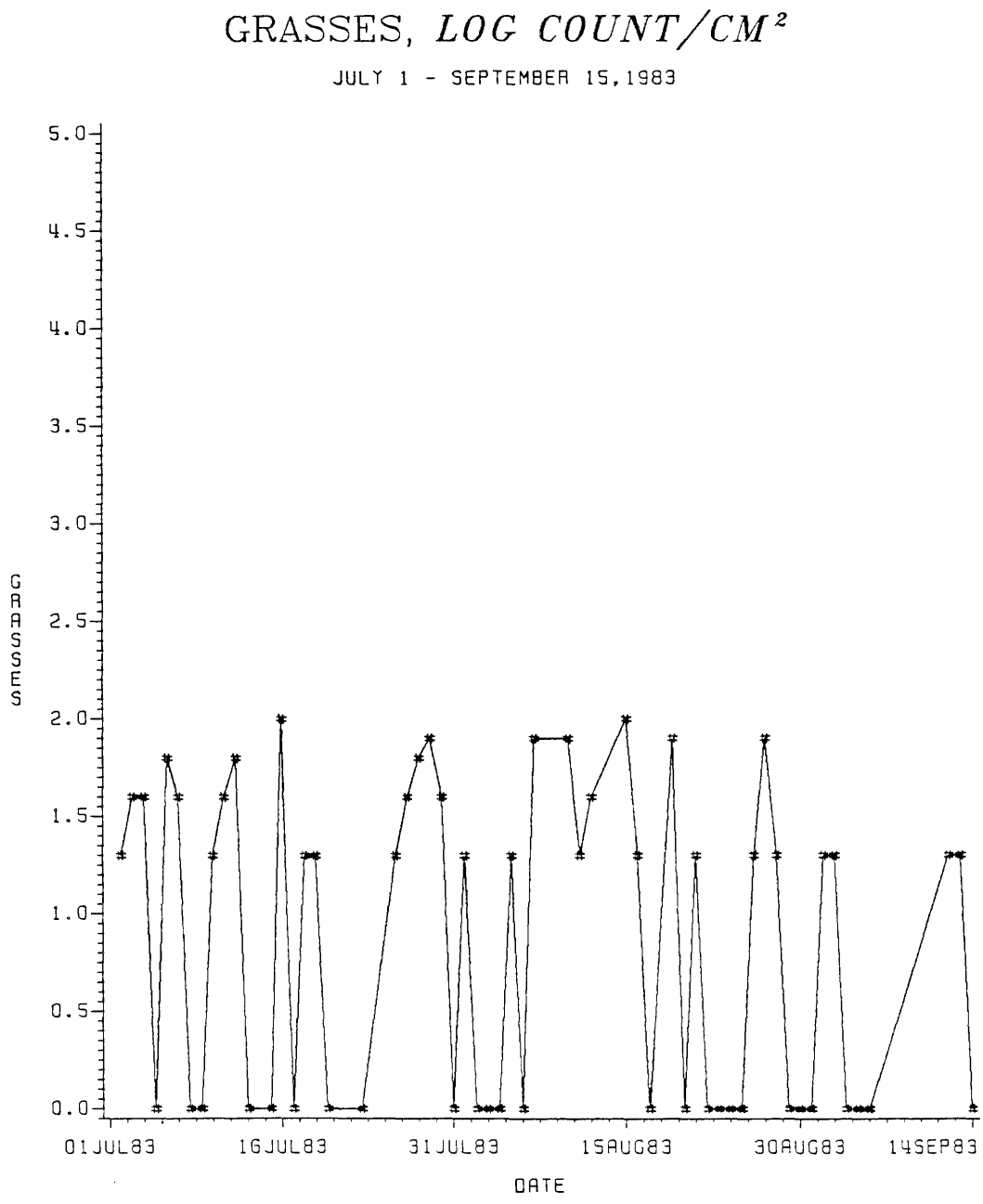
GRASSES, LOG COUNT/CM²
JULY 1 - SEPTEMBER 15,1983
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
GRASSES
01JUL83
16JUL83
31JUL83
15AUG83
30AUG83
14SEP83
DATE

Figure 18B.

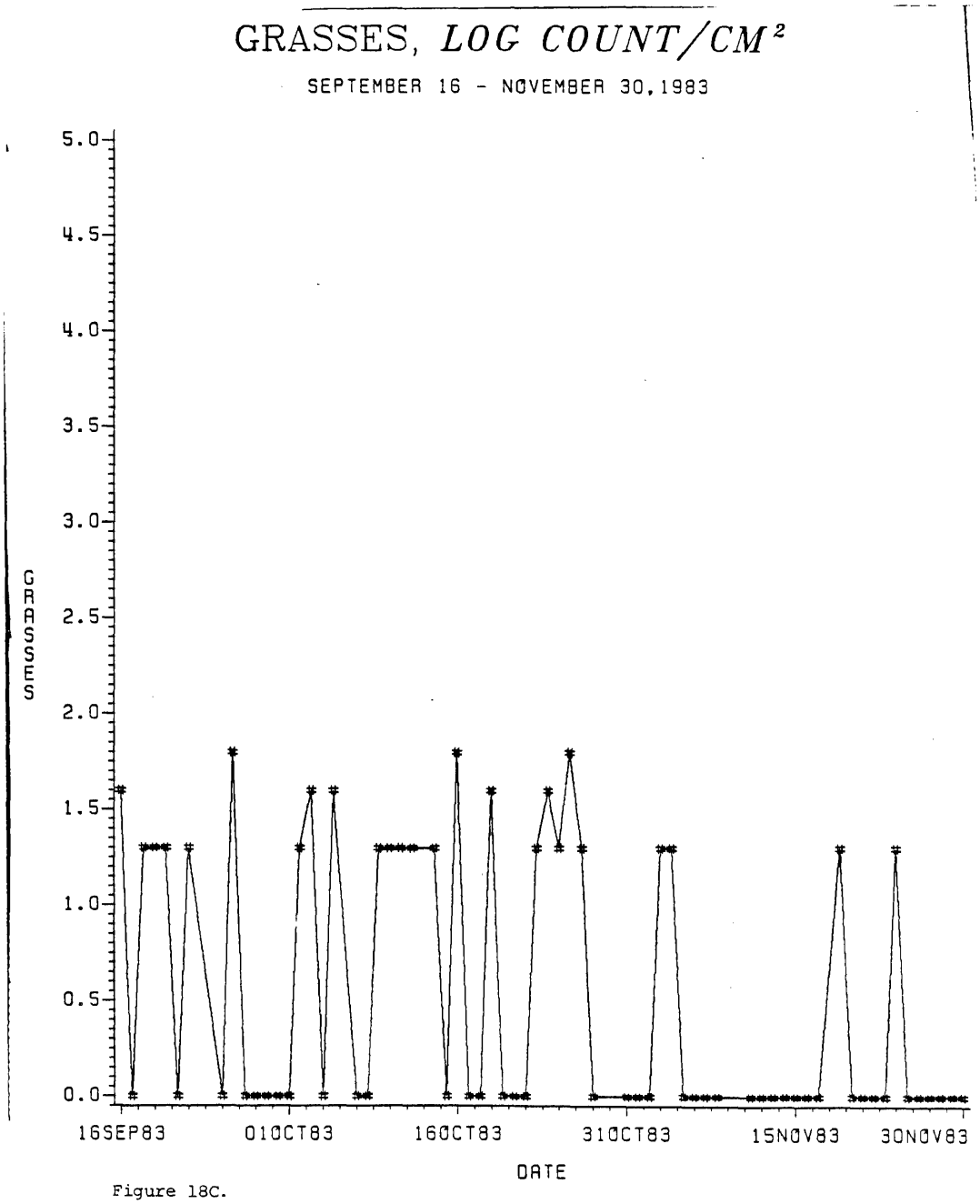
GRASSES, LOG COUNT/CM²
SEPTEMBER 16 - NOVEMBER 30,1983
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
GRASSES
16SEP83
01OCT83
16OCT83
31OCT83
15NOV83
30NOV83
DATE

Figure 18C.

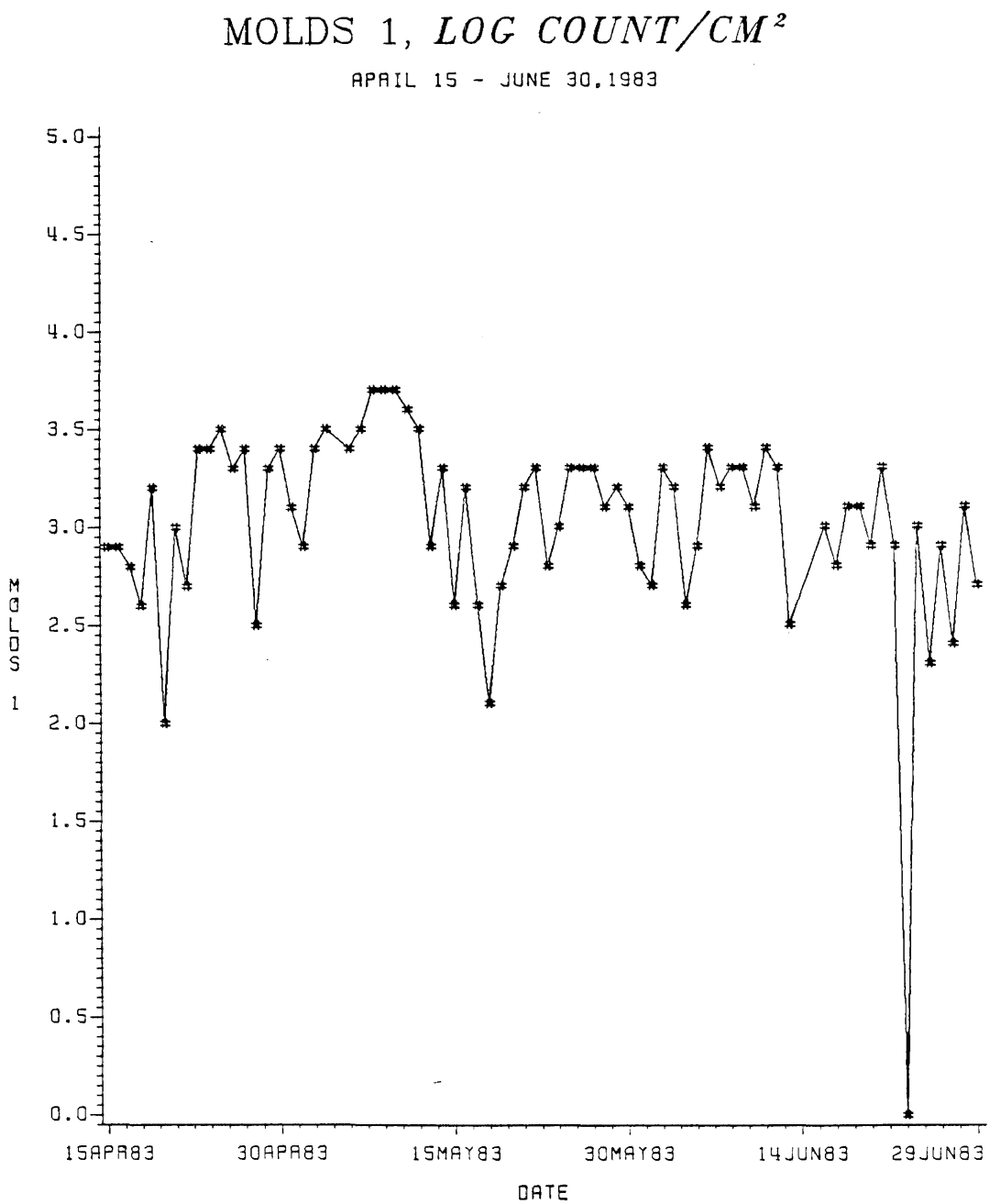

Figure 19A. Daily concentrations of atmospheric Molds 1 as the logarithm (to the base 10) of the count per square centimeter (log count/cm^2) in Glendora area.

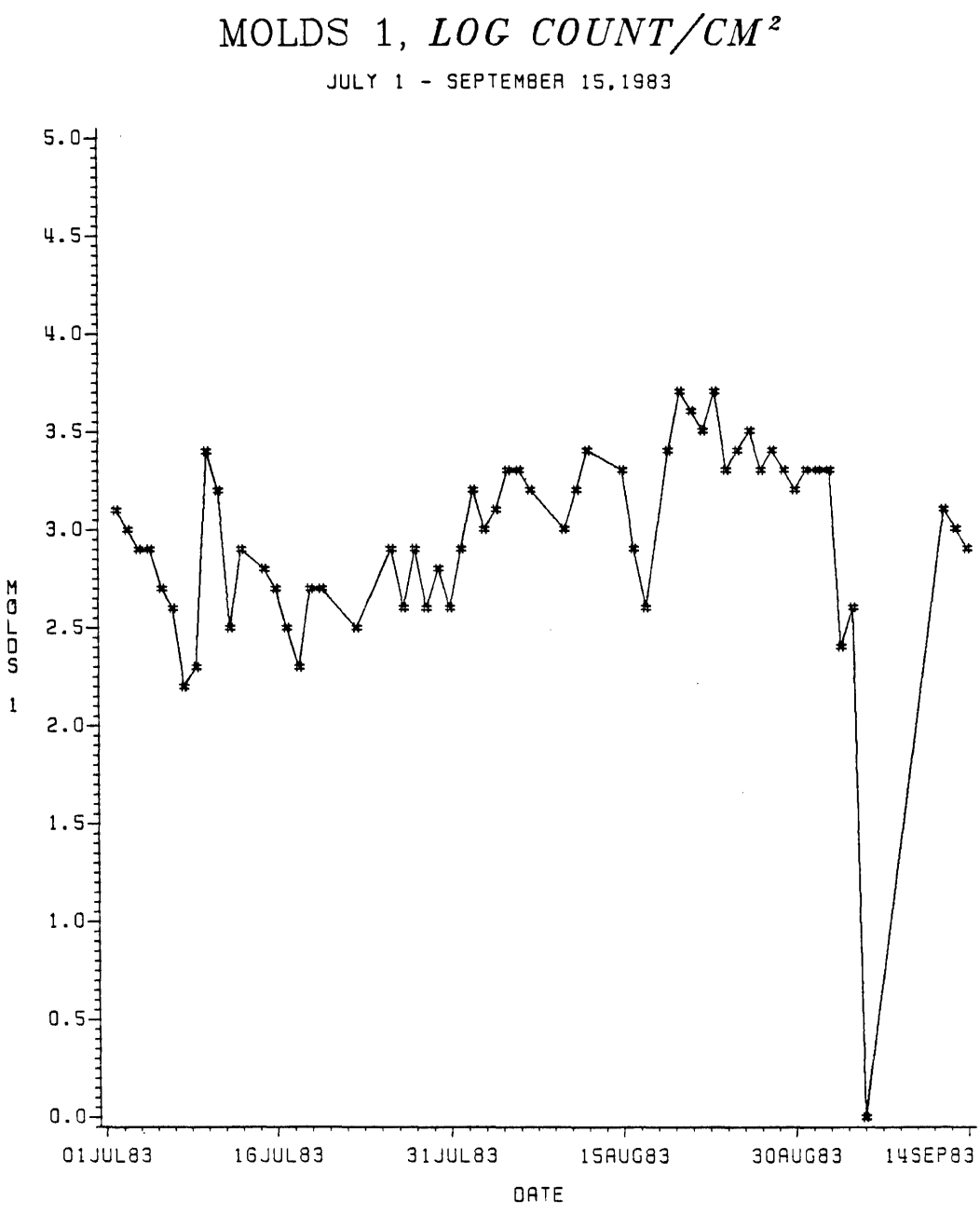
MOLDS 1, LOG COUNT/CM²
JULY 1 - SEPTEMBER 15,1983
MOLDS 1
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
01JUL83
16JUL83
31JUL83
15AUG83
30AUG83
14SEP83
DATE

Figure 19B.

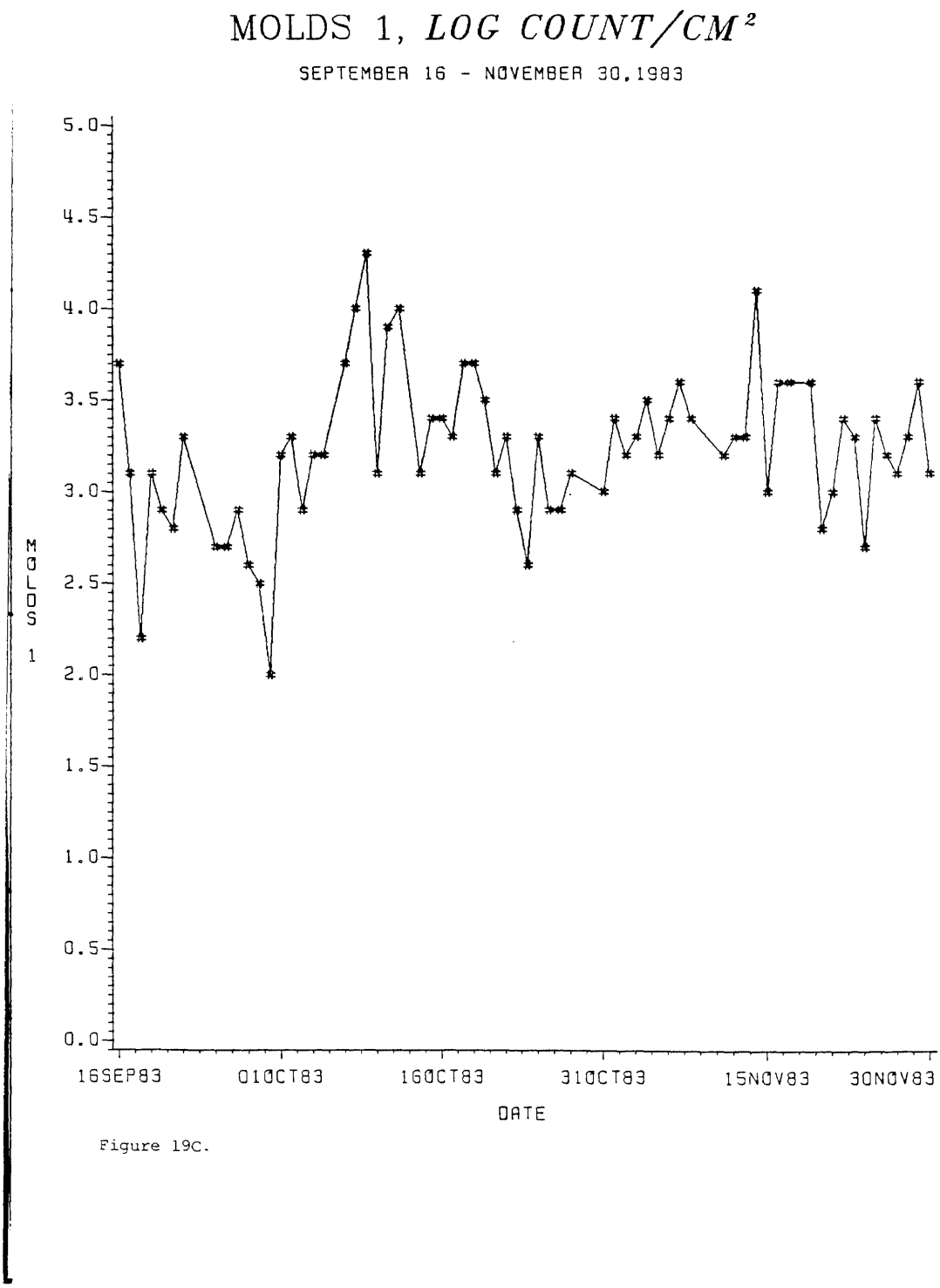
MOLDS 1, LOG COUNT/CM²
SEPTEMBER 16 - NOVEMBER 30, 1983
MOLDS 1
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
16SEP83
01OCT83
16OCT83
31OCT83
15NOV83
30NOV83
DATE

Figure 19C.

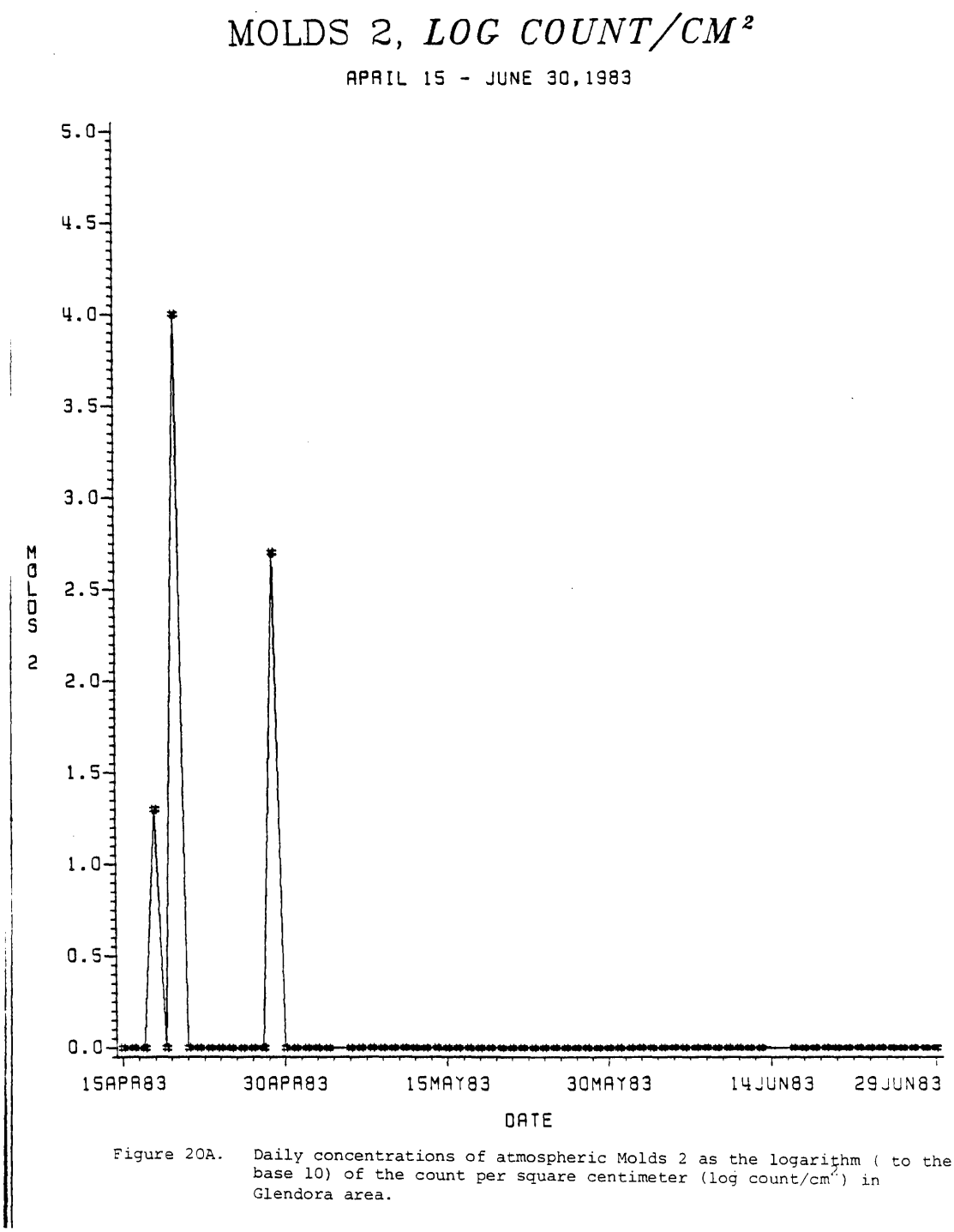

Figure 20A. Daily concentrations of atmospheric Molds 2 as the logarithm (to the base 10) of the count per square centimeter (log count/cm^2) in Glendora area.

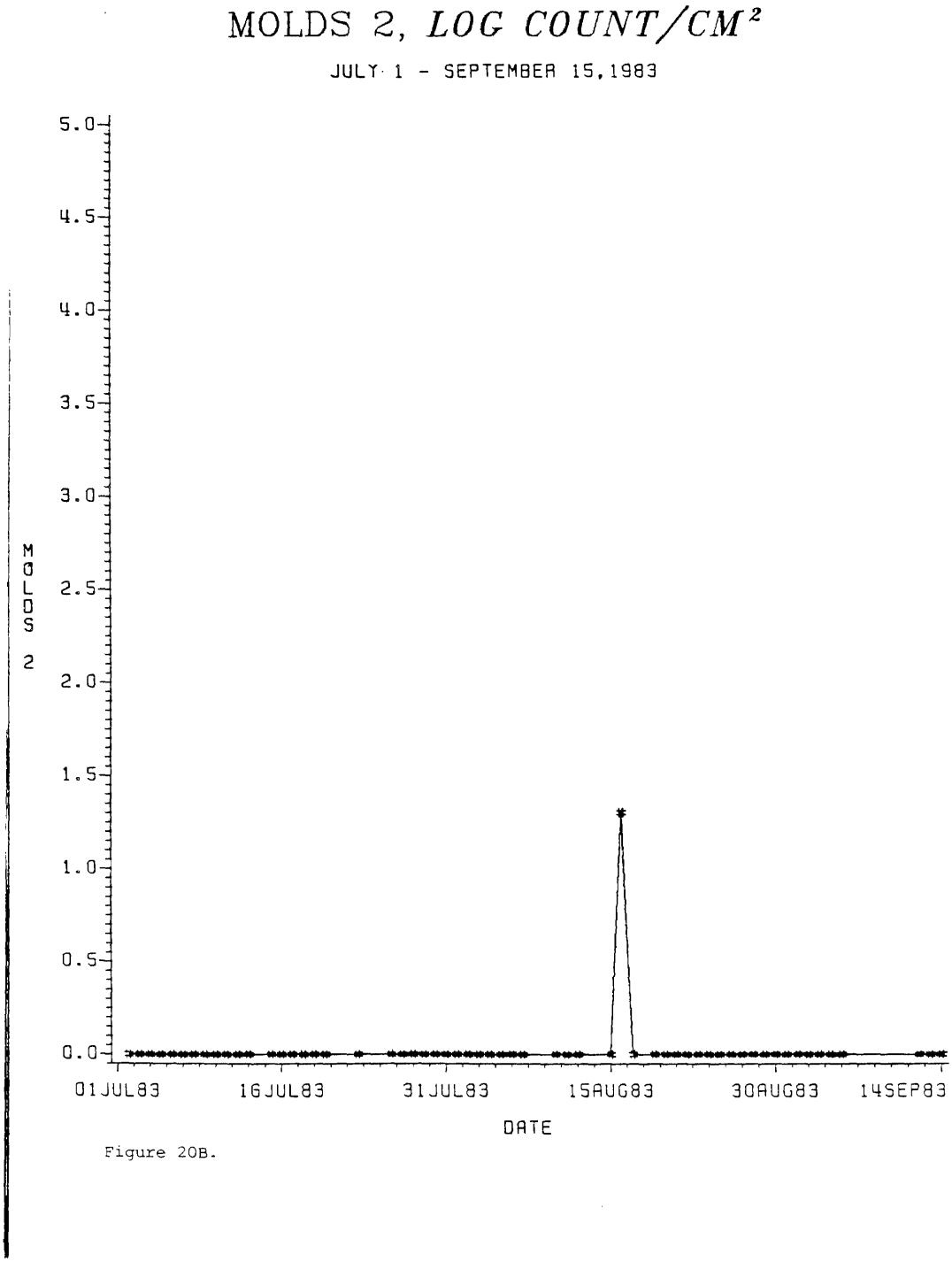
MOLDS 2, LOG COUNT/CM²
JULY 1 - SEPTEMBER 15,1983
MOLDS 2
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
01JUL83
16JUL83
31JUL83
15AUG83
30AUG83
14SEP83
DATE

Figure 20B.

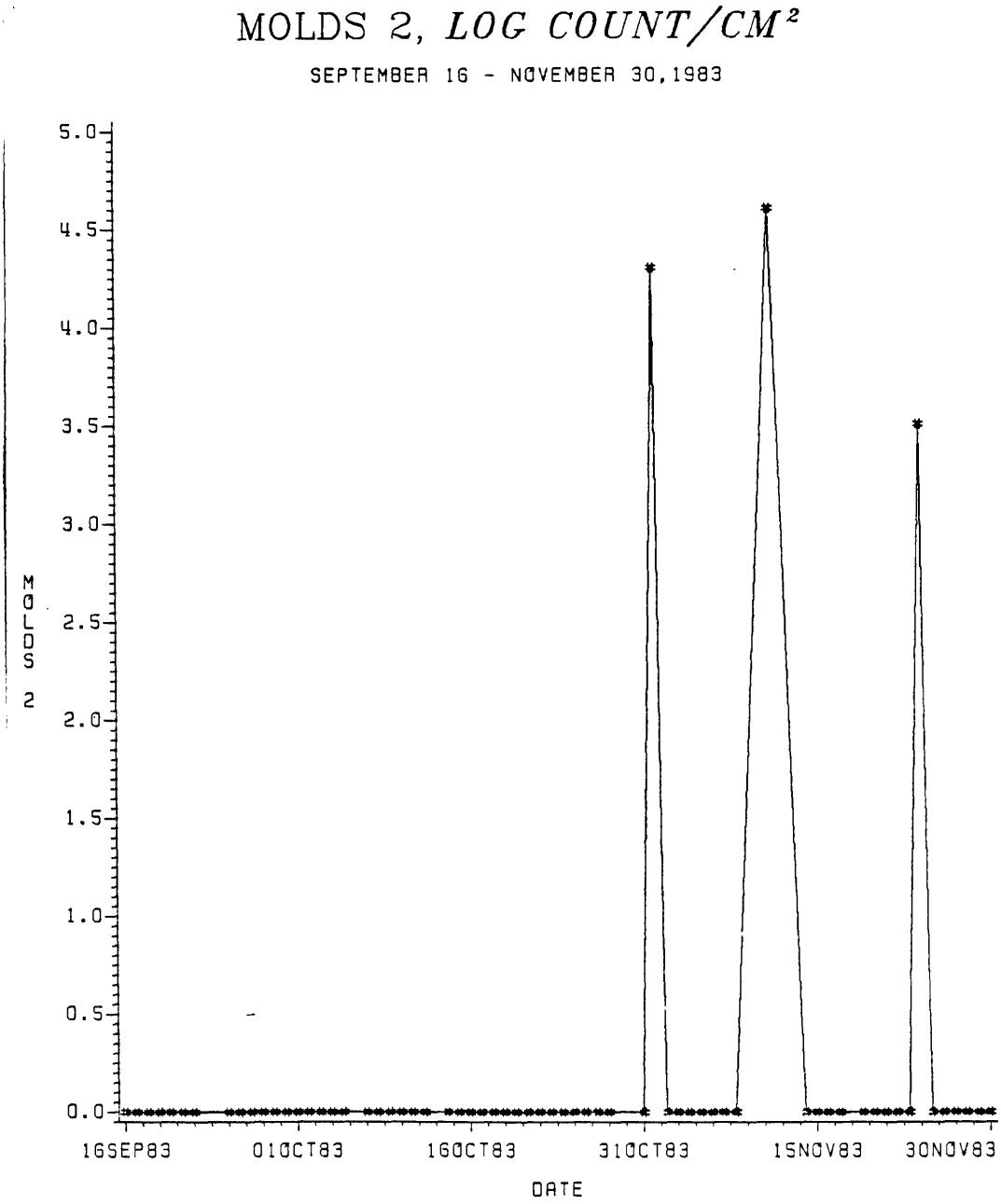
MOLDS 2, LOG COUNT/CM²
SEPTEMBER 16 - NOVEMBER 30,1983
MOLDS 2
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
16SEP83
01OCT83
16OCT83
31OCT83
15NOV83
30NOV83
DATE

Figure 20C.

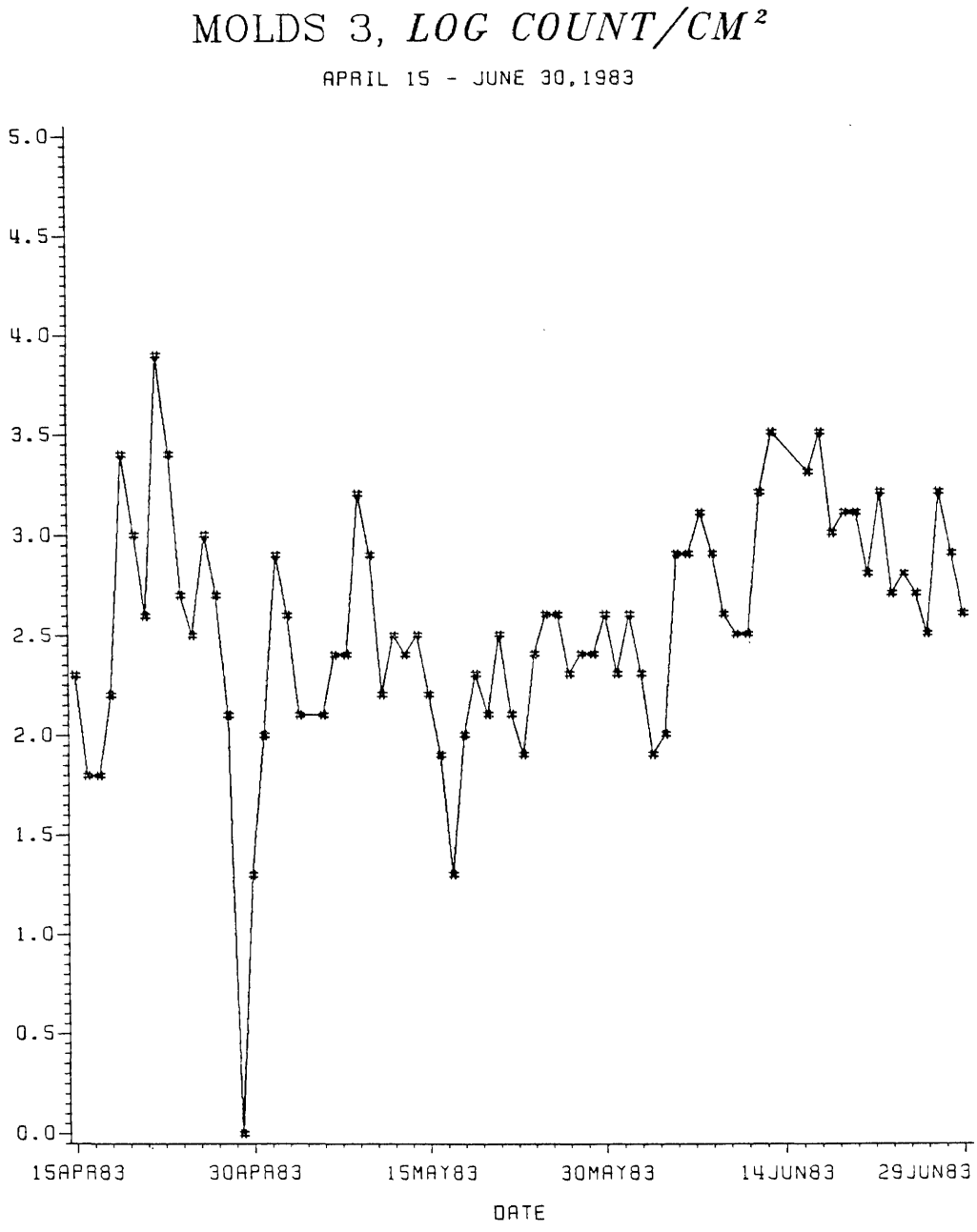

Figure 21A. Daily concentrations of atmospheric Molds 3 as the logarithm (to the base 10) of the count per square centimeter (log count/cm^2) in Glendora area.

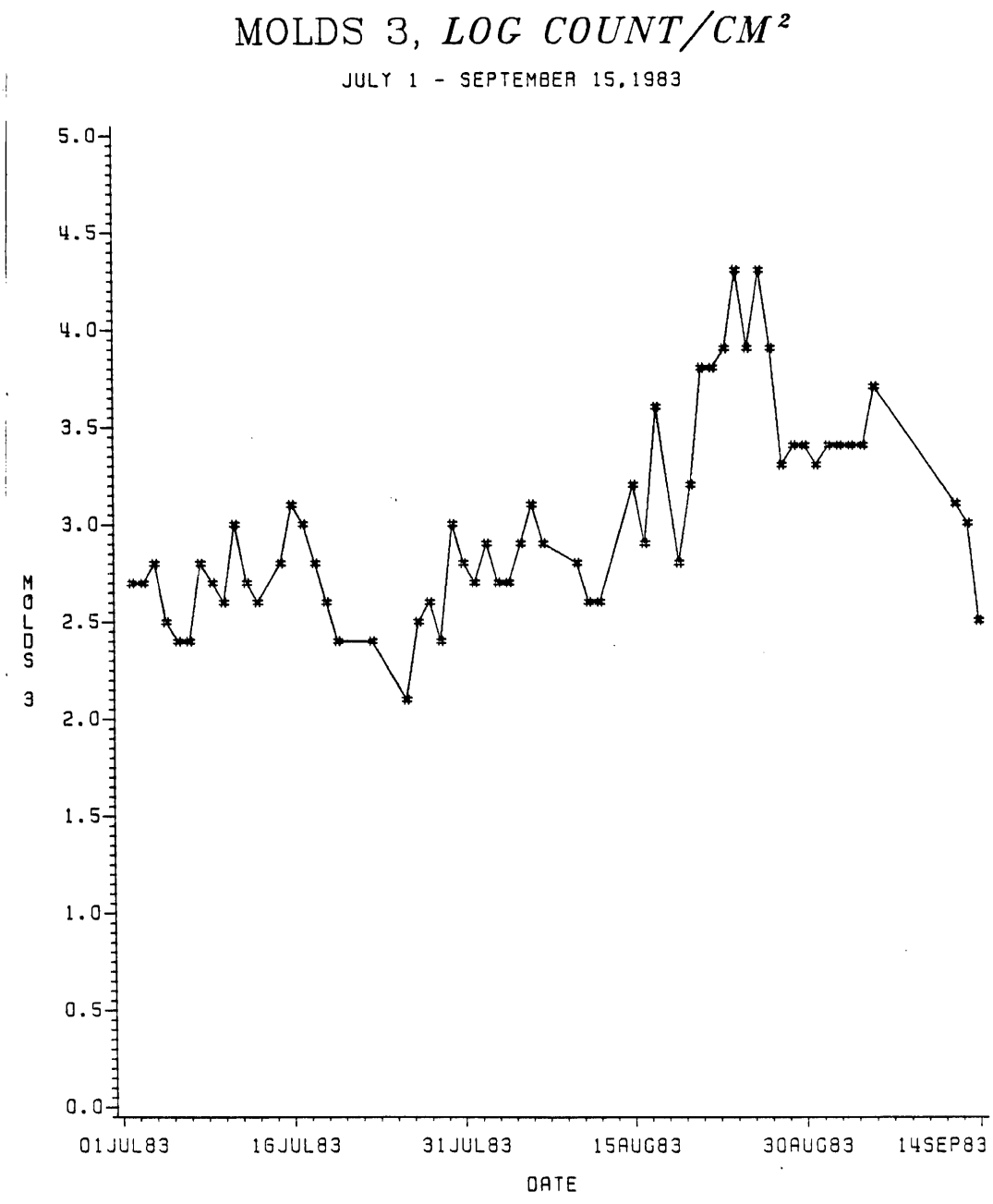
MOLDS 3, LOG COUNT/CM²
JULY 1 - SEPTEMBER 15,1983
MOLDS 3
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
01JUL83
16JUL83
31JUL83
15AUG83
30AUG83
14SEP83
DATE

Figure 21B.

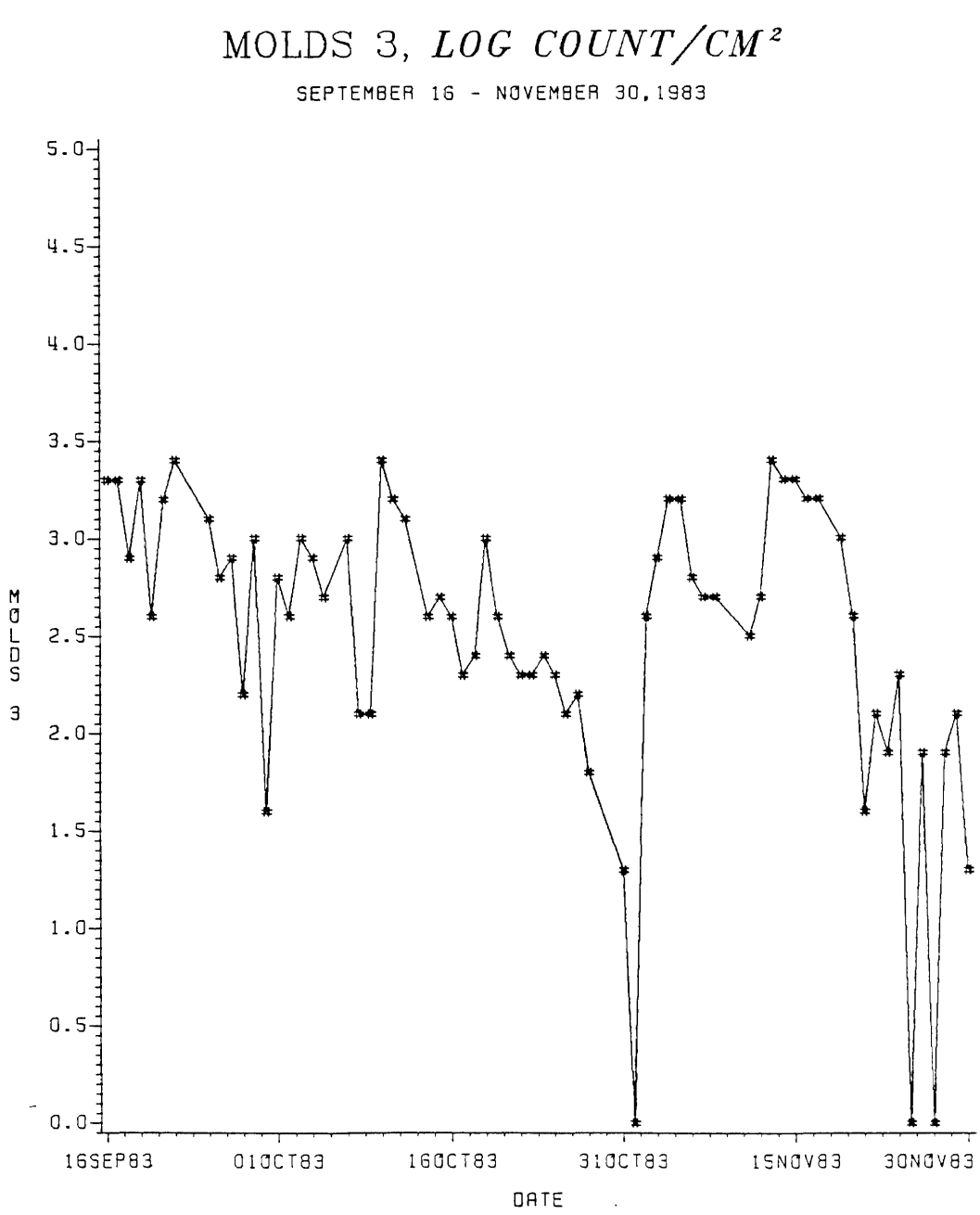
MOLDS 3, LOG COUNT/CM²
SEPTEMBER 16 - NOVEMBER 30, 1983
MOLDS 3
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
16SEP83
01OCT83
16OCT83
31OCT83
15NOV83
30NOV83
DATE

Figure 21C.

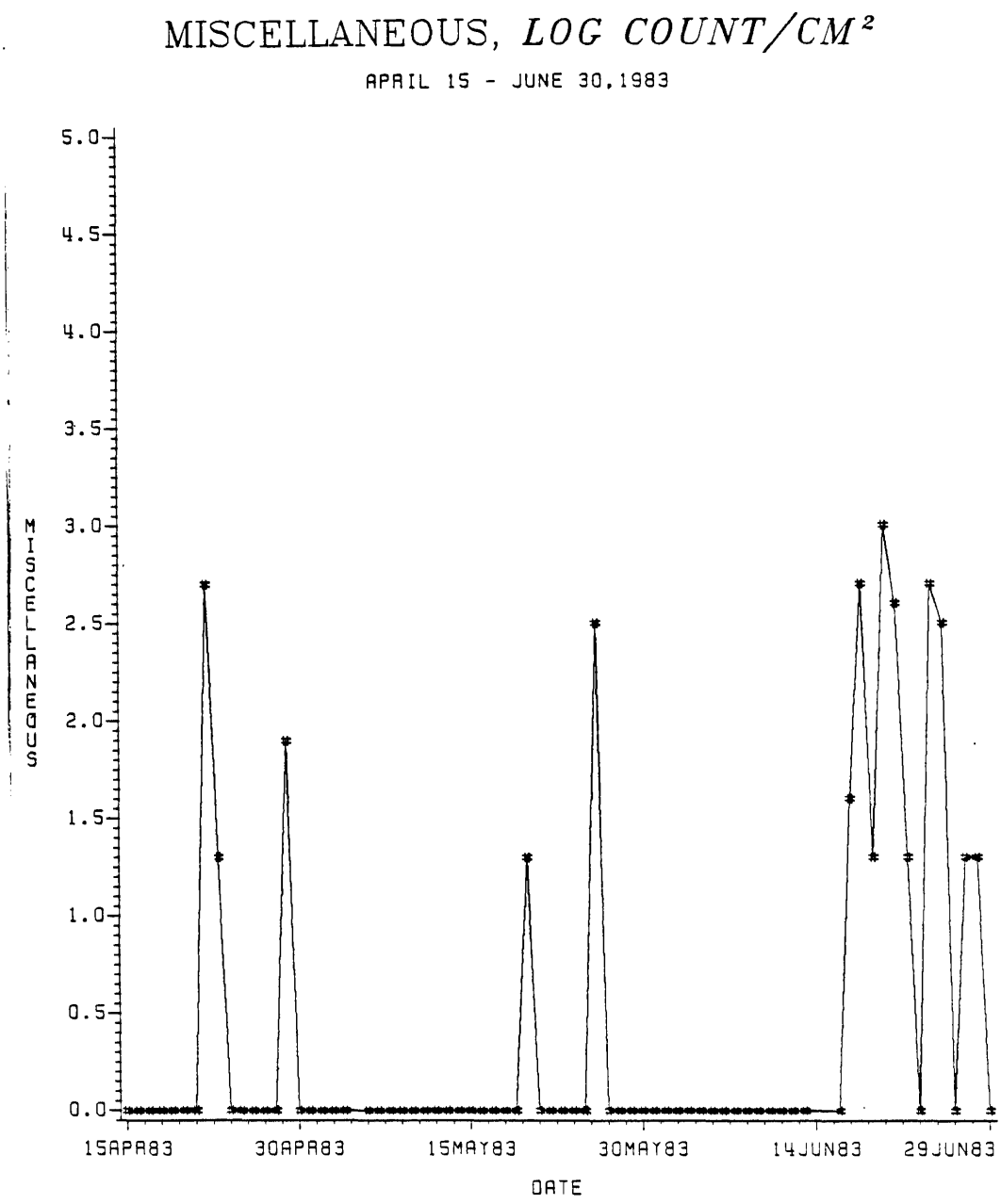

Figure 22A. Daily concentrations of atmospheric debris (Miscellaneous) as the logarithm (to the base 10) of the count per square centimeter (cm^2) (log count/cm^2) in Glendora area.

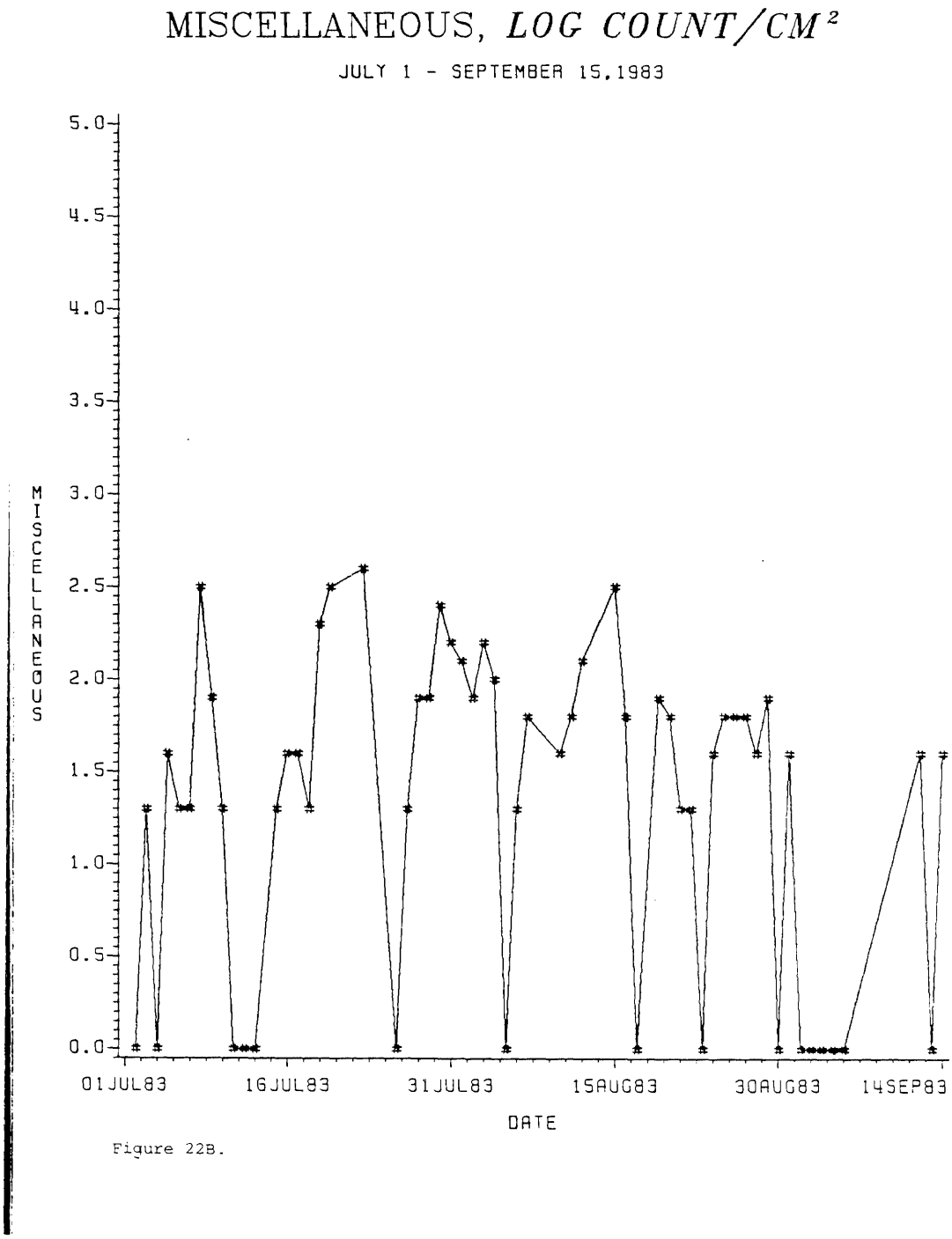
MISCELLANEOUS, LOG COUNT/CM²
JULY 1 - SEPTEMBER 15,1983
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
MISCELLANEOUS
01JUL83
16JUL83
31JUL83
15AUG83
30AUG83
14SEP83
DATE

Figure 22B.

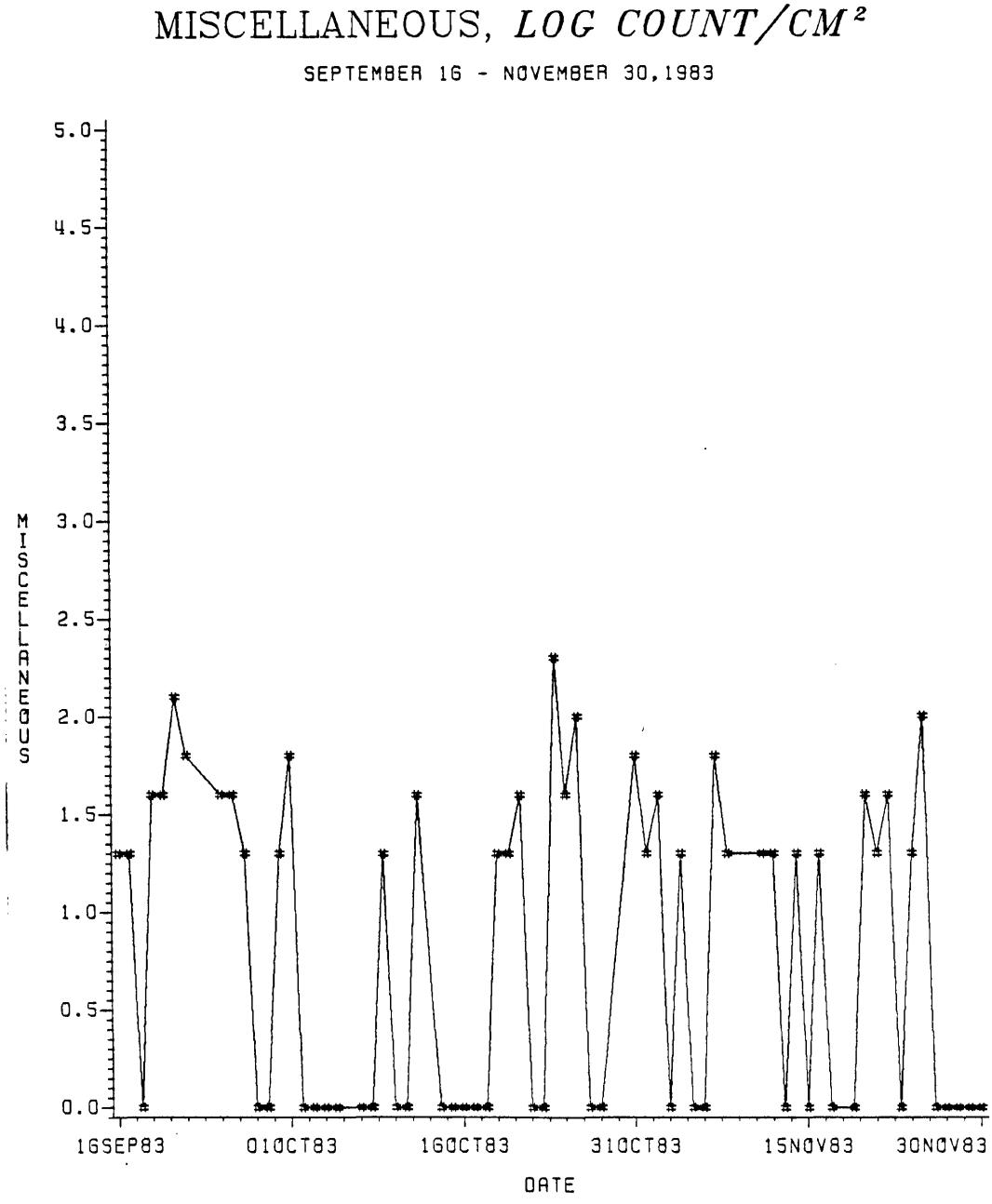
MISCELLANEOUS, LOG COUNT/CM²
SEPTEMBER 16 - NOVEMBER 30,1983
MISCELLANEOUS
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
16SEP83
01OCT83
16OCT83
31OCT83
15NOV83
30NOV83
DATE

Figure 22C.

Table 1. Baseline Demographic and Clinical Characteristics of 26 Excluded Subjects

	n=18* No. Subjects	n=8** No. Subjects	n=18+8=26*** No. Subjects
Sex:			
Male	9	5	14
Female	9	3	12
Race:			
White	14	7	21
Hispanic	1	0	1
Black	3	1	4
Employment:			
Student	5	1	6
Housewife	3	1	4
Full-time employed	4	4	8
Part-time employed	2	1	3
Retired	1	1	2
Unemployed	3	0	3
Heating System:			
Forced air	11	5	16
Floor or wall unit	7	3	10
Heating Fuel:			
Natural gas	16	8	24
Electric	2	0	2
Cooking Fuel:			
Natural gas	16	8	24
Electric	1	0	1
Not known	1	0	1
Smoking Status:			
Non-smoker	16	8	24
Smoker	2	0	2
Coexisting Atopy:	10	4	14
Eczema	1	1	2
Hay fever	8	2	10
Combinations	1	1	2

Table 1 (cont.)

	n=18* mean ± SD (range)	n=8** mean ± SD (range)	n=18+8=26*** mean ± SD (range)
Age, yrs	26.8 ± 13.1 (11-54)	45.2 ± 19.9 (11-65)	32.5 ± 16.8 (11-65)
Residence at current address, yrs	6.3 ± 6.4 (<1-20)	10.8 ± 10.6 (<1-30)	7.7 ± 7.9 (<1-30)
Travel to work (one-way), miles	6.8 ± 6.9 (0-25)	9.2 ± 9.9 (1-20)	7.9 ± 9.3 (0-25)
Asthma			
Age of diagnosis, yrs	10.4 ± 11.8 (<1-43)	19.8 ± 19.9 (<1-55)	13.3 ± 15.1 (<1-55)
Duration, yrs	16.4 ± 12.4 (<1-51)	25.5 ± 18.7 (1-49)	19.2 ± 14.8 (<1-51)
Times seen by physician for asthma in past year	7.7 ± 12.9 (0-50)	3.6 ± 4.9 (0-15)	6.4 ± 11.2 (0-50)
Pulmonary Function+			
% Predicted FVC	n=15: 92.5 ± 18.8 (54.8-119.6)	80.5 ± 11.9 (61.8-91.5)	n=23: 88.3 ± 17.5 (54.8-119.6)
% Predicted FEV_1	n=15: 82.7 ± 19.2 (35.2-110.5)	75.6 ± 17.3 (48.6-97.7)	n=23: 80.2 ± 18.5 (35.2-110.5)
% Predicted $FEF_{25-75\%}$	n=15: 68.8 ± 31.1 (15.0 ± 126.0)	51.6 ± 22.6 (23.6-82.3)	n=23: 62.8 ± 29.1 (15.0-126.0)
% Increase in Post-bronchodilator FEV_1	n=13: 11.6 ± 10.1 (0.0-36.5)	n=6: 15.4 ± 10.6 (6.6-35.8)	n=19: 12.8 ± 10.1 (0.0-36.5)

*Subjects who did not complete the study.

**Subjects who completed the study but were eventually excluded.

***All subjects excluded from final analysis.

+See Table 4 for sources of predicted values.

Table 2. Baseline Demographic and Clinical Characteristics of 83 Asthmatic Panelists

No. of Subjects

Sex - Male: 43; Female: 40

Race - White: 75; Hispanic: 7; Black: 1

Employment - Student: 26 Full-time employed: 35
Housewife: 8 Part-time employed: 6
Retired: 5 Unemployed: 3

Heating system - Forced air: 54; Floor or wall unit: 29

Heating fuel - Natural gas: 72
Electric: 9
Oil: 2

Cooking fuel - Natural gas: 83

Smoking status: Non-smokers: 76
Smokers: 7

Co-existing atopy - 36 subjects: eczema: 7
hay fever: 13
sinusitis: 4
hives: 1
combinations: 7

	Mean	SD	Median	Range
Age, yrs	32.5	17.0	30	7 - 70
Residence at current address, yrs.	8.5	7.7	7	<1 - 35
Travel to work (one-way), miles	10.5	12.4	5	0 - 50
Asthma				
Age of diagnosis, yrs	14.4	15.6	6	Birth - 57
Duration, yrs	18.0	13.7	13	1 - 50
Times seen by physician for asthma in past year	7.6	14.6	3	0 - 99

Table 3. Household Income and Educational Status of 83 Asthmatic Panelists

Annual Household Income, $	No. Subjects (%)
<5,000 - 15,999	12 (14.5)
15,000 - 39,999	46 (55.4)
40,000 - 59,999	16 (19.3)
≥60,000	7 (8.4)
No reply	2 (2.4)

Highest Educational Level Achieved	No. Subjects (%)
Grade School	25 (30.1)
Some high school	7 (8.4)
High school graduate	18 (21.7)
Some college	22 (26.5)
Bachelor or equivalent	6 (7.2)
Masters or equivalent	2 (2.4)
Doctorate or equivalent	1 (1.2)
No reply	2 (2.4)

Table 4. Baseline Pulmonary Function Results in 83 Asthmatic Panelists

	% Predicted* FVC	% Predicted* FEV_1	% Predicted* $FEF_{25-75\%}$
Mean	83.5	74.9	59.2
SD	18.6	21.6	32.4
Median	84.8	80.9	55.3
Range	33.9 - 123.7	23.8 - 110.5	9.1 - 141.3
No. Subjects with:			
≥120% Predicted*	1	0	3
100-119	11	7	7
80-99	44	36	13
60-79	17	22	13
40-59	7	8	24
20-39	3	10	11
0-19	0	0	12

	% Change in FEV_1 from Baseline FEV_1 Following Bronchodilator (n=65)
Mean	8.4
SD	11.8
Median	8.8
Range	-48.9 - 36.4
No. Subjects with:	
31-40% Change	1
21-30%	5
11-20%	15
0-10%	39
-1 to -50%	5

FVC = Forced vital capacity; FEV_1 = Forced expired volume in one second; $FEF_{25-75\%}$ = forced midexpiratory flow.

*Predicted values for adults from Morris JF. West J Med 125:110, 1976. Predicted values for children from Polgar G, Promadhat V. Pulmonary Function Testing in Children: Techniques and Standards. W.B. Saunders Company, Philadelphia, 1971.

Table 5. Evaluation of Airways Reactivity in 83 Asthmatic Panelists

	Bronchodilator (BD) Administration* Performed, n=65	Not Performed, n=18
No. Subjects With:		
A. Significant response**	10	-
B. No significant response	55	-
1. Second BD administration with significant response**	0	-
2. Positive methacholine bronchoprovocation+	3	2
3. Confirmative medical records	3	5

* Using inhaled isoproterenol.

** $\geq$15% increase in FEV_1 from baseline value.

\+ $\geq$15% decrease in FEV_1 from control value.

Table 6. Initial and Final Medication Patterns in 83 Asthmatic Panelists

Medication Regimen	Number of Subjects On April 15	On Nov. 30
MDI only	21	23
MDI + theophylline only	16	14
MDI + theophylline + oral adrenergic agent	12	10
MDI + oral adrenergic agent only	7	5
MDI + theophylline-ephedrine compound	4	3
MDI + inhaled corticosteroid + others*	11	11
MDI + oral corticosteroid + others*	5	5
MDI + oral + inhaled coricosteroid + others*	7	6
No MDI ± others*	0	6**

MDI = metered dose inhaler

*Others = theophylline and/or oral adrenergic agent

**Theophylline alone: 1 subject; theophylline + oral adrenergic agent: 3; theophylline-ephedrine: 1; no anti-asthma medication: 1

Table 7. Psychological Test Results in 71 Asthmatic Panelists (Adults Only)

	Mean Score	Standard Deviation	Range	Median
Asthma Symptom Checklist*:				
C1 (Irritability)	2.8	0.9	1.0-4.8	2.8
C2 (Fatigue)	3.3	0.9	1.2-5.0	3.2
C3 (Panic-Fear)	2.2	1.0	1.0-5.0	2
C4 (Dyspnea)	4.0	0.8	1.8-5.0	4.2
C5 (Loneliness-Anger)	1.9	0.7	1.0-4.4	2
C6 (Congestion)	3.7	0.8	1.6-5.0	3.6
C7 (Hyperventilation)	2.1	0.8	1.0-4.5	2
C8 (Hyperventilation)	2.4	0.8	1.0-4.5	2.5
Panic-Fear Symptom Scale	5.4	2.8	0-12.0	5
State-Trait Anxiety Inventory:				
State Anxiety	35.5	9.0	23.0-58.0	34
Trait Anxiety	37.8	8.4	23.0-58.0	38

*According to factors derived from this study, the eight symptom categories are composed of the following symptoms:

C1 = cranky, irritable, short tempered, edgy, frustrated with things, angry.
C2 = fatigues, tired, worn out, exhausted, weak, no energy.
C3 = frightened, afraid of being left alone, scared, panicky, worried, afraid of dying.
C4 = hard to breathe, short of breath, wheezing, uncomfortable, rapid breathing.
C5 = feel ignored, unhappy, feel isolated, mad at the world, lonely, furious, don't care about things.
C6 = coughing, mucous congestion, chest congestion.
C7 = panting, pins and needles feeling, numb, tingling in spots.
C8 = tightness in spots, dizzy, chest pain, headache.

Table 8. Psychological Test Results in 12 Asthmatic Children

	Mean Score	Standard Deviation	Median	Range
Asthma Symptom Checklist (factors derived from this study):*				
C1 (Irritability)	2.8	0.8	2.6	1.3-4.2
C2 (Fatigue)	3.1	0.9	3.0	1.6-4.3
C3 (Panic-Fear)	2.0	0.7	2.1	1.0-3.3
C4 (Dyspnea)	3.6	0.6	3.6	2.0-4.8
C5 (Loneliness-Anger)	2.2	0.7	2.0	1.0-3.6
C6 (Congestion)	3.5	0.5	3.6	2.3-4.0
C7 (Hyperventilation)	2.2	0.8	2.1	1.0-3.5
C8 (Hyperventilation)	2.8	0.6	2.8	1.8-4.0
Asthma Symptom Checklist (factors derived from Kinsman):**				
C1 (Panic-Fear)	43.1	9.7	43.9	28.6-61.8
C2 (Irritability)	47.8	9.5	48.2	32.1-61.9
C3 (Fatigue)	43.2	10.6	42.6	27.4-57.8
C4 (Hyperventilation)	53.6	6.9	52.4	42.6-64.4
C5 (Dyspnea)	41.9	10.5	40.0	16.8-57.4
C6 (Congestion)	46.2	6.9	45.6	30.2-58.0
C7 (Worry)	44.0	8.8	45.0	26.4-55.6
C8 (Anger)	52.1	13.2	50.6	34.2-78.9
C9 (Loneliness)	45.2	7.6	43.9	36.6-62.4
C10 (Rapid Breathing)	42.0	9.4	43.2	26.7-52.4
State Anxiety Inventory:				
State Anxiety	29.0	4.9	30.5	20.0-37.0
Trait Anxiety	38.4	6.6	38.5	27.0-50.0

*See Table 7 for composition of each symptom category.

**Mean score represents the standard score calculated according to reference 15.

Table 9. Ambient Concentrations of Air Pollutants in Glendora Area (April 15 - November 30, 1983)

	Ozone (O_3)	Carbon Monoxide (CO)	Sulfur Dioxide	Nitrogen Dioxide
Units	pphm*	ppm*	pphm*	pphm*
No. Days	230	230	230	230
Mean	13.8	1.5	0.83	6.4
SD	8.6	0.8	0.68	2.2
Median	13.0	1.0	1.0	6.0
Range	1.0 - 39.0	0 - 4.0	0 - 6.0	2.0 - 13.0
No. Days (Concs.)	3 (>0.35) 60 (0.20-0.34)	21 (3-4) 85 (2.0-2.9)	2 (5-6) 1 (3.0-4.9)	7 (12-13) 14 (10.0-11.9)

	Nitrogen Oxides (NOx)	Total Suspended Particulates (TSP)	Sulfates
Units	pphm*	ug/m^3**	ug/m^3**
No. Days	230	181+	181+
Mean	7.6	131.6	10.4
SD	2.4	44.1	5.9
Median	7.0	131.0	9.0
Range	2.0 - 15.0	12.0 - 270.0	1.6 - 33.3
No. Days (Concs.)	5 (14-15) 16 (12.0-13.9)	13 (200-270) 47 (150-199)	5 (>25) 8 (20-25)

	Hydrocarbons (HC)
Units	pphm carbon**
No. Days	185+
Mean	38.2
SD	11.8
Median	36.0
Range	18.0 - 89.0
No. Days (Concs.)	9 (>60) 61 (40-60)

pphm = parts per hundred million; ppm = parts per million.
*maximum hourly average concentration per day.
**24-hour concentration.
+Data unavailable for some days.

Table 10. Ambient Temperature, Relative Humidity, and Barometric Pressure in Glendora Area (April 15 - November 30, 1983)

	Temperature, °F		Relative Humidity, %		Barometric
	1 A.M.	1 P.M.	1 A.M.	1 P.M.	Pressure, mmHg
No. Days	230	200*	230	199*	225*
Mean	60.6	78.9	87.6	48.2	741.8
SD	8.1	11.7	15.5	17.8	1.9
Median	60.0	79.5	93.0	48.0	742.0
Range	37-81	56-106	14-100	14-100	737-747
No. Days (Range)	12 ($\geq$75°)	128 ($\geq$75°)	143 (>87%)	3 (>87%)	13 (>745 mmHg)
	4 ($\leq$40°)	0 ($\leq$40°)	5 (<50%)	109 (<50%)	21 (<739 mmHg)

*Data unavailable for some days.

Table 11. Correlations Between Air Pollutant Concentrations and Meteorological Data
(April 15 - November 30, 1983)

										Temperature		Humidity	
		O_3	SO_2	NO_2	NOx	CO	TSP	Sulfates	HC	1 A.M.	1 P.M.	1 A.M.	1 P.M.
O_3	r=	1.00	0.33	**0.50**	0.42	0.29	**0.66**	0.34	0.32	**0.49**	**0.52**	-0.25	-0.04
	p=	0.0000	0.0001	**0.0001**	0.0001	0.0001	**0.0001**	0.0001	0.0001	**0.0001**	**0.0001**	0.0001	0.58
SO_2	r=	0.33	1.00	0.34	0.31	0.24	0.28	0.08	0.28	0.24	0.19	-0.38	-0.04
	p=	0.0001	0.0000	0.0001	0.0001	0.0003	0.0001	0.30	0.0001	0.0002	0.0007	0.0001	0.59
NO_2	r=	**0.50**	0.34	1.00	**0.87**	**0.71**	**0.58**	0.18	0.38	0.29	0.18	-0.18	-0.01
	p=	**0.0001**	0.0001	0.0000	**0.0001**	**0.0001**	**0.0001**	0.01	0.0001	0.0001	0.009	0.005	0.87
NOx	r=	0.42	0.31	**0.87**	1.00	**0.71**	**0.48**	0.14	0.42	0.30	0.19	-0.16	-0.02
	p=	0.0001	0.0001	**0.0001**	0.0000	**0.0001**	**0.0001**	0.0001	0.0001	0.0001	0.006	0.01	0.78
CO	r=	0.29	0.24	**0.71**	**0.71**	1.00	**0.47**	0.09	0.38	0.08	-0.02	-0.16	0.03
	p=	0.0001	0.0003	**0.0001**	**0.0001**	0.0000	**0.0001**	0.21	0.0001	0.24	0.76	0.01	0.66
TSP	r=	**0.66**	0.28	**0.58**	**0.48**	**0.47**	1.00	**0.66**	0.22	0.12	0.08	-0.02	0.12
	p=	**0.0001**	0.0001	**0.0001**	**0.0001**	**0.0001**	0.0000	**0.0001**	0.008	0.09	0.32	0.83	0.12
Sulfates	r=	0.34	0.08	0.18	0.14	0.09	**0.66**	1.00	-0.01	-0.14	-0.08	0.37	0.21
	p=	0.0001	0.30	0.01	0.06	0.21	**0.0001**	0.0000	0.94	0.06	0.34	0.0001	0.008
HC	r=	0.32	0.28	0.38	0.42	0.28	0.22	-0.01	1.00	0.18	-0.02	-0.39	0.04
	p=	0.0001	0.0001	0.0001	0.0001	0.0001	0.008	0.94	0.0000	0.01	0.82	0.0001	0.66
Temp.	r=	**0.49**	0.24	0.29	0.30	0.08	0.12	-0.14	0.18	1.00	**0.50**	-0.33	0.04
1 A.M.	p=	**0.0001**	0.0002	0.0001	0.0001	0.24	0.09	0.06	0.01	0.0000	**0.0001**	0.0001	0.51
Temp.	r=	**0.52**	0.19	0.18	0.19	-0.02	0.08	-0.08	-0.02	**0.50**	1.00	-0.14	**-0.56**
1 P.M.	p=	**0.0001**	0.007	0.009	0.006	0.76	0.32	0.34	0.82	**0.0001**	0.0000	0.05	**0.0001**
Humidity	r=	-0.25	-0.38	-0.18	-0.16	-0.16	-0.02	0.37	-0.39	-0.33	-0.14	1.00	0.08
1 A.M.	p=	0.0001	0.0001	0.005	0.01	0.01	0.83	0.0001	0.0001	0.0001	0.05	0.0000	0.26
Humidity	r=	-0.04	-0.04	-0.01	-0.02	0.03	0.12	0.21	0.04	0.04	**-0.56**	0.08	1.00
1 P.M.	p=	0.58	0.59	0.87	0.78	0.66	0.12	0.008	0.66	0.51	**0.0001**	0.26	0.0000

O_3=Ozone; SO_2=Sulfur dioxide; NO_2=Nitrogen dioxide; NOx=Oxides of nitrogen; CO=Carbon monoxide; TSP=total suspended particulates; HC=Hydrocarbons.

Correlations of $r \geq 0.47$ ($p = 0.0001$) are enclosed within rectangles.

Table 12. Potential Aeroallergens in Glendora Area (April 15 - November 30, 1983)

	Trees 1	Trees 2	Shrubs 1	Shrubs 2	Grasses
No. Days	200	197	200	200	200
Daily Mean*	199.4	321.0	82.3	50.6	44.9
SD	673.1	992.2	197.5	89.8	71.4
Median	20	20	20	20	20
Range	0-5400	0-8500	0-1500	0-600	0-500
No. Days (Range)	4 (≥3000)	5 (>3000)	4 (>1000)	3 (>500)	2 (>400)
	7 (1000-2999)	13 (1000-3000)	3 (500-1000)	27 (100-500)	29 (100-400)
	7 (500-999)	5 (500-999)	32 (100-499)	26 (50-99)	25 (50-99)

	Gymnosperms	Molds 1	Molds 2	Molds 3	Misc.
No. Days	200	200	198	200	200
Daily Mean	107.1	1843.4	336.2	1164.8	46.1
SD	300.8	2115.8	2927.7	2361.8	113.4
Median	20	1360	0	480	0
Range	0-3000	0-19200	0-36000	0-20060	0-1000
No. Days (Range)	4 (>1000)	5 (>7000)	4 (≥3000)	6 (>7000)	4 (≥500)
	7 (500-1000)	12 (4000-7000)	1 (500-2999)	2 (4000-7000)	10 (200-499)
	31 (100-499)	46 (2000-3999)	1 (20-499)	16 (2000-3999)	26 (60-199)

See text for composition of each category. Data were unavailable for some days.

*Count per square centimeter.

Table 13. Daily Symptoms Reported by 83 Asthmatic Panelists (April 15 - November 30, 1983)

	Overall Asthma Rating	Wheezing Day	Wheezing Night	Shortness of Breath Day	Shortness of Breath Night
Mean*	2.1	2.2	2.2	2.2	2.2
SD	1.1	1.2	1.2	1.2	1.2
Median	1.8	2.0	2.0	2.0	2.0
Range	1-7	1-7	1-7	1-7	1-7
Total No. Measurements	15593	15305	15274	15311	15270
No. Measurements (% of total) With Ratings of ≥6:	50 (0.3%)	180 (1.2%)	174 (1.1%)	193 (1.2%)	186 (1.2%)
4.0-5.9:	1022 (6.6)	2477 (16.2)	2402 (15.7)	2755 (17.9)	2448 (16.0)

	Chest Tightness Day	Chest Tightness Night	Cough Day	Cough Night	Sputum Day	Sputum Night	Tension Day	Tension Night
Mean	2.2	2.1	1.9	1.9	1.8	1.8	1.8	1.7
SD	1.2	1.2	1.2	1.2	1.1	1.1	1.2	1.2
Median	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0
Range	1-7	1-7	1-7	1-7	1-7	1-7	1-7	1-7
Total No. Measurements	15310	15269	15303	15263	15300	15267	15224	15189
No. Measurements (% of total) With Ratings of ≥6:	188 (1.2%)	189 (1.2%)	141 (0.9%)	131 (0.8%)	108 (0.7%)	99 (0.6%)	274 (1.8%)	236 (1.6%)
4.0-5.9:	2245 (14.6)	1989 (13.0%)	1590 (10.4)	1500 (9.8)	1623 (10.6)	1565 (10.2)	1532 (10.1)	1219 (8.0)

*Rating Scale: 1 = no symptoms
2 = very mild discomfort
3 = mild discomfort
4 = moderate discomfort
5 = moderately severe discomfort
6 = severe discomfort
7 = very severe or incapacitating discomfort

Table 14. Daily Asthma Medication Index (AMI) in 83 Asthmatic Panelists (April 15 - November 30, 1983)

	AMI
Mean	9.8 units
SD	12.9
Median	4.8
Range	0 - 135.6
Total No. Measurements	15,376

Distribution of AMIs:

AMI	No. Measurements	Percent (%) of Total Measurement		
<1	4556	29.6	45.4	65.1
1.0- 3.9	2426	15.8		
4.0- 9.9	3025	19.7		
10.0-19.9	2697	17.5		
20.0-29.9	1256	8.2		
30.0-39.9	906	5.9	9.2	
40.0-49.9	285	1.9		
50.0-59.9	113	0.7		
60.0-69.9	50	0.3		
70.0-79.9	34	0.2		
80.0-89.9	11	0.07		
90.0-99.9	6	0.04		
≥100	11	0.07		

Table 15. Metered-Dose Inhaler (MDI) Usage: Nebulizer Chronolog (NC) Results in 75 Asthmatic Panelists (April 15-November 30, 1983)

	Number of Actuations During Study/Subject	Number of Daily Actuations/Subject
Mean	530.2	3.5
SD	650.4	4.7
Median	272	1.4
Range	7 - 2904	0.04 - 23.3
No. Actuations	0 - 100: 25 subjects	0.0 - 0.9 : 31 subjects
	101 - 200: 9 subjects	1.0 - 1.99: 12 subjects
	201 - 300: 6 subjects	2.0 - 4.9 : 13 subjects
	301 - 400: 3 subjects	5.0 - 7.9 : 10 subjects
	401 - 500: 5 subjects	8.0 - 10.9: 3 subjects
	501 - 600: 1 subjects	11.0 - 20.0: 5 subjects
	601 - 700: 3 subjects	20.0 - 30.0: 1 subjects
	701 - 800: 2 subjects	
	801 - 900: 1 subjects	
	901 - 1000: 5 subjects	
	1001 - 1200: 5 subjects	
	1201 - 1800: 6 subjects	
	2500 - 3000: 3 subjects	

Table 16. Metered-Dose Inhaler (MDI) Usage: Nebulizer Chronolog (NC) Versus Daily Diary Results in 75 Asthmatic Panelists (April 15 - November 30, 1983)

	Usage Pattern: NC > Diary	NC = Diary	NC < Diary	Total
No. Subjects (%) with Most Frequent Pattern	11 (14%)	50 (67%)	14 (19%)	75
No. Subject-Days (%) in Each Pattern	2700 (22%)	6850 (56%)	2728 (22%)	12,278

NC - Diary Difference:

Mean 0.44

SD 2.26

Median 0.08

Range -6.4 to 10.6

Ranges of NC-Diary Differences	-1.2 to -6.4:	6 subjects	(8%)
	-1.1 to 1.1:	60 subjects	(80%)
	1.2 to 6.0	6 subjects	(8%)
	6.1 to 10.6:	3 subjects	(4%)

Table 17. Daily Peak Expiratory Flow Rate (PEFR) in 83 Asthmatic Panelists (April 15 - November 30, 1983)

	Day PEFR, liters/minute	Night PEFR, liters/minute
Mean	367.1	366.2
SD	131.2	131.3
Median	380	380
Range	50-700	50-790
Total No. of measurements	15,213	15,184

Distribution of PEFR

Daily PEFR	No. Measurements	% of Total Measurements	No. Measurements	% of Total Measurements
≥700	73	0.5	131	0.9
600-699	495	3.3	451	3.0
500-599	2041	13.4	1861	12.3
400-499	4075	26.8	4143	27.3
300-399	4551	29.9	4607	30.3
200-299	2046	13.4	2164	14.2
100-199	1677	11.0	1574	10.4
<100	255	1.7	253	1.6

Table 18. Per Cent of Predicted of Average Peak Expiratory Flow Rates (PEFR) in 83 Asthmatic Panelists (April 15-November 30, 1983)

	Average Day PEFR, % Predicted*	Average Night PEFR, % Predicted*
Mean	87.4	87.2
SD	25.1	24.7
Median	90.8	88.7
Range	24.8-156.5	25.3-154.4

Distribution of Average PEFR % Predicted PEFR*	No. Subjects (%)	No. Subjects (%)
≥101	24 (28.9%)	24 (28.9%)
80-100	31 (37.3)	30 (36.1)
70-79	9 (10.8)	11 (13.3)
60-69	7 (8.4)	6 (7.2)
50-59	5 (6.0)	5 (6.0)
40-49	4 (4.8)	4 (4.8)
30-39	1 (1.2)	1 (1.2)
20-29	2 (2.4)	2 (2.4)

*Predicted values from Knudson RJ, Slatin RC, Lebowitz MD, Burrows B. Am Rev Respir Dis 113:587, 1976.

Table 19. Correlation of Asthma Attacks to Average Asthma Medication Index (AMI) and Metered-Dose Inhalers (MDI) Use in 83 Asthmatic Panelists (4/15/84 - 11/30/83)

	AMI		MDI	
	r	p	r	p
Day				
No. asthma attacks	0.22	0.04	0.44	0.0001
Duration of asthma attacks	0.26	0.017	-0.09	0.38
Night				
No. asthma attacks	0.20	0.06	0.42	0.0001
Duration of asthma attacks	0.29	0.007	-0.04	0.74
Day and Night (Total)				
No. asthma attacks	0.29	0.007	0.08	0.48
Duration of asthma attacks	0.26	0.014	0.01	0.90

Table 20. Daily Symptom Score, Asthma Medication Index, and Peak Expiratory Flow Rate (PEFR) in 83 Asthmatic Panelists According to Ozone Concentrations (April 15 - November 30, 1983)

	Daily Maximum Hourly Average Concentration of Ozone		
	< 0.12 ppm	0.12-0.19 ppm	> 0.20 ppm
Symptom Score			
Mean	2.1	2.1	2.1
SD	1.1	1.0	1.1
Range	1-7	1.0-6.8	1.0-6.2
Asthma Medication Index			
Mean	9.8	9.7	10.1
SD	12.4	12.7	14.2
Range	0-102	0-126	0.0-135.6
Day PEFR, liters/min*			
Mean	365.2	369.8	367.4
SD	130.9	129.9	132.8
Range	50-770	50-760	60-750
Night PEFR, liter/min*			
Mean	364.8	368.6	366.1
SD	130.8	130.4	133.1
Range	50-790	50-750	60-760

ppm = parts per million.

*p <0.01 for ozone category by two-way ANOVA when one factor is ozone level and the second factor is subject.

The p value for subjects was ignored because we wished to remove the effect of subjects in this analysis.

TABLE 21. SUMMARY OF MULTIPLE REGRESSION ANALYSES

DEPENDENT VARIABLE	INDEPENDENT VARIABLES *	COEFFICIENTS WITH SIGNIFICANT T'S (SIGN OF COEFFICIENT AND P ARE GIVEN IN PARENTHESES) *
A. TEST FOR DEPENDENCE OF SYMPTOMS ON MEDICATION USE:		
SYMPTOMS	MEDICATION	MEDICATION(+,.00008)
SYMPTOMS	MEDICATION(T-1)	MEDICATION(T-1)(+,.0012)
SYMPTOMS	MEDICATION(T-2)	MEDICATION(T-2)(+,.0167)
SYMPTOMS	MEDICATION(T-3)	
SYMPTOMS	AVERAGE OF MEDICATION(T,T-1)	AVERAGE OF MEDICATION(T,T-1)(+,.00053)
SYMPTOMS	AVERAGE OF MEDICATION(T-1,T-2)	AVERAGE OF MEDICATION(T-1,T-2)(+,.0087)
SYMPTOMS	AVERAGE OF MEDICATION(T,T-1,T-2)	AVERAGE OF MEDICATION(T,T-1,T-2)(+,.0019)
SYMPTOMS	AVERAGE OF MEDICATION(T,T-1,T-2,T-3)	AVERAGE OF MEDICATION(T,T-1,T-2,T-3)(+,.0044)
B. TEST FOR EFFECT OF NON-POLLUTANT ENVIRONMENTAL FACTORS:		
SYMPTOMS	ALL ALLERGENS (AS LOG OF READING)	
MEDICATION	ALL ALLERGENS (AS LOG OF READING)	MOLD1(-,.0027)
PF, NIGHT	ALL ALLERGENS (AS LOG OF READING)	
PF, DAY	ALL ALLERGENS (AS LOG OF READING)	TREES1(-,.0056)
SYMPTOMS	TEMP(1AM), TEMP(1PM), HUMIDITY(1AM), HUMIDITY(1PM)	
MEDICATION	TEMP(1AM), TEMP(1PM), HUMIDITY(1AM), HUMIDITY(1PM)	
PF, NIGHT	TEMP(1AM), TEMP(1PM), HUMIDITY(1AM), HUMIDITY(1PM)	
PF, DAY	TEMP(1AM), TEMP(1PM), HUMIDITY(1AM), HUMIDITY(1PM)	
SYMPTOMS	TEMP(1PM), HUMIDITY(1PM) FROM ONTARIO	
MEDICATION	TEMP(1PM), HUMIDITY(1PM) FROM ONTARIO	
PF, NIGHT	TEMP(1PM), HUMIDITY(1PM) FROM ONTARIO	
PF, DAY	TEMP(1PM), HUMIDITY(1PM) FROM ONTARIO	
C. TEST FOR EFFECT OF POLLUTANTS:		
SYMPTOMS	CO, NOX, NO2, SO2, OZONE	
MEDICATION	CO, NOX, NO2, SO2, OZONE	
PF, NIGHT	CO, NOX, NO2, SO2, OZONE	
PF, DAY	CO, NOX, NO2, SO2, OZONE	
SYMPTOMS	CO, NO2, SO2, OZONE, SULFATES, TSP	
MEDICATION	CO, NO2, SO2, OZONE, SULFATES, TSP	
PF, DAY	CO, NO2, SO2, OZONE, SULFATES, TSP	
PF, NIGHT	CO, NO2, SO2, OZONE, SULFATES, TSP	TSP(+,.0052)
SYMPTOMS	CO, SO2, NO2, TSP, SULFATE, HYDROCARBONS, OZONE	
MEDICATION	CO, SO2, NO2, TSP, SULFATE, HYDROCARBONS, OZONE	CO(+,.0158)
PF, DAY	CO, SO2, NO2, TSP, SULFATE, HYDROCARBONS, OZONE	
PF, NIGHT	CO, SO2, NO2, TSP, SULFATE, HYDROCARBONS, OZONE	
SYMPTOMS	EACH SEPARATELY: SULFATE, TSP, NO2, OZONE, CO,	
MEDICATION	HYDROCARBONS, BOTH T AND T-1 SEPARATELY, E.G.,	
PF, NIGHT	SYMPTOMS VS. SULFATE, SYMPTOMS VS. SULFATE(T-1),	
PF, DAY	MED VS. SULFATE, ETC., SYMPTOMS VS. TSP, SYMPTOMS VS. TSP(T-1), ETC. (48 TOTAL RUNS)	TSP(T)(+,.045) (PF, DAY IS DEPENDENT VARIABLE)

(TABLE 21, cont.)

DEPENDENT VARIABLE	INDEPENDENT VARIABLES *	COEFFICIENTS WITH SIGNIFICANT T'S (SIGN OF COEFFICIENT AND P ARE GIVEN IN PARENTHESES) *
D. TEST FOR EFFECT OF OZONE ALONE, INCLUDING DELAYED EFFECT:		
SYMPTOMS	OZONE	
MEDICATION	OZONE	
PF, NIGHT	OZONE	
PF, DAY	OZONE	
SYMPTOMS	OZONE, OZONE(T-1), OZONE(T-2), OZONE(T-3)	
MEDICATION	OZONE, OZONE(T-1), OZONE(T-2), OZONE(T-3)	
PF, NIGHT	OZONE, OZONE(T-1), OZONE(T-2), OZONE(T-3)	
PF, DAY	OZONE, OZONE(T-1), OZONE(T-2), OZONE(T-3)	
SYMPTOMS	AVERAGE OF OZONE(T,T-1)	
MEDICATION	AVERAGE OF OZONE(T,T-1)	
PF, NIGHT	AVERAGE OF OZONE(T,T-1)	
PF, DAY	AVERAGE OF OZONE(T,T-1)	
SYMPTOM	AVERAGE OF OZONE(T,T-1,T-2)	
MEDICATION	AVERAGE OF OZONE(T,T-1,T-2)	
PF, NIGHT	AVERAGE OF OZONE(T,T-1,T-2)	
PF, DAY	AVERAGE OF OZONE(T,T-1,T-2)	
SYMPTOMS	AVERAGE OF OZONE(T,T-1,T-2,T-3)	
MEDICATION	AVERAGE OF OZONE(T,T-1,T-2,T-3)	
PF, NIGHT	AVERAGE OF OZONE(T,T-1,T-2,T-3)	
PF, DAY	AVERAGE OF OZONE(T,T-1,T-2,T-3)	
E. TEST FOR EFFECT OF OZONE, ACCOUNTING FOR MEDICATION USE AND PREVIOUS DAY'S SYMPTOMS:		
SYMPTOMS	OZONE, OZONE(T-1), MEDICATION, MED(T-1), SYMPTOMS(T-1)	MEDICATION(+,.00005), MEDICATION(T-1)(-,.00010) SYMPTOMS(T-1)(+,<.00001)
SYMPTOMS	OZONE, OZONE(T-1), MEDICATION(T-1), SYMPTOMS(T-1)	SYMPTOMS(T-1)(+,<.00001)
MEDICATION	OZONE, OZONE(T-1), MEDICATION(T-1), SYMPTOMS(T-1)	SYMPTOMS(T-1)(+,.00044), MEDICATION(T-1)(+,<.00001)
PF, DAY	OZONE, OZONE(T-1), MEDICATION(T-1), SYMPTOMS(T-1)	SYMPTOMS(T-1)(-,<.00001)
PF, NIGHT	OZONE, OZONE(T-1), MEDICATION(T-1), SYMPTOMS(T-1)	SYMPTOMS(T-1)(-,<.00001)
SYMPTOMS	OZONE, OZONE(T-1), OZONE(T-2), OZONE(T-3), SYMPTOMS(T-1), MEDICATION(T-1)	SYMPTOMS(T-1)(+,<.00001)
F. TEST FOR EFFECT OF OZONE, ACCOUNTING FOR PREVIOUS DAY'S VALUE OF DEPENDENT VARIABLE:		
SYMPTOMS	OZONE, SYMPTOMS(T-1)	SYMPTOMS(T-1)(+,<.00001)
PF, NIGHT	OZONE, PF,NIGHT(T-1)	PF,NIGHT(T-1)(+,<.00001)
PF, DAY	OZONE, PF,DAY(T-1)	PF,DAY(T-1)(+,<.00001)

(TABL 1, cont.)

DEPENDENT VARIABLE	INDEPENDENT VARIABLES *	COEFFICIENTS WITH SIGNIFICANT T'S (SIGN OF COEFFICIENT AND P ARE GIVEN IN PARENTHESES) *
G. TEST FOR EFFECT OF OZONE ON THE (POSSIBLY) MOST SENSITIVE SUBJECTS:		
PERFORMED ON THOSE SUBJECTS WHOSE OZONE COEFFICIENTS ARE IN THE TOP QUARTILE FOR DEPENDENT = A*OZONE + B :		
SYMPTOMS	OZONE, OZONE(T-1), OZONE(T-2), OZONE(T-3)	OZONE(+,<.00001)
MEDICATION	OZONE, OZONE(T-1), OZONE(T-2), OZONE(T-3)	OZONE(+,.00004)
PF, NIGHT	OZONE, OZONE(T-1), OZONE(T-2), OZONE(T-3)	OZONE(-,<.00001)
PF, DAY	OZONE, OZONE(T-1), OZONE(T-2), OZONE(T-3)	OZONE(-,.00001), OZONE(T-2)(+,.024)
PERFORMED ON THOSE SUBJECTS WHOSE OZONE COEFFICIENTS ARE IN THE TOP QUARTILE FOR DEPENDENT = A*OZONE(T-1) + B :		
SYMPTOMS	OZONE, OZONE(T-1), OZONE(T-2), OZONE(T-3)	OZONE(T-1)(+,.00001)
MEDICATION	OZONE, OZONE(T-1), OZONE(T-2), OZONE(T-3)	OZONE(T-1)(+,<.00001), OZONE(T-2)(-,.00075)
PF, NIGHT	OZONE, OZONE(T-1), OZONE(T-2), OZONE(T-3)	OZONE(T-1)(-,<.00001), OZONE(T-2)(+,.008)
PF, DAY	OZONE, OZONE(T-1), OZONE(T-2), OZONE(T-3)	OZONE(T-1)(-,<.00001), OZONE(T-2)(+,.014)
H. TEST FOR EFFECT OF OZONE IN INCREASINGLY LARGER GROUPS OF THE (POSSIBLY) MOST SENSITIVE SUBJECTS, ACCOUNTING FOR PREVIOUS DAY'S VALUE OF DEPENDENT VARIABLE:		
PERFORMED ON THOSE SUBJECTS WHOSE AVERAGE OF THE OZONE COEFFICIENTS FOR EACH OF DEPENDENT = A*OZONE + B*DEPENDENT(T-1) + C , (WHERE DEPENDENT IS SYMPTOMS, DAY PF AND NIGHT PF) ARE THE 20 HIGHEST:		
SYMPTOMS	OZONE, SYMPTOMS(T-1)	OZONE(+,.0073), SYMPTOMS(T-1)(+,<.00001)
MEDICATION	OZONE, MEDICATION(T-1)	MEDICATION(T-1)(+,<.00001)
PF, NIGHT	OZONE, PF,NIGHT(T-1)	OZONE(-,<.00001), PF,NIGHT(T-1)(+,<.00001)
PF, DAY	OZONE, PF,DAY(T-1)	OZONE(-,<.00001), PF,DAY(T-1)(+,<.00001)
PERFORMED ON THOSE SUBJECTS WHOSE AVERAGE OF THE OZONE COEFFICIENTS FOR EACH OF DEPENDENT = A*OZONE + B*DEPENDENT(T-1) + C , (WHERE DEPENDENT IS SYMPTOMS, DAY PF AND NIGHT PF) ARE THE 25 HIGHEST:		
SYMPTOMS	OZONE, SYMPTOMS(T-1)	OZONE(+,.00090), SYMPTOMS(T-1)(+,<.00001)
MEDICATION	OZONE, MEDICATION(T-1)	MEDICATION(T-1)(+,<.00001)
PF, NIGHT	OZONE, PF,NIGHT(T-1)	OZONE(-,<.00001), PF,NIGHT(T-1)(+,<.00001)
PF, DAY	OZONE, PF,DAY(T-1)	OZONE(-,<.00001), PF,DAY(T-1)(+,<.00001)
PERFORMED ON THOSE SUBJECTS WHOSE AVERAGE OF THE OZONE COEFFICIENTS FOR EACH OF DEPENDENT = A*OZONE + B*DEPENDENT(T-1) + C , (WHERE DEPENDENT IS SYMPTOMS, DAY PF AND NIGHT PF) ARE THE 30 HIGHEST:		
SYMPTOMS	OZONE, SYMPTOMS(T-1)	OZONE(+,.00034), SYMPTOMS(T-1)(+,<.00001)
MEDICATION	OZONE, MEDICATION(T-1)	MEDICATION(T-1)(+,<.00001)
PF, NIGHT	OZONE, PF,NIGHT(T-1)	OZONE(-,<.00001), PF,NIGHT(T-1)(+,<.00001)
PF, DAY	OZONE, PF,DAY(T-1)	OZONE(-,<.00001), PF,DAY(T-1)(+,<.00001)
PERFORMED ON THOSE SUBJECTS WHOSE AVERAGE OF THE OZONE COEFFICIENTS FOR EACH OF DEPENDENT = A*OZONE + B*DEPENDENT(T-1) + C , (WHERE DEPENDENT IS SYMPTOMS, DAY PF AND NIGHT PF) ARE THE 35 HIGHEST:		
SYMPTOMS	OZONE, SYMPTOMS(T-1)	OZONE(+,.00032), SYMPTOMS(T-1)(+,<.00001)
MEDICATION	OZONE, MEDICATION(T-1)	MEDICATION(T-1)(+,<.00001)
PF, NIGHT	OZONE, PF,NIGHT(T-1)	OZONE(-,.00002), PF,NIGHT(T-1)(+,<.00001)
PF, DAY	OZONE, PF,DAY(T-1)	OZONE(-,<.00001), PF,DAY(T-1)(+,<.00001)

(TABLE 21, cont.)

DEPENDENT VARIABLE	INDEPENDENT VARIABLES *	COEFFICIENTS WITH SIGNIFICANT T'S (SIGN OF COEFFICIENT AND P ARE GIVEN IN PARENTHESES) *
PERFORMED ON THOSE SUBJECTS WHOSE AVERAGE OF THE OZONE COEFFICIENTS FOR EACH OF DEPENDENT = A*OZONE + B*DEPENDENT(T-1) + C , (WHERE DEPENDENT IS SYMPTOMS, DAY PF AND NIGHT PF) ARE THE 40 HIGHEST:		
SYMPTOMS	OZONE, SYMPTOMS(T-1)	OZONE(+,.0032), SYMPTOMS(T-1)(+,<.00001)
MEDICATION	OZONE, MEDICATION(T-1)	MEDICATION(T-1)(+,<.00001)
PF, NIGHT	OZONE, PF,NIGHT(T-1)	OZONE(-,.00016), PF,NIGHT(T-1)(+,<.00001)
PF, DAY	OZONE, PF,DAY(T-1)	OZONE(-,.00010), PF,DAY(T-1)(+,<.00001)
PERFORMED ON THOSE SUBJECTS WHOSE AVERAGE OF THE OZONE COEFFICIENTS FOR EACH OF DEPENDENT = A*OZONE + B*DEPENDENT(T-1) + C , (WHERE DEPENDENT IS SYMPTOMS, DAY PF AND NIGHT PF) ARE THE 45 HIGHEST:		
SYMPTOMS	OZONE, SYMPTOMS(T-1)	OZONE(+,.0016), SYMPTOMS(T-1)(+,<.00001)
MEDICATION	OZONE, MEDICATION(T-1)	MEDICATION(T-1)(+,<.00001)
PF, NIGHT	OZONE, PF,NIGHT(T-1)	OZONE(-,.00014), PF,NIGHT(T-1)(+,<.00001)
PF, DAY	OZONE, PF,DAY(T-1)	OZONE(-,.00037), PF,DAY(T-1)(+,<.00001)
PERFORMED ON THOSE SUBJECTS WHOSE AVERAGE OF THE OZONE COEFFICIENTS FOR EACH OF DEPENDENT = A*OZONE + B*DEPENDENT(T-1) + C , (WHERE DEPENDENT IS SYMPTOMS, DAY PF AND NIGHT PF) ARE THE 50 HIGHEST:		
SYMPTOMS	OZONE, SYMPTOMS(T-1)	OZONE(+,.0094), SYMPTOMS(T-1)(+,<.00001)
MEDICATION	OZONE, MEDICATION(T-1)	MEDICATION(T-1)(+,<.00001)
PF, NIGHT	OZONE, PF,NIGHT(T-1)	OZONE(-,.00012), PF,NIGHT(T-1)(+,<.00001)
PF, DAY	OZONE, PF,DAY(T-1)	OZONE(-,.00081), PF,DAY(T-1)(+,<.00001)
PERFORMED ON THOSE SUBJECTS WHOSE AVERAGE OF THE OZONE COEFFICIENTS FOR EACH OF DEPENDENT = A*OZONE + B*DEPENDENT(T-1) + C , (WHERE DEPENDENT IS SYMPTOMS, DAY PF AND NIGHT PF) ARE THE 55 HIGHEST:		
SYMPTOMS	OZONE, SYMPTOMS(T-1)	OZONE(+,.0046), SYMPTOMS(T-1)(+,<.00001)
MEDICATION	OZONE, MEDICATION(T-1)	MEDICATION(T-1)(+,<.00001)
PF, NIGHT	OZONE, PF,NIGHT(T-1)	OZONE(-,.00085), PF,NIGHT(T-1)(+,<.00001)
PF, DAY	OZONE, PF,DAY(T-1)	OZONE(-,.0027), PF,DAY(T-1)(+,<.00001)
PERFORMED ON THOSE SUBJECTS WHOSE AVERAGE OF THE OZONE COEFFICIENTS FOR EACH OF DEPENDENT = A*OZONE + B*DEPENDENT(T-1) + C , (WHERE DEPENDENT IS SYMPTOMS, DAY PF AND NIGHT PF) ARE THE 60 HIGHEST:		
SYMPTOMS	OZONE, SYMPTOMS(T-1)	OZONE(+,.012), SYMPTOMS(T-1)(+,<.00001)
MEDICATION	OZONE, MEDICATION(T-1)	MEDICATION(T-1)(+,<.00001)
PF, NIGHT	OZONE, PF,NIGHT(T-1)	OZONE(-,.0016), PF,NIGHT(T-1)(+,<.00001)
PF, DAY	OZONE, PF,DAY(T-1)	OZONE(-,.018), PF,DAY(T-1)(+,<.00001)
PERFORMED ON THOSE SUBJECTS WHOSE AVERAGE OF THE OZONE COEFFICIENTS FOR EACH OF DEPENDENT = A*OZONE + B*DEPENDENT(T-1) + C , (WHERE DEPENDENT IS SYMPTOMS, DAY PF AND NIGHT PF) ARE THE 63 HIGHEST:		
SYMPTOMS	OZONE, SYMPTOMS(T-1)	OZONE(+,.031), SYMPTOMS(T-1)(+,<.00001)
PF, NIGHT	OZONE, PF,NIGHT(T-1)	OZONE(-,.003), PF,NIGHT(T-1)(+,<.00001)
PF, DAY	OZONE, PF,DAY(T-1)	PF,DAY(T-1)(+,<.00001)

(TABLE 1, cont.)

DEPENDENT VARIABLE	INDEPENDENT VARIABLES *	COEFFICIENTS WITH SIGNIFICANT T'S (SIGN OF COEFFICIENT AND P ARE GIVEN IN PARENTHESES) *

I. TEST FOR EFFECT OF OZONE ON THE (POSSIBLY) MOST SENSITIVE SUBJECTS AS MEASURED BY ANY OF THE OUTCOME VARIABLES RATHER THAN JUST THE ONE CORRESPONDING TO EACH REGRESSION ANALYSIS (SEE TEXT):

PERFORMED ON SUBJECTS WHOSE COEFFICIENTS FOR OZONE ARE IN THE TOP QUARTILE FOR 2 OF 3 OF THE REGRESSIONS OF THE TYPE DEPENDENT = A*OZONE + B*DEPENDENT(T-1) + C, WHERE DEPENDENT IS SYMPTOMS, PF,DAY AND PF,NIGHT:

SYMPTOMS	OZONE, SYMPTOMS(T-1)	OZONE(+,.0168), SYMPTOMS(T-1)(+,<.00001)
MEDICATION	OZONE, MEDICATION(T-1)	MEDICATION(T-1)(+,<.00001)
PF, NIGHT	OZONE, PF,NIGHT(T-1)	OZONE(-,.00079), PF,NIGHT(T-1)(+,<.00001)
PF, DAY	OZONE, PF,DAY(T-1)	OZONE(-,<.00001), PF,DAY(T-1)(+,<.00001)

PERFORMED ON SUBJECTS WHOSE COEFFICIENTS FOR OZONE ARE IN THE TOP QUARTILE FOR 1 OF 3 OF THE REGRESSIONS OF THE TYPE DEPENDENT = A*OZONE + B*DEPENDENT(T-1) + C, WHERE DEPENDENT IS SYMPTOMS, PF,DAY AND PF,NIGHT:

SYMPTOMS	OZONE, SYMPTOMS(T-1)	OZONE(+,.0013), SYMPTOMS(T-1)(+,<.00001)
MEDICATION	OZONE, MEDICATION(T-1)	MEDICATION(T-1)(+,<.00001)
PF, NIGHT	OZONE, PF,NIGHT(T-1)	OZONE(-,<.00001), PF,NIGHT(T-1)(+,<.00001)
PF, DAY	OZONE, PF,DAY(T-1)	OZONE(-,.00009), PF,DAY(T-1)(+,<.00001)

* (T) = DATA FOR THE SAME DAY AS THE DEPENDENT VARIABLE
(T-1) = DATA FROM THE DAY BEFORE THAT OF THE DEPENDENT VARIABLE
(T-2) = DATA FROM TWO DAYS BEFORE THAT OF THE DEPENDENT VARIABLE
(T-3) = DATA FROM THREE DAYS BEFORE THAT OF THE DEPENDENT VARIABLE

SYMPTOMS = AVERAGE SYMPTOM SCORE.
MEDICATION = ASTHMA MEDICATION INDEX (AMI).
PF, NIGHT = PEAK EXPIRATORY FLOW RATE (PEFR) AT NIGHT.
PF, DAY = PEAK EXPIRATORY FLOW RATE (PEFR) DURING DAY.

SIGNIFICANT T'S ARE THOSE WITH P<.05

Table 22. Differences in Baseline Demographic, Clinical, and Physiological Characteristics Between Responders to Ozone and Respective Remainders of Group

Variable	Responders-1 (n=27) vs. n=56	Responders-2 (n=12) vs. n=71
1. Asthma Worsened by:		
a. Tension	NS (p=0.123)*	NS (p=0.626)*
b. Exercise	NS (p=0.654)	NS (p=0.174)
c. Smog	NS (p=0.497)	NS (p=0.355)
d. Animals	NS (p=0.538)	NS (p=0.295)
e. Plants	NS (p=0.099)	NS (p=0.234)
2. Atopies Combined	NS (p=0.497)	NS (p=0.239)
3. Smoking	NS (p=0.590)	NS (p=0.680)
4. Employment Status	NS (p=0.700)	NS (p=0.821)
5. Duration of Residence	NS (p=0.400)	NS (p=0.888)
6. Change in Breathing at Work	NS (p=0.420)	NS (p=0.125)
7. Age	NS (p=0.611)	NS (p=0.424)
8. Heating System	NS (p=0.705)	NS (p=0.538)
9. Heating Fuel	NS (p=0.599)	NS (p=0.170)
10. Cooking Fuel	NS (p=0.080)	NS (p=0.237)
11. Sex	NS (p=0.345)	NS (p=0.892)
12. Race	NS (p=0.233)	NS (p=0.326)
13. Education	NS (p=0.389)	NS (p=0.053)
14. % Predicted FEV_1	NS (p=0.625)	NS (p=0.421)
15. Steroid Use	NS (p=0.786)	NS (p=0.203)
16. Age	NS (p=0.303)	NS (p=0.228)
17. Income	NS (p=0.658)	NS (p=0.803)
18. Hours Indoors during:		
a. Fall	NS (p=0.976)	NS (p=0.318)
b. Spring	NS (p=0.894)	NS (p=0.219)
c. Summer	NS (p=0.430)	NS (p=0.293)
19. Duration of Asthma	NS (p=0.263)	NS (p=0.750)
20. % Predicted:		
a. FEV_1	NS (p=0.528)	NS (p=0.480)
b. FVC	NS (p=0.296)	NS (p=0.478)
c. $FEF_{25-75\%}$	NS (p=0.834)	NS (p=0.521)
21. Percent FEV_1/FVC	NS (p=0.738)	NS (p=0.465)

*Items 1-15 are based on chi-square or Fisher's exact test. Items 16-21 are based on t-tests.

Table 23. Differences in Mean Dependent Variables Between Responders to Ozone and Respective Remainders of Group

Variable	Responders-1 (n=27) vs. n=56	Responders-2 (n=12) vs. n=71
Mean Symptom Score	NS (p=0.078)+	NS (p=0.054)
Mean Day PEFR	NS (p=0.368)	NS (p=0.535)
Mean Night PEFR	NS (p=0.362)	NS (p=0.608)
Asthma Medication Index (AMI), overall	NS (p=0.466)	NS (p=0.244)
AMI, on smoggy days*	NS (p=0.351)	NS (p=0.199)
AMI, on clean days**	NS (p=0.482)	NS (p=0.244)

*7/26/83-8/8/83 and 9/1/83-9/14/83.

**4/15/83-4/28/83 and 11/6/83-11/30/83.

+Based on t-tests.

Table 24. Differences in Hours Spent Outdoors (12 noon - 6 P.M.) Between Responders to Ozone and Respective Remainders of Group

	Responders-1 (n=27) vs. n=56	Responders-2 (n=12) vs. n=71
During Smoggy Days*:		
Weekdays		
Average no. hours ± SD	2.2±1.4 vs 2.2±1.4	2.4±1.7 vs 2.2±1.4
Significance (t-test)	NS (p=0.768)	NS (p=0.519)
Weekends		
Average no. hours ± SD	2.9±1.5 vs 3.1±1.4	3.2±1.6 vs 3.1±1.4
Significance (t-test)	NS (p=0.694)	NS (p=0.662)
During Clean Days**:		
Weekdays		
Average no. hours ± SD	2.3±1.3 vs 2.1±1.5	2.5±1.6 vs 2.1±1.4
Significance (t-test)	NS (p=0.530)	NS (p=0.349)
Weekends		
Average no. hours ± SD	3.2±1.4 vs 3.1±1.6	3.5±1.7 vs 3.1±1.4
Significance (t-test)	NS (p=0.634)	NS (p=0.412)

*7/26/83 - 8/8/83 and 9/1/83 - 9/14/83.

**4/15/83 - 4/28/83 and 11/6/83 - 11/30/83.

Table 25. Significant Relationships* Between Asthma Symptom Checklist Results (Adults Only) and Average Slope Coefficients for Ozone

Category of Asthma Symptom Checklist (Kinsman)	Group Score**	Dependent Variable and Ozone Coefficient+	P Value
C 1 Panic-Fear	Moderate	Symptoms-Low	0.034
C 3 Fatigue	High	Night PEFR-Low	0.059
C 3 Fatigue	High	Night PEFR-Low	0.014
C 4 Hyperventilation	High	Day PEFR-Low	0.011
C 5 Dyspnea	High	Day PEFR-Low	0.042
C 6 Congestion	High	Day PEFR-Low	0.046
C 6 Congestion	High	Night PEFR-Low	0.039
C10 Rapid Breathing	High	Day PEFR-Low	0.037
C10 Rapid Breathing	High	Night PEFR-Low	0.038

*Based on two-way ANOVA of multiple regressions for individual slope coefficients for ozone (across sex and symptom category score). Other symptom categories were not significant ($p>>0.05$).

**High = upper 25% of group scores; moderate = middle 50%; low = lower 25%.

+A low ozone coefficient indicates a negative slope coefficient for ozone from multiple regressions, i.e., the dependent variable worsens when ozone increases.

Table 26. Differences in Asthma Symptom Checklist (Adults Only) Results Between Responders to Ozone and Respective Remainders of Group

Variable	Responders-1 (n=25) vs n=46	Responders-2 (n=12) vs n=59
Asthma Symptom Checklist (factors derived from this study):		
C1 (Irritability)	NS (p=0.874)*	NS (p=0.622)*
C2 (Fatigue)	p=0.044	NS (p=0.076)
C3 (Panic-Fear)	NS (p=0.548)	NS (p=0.255)
C4 (Dyspnea)	NS (p=0.107)	NS (p=0.079)
C5 (Loneliness-Anger)	NS (p=0.472)	NS (p=0.369)
C6 (Congestion)	NS (p=0.254)	NS (p=0.325)
C7 (Hyperventilation)	NS (p=0.112)	p=0.013
C8 (Hyperventilation)	NS (p=0.290)	NS (p=0.316)
Asthma Symptom Checklist (factors derived from Kinsman):		
C1 (Panic-Fear)	NS (p=0.304)	NS (p=0.151)
C2 (Irritability)	NS (p=0.836)	NS (p=0.565)
C3 (Fatigue)	p=0.044	NS (p=0.076)
C4 (Hyperventilation)	NS (p=0.342)	NS (p=0.152)
C5 (Dyspnea)	NS (p=0.264)	NS (p=0.138)
C6 (Congestion)	NS (p=0.130)	NS (p=0.213)
C7 (Worry)	NS (p=0.588)	NS (p=0.422)
C8 (Anger)	NS (p=0.614)	NS (p=0.487)
C9 (Loneliness)	NS (p=0.366)	NS (p=0.283)
C10 (Rapid Breathing)	p=0.019	p=0.002

*Based on t-tests.