

Reliability of the model MC-311 MDI Chronolog

Frederick S. Wamboldt, MD,^{a,c} Bruce G. Bender, PhD,^{b,c} Shannon L. O'Connor, PhD,^a Leslie A. Gavin, PhD,^{b,c} Marianne Z. Wamboldt, MD,^{b,c} Henry Milgrom, MD,^{b,d} Stanley J. Szeffler, MD,^{b,d,e} David Iklé, PhD,^{a,b} and Cynthia Rand, PhD^f *Denver, Colo, and Baltimore, Md*

Background: The Model MC-311 MDI Chronolog (Medtrac Technologies, Lakewood, Colo) is an electronic device for monitoring adherence to metered-dose inhalers (MDIs). It is a thermistor-actuated, microprocessor-equipped device that dispenses inhaled medication while recording the date and time of each canister activation.

Objective: We evaluated the reliability of the MC-311 MDI Chronolog to determine whether the model could accurately record and report the date, time, and number of MDI actuations.

Methods: Twenty-four of the MC-311 Chronologs were discharged at 8 hourly intervals across 8 days. Battery voltage was assessed before and after the experiment. The mouthpieces of 12 Chronologs were washed daily.

Results: By using generous criteria for acceptable reliability, only 10 of 24 (42%) were rated as acceptable. None of these 10 Chronologs recorded 320 or greater actuations (mean $\pm$ SD, 293.9 ± 13.3 ; range, 266 to 308); all reliable Chronologs underestimated MDI activation. An additional 6 devices had an initial signature of erroneous recordings dating from device initialization. After removing this signature, the remaining data showed acceptable reliability. All the remaining Chronologs judged to be unacceptable showed time series patterns of seizures (ie, bursts of clustered, erroneous records). Seizures were distributed across trial days, were associated with washing, and preceded all 4 cases of battery failure. Damage to the thermistor is the likely cause of seizure-pattern failures.

Conclusions: In summary, because of a combination of a clear underreporting bias with frequent initialization and seizure-pattern failures, the Model MC-311 MDI Chronolog is not recommended for use in clinical care or research (*J Allergy Clin Immunol* 1999;104:53-7.)

Key words: Metered-dose inhaler, MDI Chronolog, asthma treatment adherence

Abbreviation used

MDI: Metered-dose inhaler

Available research evidence clearly indicates the tremendous costs of nonadherence with prescribed asthma treatment caused by compromised treatment effectiveness, including increased morbidity, mortality, health care use costs, and socio vocational impairments.^{1,2} Therefore it is not surprising that interest in the measurement of patient adherence behaviors is growing, with a variety of novel approaches, including electronic monitoring devices, showing particular promise. For example, studies with earlier versions of the MDI Chronolog, a microchip-equipped dispenser that records the date and time of each dose taken of an aerosolized anti-asthma medication, have shown that previous estimates of adherence (eg, diary cards, canister weights, and pill counts) consistently overestimate patient adherence, sometimes by surprisingly large margins.³⁻⁹ These discrepancies have been shown to persist in clinical trials even when subjects are fully aware of the MDI Chronolog's recording capability and are provided explicit feedback about their own personal medication use patterns.⁷⁻¹⁰ Finally, devices like the MDI Chronolog, by providing detailed time series of medication use, also allow the conceptualization of patient adherence to develop beyond simple dichotomies of compliant/noncompliant. Patterns of adherence that can be detected with the MDI Chronolog include consistency of use, binge (presumably rescue only) use, and "dumping"¹⁰ (typically defined as canister activation of at least 100 times per day, usually occurring just before a scheduled return visit).

Unfortunately, subsequent to the above-cited research, the sensor system in the MDI Chronolog was changed from a micromechanical switch to a thermistor-based sensor. Several recent reports have suggested that these newer devices may be less reliable than their predecessors,¹¹⁻¹³ with two studies suggesting that battery failure is a major problem.^{12,13} Accordingly, we designed an experiment to evaluate the reliability of the thermistor-actuated Model MC-311 MDI Chronolog and to examine possible mechanisms for failure of these devices.

METHODS

Twenty-four Model MC-311 MDI Chronologs (Firmware Version Rev. F; Medtrac Technologies, Lakewood, Colo) were initial-

From the Departments of ^aMedicine and ^bPediatrics, National Jewish Medical and Research Center, Denver; the Departments of ^cPsychiatry, ^dPediatrics, and ^ePharmacology, University of Colorado Health Sciences Center, Denver; and ^fthe Division of Pulmonary and Critical Care Medicine, Johns Hopkins University Medical Center, Baltimore.

Supported in part by National Institutes of Health grants R01-HL53391, R01-HL48999, N01-HL16044, and M01-RR00051.

Presented at the 1997 American Lung Association/American Thoracic Society International Conference, San Francisco, California, May 1997.

Received for publication Nov 24, 1998; revised Feb 8, 1999; accepted for publication Feb 10, 1999.

Reprint requests: Frederick S. Wamboldt, MD, National Jewish Medical and Research Center, 1400 Jackson St, F301, Denver, CO 80206.

Copyright © 1999 by Mosby, Inc.

0091-6749/99 \$8.00 + 0 1/1/97841

TABLE I. Protocol for the Model MC-311 MDI Chronolog reliability assessment experiment

Days 1, 3, 5, and 7	
8:30 AM	Weigh all MDIs 3 times
9:00 AM	Two discharges at 1-second intervals
10:00 AM	Two discharges at 2-second intervals
10:30 AM	Weigh all MDIs 3 times
11:00 AM	Two discharges at 1-second intervals
12:00 PM	Two discharges at 2-second intervals
12:30 PM	Weigh all MDIs 3 times
1:00 PM	Eight discharges at 6-second intervals
2:00 PM	Eight discharges at 8-second intervals
2:30 PM	Weigh all MDIs 3 times
3:00 PM	Eight discharges at 6-second intervals
4:00 PM	Eight discharges at 8-second intervals
4:30 PM	Weigh all MDIs 3 times
4:45 PM	Wash for all odd numbered MDIs
Days 2, 4, 6, and 8	
8:30 AM	Weigh all MDIs 3 times
9:00 AM	Eight discharges at 1-second intervals
10:00 AM	Eight discharges at 2-second intervals
10:30 AM	Weigh all MDIs 3 times
11:00 AM	Eight discharges at 1-second intervals
12:00 PM	Eight discharges at 2-second intervals
12:30 PM	Weigh all MDIs 3 times
1:00 PM	Two discharges at 6-second intervals
2:00 PM	Two discharges at 8-second intervals
2:30 PM	Weigh all MDIs 3 times
3:00 PM	Two discharges at 6-second intervals
4:00 PM	Two discharges at 8-second intervals
4:30 PM	Weigh all MDIs 3 times
4:45 PM	Wash all odd numbered MDIs

Each MDI was discharged daily, shaking 5 times before each set of activations according to the above schedule.

ized by using the MDI Chronolog Display Software Version 3.0. Twelve MDI Chronologs fitted with Proventil canisters, 12 Chronologs fitted with Vanceril canisters, 4 standard Proventil metered-dose inhalers (MDIs), and 4 standard Vanceril MDIs were discharged after 5 vigorous shakes at 8 hourly intervals beginning at 9 AM on each of 8 days (ie, Tuesday through Friday in 2 consecutive weeks). Medication canisters were replaced at the start of the second week. Two new 3-volt lithium batteries (Eveready CR2032) were installed in each Chronolog before the start of the trial. Battery voltage was assessed before and after the experiment by using a Radio Shack Battery Tester (Model #22-090). All Chronologs demonstrated a reading of at least 5.8 volts before the start of the trial. Other factors manipulated within the design were (1) medication amount dispensed at each time point (2 vs 8 puffs), (2) rate of MDI activation (≤ 2 seconds between activation vs 6 to 8 seconds between activation); and (3) frequency of mouthpiece washing (daily vs none). The mouthpieces of the 12 Chronologs given odd numbers (6 Proventil and 6 Vanceril) were removed and washed daily after the recommended procedures detailed in the *MDI Chronolog & Display Software (v 3.0) Users Manual* (Medtrac Technologies, 1995). This procedure lead to each MDI Chronolog being discharged 160 times on each canister for a total of 320 actuations across the trial for each MDI Chronolog. A summary of the experimental protocol is shown in Table I. The repeated-measures experimental design was stratified by device, medication, and washing with within-device factors of amount dispensed and activation rate. Data were entered and analyzed in JMP (SAS Institute Inc,

Cary, NC). Statistical analyses were performed by using descriptive statistics and by using Fisher's exact test for comparison of proportions.

RESULTS

Reliability was assessed in several ways. First, the data were summarized in a contingency table listing number of actuations for each Chronolog by hour of the day (collapsed across all trial days). A Chronolog was deemed to have acceptable reliability if the total number of actuations recorded was within 20% of the expected 320 actuations and if no discharges were recorded between 6 PM to 8 AM. By using these generous criteria, only 10 of the 24 MDI Chronologs (42%) were rated as acceptable. None of these 10 Chronologs recorded 320 or more actuations (mean $\pm$ SD, 293.9 $\pm$ 13.3; range, 266 to 308).

Second, the activation data time series observed for each device was plotted against the expected activation time series. Fig 1 is an example of the plot obtained from a Chronolog deemed acceptable by the above-described reliability criteria.

Further inspection of these plots revealed that 6 additional devices had an initial signature of erroneous recordings dating from the device's initialization and preceding the experiment's start (Fig 2). After removing this signature, the remaining data showed acceptable reliability by the above criteria (Fig 2). Our experiment provides no explanation for these apparent errors during initialization. Nonetheless, if one discounts this as a "recoverable failure," 16 of the 24 MDI Chronologs (67%) could be considered reliable according to these more generous criteria.

All Chronologs still being judged as unacceptable showed time series patterns that had bursts of clustered, erroneous records or "seizures" (Fig 3). The first seizure observed in each of these devices was distributed across trial days, with 2 occurring on trial day 1, 3 on trial day 2, and 1 each on trial days 3, 4, and 6. Seven of the 8 devices that failed because of seizures were in the wash condition ($P \leq .001$, Fisher's exact test).

Battery failure was defined as follows: (1) an absent LED light display during attempted actuation at trial end (an internal indication of Chronolog failure); and (2) confirmation of inadequate battery voltage determined by battery testing. Four cases of battery failure were observed. All instances of battery failure occurred in Chronologs that had demonstrated seizures ($P \leq .001$, Fisher's exact test).

DISCUSSION

Overall, reliability of the Model MC-311 MDI Chronolog was low, with our estimates of reliability ranging from 42% to 67%, depending on the set of criteria used. In any case, the sensor system of these Chronologs always underestimated MDI activation by slightly over 8% on average. A specific and unexplained error in the initialization process was observed in 6 of the 24 Chronologs (25%). Fortunately, this problem did not appear to contaminate subsequent data recording. Indeed,

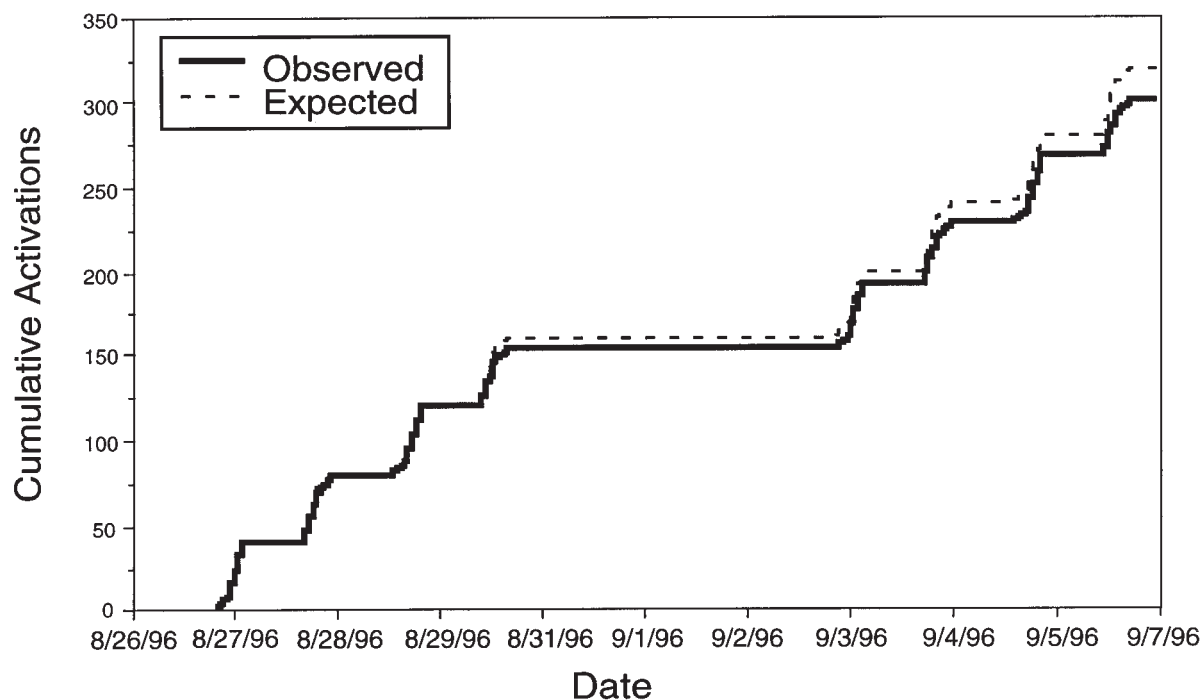


FIG 1. Expected and observed cumulative activation counts of an MDI Chronolog showing acceptable reliability.

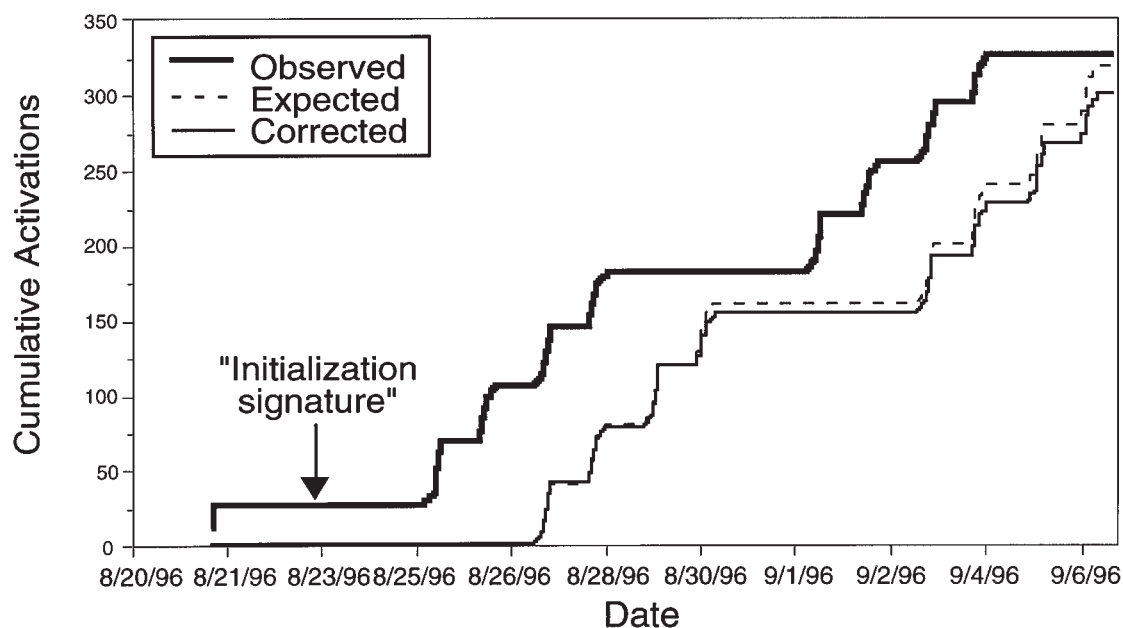


FIG 2. Expected, observed, and corrected cumulative activation counts of an MDI Chronolog showing the "faulty initialization signature" failure pattern.

once the "signature" of this error was removed, the resulting data time series exhibited acceptable reliability. Seizure-pattern activation time series were observed in all 8 of the Chronologs judged as unacceptable, and therefore seizures appear to be, at minimum, a marker of unreliability. Because the first observed seizure occurred on 5 of

the 8 days of the trial, it may prove difficult to weed out at-risk Chronologs through a pretesting procedure. Battery failure, which has been previously identified as a mechanism of MDI Chronolog failure,^{12,13} always occurred after seizures and, accordingly, appears to be a secondary problem. Furthermore, mouthpiece washing

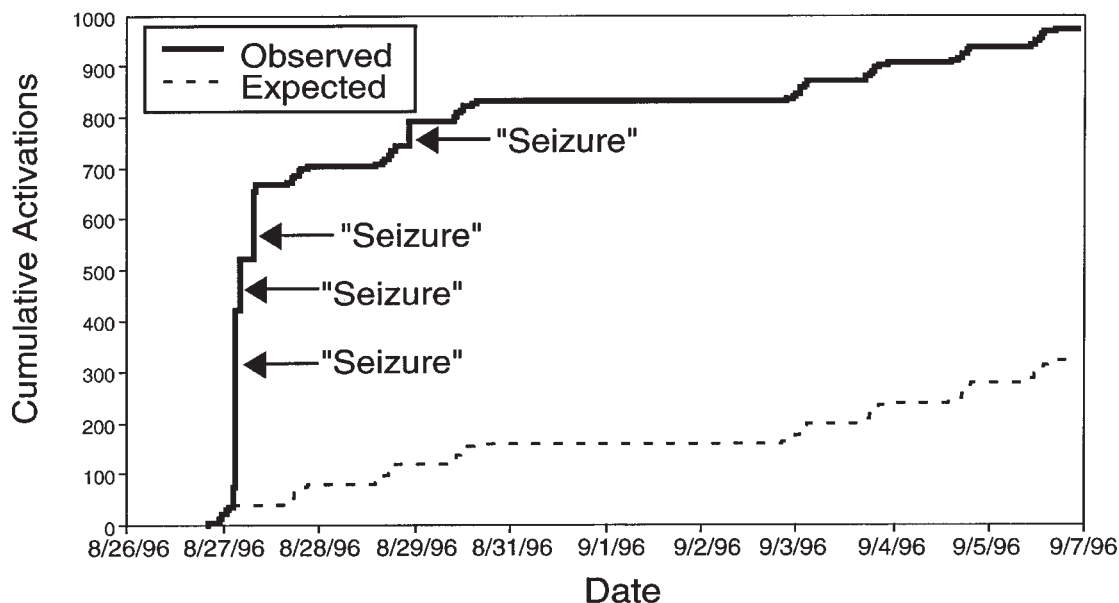


FIG 3. Expected and observed cumulative activation counts of an MDI Chronolog showing "seizures."

strongly was associated with seizures, with 7 of the 8 devices demonstrating seizures being in this condition. Presumably, the act of removing and replacing the mouthpiece during washing caused physical damage to the activation-recording thermistor, which is precariously placed in the medication outflow stream. This suggests that a vulnerable and delicate thermistor is the primary cause of unreliability in these devices. It is important to underscore that this experiment was conducted in a controlled laboratory by personnel who were trained in the handling of the Chronologs by representatives of the manufacturer. Accordingly, one would expect that rates of failure may well be much higher in field studies using the Chronolog.

Two important further points must be made concerning this reliability trial. First, the phenomenon of seizures that we report herein does not correspond in any way to the above-mentioned phenomenon of canister "dumping" identified in subjects in clinical trials by Rand et al¹⁰ in at least 2 regards. First, although dumping was specifically defined by Rand and associates as canister activation of at least 100 times per day, the dumping episodes predominantly occurred right before a scheduled return visit when the research subject knew that their returned MDI canisters would be weighed as a measure of medication adherence. However, in the present experiment, seizures were essentially equally distributed across the days of the trial. Second and most important, the version of the MDI Chronolog used in this prior study was an earlier version that used a microswitch to record canister activation rather than the current thermistor-based sensor system, which we identified as the likely cause of seizures and failure in this experiment.

The second important point concerning this study is that representatives of the manufacturer of the MDI

Chronolog were both supportive and responsive across this trial, despite the extremely unfavorable reliability results observed. To our knowledge, this is the most rigorous trial concerning the reliability of a respiratory medication adherence measuring device done in collaboration with a device manufacturer, although totally independent in design and conduct, that has achieved peer-reviewed publication. We laud this manufacturer for recognizing the importance of such independent testing for the long-term interests of their product line. Indeed, the manufacturers have recalled outstanding units and withdrawn the Model MC-311 MDI Chronolog from the market and now offer a redesigned electronic adherence measurement device, the MDI Log, which features a different sensor system among a variety of improvements.

Other electronic devices are now marketed to track patient adherence to asthma treatment, although with a few promising exceptions,¹⁴ almost no independent studies of the reliability of these devices have been published. In addition to the Medtrac MDI Chronolog, the Doser (MediTrack Products, Hudson, Mass) can record daily use of inhaled medications. The Electronic Drug Exposure Monitor (AARDEX, Inc, Palo Alto, Calif) monitors tablet use, whereas the AirWatch (ENACT Health Management Systems, Mountain View, Calif) and Asthma Monitor I (Ferraris Medical Inc, Holland, NY) record peak flow readings. Finally, the Smartmist (Aradigm Corporation, Hayward, Calif) records both inhaled medication use and peak flows. We encourage these other manufacturers to follow Medtrac's lead in supporting rigorous, independent testing to ensure that the adherence recording devices with the highest possible quality are available for clinical research and practice.

In summary, because of a combination of a clear under-reporting bias with frequent initialization and seizure-pat-

tern failures, the Model MC-311 MDI Chronolog is not recommended for use in clinical care or research. Manufacturers of electronic adherence monitoring devices are encouraged to provide better documentation of the reliability of their instruments in both laboratory and field settings, including research published in peer-reviewed journals. Behavioral scientists using these devices in studies of treatment adherence are encouraged to take an active role in helping to specify the expectations and format for such documentation.

We thank Sandra McTaggart and Lisa Meltzer for graciously providing the finger power required for this experiment, Medtrac Technologies for supplying the Model MC-311 MDI Chronologs, and Schering Corporation for donating the MDI canisters.

REFERENCES

1. Creer TL, Bender BG. Pediatric asthma. In: Roberts M, editor. The handbook of pediatric psychology. 2nd ed. New York: Plenum; 1994.
2. Bender B, Milgrom H. Adherence in pediatric asthma. *Asthma Management* 2000;196;1:7-10.
3. Coutts JAP, Gibson NA, Paton JY. Measuring compliance with inhaled medication in asthma. *Arch Dis Child* 1992;67:332-3.
4. Mawhinney H, Spector SL, Kinsman RA, Siegel SC, Rachelefsky GS, Katz RM, et al. Compliance in clinical trials of two nonbronchodilator, antiasthma medications. *Ann Allergy* 1991;66:294-9.
5. Mawhinney H, Spector SL, Heitjan D, Kinsman RA, Dirks JF, Pines I. As-needed medication use in asthma: usage patterns and patient characteristics. *J Asthma* 1993;30:61-71.
6. Milgrom M, Bender B, Ackerson L, Bowry P, Smith B, Rand C. Non-compliance and treatment failure in children with asthma. *J Allergy Clin Immunol* 1996;98:1051-7.
7. Nides MA, Tashkin DP, Simmons MS, Wise RA, Li VC, Rand CS. Improving inhaler adherence in a clinical trial through the use of the nebulizer chronolog. *Chest* 1993;104:501-7.
8. Spector SL, Mawhinney H. Aerosol inhaler monitoring of asthmatic medication. In: Cramer JA, Spilker B, editors. Patient compliance in medical practice and clinical trials. New York: Raven Press; 1991.
9. Tashkin DP, Rand C, Nides M, Simmons M, Wise R, Coulson AH, et al. A nebulizer chronolog to monitor compliance with inhaler use. *Am J Med* 1991;91:335-65.
10. Rand CS, Wise RA, Nides M, Simmons MS, Bleecker ER, Kusek JW, et al. Metered-dose inhaler adherence in a clinical trial. *Am Rev Respir Dis* 1992;146:1559-64.
11. Bender B, Ackerson L, Milgrom H, Rand C. Metered dose inhaler chronologs [abstract]. *Am J Respir Crit Care Med* 1997;155:A259.
12. Gong H, Simmons M, Clark V, Tashkin D. Metered-dose inhaler usage in subjects with asthma. Comparison of nebulizer chronolog and daily diary recording. *J Allergy Clin Immunol* 1988;82:5-10.
13. Brueckner JW, Marshik P, Sherman J, Hendeles L. Reliability of the Medtrac MDI Chronolog. *J Allergy Clin Immunol* 1997;100:488-91.
14. Simmons MS, Nides MA, Kleerup EC, Chapman KR, Milgrom H, Rand CS, et al. Validation of the Doser, a new device for monitoring metered-dose inhaler use. *J Allergy Clin Immunol* 1998;102:409-13.

Bound volumes available to subscribers

Bound volumes of The Journal of Allergy and Clinical Immunology are available to subscribers (only) for the 1999 issues from the Publisher, at a cost of \$107.00 for domestic, \$136.96 for Canadian, and \$128.00 for international subscribers for Vol. 103 (January-June) and Vol. 104 (July-December). Shipping charges are included. Each bound volume contains a subject and author index, and all advertising is removed. Copies are shipped within 30 days after publication of the last issue in the volume. The binding is durable buckram with the journal name, volume number, and year stamped in gold on the spine. *Payment must accompany all orders.* Contact Mosby, Inc., Subscription Services, 11830 Westline Industrial Dr., St. Louis, MO 63146-3318; phone 1 (800) 453-4351 or (314) 453-4351.

Subscriptions must be in force to qualify. Bound volumes are not available in place of a regular journal subscription.