

# Home monitoring of warfarin therapy in children with a whole blood prothrombin time monitor

P. Massicotte, MD, V. Marzinotto, RN, P. Vegh, M. Adams, and M. Andrew, MD

From the Children's Hospital at Chedoke-McMaster, Hamilton, Ontario, and the Hospital for Sick Children, Toronto, Ontario, Canada

We prospectively evaluated a capillary whole blood prothrombin time (PT) monitor (Biotrack, Ciba Corning) in an outpatient pediatric anticoagulation clinic (40 clinic patients) and in age-matched healthy subjects (30 control subjects). Subsequently, 23 children requiring warfarin therapy were placed on a home program (home patients) using the PT monitor; their parents were trained and the results followed by clinic staff. The PT results were reported as internationalized normalized ratios (INRs). The laboratory and PT-monitor INR values were similar for the clinic patients and the control subjects ( $y = 0.76x + 0.38$ ;  $r = 0.93$ ;  $p < 0.001$ ). The accuracy of the PT monitor (the difference between INR values and the laboratory INR) was best at an INR of 2.5 to 3.5; 90% of paired INR values were within 0.8 INR units. The average duration of monitoring for home patients was 13 months (range, 2 to 60 months). They had an average of 3 dose measurements (range, 1 to 11 measurements) and 1.8 dose changes (range, 0.6 to 4.5 changes) per month. Of the 599 measurements, 63% were within the therapeutic range, similar to those for clinic patients; the dose requirements were also similar. There was 1 significant bleeding event, a subdural hematoma in a patient with an INR of 4.1, and 1 catheter-related thrombotic event with an INR of 1.2; both children recovered. Of the 23 families, one discontinued home monitoring because of parental discomfort, 2 children died of their primary disease, 6 completed warfarin therapy, and 14 remain on the home program. We conclude that the whole blood PT/INR monitor is safe and offers practical advantages to children requiring anticoagulation. (J PEDIATR 1995;127:389-94)

Orally administered anticoagulants are used prophylactically and therapeutically for a variety of inherited and acquired disorders.<sup>1,2</sup> Warfarin, a competitive inhibitor of vitamin K, is commonly used because of its predictable onset and du-

ration of action.<sup>3,4</sup> Unfortunately, warfarin's anticoagulant activity must be closely monitored to avoid both hemorrhagic and thromboembolic complications; the prothrombin time is usually used to monitor the anticoagulant effect.<sup>5</sup>

Supported by a grant-in-aid from the Medical Research Council of Canada. Dr. Andrew is a Career Investigator of the Heart and Stroke Foundation of Ontario, and Dr. Massicotte is a Research Fellow of the Heart and Stroke Foundation of Ontario.

Submitted for publication Nov. 15, 1994; accepted April 10, 1995.

Reprint requests: M. Andrew, MD, Hamilton Civic Hospitals Research Centre, Henderson General Division, 711 Concession St., Hamilton, Ontario L8V 1C3, Canada.

Copyright © 1995 by Mosby-Year Book, Inc.  
0022-3476/95/\$5.00 + 0 9/20/65557

CHD	Congenital heart disease
DVT	Deep vein thrombosis
INR	International Normalized Ratio
PE	Pulmonary embolism
PT	Prothrombin time

Warfarin therapy requires more frequent monitoring in children than in most adults because of the complexity and labile nature of their primary problems.<sup>2</sup> Venipuncture in children is frequently difficult, particularly in the presence

of primary medical problems that have necessitated frequent venous access. The problem of safely monitoring warfarin therapy in children has served as a deterrent to its use.

Recently portable monitors that measure PT values using capillary whole blood have been tested in adults receiving warfarin.<sup>6-10</sup> Whole blood PT monitors offer a potentially important extension of warfarin therapy in children. Therefore we prospectively evaluated a whole blood PT monitor when used in healthy children and in consecutive children requiring warfarin therapy.

## METHODS

**Patient population.** Three patient populations were evaluated. The first group comprised healthy, age-matched subjects (control subjects) who were having routine blood work performed before elective outpatient surgery at the Children's Hospital at Chedoke-McMaster, Hamilton, Ontario, Canada. The second group comprised consecutive children requiring warfarin therapy and monitored through a pediatric outpatient anticoagulation clinic (clinic patients) at the Hospital for Sick Children, Toronto, Ontario, Canada. The third group comprised children from both institutions who required warfarin therapy (home patients) and in whom one of the following problems was present: difficult venous access that hindered warfarin therapy; geographic isolation without laboratory services that could meet the needs of pediatric patients; and patients with labile coagulation function who required monitoring two or three times a week. The protocol was approved by institutional ethical review boards, and informed consent was obtained. Patients were monitored with one of three target ranges of International Normalized Ratios: usual therapeutic range (INR 2.0 to 3.0); range for patients with prosthetic valves (INR 2.5 to 3.5); and prophylactic dose range (INR 1.4 to 1.9). All whole blood PT monitor measurements were made on blood obtained by finger stick. All INR values determined in the laboratory were on blood obtained by venipuncture.

**Blood sampling.** Platelet-poor plasma was obtained from whole blood anticoagulated with sodium citrate, followed by centrifugation at 3000g for 20 minutes. The laboratory PT was measured by the automated coagulation laboratory machine (Instrumentation Laboratory S.P.A., Milan, Italy) using Thromborel-S (Behring Diagnostics, Inc., Montreal, Quebec, Canada), a thromboplastin with an International Sensitivity Index of 1.1. A second blood sample was anticoagulated with ethylenediaminetetraacetic acid to measure hematocrit (Coulter, Inc., Hialeah, Fla.). Hematocrit and hemoglobin values were determined with the use of automatic counters (Coulter). The capillary blood samples were collected with an automated device (Tenderlet device, International Technidyne, Edison, N.J.), either from a finger stick in children or a heel stick in young infants.

**Whole blood prothrombin time monitor.** The whole blood PT monitor (Ciba Corning Diagnostic 512 Coagulation Monitor [CCD Monitor], Ciba Corning Diagnostics Corp., Medfield, Mass.) was used in this study, described previously.<sup>6</sup> In brief, a plastic reagent cartridge is placed in the monitor for warming at 37° C. One drop of fresh whole blood, obtained by finger or heel stick, is placed in the small reservoir in the cartridge. The PT is determined by the amount of time required for blood to flow by capillary action through a channel, between the initial reservoir and a mixing chamber, that is coated with a rabbit brain thromboplastin. The cessation of blood flow (i.e., clotting) is sensed by variation in the light scatter caused by the movement of erythrocytes. The change in light scattering is detected by a photodetector and converted into an electric signal that is analyzed by a microprocessor and displayed on a screen as the PT and the International Normalized Ratio. The International Sensitivity Index of the thromboplastin reagent is 2.04. After a PT-INR value is displayed, a new cartridge is inserted for the next test. Each test requires approximately 1 minute.

**Patient education for home monitoring.** The nurse coordinator (V.M.) of the anticoagulation clinic taught the parent(s) to use the whole blood PT-INR monitor. Before home use, the parents had to demonstrate their ability to use the whole blood PT-INR monitor successfully on at least three separate occasions. The families recorded all PT-INR values, and any warfarin dose changes, on a calendar. The nurse coordinator was in contact with the families at least weekly by telephone and after every home test. The medical team (nurse coordinator and physician) adjusted the warfarin doses on the basis of the whole blood monitor PT-INR values, using a previously validated nomogram.<sup>2</sup> The family was instructed when to perform the test and when to call results to the anticoagulation clinic nurse coordinator. If the INR was not in the therapeutic range, the test was repeated and an appropriate clinical decision made. If the INR was greater than 4.5 on repeated testing, the child was brought to the hospital for a confirmatory test.

**Statistical analyses.** Correlations between the whole blood monitor and laboratory PT-INR reference values were statistically evaluated by linear regression. Clinical information is presented descriptively. Mean values between groups were assessed with the Student *t* test and Bonferroni correction for multiple measurements. Unless otherwise indicated, *p* values less than 0.05 were considered statistically significant.

## RESULTS

### Patient populations

**Control subjects.** There were 30 healthy, age-matched control subjects (16 males) with a median age of 9 years and a range of 1 to 16 years. These 30 children had routine blood

studies performed in the pediatric outpatient clinic before elective outpatient surgery for dental work (n = 13), placement of myringotomy tubes (n = 14), hernia repair (n = 1), strabismus repair (n = 1), and cleft lip repair (n = 1).

**Clinic patients.** Forty consecutive children (21 boys) had been receiving warfarin for at least 4 weeks and attending the anticoagulation clinic; their median age was 14 years (range, 1 to 18 years). The medical problems necessitating therapy with warfarin were congenital heart disease with a mechanical heart valve (n = 13), CHD without a mechanical valve (n = 11), and deep venous thrombosis with pulmonary embolism (n = 16). The most common CHD without mechanical valves included the Fontan procedure and cardiomyopathy. The underlying causes of DVT with PE were cancer, trauma or surgery, systemic lupus erythematosus, and nephrotic syndrome.

**Home patients.** The parents of 23 children (13 boys) were trained to use the whole blood PT-INR monitor at home; their median age was 3 years (range, 5 months to 14 years), and four children were less than 1 year of age. The medical problems necessitating warfarin therapy were CHD with a mechanical heart valve (n = 4), CHD without a mechanical valve (n = 9), DVT with PE (n = 10), and stroke (n = 1). The most common CHDs without mechanical valves included the Fontan procedure and cardiomyopathy. The underlying causes of DVT with PE were cancer, nephrotic syndrome, congenital antithrombin deficiency, Kawasaki disease with giant coronary aneurysms, and myelomeningocele.

**Comparison of laboratory and whole blood PT-INR values.** Hematocrits were similar in the control and patient groups, and within the normal range for age. The mean whole blood monitor PT values in healthy control subjects were similar to the laboratory PT values (Table). However, the laboratory PT values for the 40 clinic patients were significantly longer than the whole blood monitor PT values ( $p < 0.01$ ), reflecting the differing sensitivities of the thromboplastin reagents (Table). In contrast, INR values were similar for laboratory and whole blood monitor values, and the INR values from the clinic patients were within the therapeutic range of 2 to 3.5. Figure 1 shows the correlation curve for INR values for the 30 control subjects and 40 clinic patients ( $y = 0.76x + 0.37$ ;  $r = 0.93$ ;  $p < 0.001$ ).

The accuracy of the whole blood monitor was assessed as the whole blood monitor INR value minus the laboratory INR (delta INR), plotted against the laboratory INR value<sup>8</sup> (Fig. 2). The agreement at an INR of 2.0 to 3.5 was within 0.8 INR unit for 90% of values. Four INRs were subtherapeutic by the laboratory method (i.e.,  $< 2.0$ ) but were therapeutic by the whole blood monitor (i.e.,  $> 2.0$ ). There were six suprathreshold INR values by the laboratory method, but all were less than 3.5 by the whole blood monitor. The INR determined by either method would have at least a 0.5

**Table.** Comparison of laboratory and Biotrack PT-INR values

	Control subjects (n = 30)	Clinic patients (n = 40)
Hematocrit	0.38 ± 0.022	0.41 ± 0.70
Laboratory		
PT	11.2 ± 0.69	27.0 ± 1.40
INR	1.0 ± 0.07	2.7 ± 0.15
Monitor		
PT	12.0 ± 0.90	18.8 ± 0.43
INR	1.0 ± 0.14	2.6 ± 0.10

There was no significant difference between INR values measured by the laboratory and those measured by whole blood monitor.

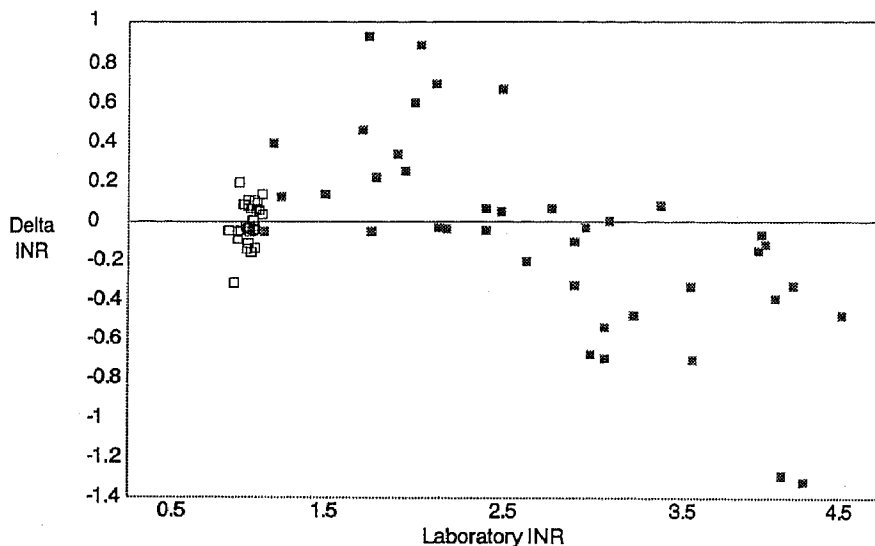
second error associated with it, thus bringing into concern those INRs either at the low end of therapeutic values (INR  $< 2.0$ ) or at the high end (INR  $> 3.5$ ) when either method is used.

#### Home monitoring of PT-INR values with the whole blood monitor

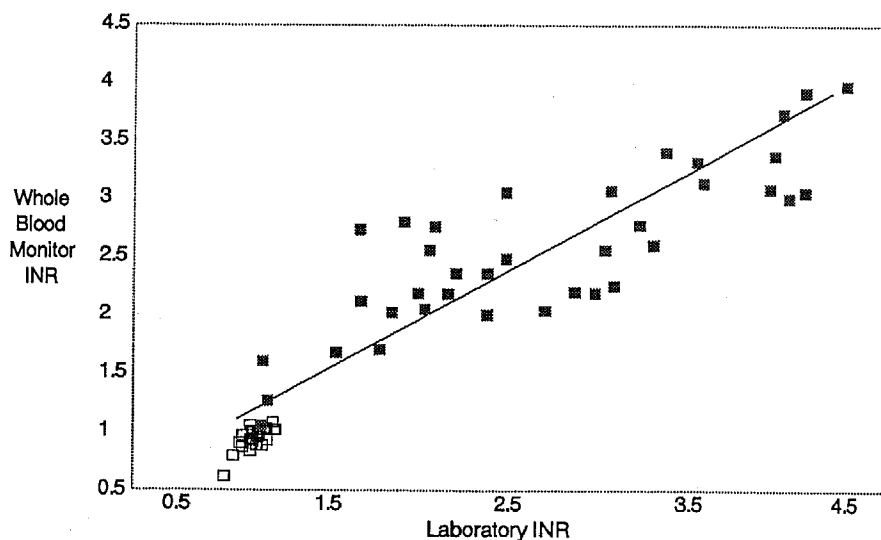
**General information.** The 23 children managed with the whole blood PT-INR monitor had a variety of medical problems (previous section) and poor venous access. Eighteen children were receiving other medications (1, one drug; 4, two drugs; 4, three drugs; 10, four or more drugs). The 18 measurements comparing the whole blood monitor INR versus the laboratory INR show no significant difference ( $p = 1.7 ± 0.16$  vs  $1.9 ± 0.16$ ). The average duration of whole blood monitoring at home was 13 months (range, 2 to 60 months). Of the 599 whole blood monitor INR measurements, 63% were within the therapeutic range. An average of three dose measurements per month were performed (range, 1 to 11 months), resulting in 1.8 dose changes per month (range, 1.0 to 4.5 changes). The average dose of warfarin required to maintain an INR value between 1.5 and 2.0 was 0.11 mg/kg per day. The average dose of warfarin required to maintain an INR between 2.0 and 3.5 was 0.30 mg/kg per day (range, 0.05 to 0.59 mg/kg per day).

**Complications.** Significant complications consisted of one subdural hemorrhage and one new thrombus. The hemorrhage occurred when the INR (4.1) was above the therapeutic range for less than 24 hours. The thrombus occurred as a result of the placement of a femoral venous line when the INR (1.2) was below the target range (1.3 to 1.9) for less than 2 days. Both problems resolved without sequelae.

**Patient and parental satisfaction.** Only one family discontinued home monitoring because of parental discomfort using the home monitor. Of the remaining 22 patients, 2 children died from their disease, and warfarin therapy was discontinued in 6 children as it was no longer necessary. The remaining 14 children continue to be monitored with the whole blood PT/INR monitor at home without difficulty.



**Fig. 1.** Correlation curve for INR values measured by a whole blood monitor and traditional laboratory tests for 30 healthy, age-matched control subjects ( $\square$ ) and 40 pediatric clinic patients ( $\blacksquare$ ) receiving oral anticoagulant therapy. The correlation was highly significant ( $y = 0.76x + 0.37$ ;  $r = 0.93$ ;  $p < 0.001$ ).



**Fig. 2.** Accuracy of the whole blood monitor was assessed as the whole blood monitor INR value minus the laboratory INR (delta INR) plotted against the laboratory INR value. The agreement at an INR of 2.0 to 3.5 was within 0.8 INR unit for 90% of values. The healthy control subjects are represented by  $\square$ . The clinic patients are represented by  $\blacksquare$ .

Repeated unsuccessful venepunctures were eliminated, as were interruption of school for older children and work for parents.

## DISCUSSION

Oral anticoagulant therapy requires close monitoring to minimize the risk of hemorrhage or recurrent thrombotic disease.<sup>11</sup> Children requiring warfarin therapy frequently have poor venous access, which inhibits optimal monitoring

and places them at increased risk of hemostatic complications. Our study showed that a whole blood PT-INR monitor gave results similar to laboratory INR values in children. Home monitoring, supervised through a pediatric anticoagulation clinic, was shown to be an effective, safe, and useful alternative to laboratory monitoring in children with difficult venous access.

Warfarin functions as an anticoagulant by competitively inhibiting vitamin K, which results in low plasma concen-

trations of factors II, VII, IX, and X. Low functional levels of these proteins prolong the PT, which is the most commonly used test to monitor warfarin therapy in North America.<sup>12</sup> Thromboplastin reagents have differing sensitivities to low levels of the vitamin K-dependent proteins, necessitating standardization of the PT.<sup>13-16</sup> The INR is accepted internationally as a standardized form of the PT and should be used for monitoring patients receiving warfarin therapy.<sup>17</sup> The usual therapeutic level for the INR is 2.0 to 3.0, although some patients (e.g., those with mechanical heart valves) may require INR values between 2.5 and 3.5 and some may need lower INR values (1.5 to 2.0).

Children requiring warfarin therapy, because of their underlying problems, are particularly prone to intercurrent infections, often require new or adjusted medications, and have rapid changes in clinical status.<sup>2</sup> A problem unique to young infants is their intake of commercial enteral formulas that contain high concentrations of vitamin K; the result is an increased requirement for warfarin by body weight, which makes infants vulnerable to excessive anticoagulation. Another problem for children is poor venous access, which can be compounded by geographic isolation without laboratory services that meet the needs of pediatric patients. For all these reasons, a monitor that measures PT-INR values for whole blood obtained by finger stick is potentially invaluable to the monitoring of warfarin therapy in children.

The correlation between values obtained with whole blood PT-INR monitors and laboratory INR values has been evaluated previously in adults.<sup>6-10, 18, 19</sup> The correlation coefficients were greater than 0.89 for PT values in all studies.<sup>6, 8, 9</sup> Only one study analyzed INR values; the correlation coefficient was 0.96.<sup>8</sup> We measured both PT and INR values in our patients. As expected, PT values measured by the monitor differed significantly from the reference laboratory values, reflecting the different sensitivities of the thromboplastin reagents. In contrast, the INR values did not differ and the correlation coefficient was 0.92, a value similar to previous results in adult patients.

The accuracy of the whole blood PT-INR monitor values can be assessed by the delta INR value, compared with the laboratory-determined INR.<sup>8</sup> One study concluded that the accuracy of the whole blood PT-INR monitor in adults was best at an INR of about 3.0; 90% of paired monitor and laboratory INRs were within 0.9 INR unit.<sup>8</sup> In our study the accuracy of the whole blood PT-INR monitor in the pediatric clinic patient population was best at INRs between 2.5 and 3.5; 90% of the paired laboratory and whole blood PT-INR values were within 0.8 INR unit.

In our home study the whole blood PT-INR monitor was successfully used for pediatric patients in whom laboratory monitoring would have been difficult or impossible. Despite numerous confounding variables, 67% of INR values were

within the target range, a percentage similar to that in children monitored by laboratory INR values.<sup>2</sup> Adverse clinical outcomes were rare and similar to those in children monitored by laboratory testing.<sup>2</sup> There was one significant bleeding event and one recurrent thrombotic event.

An INR obtained by the home monitor was not duplicated by the laboratory method unless the INR was >4.5. Figure 2 indicates that the home monitor INR could have been as high as 5.3 to 5.8. This level of INR must be managed appropriately to prevent bleeding. From the accuracy data, we therefore recommend that if the home monitor INR is greater than 3.5, determination of the INR should be repeated on the home monitor; if the value is greater than 3.5, the warfarin should be withheld until the INR (repeated daily) is again in the therapeutic range. If the INR obtained by home monitor is >4.0, the laboratory INR could be as high as 4.8 to 5.4. At this INR, a new management decision would be initiated. The clinical treatment plan would be the same as when the home monitor INR is greater than 3.5; however, if the repeated home monitor INR were greater than 3.5, a laboratory INR should be obtained and then the appropriate clinical decision made. This protocol when using the home monitor should presumably avoid bleeding in patients.

With only one exception, families preferred testing with the whole blood PT-INR to the standard method, primarily because of the minimal trauma to their child. Other advantages identified by parents included minimal interruption of work and school, ease of operation, and portability.

This study provides evidence that a whole blood PT-INR monitor for warfarin therapy can be used safely and effectively in a pediatric outpatient clinic and by parents at home. The generalizability of our findings to other centers is uncertain because our patients were followed through a large pediatric anticoagulation clinic with significant resources, which included a full-time nurse coordinator and a pediatric hematologist with clinical and research expertise in childhood thrombophilia. In Canada, the generalizability of this approach is being assessed through a national program, the Canadian Children's Thrombophilia Program. An outreach program for anticoagulation therapy in children has been established and provides access to pediatric hematologists across Canada. This type of national resource facilitates the safe and effective implementation of innovations in anticoagulation monitoring for children.

## REFERENCES

1. David M, Andrew M. Venous thromboembolism complications in children: a critical review of the literature. *J PEDIATR* 1993;123:337.
2. Andrew M, Marzinotto V, Brooker L, et al. Oral anticoagulant therapy in pediatric patients: a prospective study. *Thromb Haemost* 1994;71:265.

3. Breckenridge AM. Oral anticoagulant drugs: pharmacokinetic aspects. *Semin Hematol* 1978;15:19.
4. O'Reilly RA. Vitamin K and the oral anticoagulant drugs. *Ann Rev Med* 1976;27:245.
5. Hirsh J, Fuster V. Guide to anticoagulant therapy. II. Oral anticoagulants. *Circulation* 1994;89:1469.
6. Lucas FV, Duncan A, Jay R, et al. A novel whole blood capillary technique for measuring the prothrombin time. *Am J Clin Pathol* 1987;88:442.
7. White RH, McCurdy SA, von Marensdorff H, Woodruff DE, Leftgoff L. Home prothrombin time monitoring after the initiation of warfarin therapy. *Ann Intern Med* 1989;111:730.
8. McCurdy SA, White RH. Accuracy and precision of a portable anticoagulation monitor in a clinical setting. *Arch Intern Med* 1992;152:589.
9. Belsey RE, Fischer PM, Baer DM. An evaluation of a whole blood prothrombin analyzer designed for use by individuals without formal laboratory training. *J Fam Pract* 1991;33:266.
10. Ansell J, Holden A, Knapic N. Patient self-management of oral anticoagulation guided by capillary (finger stick) whole blood prothrombin times. *Arch Intern Med* 1989;149:2509.
11. Dalen JE, Hirsh J. American College of Chest Physicians and National Heart, Lung, and Blood Institute National Conference on Antithrombotic Therapy. *Arch Intern Med* 1986;146:462.
12. Hirsh J. Oral anticoagulant drugs: review article. *N Engl J Med* 1991;324:1865.
13. Poller L. Progress in standardization anticoagulation control. *Hematology Review* 1987;1:225.
14. Second American College of Chest Physicians Conference on Antithrombotic Therapy. *Chest* 1989;95(suppl):1S.
15. Loeliger EA. International Committee for Standardization in Hematology/International Committee of Thrombosis and Hemostasis recommendations for reporting prothrombin time in oral anticoagulant control. *Thromb Haemost* 1985;54:155.
16. Bussey HI, Force RW, Bianco TM, Leonard AD. Reliance on prothrombin time ratios causes significant errors in anticoagulation therapy. *Arch Intern Med* 1992;152:278.
17. Hirsh J. Substandard monitoring of warfarin in North America: time for change. *Arch Intern Med* 1992;152:257.
18. Jennings I, Luddington RJ, Baglin T. Evaluation of the Ciba-Corning Biotrack 512 coagulation monitor for the control of oral anticoagulation. *J Clin Pathol* 1991;44:950.
19. Weibert RT, Adler DS. Evaluation of a capillary whole-blood prothrombin time measurement system. *Clin Pharmacology* 1989;8:864.

#### AVAILABILITY OF JOURNAL BACK ISSUES

As a service to our subscribers, copies of back issues of THE JOURNAL OF PEDIATRICS for the preceding 5 years are maintained and are available for purchase from the publisher, Mosby-Year Book, Inc., at a cost of \$10.00 per issue. The following quantity discounts are available: 25% off on quantities of 12 to 23, and one third off on quantities of 24 or more. Please write to Mosby-Year Book, Inc., Subscription Services, 11830 Westline Industrial Drive, St. Louis MO 63146-3318, or call (800)453-4351 or (314)453-4351 for information on availability of particular issues. If back issues are unavailable from the publisher, photocopies of complete issues are available from UMI, 300 N. Zeeb Rd., Ann Arbor, MI 48106, (313)761-4700.