Accuracy in Using Dual-Isotope Schilling Test to Measure Urine Samples: A Multicenter Study

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As a component of our quality assurance program, this multicenter study was performed to characterize the magnitude and types of error present in measurement of typical dual-isotope Schilling test (DIST) urine samples. **Methods:** A panel of three simulated DIST urine samples was formulated corresponding to diagnoses of normal excretion, malabsorption and pernicious anemia and was distributed to eight hospitals in our regional area (three novice and five experienced users). Count-rate data and urine volume measurements from each site were analyzed for accuracy against the predicted values and a carefully measured gold standard and were correlated with the methodology and equipment used. **Results:** Three of 24 results were uninterpretable due to an overly low ratio of intrinsic factor bound to free vitamin B12 excretion (B/F ratio), inconsistent with possible diagnoses. In 20 of 21 interpretable samples, results corresponded to the appropriate diagnoses, with typical values noted in 18 of the cases and slightly atypical yet diagnostic values seen in the remaining two cases. In only one sample did values correspond to an erroneous diagnosis (low normal or partial malabsorption rather than pernicious anemia). The four major discrepancies (test failure or misdiagnosis) were largely attributable to blunders and were limited to two of the three novice sites and to a single experienced site which had grossly inaccurate raw data (background greater than sample counts). **Conclusion:** Quantitation of vitamin B12 excretion in DIST urine samples is a reliable method of evaluation when performed by reasonably experienced and competent clinical laboratories. Improved accuracy may be obtained by increasing the stochastic certainty of the count data and by more careful measurement of the sample and urine volumes.

Key words: Schilling test; quality assurance; dual-isotope studies; urine measurement

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The Schilling test, devised in 1953 (*1,2*), remains the most practical and effective method of evaluating vitamin B12 absorption following an oral test dose of radioactive cyanocobalamin (*3–6*). When urinary excretion of the labeled vitamin is low, a second stage of the test may be performed where the radiotracer is supplemented with exogenous intrinsic factor (IF) in an attempt to correct the abnormality.

To improve convenience and reliability of the examination, a dual-isotope variation was conceived by Katz et al. in 1963, which performed both stages of the test simultaneously (*7*). The commercial version of the dual-isotope Schilling test (DIST), based on modifications reported by Bell et al. (*8*), utilizes two 0.25-μg capsules of vitamin B12, one labeled with 0.8 μCi of ^{58}Co and lacking exogenous IF, the other labeled with 0.5 μCi ^{57}Co and preincubated with IF-containing human gastric secretions. Matched ^{57}Co and ^{58}Co standards, each containing 2% of the respective administered doses per milliliter, are included in the kit for reference purposes. The urine sample is identical for both phases of the examination and the ratio of IF-bound-to-unbound (free) vitamin B12 excretion (B/F ratio) may be used to evaluate the corrective effect of IF, even when urine collection is incomplete (*9*).

This investigation was initiated as part of an ongoing quality assurance program (*10*). We have occasionally noted irregular results of the DIST at our affiliated hospitals, some of which relate to biological issues involved in coadministration of the two phases of the examination (*11*), while others have been attributed to various technical faults in performance of the assay, including stochastic variation due to poor counting statistics (*12,13*). To characterize the magnitude and types of error present in the assay of the two labeled vitamin B12 moieties within DIST samples, we created a panel of three calibrated mock urine samples which were distributed to two of our own affiliated hospitals in addition to another six participating centers in our regional area. Biological issues involved in coadministration of the two vitamin B12 capsules have been previously reviewed (*11*) and were not relevant to this artificially constituted panel.

MATERIALS AND METHODS

Five two-patient DIST kits were used (Dicopac, Amersham Health Care, Arlington, Heights, IL). The contents of six ^{57}Co and seven ^{58}Co vitamin B12 capsules were each dissolved into 100 ml phosphate-buffered saline and counted on a gamma scintillation counter. They were further diluted with water to attain count-rate concentrations corresponding to the manufacturer's 2% standards at 2 wk prior to kit expiration, i.e., the conditions we wished to simulate. These preparations, tinted appropriately with yellow

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TABLE 1
Design and Formulation of Mock Urine Samples

Parameter	Urine sample A	B	C
Simulated diagnosis	Normal	Malabsorption	Pernicious anemia
Free ^{58}Co-Vitamin B12 excretion (%)	21.42	4.20	5.11
IF-Bound ^{57}Co-Vitamin B12 excretion (%)	21.70	3.90	10.30
B/F ratio	1.01	0.93	2.02
Total urine volume (ml)	1562	1451	1508
Amount 2% ^{58}Co stock added (ml)	88.88	17.43	21.19
Amount 2% ^{57}Co stock added (ml)	90.05	16.17	42.75
Amount water added (ml)	12,785.74	12,009.69	12,452.49

and blue food coloring were thereafter used as stock solutions from which the mock urine samples were constituted and as new 2% standards distributed for reference purposes.

Total urine volumes and values of total ^{57}Co and ^{58}Co vitamin B12 urinary excretion, typical for subjects with normal absorption, malabsorption and pernicious anemia (urine samples A, B and C, respectively) were selected (Table 1). Calculated amounts of the new ^{57}Co and ^{58}Co 2% standard/stock solutions were added into appropriate volumes of tap water, as measured by weighing the constituent components on sensitive electronic balances, to enable preparation of eight replicate samples (Table 1). Trace amounts of yellow food coloring were added to simulate the appearance of urine. The estimated final concentrations of isotopes were accurate to within 0.1% of the intended values. Individual urine samples were subdivided by weight into either of two types of 24-hr urine collection containers to an accuracy of within 0.01% of the intended volume.

Permission of the chief-of-service at each hospital was obtained prior to initiation of the studies, and the nature of the exercise was not disclosed to the technologists performing the procedure. Approximately 1 wk after constitution, each of the eight study sites received three filled urine collection jars, marked with fictitious names, the aliquots of 2% ^{57}Co and ^{58}Co standard solutions and copies of the worksheet accompanying the commercial kit. After each hospital's measurements and calculations were completed and returned to us, information regarding the equipment and methodology used was solicited from the technologists who performed the examination.

Based on data returned from each center, the percent per milliliter (%/ml) and total ^{57}Co and ^{58}Co excretions were calculated and used to determine the B/F ratio, according to a customized spreadsheet we developed (Quattro Pro, Borland International, Scotts Valley, CA). Standard errors of the estimate were also determined based on stochastic considerations (*14*). Unused samples of the mock urines and 2% standards were retrieved from center 8 and 5 ml volumes were carefully alliquoted and counted for 167 min each to obtain our own measured values, which were generated with a high degree of statistical validity. Measured values were compared to predicted isotope excretions calculated based on amounts of the 2% per milliliter standards added to each of the samples. Interpretation criteria were based on revised guidelines included in the commercial product information sheet (Table 2).

RESULTS

The equipment and methodology used at the eight sites are shown in Table 3. Three of the laboratories (sites 1–3) had not previously performed DIST and therefore represent a group of novice users in contrast to the remaining five sites (sites 4–8) which were using this examination and therefore constitute a relatively experienced user group. Raw data for the eight sites appear in Appendix 1 and calculated values and apparent diagnoses appear in Appendix 2.

Total Urinary Excretion

The free B12 excretion and B/F ratios for the 24 points appear in Figure 1, along with the usual range of values encountered in various disease states (*15*). Three samples had a B/F ratio less than 0.6 (B1, B2 and B8), which does not correspond to known disease states but suggests instead an erroneous result (*16*). In 20 of the remaining 21 samples, the results corresponded to the appropriate diagnoses. Eighteen results were typical of the corresponding diagnoses whereas 2 results (A8, B6) were slightly outside the usual range but still suggestive of the correct disorder. Only one sample (C2) would have been misinterpreted based on the urine measurements, indicating low-normal or partial malabsorption rather than IF-deficiency, although cautious interpretation may still have raised this possibility, based on a B/F ratio approaching 1.2.

Of the four significant discrepancies discussed above

TABLE 2
Mean Values and Usual Range (*15*)

Diagnosis	Free ^{58}Co-Vitamin B12 excretion (%)	IF-Bound ^{57}Co-Vitamin B12 excretion (%)	B/F ratio
Normal	20 (9–33)	20 (8–34)	0.7–1.2
Pernicious anemia	5 (1–10)	10 (2–15)	>1.4*
Malabsoption syndromes	4 (0–8)	4 (0–8)	0.6–1.1

*Some patients with pernicious anemia give ratios in the range of 1.2 to 1.4.

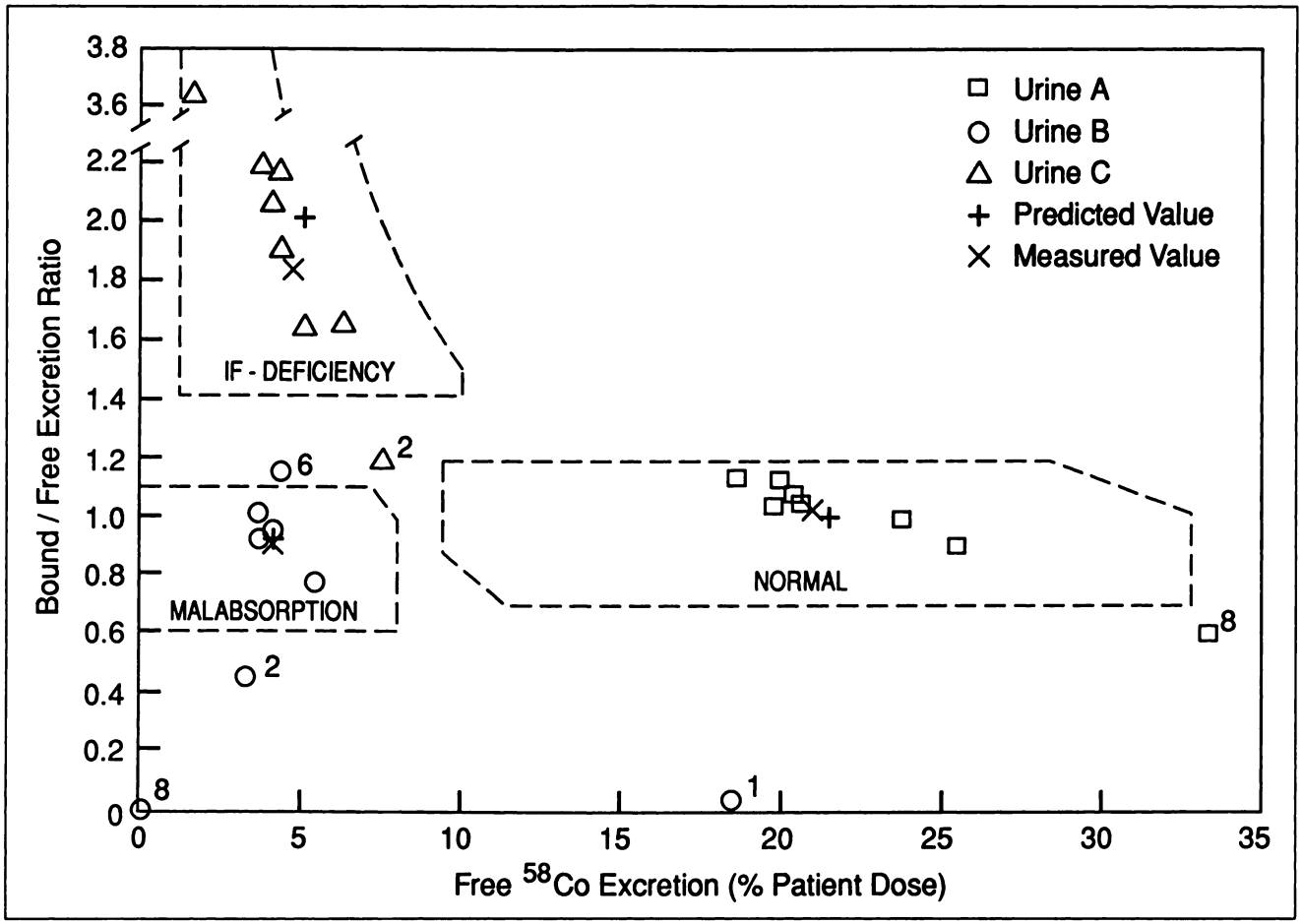

FIGURE 1. Free ^{58}Co excretion and B/F ratio for the 24 urine samples tested. Predicted values, based on the amount of stock solution added and measured values, obtained by prolonged counting of samples from site 8, are also displayed. Ranges typical of normal excretion, malabsorption and pernicious anemia, as suggested by the manufacturer, are illustrated by the dashed boxes. Values lying outside of their expected ranges have site numbers indicated to aid in identification. Because of its negative value, urine sample B, site 8, has been replotted at the origin.

(test failure or misdiagnosis), three occurred at two of the novice sites, while the fourth occurred at site 8 which had grossly flawed raw counting data (background counts were greater than urine counts, see Appendix 1). The two minor discrepancies (correct diagnosis with atypical values) occurred at sites 6 and 8, both experienced locations. For the competent sites (excluding the novice users and site 8, which had obviously flawed data) average errors (mean ± 1 s.d.) were 0.84% ± 0.74% for ^{57}Co excretion and 1.12% ± 1.07% for ^{58}Co excretion.

To further understand and characterize the cause of the observed discrepancies, the total excretion of each isotope was broken down into the independent constituent components of total urine volume and percent excretion of each isotope per milliliter.

Urine Volume

Five of the sites (1, 2, 6, 7, 8) measured urine volume by sighting the level relative to volume graduations stamped on the urine-collection container walls and they overestimated urinary volume by an average of 117 ± 27 ml (mean ± 1 s.d.) (Fig. 2). The remaining three sites measured urine volume in graduated cylinders. Two of these sites (3, 4) were accurate to within several milliliters, while site 5 consistently overestimated urine volume by 77–79 ml (Fig. 2). This inaccuracy may be related to a systematic error arising from measurement of urine volumes greater than 1 liter using a 1000-ml graduated cylinder, although a definite cause cannot be ascertained.

Percent Vitamin B12 Excretion per Milliliter and Stochastic Error of Measurement

The low counting rates seen with ^{58}Co resulted in a greater standard error of the measurement than with ^{57}Co, and, to a large degree, much of the discrepancy between observed and predicted values can be attributed to this statistical variation. In general, the observed values distributed around the predicted percent excretion, with the single exception being measurement of ^{57}Co in urine C, in which observed values and our own measurement were slightly below predicted values (Fig. 2). Further investigation of this phenomenon led to analysis of a small amount of black sediment present on the bottom of the urine C carboy which was counted and found to contain ^{57}Co ra-

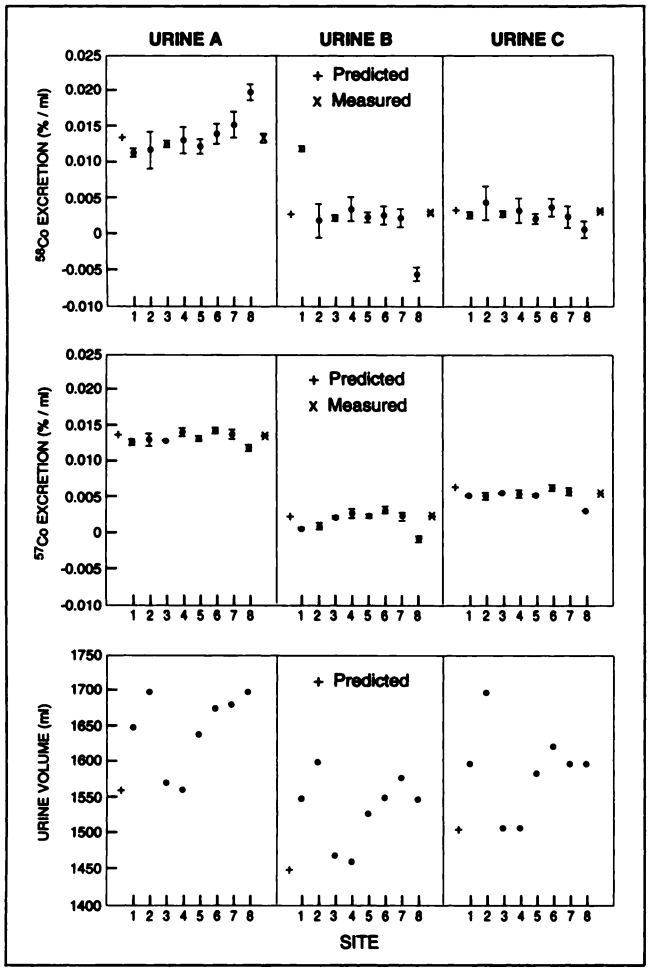

FIGURE 2. Measured urine volumes (bottom) and isotope excretions per milliliter of urine for ^{58}Co (top) and ^{57}Co (middle). Error bars represent 2 s.e.e. based on counting uncertainty.

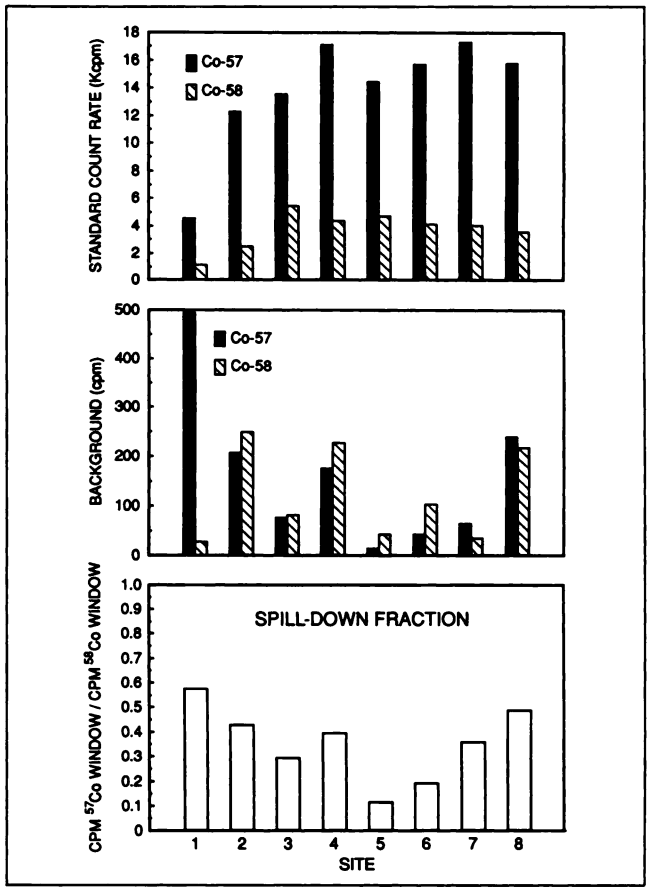

FIGURE 3. Net count rates (top) and background rates (middle) for ^{57}Co and ^{58}Co 2% standards. At each site, 1 ml standard was diluted into the measured volume, with the exception of site 1 where 6 ml were diluted into 1 liter of volume. Because sample counting was performed on different dates with differing geometries, each count rate sensitivity reflects the particular conditions under which the sample was counted and cannot be used to directly compare the sensitivity of one instrument to another.

dioactivity. The carboys containing the remainder of urine samples A and B were inspected and did not contain sediment, and our own measurements of these samples, on samples obtained from site 8, did not deviate appreciably from predicted values (Fig. 2), indicating that this was an isolated phenomenon.

DISCUSSION

When measuring DIST urine samples, diagnostic error can be attributed to inaccurate measurement of the total urine volume, statistical uncertainty due to low count lev-

TABLE 3
Equipment and Methodology

		Gamma counter			Sample counting			Volume measurement	
Site	Experience	Crystal	Analyzer	Changer	Time (min)	Volume (ml)	Duplicate	Total urine	Counting sample
1	Novice	3" END	SCA	Manual	5	1000	No	Specimen bottle	1000 ml GC
2	Novice	2"WELL	SCA	Manual	10	5	No	Specimen bottle	Micropipette
3	Novice	3"THRU	DCA	Automated	20	5	Standard, Urine	1000 ml GC	Micropipette
4	Experienced	2"WELL	SCA	Manual	10	4	No	2000 ml GC	Micropipette
5	Experienced	3"WELL	DCA	Automated	20	5	No	1000 ml GC	Micropipette
6	Experienced	2"WELL	SCA	Manual	10	4	No	Specimen bottle	Syringe
7	Experienced	3"WELL	DCA	Automated	10	2	Urine	Specimen bottle	Micropipette
8	Experienced	2"THRU	SCA	Automated	30	3	Background, Urine	Specimen bottle	Micropipette

GC=graduate cylinder; SCA=single-channel analyzer; DCA=dual-channel analyzer.

APPENDIX 1
Raw Data

Site	Measurement	Time (min)	Background	^{57}Co Standard	^{58}Co standard	Urine A	Urine B	Urine C
1	^{57}Co CPM	5	494	5026	1129	5923	1333	2628
	^{58}Co CPM	5	28	—	1131	1067	1123	282
	Urine volume (ml)					1650	1550	1600
2	^{57}Co CPM	10	207	12484	1281	644	242	382
	^{58}Co CPM	10	249	—	2738	322	262	276
	Urine volume (ml)					1700	1600	1700
3	^{57}Co CPM	20	75	13913/13372	1661/1705	565/564	164/167	278/280
	^{58}Co CPM	20	81	—	5457/5636	253/252	113/119	118/119
	Urine volume (ml)					1570	1470	1510
4	^{57}Co CPM	10	176	17309	1881	705	288	381
	^{58}Co CPM	10	227	—	4546	340	259	257
	Urine volume (ml)					1560	1460	1510
5	^{57}Co CPM	20	14	14456	551	507	109	209
	^{58}Co CPM	20	43	—	4741	190	72	71
	Urine volume (ml)					1640	1530	1585
6	^{57}Co CPM	10	44	15770	840	512	151	251
	^{58}Co CPM	10	103	—	4232	220	127	135
	Urine volume (ml)					1675	1550	1625
7	^{57}Co CPM	10	64	17369	1512	320/326	114/109	166/173
	^{58}Co CPM	10	34	—	4068	92/100	45/45	48/42
	Urine volume (ml)					1680	1580	1600
8	^{57}Co CPM	30	224/254	15999	1974	588/552	196/196	322/305
	^{58}Co CPM	30	206/229	—	3783	335/310	191/186	233/211
	Urine volume (ml)					1700	1550	1600

els and miscellaneous causes, such as inaccurate pipetting, incorrect window placement, cross-contamination of samples or other blunders. Whereas the Dicopac Users Guide (*16*) suggests a protocol for calibrating and checking energy windows on gamma counters using a "mock urine" sample, the purpose of the simulated urines in this exercise was to evaluate all aspects of DIST measurement.

The urine samples analyzed in this exercise were designed to represent a worse case scenario. To achieve this end, the samples were submitted in a routine manner, so that the technologists performing the examination were unaware of the nature of the study. The kit was distributed 1 wk prior to its simulated expiration, and the urine volumes in which the activity was diluted were in the upper range of normal. These factors combined to yield low radiocobalt concentrations with resultant poor counting statistics. Nonetheless, excretion values were chosen in the midrange of typical values, which tended to increase diagnostic accuracy because of the large changes necessary to shift values from the midpoint of a given diagnostic category into another.

Actually, quantitation of the cobalt isotopes in the Schilling samples was quite accurate, resulting in values that would have permitted correct diagnoses to be made in 20 of the 21 interpretable cases (95% frequency). Typical values were seen in 18 of these samples and atypical, although still diagnostic, results were observed in another 2. In 3 of the original 24 cases, results were identified as erroneous because of B/F ratios below 0.6, which would have necessitated repetition. In only 1 of the 24 samples would an incorrect diagnosis have been made (Fig. 1). What is remarkable is that significant errors only occurred at two of the three novice hospitals, and at site 8, which had grossly inaccurate count rate data, possibly due to invalid counting windows or contamination of the counter. With the exception of site 8, it appears that the experienced centers performed the test in a generally accurate manner, resulting in data which would have led to appropriate diagnoses. A blunder in recording or measuring one of the urine samples is the most plausible explanation for the error at site 1. The cause of errors at site 2 cannot be ascertained definitely, although the stochastic error was largest at this site. The minor error seen in the urine B sample from site 6 is possibly related to their imprecise method of measuring standard volumes with a disposable syringe.

Stochastic uncertainty due to poor counting statistics, as demonstrated by error bars in Figure 2, is a widespread, yet easily rectified, source of error which can be reduced by either increasing the volume of the samples counted or by lengthening the counting time. Counting 2 or 3 ml of urine for only 10 or 20 min, as was performed in some of the sites, is inadequate at the low isotope concentrations prevailing during the DIST. The product insert for the commercial dual-isotope kit (*15*) recommends counting "the largest practical volume" and at least 10 ml, while the

APPENDIX 2
Percent Excretion Cobalt Isotopes and Resultant Diagnosis

Site	Isotope	Urine sample A (normal) Value ± s.d.	B/F ratio	Apparent diagnosis
1	^{57}Co	21.10 ± 0.24		
			1.13 ± 0.03	Normal
	^{58}Co	18.64 ± 0.37		
2	^{57}Co	22.43 ± 0.55		
			1.12 ± 0.12	Normal
	^{58}Co	19.94 ± 2.07		
3	^{57}Co	20.32 ± 0.20		
			1.03 ± 0.02	Normal
	^{58}Co	19.71 ± 0.37		
4	^{57}Co	22.05 ± 0.45		
			1.08 ± 0.08	Normal
	^{58}Co	20.37 ± 1.36		
5	^{57}Co	21.63 ± 0.24		
			1.05 ± 0.03	Normal
	^{58}Co	20.55 ± 0.48		
6	^{57}Co	23.74 ± 0.41		
			1.00 ± 0.05	Normal
	^{58}Co	23.63 ± 1.16		
7	^{57}Co	22.99 ± 0.48		
			0.90 ± 0.05	Normal
	^{58}Co	25.51 ± 1.20		
8	^{57}Co	20.13 ± 0.29		
			0.60 ± 0.02	Atypical normal
	^{58}Co	33.38 ± 0.96		

Site	Isotope	Urine sample B (malabsorption) Value ± s.d.	B/F ratio	Apparent diagnosis
1	^{57}Co	0.86 ± 0.12		
			0.05 ± 0.01	Nondiagnostic
	^{58}Co	18.47 ± 0.36		
2	^{57}Co	1.51 ± 0.38		
			0.45 ± 0.28	Nondiagnostic
	^{58}Co	3.32 ± 1.84		
3	^{57}Co	3.48 ± 0.13		
			0.92 ± 0.07	Malabsorption
	^{58}Co	3.77 ± 0.28		
4	^{57}Co	4.24 ± 0.31		
			0.79 ± 0.18	Malabsorption
	^{58}Co	5.38 ± 1.18		
5	^{57}Co	3.88 ± 0.11		
			1.02 ± 0.09	Malabsorption
	^{58}Co	3.79 ± 0.31		
6	^{57}Co	5.06 ± 0.22		
			1.16 ± 0.24	Atypical malabsorption
	^{58}Co	4.37 ± 0.90		
7	^{57}Co	3.95 ± 0.33		
			0.96 ± 0.27	Malabsorption
	^{58}Co	4.11 ± 0.93		
8	^{57}Co	−1.89 ± 0.20		
			0.23 ± 0.03	Nondiagnostic
	^{58}Co	−8.40 ± 0.75		

APPENDIX 2 (continued)

Site	Isotope	Urine sample C (IF deficiency) Value ± s.d.	B/F ratio	Apparent diagnosis
1	^{57}Co	8.42 ± 0.13		
			1.90 ± 0.07	IF deficiency
	^{58}Co	4.43 ± 0.15		
2	^{57}Co	9.00 ± 0.46		
			1.19 ± 0.32	Low normal/Mild malabsorption
	^{58}Co	7.54 ± 1.98		
3	^{57}Co	8.59 ± 0.14		
			2.07 ± 0.15	IF deficiency
	^{58}Co	4.14 ± 0.29		
4	^{57}Co	8.53 ± 0.35		
			1.64 ± 0.39	IF deficiency
	^{58}Co	5.19 ± 1.22		
5	^{57}Co	8.42 ± 0.15		
			2.19 ± 0.19	IF deficiency
	^{58}Co	3.85 ± 0.32		
6	^{57}Co	10.42 ± 0.29		
			1.66 ± 0.26	IF deficiency
	^{58}Co	6.26 ± 0.96		
7	^{57}Co	9.34 ± 0.37		
			2.18 ± 0.49	IF deficiency
	^{58}Co	4.28 ± 0.95		
8	^{57}Co	4.89 ± 0.22		
			3.64 ± 2.19	IF deficiency
	^{58}Co	1.35 ± 0.81		

associated Users Guide (*16*) bases its examples on counting of 500-ml urine volumes. Other than site 1, which utilized a specialized counting method, none of the laboratories measured more than 5 ml of urine and, practically speaking, typical clinics do not have access to gamma counters with larger capacities. The product insert (*15*) also recommends counting for "an appropriate time," generally specified as "usually 20 min." Only three of the eight sites met or exceeded this recommendation. Counting for prolonged periods of time is possible when the gamma counter is equipped with an automatic sample changer and a multichannel analyzer that can be run overnight; with a single-well counter, it is impractical to occupy a technologist and use the device for several hours.

In several cases, error in the calculated %/ml excretion of cobalt isotopes was greater than that due to statistical variation alone (Fig. 2). This suggests that a component of the observed error originated from another source, such as imprecision in dilution of the standards, placement of windows or in pipetting of the counting samples. While counting of duplicate samples is advocated in the product insert (*15*), this was only performed on samples at three sites and on standards at one site (Table 3). Evaluation of these duplicate samples confirms that the differences between values was generally greater than that originating from counting errors alone (Appendix 1). At present, many nu-

clear medicine technologists do not perform in vitro work on a routine basis and may lack accurate pipetting and other measuring skills. Poor methodology may also be a factor, as site 6 was aliquoting volumes with disposable plastic syringes, which is an inaccurate method. Careful attention to accurate volume measurement, including use of increasingly available semiautomated electronic pipettes, may help rectify this component of error.

Count rate sensitivity for the two isotopes, in addition to the spill-down fraction, were calculated at each site based on count rates of the standard samples (Fig. 3) With the exception of site 1, which used a counter with unique geometry, count rate sensitivities were similar at the various sites. Although wherever possible, counters with a 3-inch diameter crystal are preferable to 2-inch crystals, to allow improved efficiency in detecting the energetic gamma emissions of ^{58}Co (*13*), no differences were noted between counters with 2- or 3-inch crystals in our limited sampling. Because of differences in models of counters and methods of energy calibration, it was impractical to analyze the appropriateness of the specific ^{57}Co and ^{58}Co windows. Spill-down fractions varied between 0.1 and 0.6 at the different institutions (Fig. 3), probably because of variations in the energy resolution of the detectors and the particular energy windows chosen.

As a general rule, sites that measured urine volume by graduations on the collection bottles overestimated urine volume by over 100 ml, which in turn inflated the final urinary excretion of the cobalt isotopes by 6%–7% of expected values (Fig. 2). It was not possible to retroactively identify differences between the brands of collection bottles but subsequent comparison of the bottles revealed errors of 89.8 ± 4.6 and 89.5 ± 5.3 ml (mean ± 1 s.d.) when measuring a 1508-ml sample. Measurement of the urine volume in a graduated cylinder represents a simple and reliable alternative.

CONCLUSION

Quantitation of vitamin B12 excretion in DIST samples has proven to be a reliable method in a variety of regional laboratories when performed by experienced practioners. There appears to be difficulty initiating this procedure for the first time, which is probably related to placement of the scintillation counter window settings and inexperience with the protocol. Urine volume must be measured by a reliable method, such as use of a graduated cylinder, because volume markings on the collection bottles were highly inaccurate. A widespread source of error in measurement of the cobalt isotopes stems from poor counting statistics. This can be improved by increasing the sample volume and counting time. Additional errors, such as pipetting and dilution, can be avoided by using proper techniques: We suggest counting duplicate samples to monitor precision of measurements. Mock urine samples provide an excellent method of monitoring all technical aspects involved in this test, from measurement of urine volume to calculation of percent excretions and B/F ratios, and may provide a means of overcoming the startup difficulties encountered by novice and inexperienced users.

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