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● *Paper*

PERFORMANCE OF A WELL COUNTER AND A DOSE CALIBRATOR FOR QUANTITATIVE POSITRON EMISSION TOMOGRAPHY

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***Abstract*—Quantitative nuclear medicine techniques such as positron emission tomography (PET) require precise and accurate knowledge of both the amount of radioactivity administered to a patient and the radioactivity concentration in blood as a function of time. In addition, the uncertainties in such measurements must be known so that the accuracy and precision of quantitative *in vivo* metabolic measurements may be estimated. In order to characterize and minimize the measurement errors for PET, well counter and dose calibrator performances were studied over long and short time periods using positron-emitting isotopes. To ensure accurate quantitation with well counters, the use of correction factors for sample volume and high count rate effects is essential. Only small drifts in well counter sensitivity were observed during a 24-h period, but longer-term drifts and poor performance emphasized the need for continuing quality control procedures. Similar behavior was observed for dose calibrators. Dose calibrator, rather than well counter, data should be used for PET imaging instrument calibration. The methods presented have direct application to any quantitative nuclear medicine program.**

INTRODUCTION

ONE OF the major advantages of quantitative nuclear medicine techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) is the capability of providing regional quantitative information about *in vivo* physiology when proper calibrations have been performed (Eichling et al. 1977). However, quantitative metabolic imaging using these nuclear medicine techniques requires accurate knowledge of the sensitivity of both the imaging device and the counting instrument utilized for determining the time-course of the radiotracer concentration in blood. This paper focuses on the practical performance of well counters, used for determining blood radioactivity concentrations, and dose calibrators, used for estimating activity delivered to the patient. Emphasis is made on instrument response to positron-emitting isotopes.

Although the general performance of well counters and dose calibrators has been treated in several basic nuclear medicine works (Sorenson and Phelps 1987; Rhodes 1977; Rollo 1977), their exact performance in a practical environment has not been widely reported or analyzed. Special problems associated with the calibration of well counters and dose calibrators will be examined along with specific short- and long-term variations in sensitivity encountered for two systems in use for PET. Several small enhancements to day-to-day operations and techniques which result in decreased variance in measurements of blood radioactivity will be mentioned.

METHODS

Well counter QA

The scintillation well counter detection system consisted of a 5.1-cm (2 in.)- diameter NaI well crystal-photomultiplier tube (PMT) detector assembly with a 2.22-cm (0.875 in.)-diameter, 3.94-cm (1.55 in.)-deep well. This was encased in a lead shield, approximately 50.8 mm thick in all directions, which contained a built-in preamplifier. The preamplifier output drove the linear amplifier of a preamp–amp single channel analyzer (SCA) module. The SCA window was calibrated using a multichannel analyzer (MCA) in order to accept pulses within ±18% of 511 keV. The counts were input into a custom-designed real-time printer/timer which printed the absolute time, duration of counting period, counts and sample number.

A plastic insert was designed for the well counter which snugly fit the 12-mm outside (10.5 mm inside) diameter, 10-cm-long vials typically used for blood sample collection. This improved the consistency of vial placement in the center of the well counter for each measurement with a minimum of attenuation.

The effects of sample geometry on well counter sensitivity were studied by taking known volumes, as determined by weighing, of ^{68}Ga in solution, repeatedly diluting them and reweighing the vials, and measuring the effects on the count rate. For this experiment the count rate was maintained less than 5 kcps to avoid deadtime effects. The volumes of three different samples were varied from

0.3 to 3.0 mL in increments of approximately 0.2 mL. The decay-corrected normalized results were pooled together and fit as a third-order polynomial function of volume. All subsequent calibration experiments were corrected to correspond to a 1-mL volume using the resulting function.

The well counter was tested each day using both 33 kBq (0.9 μCi) and 1550 kBq (4.2 μCi) ^{22}Na sources. This provided information about long-term drifts in well counter sensitivity. The short-term reproducibility and drift of the instrument were tested by repeatedly counting the ^{22}Na source over 12-h and 4-h periods. Additional well counter calibration experiments were performed in which activity was measured in the dose calibrator, precisely diluted, and counted.

Data on the well counter high-count-rate behavior were obtained by placing 3.7–9.2 MBq (10–25 μCi) samples of ^{11}C, ^{15}O, ^{82}Rb, ^{68}Ga and ^{18}F in vials in the well counter. The well counter was tested, using these isotopes and ^{13}N, for any isotope-dependent behavior which could result from differences in positron abundance, positron range and the presence of other radioactive emissions which could affect response in spite of detector windowing and sample encasement. The actual activities present, initially the order of tens of MBq (several mCi), were measured using the dose calibrator. The peak count rates were noted and the count rate was measured over several half-lives.

A correction for the well counter nonlinearity at high count rates was devised by fitting the following model for linear plus paralyzable behavior using nonlinear least-squares fitting routine (Marquardt 1963):

$$y = a_1 + a_2 x + \frac{a_3}{a_4 + x}, \quad (1)$$

where

$x = \log_{10}(1000C/b_f)$,
$y = \log_{10}(A)$,
b_f = the fractional positron abundance,
A = sample activity, and
C = recorded count rate.

Since the expected error for the variance of each of the counting measurement increased with the magnitude of the measurement and additional experimental errors beyond Poisson statistics could be present and causing skewness, the logarithms of the data were fit for greater statistical stability. Any errors or uncertainties in the dose-calibrator measurement were reflected as variations in the parameter a_1. The sensitivity measurement itself, a_2, was independent of the dose calibrator measurement. Long-lived contaminants and background were reflected as variations in a_1 and a_4. Adjustments required due to variations or drifts in sensitivity which do not affect count rate capability are easily made to the above calibration by modifying the parameter a_1.

A correction for positron abundance was made by dividing the measured sensitivity values (counts/activity) by the fractional positron abundance. This permitted data for different isotopes to be pooled together to obtain a single calibration curve. In addition, information obtained during the daily imaging quality assurance and well linearity tests was used to improve the calibration by replacing a_1 with a value obtained using all available data.

Dose calibrator QA

Calibrations of the dose calibrator in the PET suite were verified monthly over a 1-y period using standard ^{57}Co, ^{137}Cs, and ^{60}Co calibration sources. To determine the instrument reproducibility, these sources were measured every 30 min over a 50-h period.

Statistical analysis

Multiple analysis of variance was performed using a standard software package, SPSS*, on the well counter and dose calibrator QA data. First, scatter plots were examined. A search was made to see whether the data could be readily separated into definite periods and whether there were any abrupt changes in behavior or gradual trends. Outliers, which could influence the data unfairly by producing apparent significant drifts, were investigated. A regression was then performed. If p was close to 1.0, then a trend was suspected. The Durbin–Watson statistic was examined to determine whether or not the data were autocorrelated even after trends were removed by regression. No autocorrelations were believed present if this statistic was close to 2.0. Histograms were employed to search for any remaining outliers and bimodality of the distribution. P-p plots, plots of the observed residuals against the residuals expected from a normal distribution, were made and examined for linearity. Nonlinearity of p-p plots was interpreted as being diagnostic of deviation from a Gaussian distribution. The magnitudes and significance of changes and variations were examined.

RESULTS

Well counter performance

Well counter calibrations. The orientation of a 33 kBq (0.9 μCi) ^{22}Na calibration source and blood vials in the well counter was found to cause variations in count rate up to 1.5%, which was decreased to less than 1% by the use of the plastic positioning insert.

The results of the volume effects experiment, utilizing the 12-mm outside diameter, 10-cm-long vial, are shown in Fig. 1. An increase in sample volume from 1 to 2 mL decreased the relative sensitivity of the well counter by approximately 3.4%. The best polynomial fit to the data was:

$$\mathrm{VCF} = 1.014 - 0.014V + 0.00720V^2 - 0.00584V^3, \quad (2)$$

* Statistical Package for the Social Sciences (SPSS), SPSS Inc., 444 North Michigan Ave., Chicago, IL 60611.

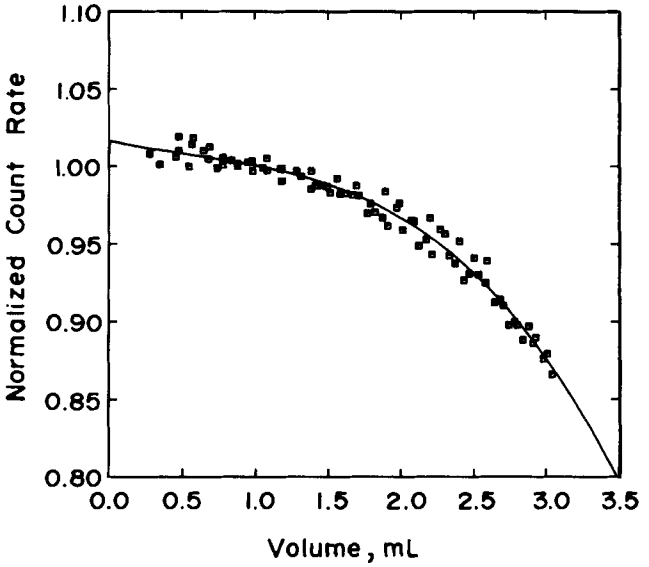

Fig. 1. Results of experiment for determining effects of sample volume on well counter sensitivity for the 12-mm outside diameter, 10-cm-long vial. Decay-corrected, normalized data for count rate are plotted as a function of volume.

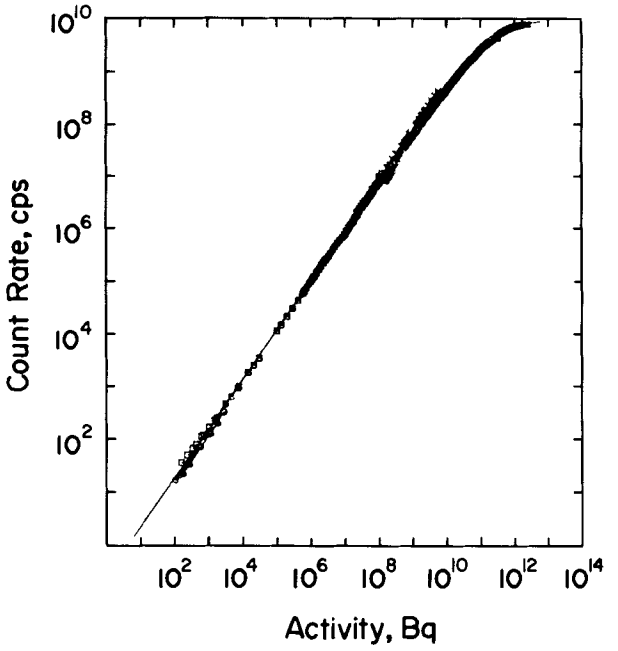

Fig. 2. Results of several well counter decay experiments obtained using ^{18}F, showing data and fitted calibration curves.

where VCF = the volume correction factor or count rate relative to a 1-mL sample volume, and V = volume of sample in mL.

The fit falls within ±2% of all data points and is specific to the vial type and range of volumes tested, between 0.3 and 3.0 mL for the reported fit. To correct count rates obtained at volumes other than 1 mL to correspond to those which would be obtained for volumes of 1 mL, the count rates must be divided by the VCF. For precise work involving samples having different volumes, use of a volume-correction factor such as this is indicated.

Data pooled for several decay experiments utilizing ^{18}F appear in Fig. 2. The average peak count rate observed for ^{11}C, ^{15}O and ^{18}F was 3.3 ± 2 kcps, while the peak count rates for ^{68}Ga and ^{82}Rb, which emit photons in addition to the 511-keV annihilation photons, were observed to be 33.5 ± 0.1 and 27 ± 7 kcps, respectively.

Calibration coefficients for each isotope and for the pooled data are shown in Table 1. It should be noted that these specific values are only applicable to the particular system studied under the given conditions of operation, and experiments would need to be repeated for other settings or equipment. Discrepancies in some coefficients were believed to be due to the varying response of the dose calibrator, used for the absolute determination of activity, to different isotopes. For the global fit the uncertainties in the coefficients a_1, a_2, a_3 and a_4 were ±11%, ±1.2%, ±20% and ±1.0%, respectively. These would produce uncertainties in the computed activity of 0.01% to 8% at 5 cps and 0.1% to 13% at 37 kcps. The calibration data are only valid for samples having count rates less than approximately 33 kcps.

Plots of the count rates observed as a function of time revealed not only nonlinearities in well counter behavior but also the presence and amounts of any radioisotopic impurities in the samples. These impurities included ^{11}C in ^{15}O, ^{68}Ge in ^{68}Ga, and ^{82}Sr in ^{82}Rb. The amount of ^{11}C in ^{15}O depended upon the date of the experiment and the methods employed for the ^{15}O production. The well counter decay experiments revealed approximate breakthroughs of 3.2×10^{-6} and 5.5×10^{-7} for the $^{68}Ge/^{68}Ga$ and $^{82}Sr/^{82}Rb$ generators, respectively.

Daily well counter QA. The daily well counter data included not only drifts in the well counter but also in

Table 1. Polynomial fits of well counter calibration data for the specific system tested.

$$y = a_1 + a_2 * x + \frac{a_3}{a_4 + x}$$

where x = log(0.6*C/b_f),
y = log(0.27*A),
b_f = the fractional positron abundance,
A = sample activity (Bq),
and C = recorded count rate (cps).

Isotope	N_1[a]	a_1	N_2[b]	a_2	a_3	a_4
^{68}Ga	4	0.8061	3	1.0159	0.2277	10.0302
^{18}F	1	0.6043	2	1.0365	0.2121	10.0836
^{11}C	14	0.7775	1	1.0141	0.2246	10.1526
^{13}N	1	0.7649	1	1.0096	0.2760	10.3080
^{15}O	1	1.990	1	1.0047	0.1393	10.0320
^{82}Rb	1	0.7692	2	1.0323	0.2310	10.0013
Overall		0.7729		1.0214	0.2209	10.1013

a Number of experiments used for determination of a_1
b Number of experiments used for determination of a_2, a_3, and a_4

the dose calibrator. There was more experimental error and uncertainty in these experiments than for those involving long-lived solid check sources, since activity was measured in the dose calibrator, mixed and diluted. The short half-lives of the isotopes used in these experiments made experimental timing even more critical. These data can, however, provide information about the sensitivity of the system for the same source geometry and activity as the actual patient blood samples.

The complete data set included 77 points obtained over an 8-mo period. When the entire data set was treated as a whole, a slightly significant decreasing trend appeared, with $p = 0.0622$. Here "p" refers to the conventional probability value or p value, which would indicate a significant effect when its value is <0.05. However, examination of the scatter diagrams revealed that the trend was actually false, and caused by two outliers; one early high outlier and one later low outlier. When these outliers were removed, it became apparent from the scatter plots, shown in Fig. 3, that the distribution was probably bimodal. The data were broken down into groups in terms of the size of the phantom employed (some were of different lengths and diameters) to see if this explained the long tails and many outliers which remained. Phantom type did not, however, significantly correlate with measured sensitivity value or explain the distribution's bimodality. Errors in the dilution factors also did not explain the observations.

Further examination of the scatter plot revealed that the daily well QA data could be broken down into two periods of slightly different sensitivities. These two time periods were then analyzed separately. During the first time period, no significant trend was observed, with $p = 0.808$. The standard deviation during this time period was observed to be 4.5%, the tails of the distribution were long, and the p-p plot was not linear. In addition, the percent variation between the minimum and maximum sensitivities was 26%. It should be noted that the minimum-to-maximum variation is simply an indication of the outer limits or extremes of the data. In fact, 95% of all the data should fall within two standard deviations, or ±9% for this case, of the mean. From the scatter diagram, it was noticed that seven of the ten most pronounced outliers for the period occurred during the first 14 d, indicating some learning effect for the experimental procedure. When these first points were omitted, the percent variation from the minimum to the maximum was reduced to 18% and the standard deviation was reduced to 3.7%. Following the first time period, a definite change abruptly occurred, and the sensitivity was decreased by 3.5%. During this final period, the well counter remained stable with a standard deviation 4.2%, a minimum-to-maximum variation of 31%, and no significant trend ($p = 0.869$). The higher deviations in the data reflect variations in the dose calibrator and other experimental errors. A value of Durbin–Watson coefficient near two for a data set should indicate an absence of significant autocorrelations. For these data, the Durbin–Watson statistic was 1.71, indicating that no significant autocorrelation was observed. Autocorrelation would indicate some underlying relationship among data points. This dependence could be due to some physical process, such as a systematic drift, which may relate to a trend.

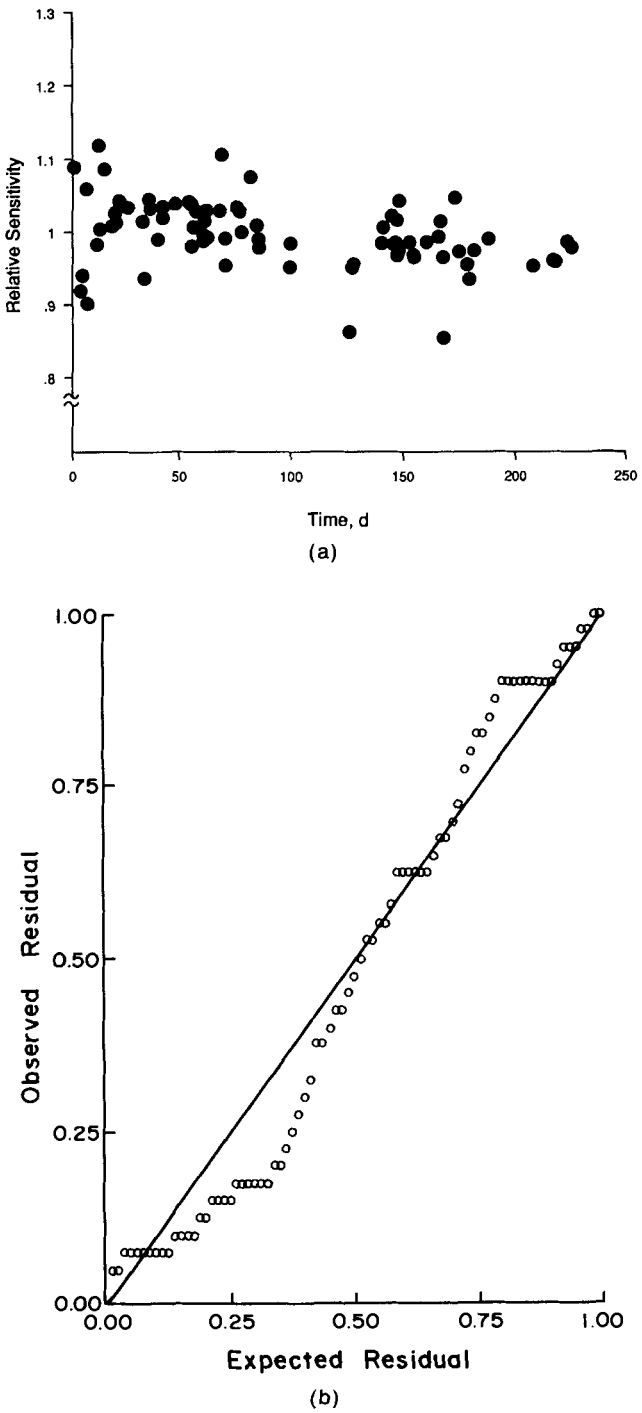

Fig. 3. Results of daily well QA experiments obtained over several months using a variety of short-lived PET isotopes. (a) Scatter plot, with two outliers removed; (b) P-p plot.

Short-term well counter performance. A scatter plot, shown in Fig. 4a, of the counts obtained for a ^{22}Na check source over a 12-h period revealed two trends: 1) an in-

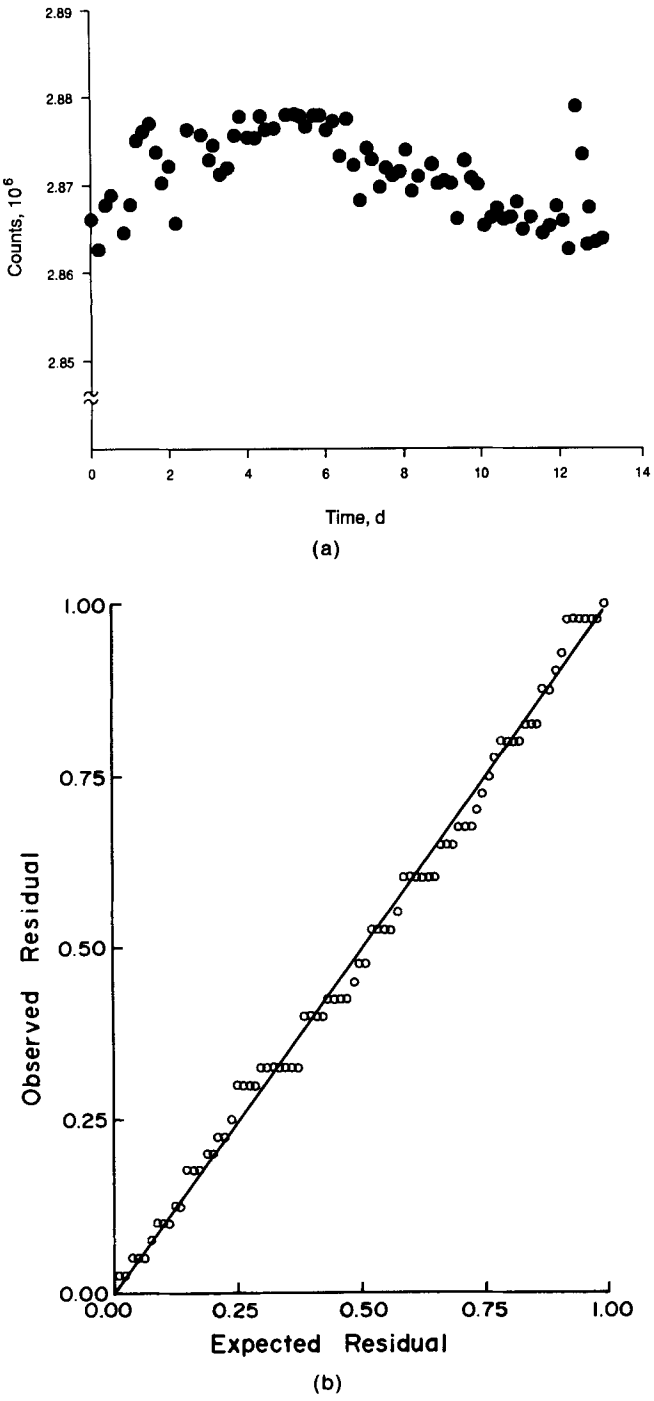

Fig. 4. Short-term well counter repeatability test obtained using a ^{22}Na source over a 12-h period. (a) Scatter plot; (b) *P-p* plot.

crease in count rate during the initial 7-h period of the experiment, from 9 p.m. to 4 a.m. ($p < 0.0001$), and 2) a decrease in count rate during the final portion of the experiment, conducted between 4 a.m. and 10:30 a.m. ($p = 0.0001$). However, the upward increase was only 0.4%, with the standard deviation 0.01%. For the second period the decrease was less than 0.04% and the standard deviation was 0.0007%. The difference between the minimum and maximum measured well counter sensitivity over the entire 12-h period remained 0.56%. Significant auto-correlation occurred, with a Durbin-Watson statistic of 0.75. However, this can be ignored because the total variations are small. Counting statistics for this experiment were constant at 0.06%. The *p-p* plot, included in Fig. 4b, was linear and thus indicated a normal distribution. An increase of 0.4% in count rate occurred during the last hour of the experiment. This coincided with the delivery of activity for another experiment, which caused a slight increase in background. This is an unfortunate event resulting from a practical space limitation which is, unfortunately, suffered by many clinically based facilities.

Figure 5a shows a scatter plot of the data obtained by repeatedly counting the ^{22}Na source in the well counter over a 4-d period. Although several trends may be apparent in the data, the standard deviation of the count rate was less than 1.6% for the entire period. The minimum and maximum values of measured sensitivity differed by less than 0.7% from each other. Figure 5b is a *p-p* plot of the results. These indicate the normality of the distribution of the values, which has a Durbin-Watson statistic of 0.46.

Long-term well counter drift. The scatter plot, appearing in Figure 6a, and regression analysis of the counts resulting from the ^{22}Na obtained as a function of time showed no significant trend for 26 points taken over a 70-d period. A normal distribution was indicated by closeness of normalized *p-p* plots of standardized residuals, shown in Fig. 6b, to a straight line.

Noise was Gaussian, and the observed standard deviation, 1.5%, was not much greater than the Poisson counting statistics noise, 0.55%. No significant correlation was observed for values obtained on successive days, with a Durbin–Watson statistic of 1.33, which is equivalent to a correlation coefficient of 0.3. This correlation was of little consequence because of the small overall observed standard deviation of the measurements.

For the first 14-d period during which the long-term well counter drift experiment was performed, the observed standard deviation was 1.17 times that measured subsequently. The improvement in performance was due to the well counter peaking or window-centering procedure and the plastic insert which provided more repeatable repositioning. The initial period was followed by a 70-d period of well counter stability. Then a drop in sensitivity of 21% occurred. Maintenance work was done on the well counter. However, the sensitivity never returned to its original value over the next 150-d period, remaining 10% lower than in the previous period. The sensitivity was stable over that time period with a standard deviation of 3.4%.

Dose calibrator performance

Short-term dose calibrator performance. No significant trends in measured response were observed for the

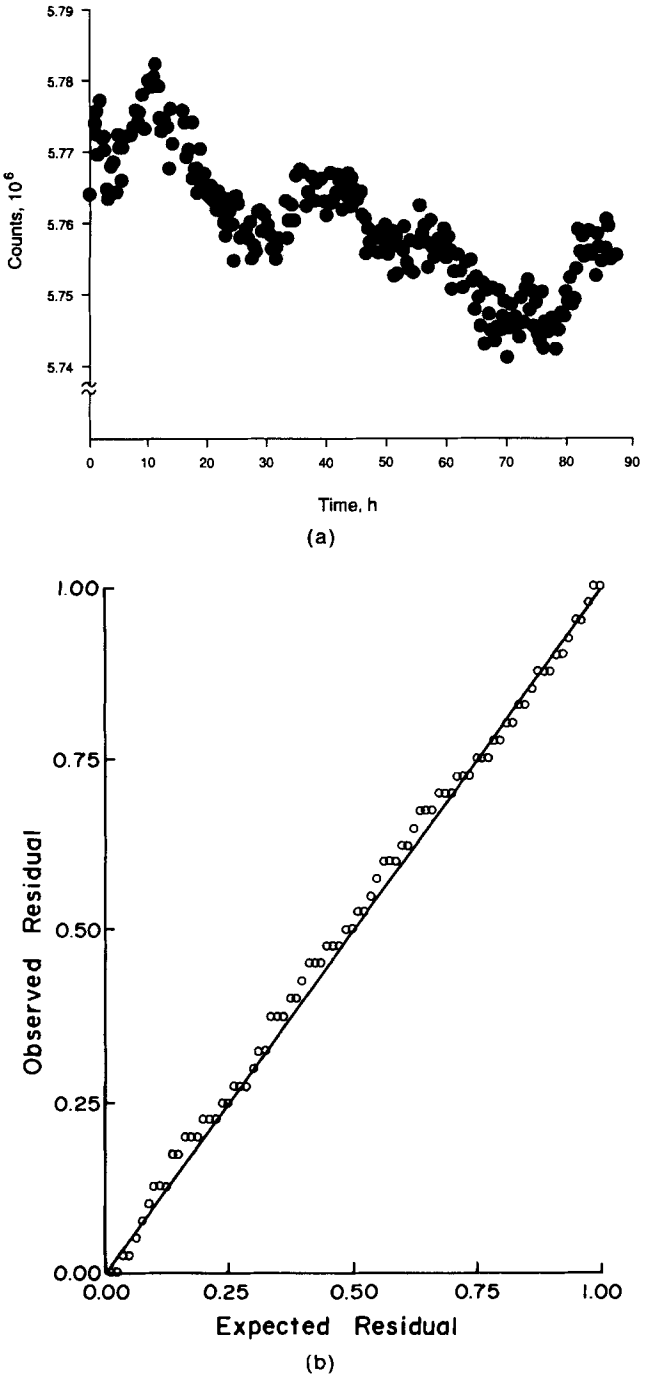

Fig. 5. Four-day well counter drift test obtained using ^{22}Na. (a) Scatter plot; (b) *P-p* plot.

^{57}Co, ^{60}Co and ^{137}Cs check sources in the dose calibrator over a 50-h period. The Durbin–Watson statistic, having values of 1.84, 2.06 and 2.26 for the three sources, indicated no strong autocorrelations for the data. The standard deviations of the 36 data points were all less than 0.64%, indicating very good short-term performance of the dose calibrator. The distributions did, however, exhibit fairly long tails, but the percentage difference between the minimum and maximum was only 3%. There was no significant correlation among measurements made with the three sources.

Long-term dose calibrator performance. Since dose calibrator performance was only monitored once a month over a 1-y period, it is difficult to make definite conclusions

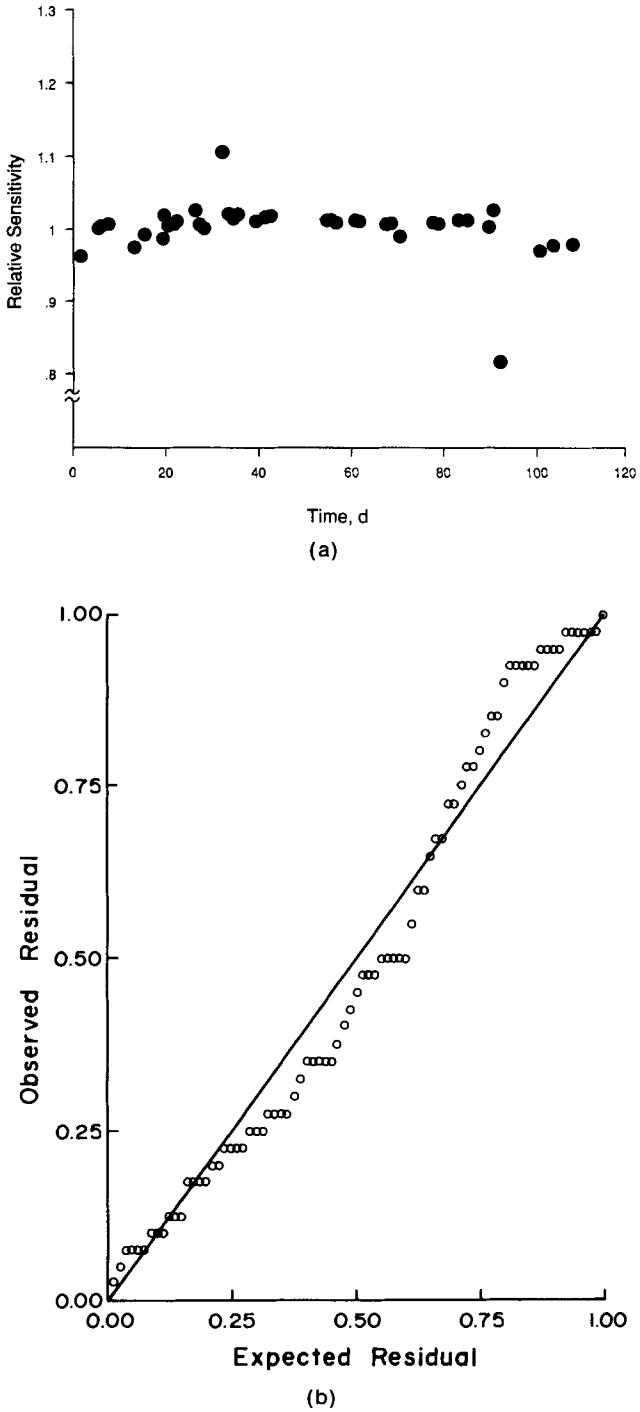

Fig. 6. Long-term well counter drift test obtained using a ^{22}Na source over a 104-d period. (a) Scatter plot; (b) *P-p* plot.

about dose calibrator drift and overall performance. No significant trends or temporal drifts were observed, with $p = 0.835$, 0.0834 and 0.658 for the ^{57}Co, ^{137}Cs and ^{60}Co sources. In addition, autocorrelation was not significant, with Durbin–Watson statistics of 2.71, 2.62 and 1.83. Standard deviations were observed to be 0.4% to 1.1%, and the maximum difference between any two points was 4.2%.

DISCUSSION AND CONCLUSIONS

Use of a specially designed plastic insert reduced the errors introduced by sample positioning in the well counter to less than 1%. Care must be taken that well counter peaking or centering procedures are accurate. Third-order polynomials may provide excellent fits to detected count rate as a function of sample volume for blood vials and should be determined and applied in situations for which different volumes of samples are to be studied. Understanding of the behavior of the well counter for high count rates is essential for accurate PET quantitation, especially when high dosages of short-lived isotopes are to be injected into patients. Although well counter sensitivity may drift during the day, the magnitudes of these drifts are small. For the experiments reported, an extreme range of variation of <1% was observed in sensitivity over a 12-h period. Typically, 95% of all readings fell within ±4% for a 4-d period. Over an 8-mo period, 95% of all readings fell within ±7–9%. Daily QA of well counters is, however, recommended for detecting longer-term drifts and poor performance.

The dose calibrator tested did not show substantial variability, with standard deviations of less than 2% for 50-h and 1-y periods. Long-term monitoring of dose calibrator performance, preferably using longer-lived calibrated check sources with cross-referencing to other dose calibrators, whenever possible, is a highly recommended procedure to be included in any quantitative nuclear medicine quality assurance program for the detection of instrument problems.

When dose calibrator data are used to normalize PET-imaging instrument sensitivities, the standard deviation of the sensitivity values is one half that obtained for well counter-normalized data. Although dose calibrator-normalized data are preferable to well counter-normalized data for monitoring quantitative PET-imaging instrument performance because of the experimental uncertainties which are introduced, it is relative well counter-imaging sensitivity that is of interest for calibrating patient studies. Well calibration data obtained during the daily PET-imaging instrument QA also provide indications of well counter behavior. Collection of well counter data as a part of the daily PET imaging QA procedure is thus strongly recommended.

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