Quality Control in Nuclear Medicine Procedures

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Application of the scientific method to medicine in the last century has resulted in revolutionary advances in medical science. The scientific method depends first on observation during which phenomena are recorded with as much precision as possible. These observations may be purely qualitative; for example, children with congenital heart disease often assume a squatting position. There is general agreement that quantitative relationships are more precise and some have suggested that the term "scientific method" be restricted to quantitative observations which can be subjected to mathematical manipulation although this is perhaps too restrictive. It is hard to conceive what life without weights and measures would be like, for these are among the most primitive tools of man. Length was measured by fingers, hands, and arms; time by the periods of the sun, moon, and stars. The capacity of a vessel was measured by the number of seeds contained within it; for instance, a "carat," still used as a measure for gems, was derived from the carob seed.

For measurements to become a measurement system it was necessary that standardization be introduced. Tradition holds that King Henry I decreed that the yard be the distance from the tip of his nose to the end of his thumb. This was the first of a series of royal edicts which achieved some degree of standardization.

The need for a single worldwide coordinated measurement system was recognized over 300 years ago and in 1790, in the midst of the French Revolution, the French Academy of Sciences was directed by the National Assembly to "deduce an invariable standard for all the measures and all the weights." Length was related to the earth's circumference, and volume and weight derived from length, thus relating the basic units to nature and to each other. Most countries now use a system evolved from these units. Meters, kilograms, seconds, amperes, degrees Kelvin, moles, and candela measure length, mass, time, electric current, temperature, amount of substance, and luminous intensity, respectively. As we shall see, measurement, standardization, and quality control are interdependent and closely related.

In nuclear medicine, as in all sciences, we observe, describe, measure, and interpret. We group phenomena on the basis of similarities whether they are chemical elements with similar properties or patients with similar manifestations of disease. The variation among the individual parts of the group is an important characteristic of the group. Once we define a grouping in the scientific sense, we must state also the degree of tolerance that is acceptable. All of our scientific measurements and laws are subject to some degree of variance or, in a sense, to some degree of error. Modern physics today accepts the fact that there are no mathematically exact laws in nature and that the best we can attain are probabilities.

Basic Considerations

In the day-to-day practice of nuclear medicine, we must deal continually with variance, probabilities, accuracy, precision, calibration, and standardization. Quality control can be viewed as control of variance. We must decide which measurements we must make to ensure quality, what limits of variability (variance) are acceptable, how often such measurements should be made, and who is responsible for making them. We attach particular importance to measurements and

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quantity. We may speak of an object as being light or heavy but only when we express its weight in grams or pounds can we make a quantitative statement about its lightness or heaviness.

Quality control must be maintained throughout the application of radioactive tracers in medicine, from the decision to carry out a specific study to the final reporting of the results and recording of data in the patient's medical record. It is helpful to subdivide the various components of the procedures.

Identification of the patient's problems and the measurements to be made. Patients come to physicians because of problems. The diagnostic process depends upon progressively more precise identification of the problems. The patient may view his problem as one of weakness, the physician may observe that he is pale, the nuclear medicine consultant may determine that the patient's red blood cells are being destroyed at an abnormally rapid rate in the spleen. The problem has been defined with more precision and therapy can be planned more specifically.

It is helpful to ascertain the resolution requirements of the patient's problem in terms of functional, spatial, and temporal resolution. Radioactive tracers permit us to measure body functions. At times measurement of a single function such as phagocytosis of particles by the reticuloendothelial cells of liver may be all that is needed to solve the problem. At other times several functions of the liver will have to be measured, for example, regional blood flow, blood volume, and parenchymal cell function. Having determined which functions are to be measured, the next decision is the degree of spatial resolution required. For example, if we are concerned only with the absorption of radioactive iron from the intestinal tract, we need only administer an oral dose of the tracer and monitor the total-body content of radioactivity in a whole-body counter without being concerned with where the tracer is located within the body. On the other hand, if the patient's problem requires that we know the relative function of each of the two kidneys, our measurements must be able to separate their respective functions and we will need instruments with better spatial resolution than the whole-body counter. In another example, we may have to determine whether a brain tumor is located in the posterior fossa of the brain. This will require even greater spatial resolution and necessitate the use of a different instrument. Each measuring device must be able to make measurements that are within the tolerable errors determined by the patient's problem.

Next we consider the temporal resolution requirements of the problem. Are we to measure a slow process such as bone metabolism or a fast process such as the beating of the heart? If we measure the latter with a radioactive gas, such as ^{133}Xe and an instrument with an excessively long deadtime, gross errors may result because of inadequacy of temporal resolution.

Analysis of Variance

Certain characteristics of the normal human body such as temperature vary only slightly from one person to another (interpersonal variation) or from one time to another in the same person (intrapersonal variation). Others such as basal metabolic rate are considerably more variable. It is not unusual for some characteristics such as serum thyroxine levels to vary several hundred percent in healthy individuals. To express variance we use the principle of the normal distribution, first described by Gauss, which permits us to measure the standard deviation, using the formula

$$S^2 = \frac{\Sigma (X_i - \bar{X})^2}{n}$$

where S^2 = variance, S = the standard deviation, X_i are the individual measurements, $\bar{X}$ is the mean, and n = the number of observations. Knowing the mean and standard deviation of a series of measurements tells us how variable the characteristic is. In most cases, the between-person variance is greater than the variance from one time to another within the same individual. Since it can be shown that variances (but not standard deviations) from independent sources are additive, total variation in a series of measurements is the sum of that arising from normal biological variation and that arising from random analytical error. These two variances make up the total variance among healthy persons. Calculation of the numerical values for these two components, biological and laboratory variance, is called a component-of-variance analysis and is an important principle of quality control (Table 1). As a practical example of components-of-variance analysis we may choose a common in vitro test performed in nuclear medicine laboratories, the serum thyroxine level. Analytical error for the test arises both within a single run and between runs of the test. The variance between runs reflects the failure to exactly reproduce test conditions because of a change either in the analytical reagents or of techniques. It is measured by running two normal control sera in each test and establishing for each control a chart with mean and standard deviation

Table 1. Quality Control in In Vitro Studies

Component	How measured	What it measures
	Analytical error (variance)	
Between run	Control sera	Change in reagents or techniques
In run	Duplicate samples	Technical precision
	Biological variance	
Between person	Samples from normal subjects	Normal distribution
Within person	Repeated samples from one subject	Individual fluctuation

calculated when about 20 values have been obtained. A range which includes two standard deviations above and below the mean demonstrates test reproducibility. Within-run variance is a measure of technical precision and is measured by assaying each sample (control sera, standard concentrations, and test sera) in duplicate.

The normal individual has some fluctuation in his day-to-day blood level of thyroxine and this is determined by repeating the assay from one subject on several occasions. By establishing what is normal fluctuation, pathological changes in progressive disease or the effect of treatment can be determined.

The establishment of a normal range for the test is dependent on the between-person variance of disease-free subjects. The normal range is usually taken as values between two standard deviations above and below the mean for these subjects.

Regional function measurements. Up to now we have considered only in vitro procedures in which the data are reported in numerical form. The same principles apply to in vivo measurements of radioactivity within the body despite the fact that frequently the data are presented in the form of a picture rather than in numerical form. Again the sources of error are multiple and the position is clarified if the components of the process are subdivided and quality control is applied at each stage. Tables 2 and 3 divide patient, radiopharmaceutical, and instrument as the major components and subdivides the minor components contained within.

The patient. The patient is central to all diagnostic departments and the study is performed to answer specific questions. The nuclear medicine physician must obtain either by direct consultation with the referring physician and the patient or by way of a requisition form the following information:

1. Patient data (name, age, sex),
2. Data recall information (history or social security number),
3. Study required,
4. Questions to be answered,
5. Relevant clinical findings,
6. A priori diagnosis.

A formal report is issued at the completion of the study and has three sections—description, interpretation, and comments as to further studies or repeat examination should these be required.

Table 2. Quality Control for Patient and Radiopharmaceutical

What is to be monitored	How monitored	How often	Who is responsible
Patient			
1. Is the correct study being performed?	Consultation with referring physician	Before scheduled	Physician
2. Satisfactory information	Requisition/report form Clinical evaluation	After study	Physician
3. Accurate interpretation	Followup	When information becomes available	Physician
4. Positive identification	Verbal or personal communication, wrist band if available	Before nuclide is administered	Technologist
5. Correct preparation	Verbal request	Before nuclide is administered	Technologist
Radiopharmaceutical			
1. Pyrogens	Pyrogen test (USP)		
2. Microorganisms	Sterility test (USP)		
3. Efficacy	Tissue distribution or chromatography		
4. Radiochemical purity	Spectroscopic analysis		
5. Radionuclidic purity	Beta/gamma spectroscopy		
6. Physical properties	Microscopy		
7. Radionuclidic concentration	Ionization chamber assay		
Commercially compounded		Before use	Manufacturer
Commercial kit preparations and generators		Before use	Manufacturer 1, 2 Pharmacist 3–7
In-house preparations		Before use	Pharmacist

Table 3. Instrument Function Quality Control

What is to be monitored	How monitored	How often	By whom
Well counters and external detectors			
System resolution	FWHM	Monthly	Technologist
System linearity	Two nuclides with widely separated photopeaks	Monthly	
Background	Background control chart	Daily	
Stability of counting rate	Long-lived standard control chart	Daily	
Spectrometer calibration	Peak with nuclide with photopeak near nuclide to be counted	Daily	
Rectilinear scanners			
Photorecorder calibration	Counts/cm²/film density	3 monthly	
	Effect of contrast enhancement	3 monthly	
Spatial resolution	Phantom studies	Initial evaluation only	
Scintillation cameras			
Stability of counting rate	Long-lived standard control chart	Daily	
Spectrometer calibration	Peak with nuclide to be used	Daily	
Field uniformity check	Disk source ^{57}Co or ^{99m}Tc	Daily	
Spatial resolution	Lead bar phantom or line source phantom	Daily	
Ionization chambers			
Contamination	Background count	Daily	
Stability of counting rate	Long-lived standard count	Daily	

All patients should be followed up to improve the accuracy of the interpretation.

The radiopharmaceutical. In regional function measurements, the patient is injected with a radioactive tracer referred to as a radiopharmaceutical. Improper quality control of the radiopharmaceutical can result in unnecessary radiation of the patient, inaccurate information, or needless repetition of studies. The radiopharmaceutical must not contain impurities such as microorganisms or pyrogens and must be chemically, radiochemically, and radionuclidically pure.

Chemical purity is usually established by spectroscopic measurements, radionuclidic purity by gamma spectrometry, and radionuclidic concentrations by beta and gamma measurements. Pharmaceutical controls include chemical identification, physical controls, such as particle size in the case of some radiopharmaceuticals, and biological controls. These usually involve measurement of the distribution of the tracer in animals after intravenous injection, pyrogen testing, and sterility. The initial responsibility for radiopharmaceutical controls rests with the pharmaceutical manufacturer; where chemical processes are performed within the hospital laboratory, additional responsibility falls on the radiopharmacist.

The radiopharmacist is issued with the manufacturer's instructions for making up the agent with the implied understanding that it will be efficacious, free of impurities, and safe for clinical use. Because he adds the radioactive ingredients, however, he must test the finished product for radioactive concentration, for radioactive contamination, and for efficient labeling. For molybdenum generator-eluted technetium, ^{99}Mo can be detected by counting in a high-energy window (600–900 keV) or through a ¼-in. lead container which will shield the 140 keV of ^{99m}Tc but not the ^{99}Mo. Paper or thin-layer chromatography will separate bound from unbound technetium quickly and with a minimum of equipment. The final product is assayed in a dose calibrator, labeled with the agent name, concentration, and time of assay. Further instructions prior to administration, such as dispersal of particles, should be conveyed to the person administering the agent.

The Joint Committee on Accreditation of Hospitals has laid guidelines for nuclear medicine and requires that radiopharmaceutical records "include at least the following information: A) dates, amounts and methods of receipts and disposal; B) supplier and lot number, and where applicable; C) the use, date, amount, and identity of any recipient."

RADIOPHARMACEUTICAL QUALITY CONTROL	
What is to be monitored	How monitored
Radionuclidic purity	Check for contaminants
Radiochemical purity	Thin-layer or paper chromatography
Radionuclidic concentration	Ionization chamber assay

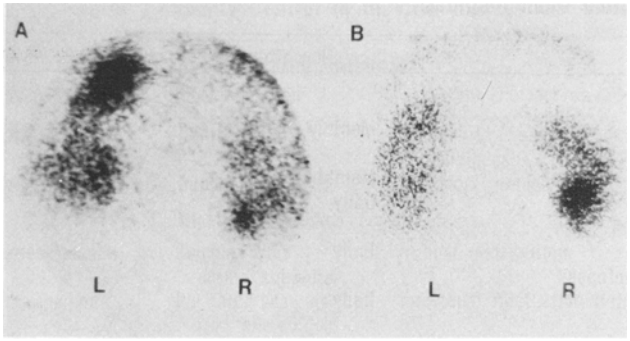


FIG. 1. (A) Renal scan with poorly labeled ^{99m}Tc-DTPA showing gastric uptake overlying upper pole of left kidney. (B) Repeat study using ^{113m}In-DTPA.

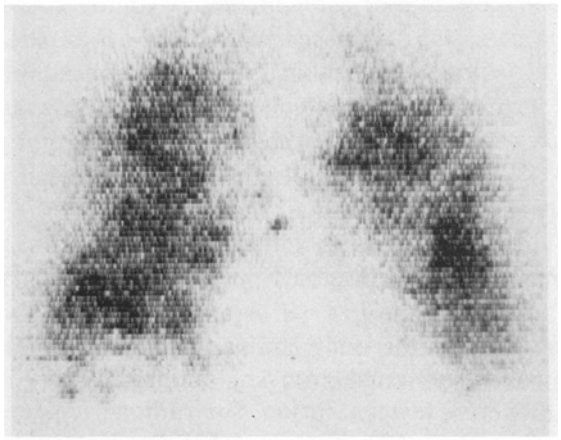


FIG. 2. Lung scan. Multiple "hot" areas due to radiopharmaceutical clumping.

Figures 1 and 2 demonstrate the importance of these techniques. The scan in Figure 1 shows a renal scan using DTPA poorly labeled with ^{99m}Tc. Free $^{99m}TcO_4^-$ has accumulated in the stomach giving a region of increased activity adjacent to the upper pole of the left kidney. Recognition of the problem prompted a repeat study performed with ^{113m}In-DTPA and clarified the picture. The lung scan in Fig. 2 shows clumping of particles to give a characteristic "hot spot" pattern. This artifact was caused by failure to redisperse the particles which clump on standing. An identical pattern may be caused when blood is allowed to mix in the syringe with the particles, with the formation of microradioactive emboli.

Instrument function. The four types of instruments commonly found in nuclear medicine laboratories are low-spatial resolution detectors (gamma probe systems, well counters), rectilinear scanners, scintillation cameras, and ionization chambers (dose calibrators). Each instrument must have its electronic stability checked at specified intervals. The results of all checks are entered in the instrument log, as are the results of maintenance performed (Table 3). The Joint Committee on Accreditation of Hospitals specifies also that the technologist or service source be identified. The performance of the individual checks is well covered in procedural manuals and interpretation only will be stressed (*1*, 2).

Low-spatial Resolution Detectors

Included in this section are external probe detectors and well counters.

Energy resolution. The manufacturer will specify the expected full width at half-maximum (FWHM) and the resolution obtained should be checked on installation. A sudden change of the order of 2% is not specific but indicates a major problem, such as a defective crystal.

System linearity. Following calibration, linearity should be tested by plotting spectra on two or more well-separated photopeak energies. Nonlinearity can be corrected for by graphing expected photopeak against experimental photopeak or a full spectrum plotted for each new nuclide used.

Background. A control chart is established for background in the spectral range being used for assays. This is a check for contamination as well as for electronic or room background changes.

Stability of counting rate. The stability of counting rate is plotted on a control chart with 95% confidence limits. A long-lived standard is used and correction applied to the limits for the expected standard radioactive decay. Recurring values outside the upper or lower limit indicates electronic malfunction.

Spectrometer calibration. Either the nuclide to be used for the study or one with a similar photopeak (e.g., "mock ^{131}I") may be used. A long-lived nuclide can be used to check system linearity and stability in the range to be utilized at the same time.

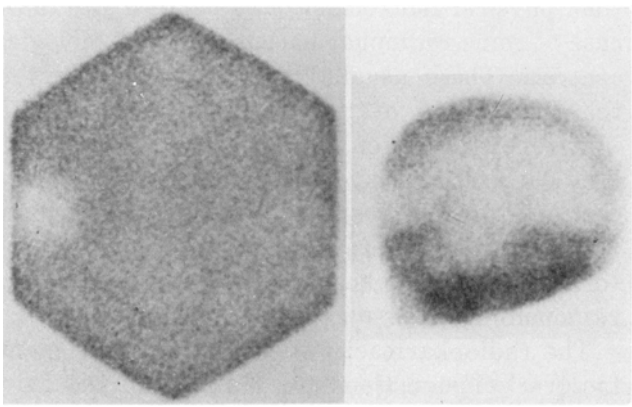


FIG. 3. Flood field with photomultiplier-tube dysfunction. Reduced activity on lateral brain scan corresponds to this area.

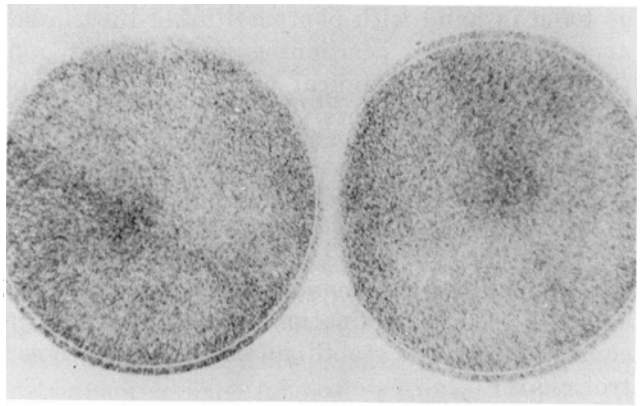


FIG. 4. Flood field in two orientations showing area of increased activity traversing image. This was caused by crack in collimator during manufacture.

Rectilinear Scanner

The checks outlined before are performed. In addition, the photorecording and spatial resolution of the system are evaluated initially and, if necessary, following service checks.

Density strips. Intensity settings, line spacing, and scan speed settings to produce a net density on film of no higher than 1.5 are calibrated for different count densities. The effect of contrast enhancement is assessed by varying the counting rate at fixed contrast enhancement settings.

Spatial resolution. Spatial resolution is a function of the collimator rather than the electronics and is expected to remain stable.

Scintillation Camera

Stability of counting rate and field uniformity can be assessed with a long-lived source incorporated in a solid disk large enough to cover the collimator face. The field uniformity check is necessary in conjunction with the clinical images to assess real abnormalities. The nonuniformity was due to photomultiplier tube dysfunction in Fig. 3. A defective collimator was responsible in Fig. 4.

Spectrometer calibration. Each nuclide in use is peaked on the visual multichannel analyzer or ratemeter provided. A symmetrical window over the photopeak is necessary because the photomultiplier tubes are balanced by the manufacturer for this setting. The effect of an asymmetrical high window with reduced response centrally is

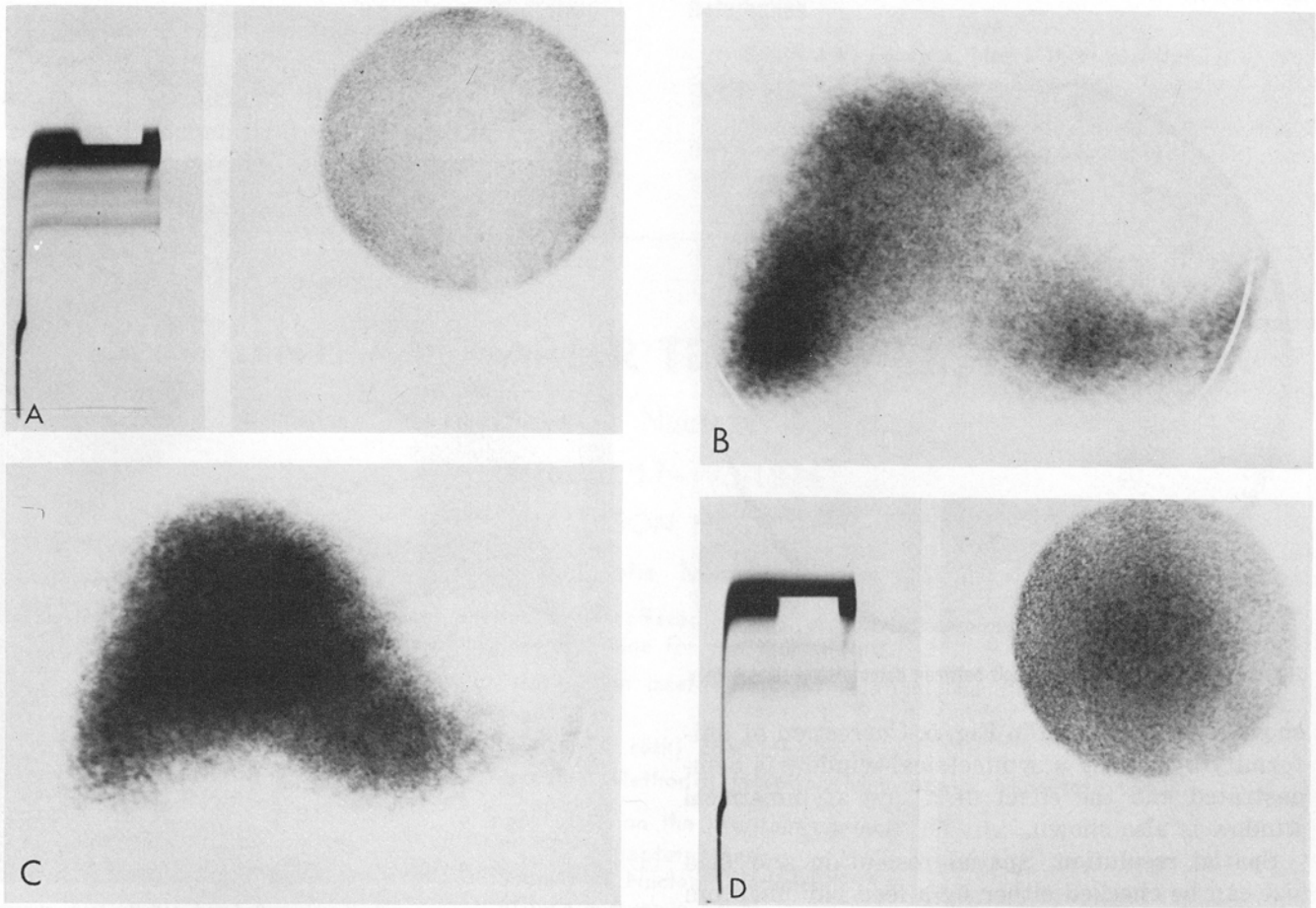


FIG. 5. (A) Spectrum and flood field—asymmetrical high window, ^{99m}Tc. (B) Liver scan with spectrum set as in (A). (C) Liver scan repeated with symmetrical window. (D) Effect of asymmetrical low window on flood field.

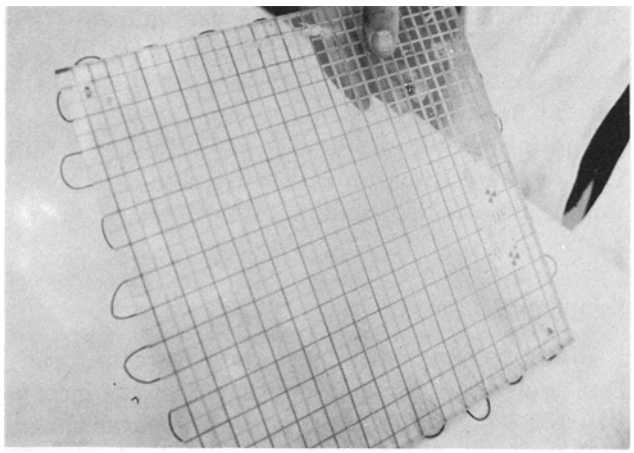


FIG. 6. Line-source phantom, grid pattern.

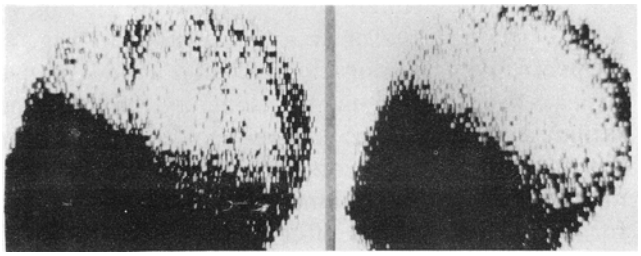


FIG. 7. Brain scan. Lateral view with anterior view superimposed and repeated lateral view.

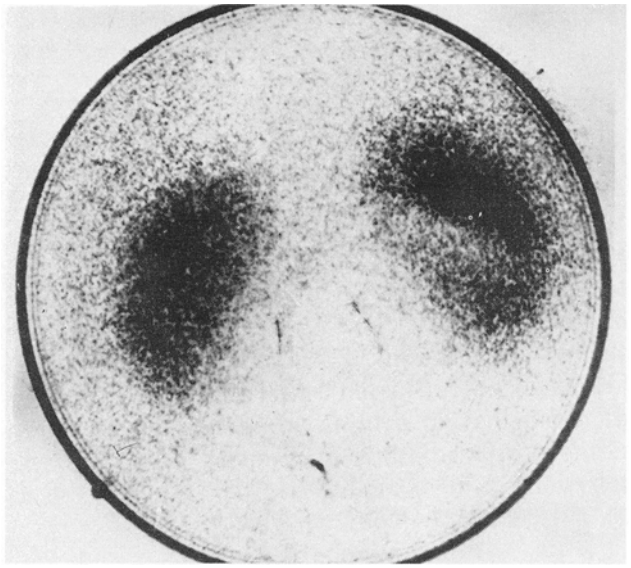


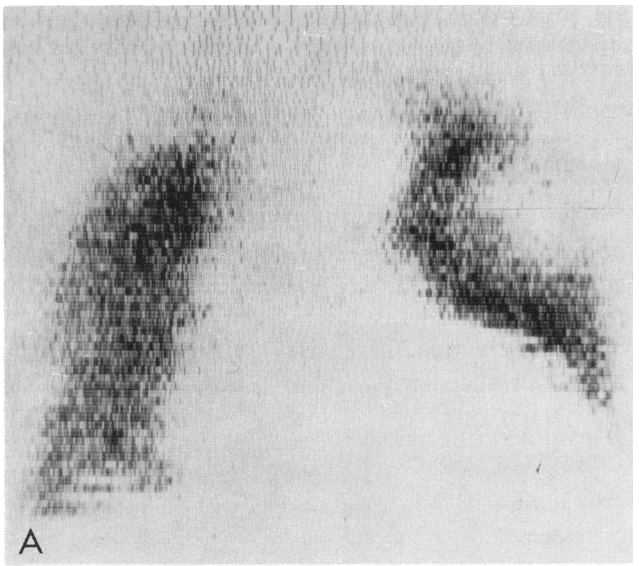
FIG. 8. Artifact caused by metal bolt between detector and right kidney.

shown on a liver scan in Fig. 5. Correction of uniformity by setting a symmetrical window is demonstrated and the effect of a low asymmetrical window is also shown.

Spatial resolution. Spatial resolution and field size can be checked either by a lead bar phantom or by a line source arranged in a grid or parallel pattern Fig. 6. Changes in these parameters often go hand in hand with photomultiplier-tube imbalance because XY positioning is dependent upon them. Cameras in clinical use should be capable of resolving ¼-in. bars and as newer, upgraded instruments become widely available the resolution requirement could be expected to drop.

Ionization Chambers

Dose calibrators should be assessed daily for evidence of contamination (background count control chart) and stability (standard source control chart).



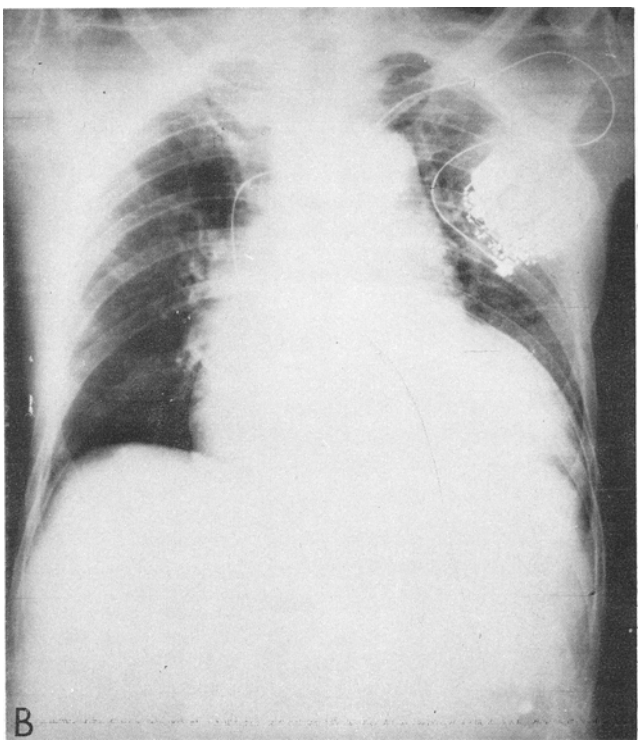


FIG. 9. (A) Lung scan, anterior view. Reduced activity from superolateral portion of left lung. (B) Radiological examination shows cardial pacemaker implanted in left infraclavicular fossa.

The Clinical Study

The technologist has responsibility for the actual production of the study and coordinates activities from the administration of the nuclide to the patient's discharge from the department. Positive identification of patients and images and the production of technically pleasing images is part of this responsibility. To assist in the reliability of performance, each procedure should be the subject of a check list so that no step is omitted. Such a procedure check list should be made up for each instrument in each laboratory and guidelines are given below in an example:

1. Check requisition for study,
2. Select collimator, load film,
3. Intensity, scan speed or present counts
4. Correct patient positions, special positions,
5. Identify and develop film, mount, and check.

Figures 7, 8, and 9 show examples of uncommon but recognizable artifacts. The superimposition of an anterior and a lateral brain scan when the cassette was not changed was quickly recognized and repeated. The linear region of reduced uptake in the right kidney region was caused by a metal bolt between patient and detector. A further illustration of artificially reduced photon reduction serves to demonstrate the collaborative use of radiology in demonstrating the position of a cardiac pacemaker in the left infraclavicular fossa.

Conclusion

Quality control in nuclear medicine is based on answering the following questions: What performance parameters must be monitored? How are we to monitor them? What degree of variation is acceptable? Who will be responsible for the monitoring? How often need the measurement be made?

Nuclear medicine procedures involve the use of radiopharmaceuticals and instruments, as well as interactions among the referring physician, nuclear physician, patient, and technologist; each must have a systematic quality-control program.

By insisting on a high standard of performance and developing a reasonable, practical, and continuing quality-control program, the nuclear medicine department can raise the general level of diagnostic excellence and contribute most effectively to improving medical care.

Acknowledgments

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