A Review of Neutron Activation Analysis In Medicine

D. E. Raeside

University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma

What is neutron activation analysis? How does it relate to nuclear medicine? Many nuclear medicine procedures expose the patient to the risks of ionizing radiation interacting within the human body. A method which circumvents these risks is available, however, for special circumstances—it is the method of neutron activation analysis. The method is most advantageous in situations where it is imperative that radiation dose to the patient be avoided, such as in the case of children or pregnant women.

The diagnostic procedures of nuclear medicine depend primarily on the fact that the biologic systems of the human body are unable to distinguish between the radioactive form of a substance and the nonradioactive form of the same substance. This makes it possible to determine the manner in which diseases alter body functions by a tracer technique, that is, the observation of the spatial and temporal progression of a distribution of a radioactive substance placed in the body. The ultimate aim being, of course, to correlate the observed body function with a specific disease.

In ordinary (non-nuclear) medicine the traditional approach is to obtain a sample from the biologic system of the body under study and analyze its composition by the standard tools of chemical analysis. This approach, however, is limited to cases where the sample obtained is not extremely small or where the element of interest in the sample is available in more than a trace amount. The situation where the sample is extremely small or where the element of interest is present in a trace amount is well suited, on the other hand, to analysis by the method of neutron activation analysis.

In the method of neutron activation analysis a sample from the biologic system of the body under study is irradiated with neutrons and various elements of the sample become radioactive (to differing degrees). An examination of the radiations associated with the radioactive sample allows an inference to be made concerning the amounts of the various elements in the sample. For certain elements, the method of neutron activation analysis is the most sensitive method of quantitative analysis known.

Why learn about neutron activation analysis? Since nuclear medicine laboratories have the necessary counting equipment and expertise for neutron activation studies, it is only reasonable to expect workers in nuclear medicine to be familiar with this powerful technique. It is hoped that this review article will provide the reader with sufficient background to understand and intelligently evaluate the neutron activation analysis papers which regularly appear in the *Journal of Nuclear Medicine*. To put this newly acquired knowledge to use, it is recommended that the reader study the following recent investigations:

1. The measurement of total-body calcium, sodium, chlorine, and nitrogen, by Cohn and Dombrowski (*1*).
2. The determination of calcium in biological samples by Weber and Andrews (*2*).
3. The human tissue trace element study of Budinger, et al (*3*) (in this work, data are presented on 40 trace elements in human tissues, with 2 of these 40, hafnium and tantalum, not previously known to exist in human tissues).

Principles of Neutron Activation

Scope of discussion. Neutron physics is a specialized and highly sophisticated branch of physics. This discussion will touch only a few of its

For reprints contact: D. E. Raeside, Dept. of Radiological Sciences, University of Oklahoma Health Sciences Center, Box 26901, Oklahoma City, Okla. 73190.

surface features, namely, the common neutron sources, the fundamental equation of neutron activation, and the common interactions between neutrons and atomic nuclei. We begin with an outline of the basic ideas related to nuclear reactions.

Nuclear reaction equations. Let ${}_{Z}X^{A}$ represent a nucleus X with atomic number Z and mass number A. With this notation we can write "reaction formulas" such as,

$$ {}_4Be^9 + {}_2He^4 \rightarrow {}_6C^{12} + {}_0n^1 + 5.708 \text{ MeV} $$

and

$$ {}_4Be^9 + \gamma \rightarrow {}_4Be^8 + {}_0n^1 - 1.666 \text{ MeV} $$
$$ \hookrightarrow {}_2He^4 + 0.094 \text{ MeV} $$

In the first of these reactions, ${}_4Be^9$ (α,n) ${}_6C^{12}$, an alpha-particle (${}_2He^4$) combines with a ${}_4Be^9$ nucleus to form a ${}_6C^{12}$ nucleus, ejecting a neutron in the process. The second reaction, ${}_4Be^9$ (γ,n) ${}_4Be^8$, represents gamma-ray bombarding a ${}_4Be^9$ nucleus with sufficient energy (in excess of 1.666 MeV) to produce a ${}_4Be^8$ nucleus and a free neutron (the half-life of ${}_4Be^8$ is extremely short, so ${}_4Be^8$ decays into two alpha-particles which share 0.094 MeV for their kinetic energies). Note that in each of the above two reaction formulas the units are understood to be energy units for each entry. This means that all atomic masses should be expressed in MeV (1 atomic mass unit = 9.31478 MeV). For the ${}_4Be^9$ (α,n) ${}_6C^{12}$ reaction, the principle of conservation of mass energy requires that an amount of energy equal to 5.708 MeV be liberated in the reaction because

$$ \begin{aligned} &M(Be^9) + M(He^4) - M(C^{12}) - M(n^1) \\ &\quad = (9.31478)\,(9.01219 + 4.002603 - \\ &\qquad 12.000000 - 1.008665) \text{ MeV} \\ &\quad = +5.708 \text{ MeV} \end{aligned} $$

where $M(\cdot)$ denotes a mass in atomic mass units. Similarly, for the ${}_4Be^9(\gamma,n){}_4Be^8$ reaction, an amount of energy equal to 1.666 MeV must be supplied because

$$ \begin{aligned} &M(Be^9) + M(\gamma) - M(Be^8) - M(n^1) \\ &\quad = (9.31478)\,(9.01219 + 0.0 - \\ &\qquad 8.005308 - 1.008665) \text{ MeV} \\ &\quad = -1.666 \text{ MeV} \end{aligned} $$

It is important to note the algebraic sign that arises from the computation of the difference between the mass of the initial system and the mass of the final system (the so-called Q-value of the reaction). If the Q-value is positive the reaction supplies kinetic energy to the final products, whereas if the Q-value is negative the reaction will not take place unless the incident particle (or radiation) has an energy in excess of this number (for this reason 1.666 MeV is said to be the "threshold energy" of the ${}_4Be^9(\gamma,n){}_4Be^8$ reaction). Those reactions in which the Q-value is positive will make energy available to the ejected neutron but the exact value of this energy will depend on several factors: the angle at which the neutron is emitted (measured relative to the line along which the bombarding particle is incident), the energy of the bombarding particle, and whether the product nucleus is left in an excited state or not.

Since a great many reactions can be written which satisfy the conservation of mass-energy principle, how do we know which reactions will actually take place? Obviously, the answer to this question requires an experimental determination of the probabilities of occurrence of the various reactions. This information is often available and it is expressed as the reaction "cross section," a quantity proportional to the reaction probability. The units of cross section are the units of area (cm^2). Since cross sections for nuclear reactions are usually extremely small, a special unit called the "barn" has been adopted: 1 barn = 10^{-24} cm^2. Because of competition between the various possible reaction processes, reaction probabilities usually change as the energy of the bombarding radiation increases or decreases.

Neutron sources. The simplest neutron sources are those using radioactive sources. Such neutron sources have the advantages of being small (in fact, they are usually portable) and relatively inexpensive. They have one severe disadvantage, however; their usable neutron flux is ordinarily about a billion times smaller than common nuclear reactors. One of the more popular of these neutron sources is the ^{210}Po—Be source (it was used in many historically important experiments such as the discovery of neutrons). One disadvantage of the ^{210}Po—Be configuration is the short half-life of ^{210}Po (138.4 days). A long-lived neutron source can be obtained by alloying plutonium (^{239}Pu) with beryllium. The half-life of ^{239}Pu is 2.44×10^4 years. Another radioactive neutron source that has recently become available is ^{252}Cf ($T_{1/2} = 2.65$ years). This radioactive nuclide is manufactured from ^{239}Pu by a sequence of neutron captures in a so-called high-flux isotope reactor. As 1 gm of ^{252}Cf undergoes fission, about 10^{12} neutrons/sec are emitted. Of the commonly available radioactive neutron sources, ^{252}Cf is the best neutron producer.

Accelerators are able to impart sufficient energy to charged particles to enable them to exceed the threshold energy for the release of neutrons in certain targets; hence, they are important sources of neutrons. In recent years, cyclotrons, Van de Graaf accelerators, and Cockcroft-Walton accelerators have become available for use in medicine. The usable neutron flux that can be obtained from small accelerators is usually

in the range $10^6 - 10^{11}$ n/s·cm². Although this range is significantly greater than that which can be obtained from radioactive neutron sources, it is still less than the usable neutron flux of $10^{12} - 10^{14}$ n/s·cm² obtainable with common reactors.

Neutron interactions. The most important neutron interactions for neutron activation are the interactions occurring between nuclei and thermal neutrons (neutrons having energies on the order of 10^{-2} eV). There are four of these processes to be considered (not all of equal importance for our purposes); three of them are summarized by the following reaction equations:

$$_zX^A + {}_0n^1 \rightarrow {}_zX^{A+1} + \gamma + Q$$
$$_zX^A + {}_0n^1 \rightarrow {}_{z-1}X^A + {}_1H^1 + Q$$
$$_zX^A + {}_0n^1 \rightarrow {}_{z-2}X^{A-3} + {}_2He^4 + Q$$

where Q denotes the reaction energy. The fourth process is fission, that is, the breakup of a very heavy nucleus into intermediate-sized nuclear fragments. By far the most important interaction between nuclei and thermal neutrons for the method of neutron activation analysis is the (n, γ) reaction in which a target nucleus captures a neutron and immediately emits gamma rays, leaving a product nucleus which is often unstable. This unstable product nucleus then decays with the emission of characteristic radiations at a rate determined by its half-life. The (n,p) and the (n,α) reactions usually are observed only with fast neutrons (neutrons having energies between 10^4 eV and 10^7 eV), but for very light nuclei the (n,p) and (n,α) reactions have substantial probabilities for thermal neutrons.

The fundamental equation of neutron activation analysis. Consider bombarding some species of nuclei with neutrons to produce a new radioactive species of nuclei. Let N denote the total number of these nuclei in a given sample, σ denote the interaction cross-section for the particular neutron energy being utilized in the irradiation, and F denote the neutron flux (F is the number of neutrons impinging upon a unit area of the sample in 1 sec). Then the rate of production of new nuclei, dn/dt, as a result of the interaction between the bombarding neutrons and the target nuclei is given by $dn/dt = N\sigma F$, where n is the number of new nuclei produced in the time t. For the case that the nuclei produced are radioactive, a competing decay process must be taken into account to properly determine the rate of production of new nuclei; thus,

$$dn/dt = N\sigma F - \lambda n$$

where $\gamma = \ln(2)/T_{1/2} = 0.693/T_{1/2}$ ($T_{1/2}$ being the characteristic half-life of the new nuclei). The solution of the above differential equation is

$$n = (n\sigma F/\lambda)(1 - e^{-\lambda t})$$

The quantity of direct interest, however is not n but the activity, $A = \lambda n$:

$$A = N\sigma F (1 - e^{-\lambda t})$$

We shall call this equation the fundamental equation of neutron activation analysis.

It should be pointed out that an important assumption is implicit in the fundamental equation. The assumption is that a negligible fraction of the target is activated, so that the number of nuclei available for activation during irradiation is effectively constant. This assumption is almost always valid.

The factor $1 - e^{-\lambda t}$ appearing in the fundamental equation varies from 0 to 1, as t varies from 0 to ∞. For this reason $N\sigma F$ is called the saturation activity. Note that if irradiation lasts for one half-life, the resulting activity is $N\sigma F/2$. It is often possible to perform rapid calculations of this kind because the factor $1 - e^{-\lambda t}$ is particularly simple when t is an integral multiple of $T_{1/2}$. For example, note that little is gained by irradiating a sample for longer than three half-lives. In general, the shortest irradiation time possible is recommended consistent with obtaining sufficient activity for good counting statistics to prohibit the buildup of long-lived contaminants.

If, following irradiation of the sample, some time passes before analysis is performed (say, to allow short-lived contaminants to decay), then an exponential decay factor must be applied to the fundamental equation: $A \rightarrow N\sigma F(1 - e^{-\lambda t})e^{-\tau t}$, where τ is the time that has elapsed between the end of irradiation and the analysis of the sample.

In neutron activation the neutron flux is often not well known; therefore, it is desirable to develop a technique which circumvents requiring knowledge of the neutron flux. This can be done if a precisely known amount of the element of interest is irradiated simultaneously with the sample. Let us derive the appropriate formula (unprimed quantities will refer to the sample and primed quantities to the precisely known standard). The activity of the element of interest in the sample at the completion of irradiation, A, is given by

$$A = N\sigma F (1 - e^{-\lambda t})$$

and the activity of the standard at the completion of irradiation, A′, is given by

$$A' = N'\sigma F(1 - e^{-\lambda t})$$

Because the sample and the standard are irradiated simultaneously in close proximity to one another, there is no need to place primes on σ, F, or t. By forming the ratio A/A′ we obtain, through the cancellation of σ, F and $1 - e^{-\lambda t}$, a simple expression relating A, A′, N, and N′:

$$A/A' = N/N'$$

Since $N = mA_o/M$ and $N' = m'A_o/M$, where m and m′ denote the masses of the element of interest in the sample and the standard, respectively, and A_o is Avogadro's number and M is the atomic mass, we can write:

$$A/A' = m/m'$$

If the sample and standard are counted one immediately following the other, for identical short time intervals, with the same counting equipment, and in the same counting geometry,

$$n = e\,A$$
$$n' = e\,A'$$

where n and n′ denote the number of counts recorded for the sample element of interest and the standard, respectively, and e denotes a common factor accounting for detector efficiency, counting geometry, and absorption of the radiation in the intervening media between the source and the detector. Thus,

$$m = m'\,(n/n')$$

This expression, of course, will be valid only if the half-life pertinent to this discussion is sufficiently large to allow the time interval between counting of the sample and counting of the standard to be ignored. If a half-life correction is required, then this formula for m must be modified by the appropriate exponential factor.

It is good practice to select the amount of the standard so that A and A′ are approximately equal. This will insure minimum gain shift when the sample and standard are brought successively to the counting apparatus and also make it possible to ignore "deadtime" effects.

Sample counting. The radiation usually counted in an application of the formula $m = m'(n/n')$ is beta or gamma radiation. Consider the case where gamma radiation is counted. If there are sound reasons for believing that no interfering activity has been produced in the activation of the sample (or, if the interfering gamma radiation that is produced has a spectrum of energies lying below the energy of a gamma ray associated with the element of interest), then the counting system can be simple: NaI(Tl)-photomultiplier assembly, preamplifier, amplifier, discriminator (to reject low-energy pulses associated with the type of interference just mentioned), and scaler. If, on the other hand, interfering radiations are present which give rise to gamma rays of higher energy than the gamma rays in the element of interest, then the counting system may have to be NaI(Tl)-photomultiplier assembly [or lithium-drifted germanium, Ge(Li), detector to separate closely spaced photopeaks], preamplifier, amplifier, and multichannel analyzer.

Neutron Activation in Medicine

Representative applications of neutron activation analysis in medicine. Neutron activation analysis is well suited for determination of the quantity of sodium in biologic samples. There is but a single stable isotope of the element sodium (^{23}Na) and only one radioactive isotope (^{24}Na) is produced in the capture of thermal neutrons by naturally occurring sodium (the probability of "double capture", that is, the production of ^{25}Na is negligible). The half-life of ^{24}Na is 15 hr and more than 99% of the decay involves two gamma rays, their energies being 2.75 MeV and 1.37 MeV, in cascade. Detection of this pair of gamma rays is easily accomplished with an ordinary scintillation crystal. In applying the method of neutron activation to a determination of sodium in blood serum, Spencer, Mitchell, and King (*4*) have shown that the method is both rapid and accurate.

Another use of neutron activation analysis in medicine is found in the study conducted by Cardarelli, Podolsky, and Burrows (*5*). These investigators determined the amount of iodine in stable iodinated insulin. Since there is only one stable isotope of iodine (^{127}I), just one radioactive isotope of iodine is produced in the irradiation of natural iodine by thermal neutrons (the probability of "double capture" is negligible). The isotope produced is ^{128}I with a half-life of about 25 min. Cardarelli, Podolsky, and Burrows counted their samples using both a high-resolution Ge(Li) spectrometer (no chemical extraction of the iodine being necessary) and a high-efficiency NaI(Tl) well spectrometer (postirradiation chemistry was performed to remove the sodium and chlorine interferences masking the presence of iodine).

Trace element analysis. It is well known that excess or deficiency of trace elements in humans can be correlated with disease and it is reasonable to expect that the method of neutron activation analysis can provide a sensitive method of measuring trace elements in humans. The early determination of trace amounts of manganese in human blood by Bowen (*6*) was an attempt to formulate a simple, routine technique which could compete effectively with the results that only skilled workers could obtain in analyzing trace amounts of manganese by conventional methods of analysis. Bowen noted the difficulty in finding preirradiation sample handling equipment that did not transfer manganese to the sample. Even after washing the polyethylene sample tubes in nitric and hydrochloric acids, detectable amounts of manganese still remained on them. Since stainless steel contains manganese, no stainless steel was allowed to contact the sample in Bowen's work and the sub-

jects were pricked with sharp silica fragments to obtain the blood samples. After irradiating the samples in a reactor, it was necessary to perform postirradiation chemical separation to remove sodium, potassium, chlorine, bromine, iodine, and phosphorus. Following these chemistry procedures, the samples were counted. To verify that no interfering activities were present, the half-life of the sample activity was measured and found to agree with the accepted half-life of ^{56}Mn. Since blood contains a significant amount of iron, it was necessary to consider the capture of fast neutrons by ^{56}Fe [through the reaction ^{56}Fe(n,p)^{56}Mn]. Because the fast neutron flux of the reactor used in Bowen's study was poorly known, it was not possible to calculate accurately the amount of ^{56}Mn produced through the capture of fast neutrons by ^{56}Fe; Bowen estimated that about 20% of the measured activity was due to this mode of production. In another paper on the determination of manganese in man (human urine) using the method of neutron activation analysis, Moav (*7*) points out that conventional methods of analysis are not well suited for a determination of trace amounts of manganese such as are found in urine (manganese excretion is primarily fecal), and, in fact, the manganese concentration in some samples from normal subjects is below the detection limit of conventional methods. Moav irradiated urine samples for 5 min in a reactor neutron flux of 7.13×10^{12} n/s·cm^2 (the ratio of thermal neutrons to fast neutrons was 3–1). Postirradiation chemical separation of the manganese from sodium, potassium, and chlorine was required (even after completion of the separation a small amount of sodium remained); the separated samples were analyzed with a NaI(Tl) spectrometer which incorporated a multichannel analyzer. The intensity of the 0.847-MeV photopeak of ^{56}Mn was taken as a measure of the ^{56}Mn activity, and comparison with a standard, made it possible to estimate the amount of manganese present in the sample. For the given experimental conditions, the minimum detectable amount of manganese was found to be 5×10^{-9} gm. Moav determined that the possible fast neutron reactions that might lead to the production of ^{56}Mn [namely the ^{59}Co(n,α)^{56}Mn and ^{56}Fe(n,p) ^{56}Mn reactions] contributed negligibly to the observed spectrum and verified that no portion of the 0.847-MeV photopeak intensity was associated with the decay of some unknown interference by showing that the half-life of the 0.847-MeV photopeak was in agreement with the accepted ^{56}Mn half-life. The major point of Moav's study was the demonstration that after administration of EDTA (ethylenediaminetetraacetate) the manganese content of human urine was significantly elevated in comparison with the manganese content of the urine of untreated subjects.

References

1. Cohn SH, Dombrowski CS: Measurement of total-body calcium, sodium, chlorine, nitrogen, and phosphorus in man by in vivo neutron activation analysis. *J Nucl Med* 12: 499–505, 1971

2. Weber, DA, Andrews HL: Neutron activation analysis of calcium in biological samples. *J Nucl Med* 13: 293–299, 1972

3. Budinger TF, Farwell JR, Smith AR, et al: Human tissue trace-element detection by neutron activation without chemical separation. *Int J Appl Radiat Isot*, 23: 49–56, 1972

4. Spencer RP, Mitchell TG, King ER: Neutron activation of sodium in blood serum. *J Lab Clin Med* 50: 646–652, 1957

5. Cardarelli JA, Podolsky S, Burrows BA: Analysis of stable iodinated insulin by neutron activation techniques. *Int J Appl Radiat Isot* 21: 513–517, 1970

6. Bowen, HJM: The determination of manganese in biological material by activation analysis, with a note on the gamma spectrum of blood. *J Nucl Energy* 3: 18–24, 1956

7. Moav B: The determination of manganese in urine by neutron activation analysis. *Int J Appl Radiat Isot* 16: 365–369, 1965