



## Chapter 17

# Multi-element Analysis of the Living Human Body by Neutron Activation Analysis

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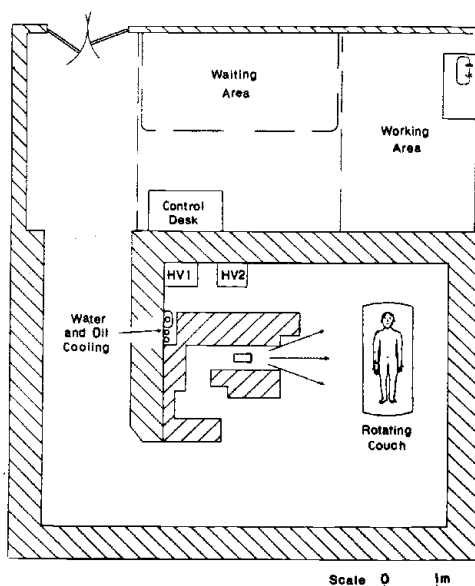
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### INTRODUCTION

In clinical investigation we often need to know the total amount of an element in the body of a patient. For example, in studying malnutrition, we may wish to estimate total body nitrogen, because this is a direct measure of the body's protein content; it would be extremely useful to be able to measure changes in body calcium when investigating and treating bone disease; an estimate of total body potassium is invaluable when investigating electrolyte disturbances.

Another chapter in this book (see p.111)<sup>1</sup> describes how total-body potassium can be measured by virtue of the natural radioactivity of the element, and how other elements can be measured by adapting the well-established analytical technique of neutron activation analysis for use *in vivo*. This technique allows us to measure the body contents of nitrogen, sodium, phosphorus, chlorine, calcium, hydrogen and oxygen<sup>2</sup>, and is being developed independently at a number of centres. The principle of *in vivo* activation is the same as *in vitro*. The sample, in this case the patient, is irradiated and the induced radioactivities measured by a detector, a whole-body counter. However, because the sample is a living subject, severe constraints of 'sample handling' have to be imposed giving a reduction, compared to *in vitro* analysis, not only in the number of elements that can be measured but also in accuracy and precision. The chief limitation is caused by the large bulk of the patient, of the order of 60 kg, compared to the small samples used in *in vitro*. Thermal neutrons do not penetrate to the deeper tissues of the body and we therefore irradiate the subject with fast neutrons, which are moderated within the body itself to thermal energies. We therefore have fast and thermal neutrons throughout the body producing radioactive isotopes by both fast and slow neutron reactions. Because neutrons are moderated and captured as they traverse tissue, there is a decrease in both the fast and thermal fluences with depth<sup>3</sup>. Even with bi-lateral irradiation there is a decrease in both with the fast fluence showing the greatest change<sup>4</sup>; its value at the centre of the body is 40% of that at the surface, in the Leeds irradiation facility. Consequently the distributions of the various induced activities are not uniform in the body and the method is dependent upon the size of the subject; this causes the major problem in calibrating the *in vivo* technique.

In *in vitro* analysis, standards containing known amounts of the element to be estimated are made to match the size and composition of the samples. Both samples and standards are then irradiated and counted in the same geometries so correcting automatically for the variations in neutron fluence and counting sensitivity throughout the volume of the sample. It is impossible in *in vivo* analysis to make standards to match each person being measured because subjects come in large ranges of size, shape and composition. Instead we calibrate the method by taking into account body size.



1. The Leeds neutron irradiation facility.

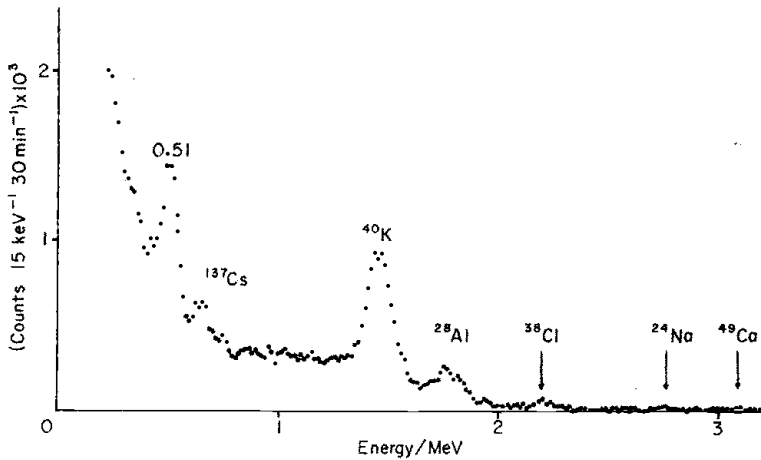
Another problem is that of radiation dose. In *in vitro* work samples are left in a neutron field for the time required to give sufficient statistical accuracy; living tissue placed in the same position would perhaps receive thousands of rem. However, in *in vivo* activation we are limited to the radiation dose we can deliver to the subject; normally we do not give more than 1 rem by neutron irradiation. The need to give as little dose as possible leads to the use of whole body monitors with large radiation detectors and to the inability to resolve and measure most elements in minor concentration in the body.

Several centres have installed equipment to carry out *in vivo* neutron activation analysis, and each has found its own solutions to the technical problems<sup>2</sup>. At Leeds we have concentrated initially on measuring nitrogen and sodium. We estimate nitrogen by measuring the 0.51 MeV annihilation radiation from the isotope nitrogen-13 produced by the fast neutron reaction  $^{14}\text{N}(n, 2n)^{13}\text{N}$ . Sodium is estimated using the thermal reactions  $^{23}\text{Na}(n, \gamma)^{24}\text{Na}$ ; sodium-24 emits gamma rays at two energies, 1.37 MeV and 2.75 MeV. In this paper we describe our installation and our approach to the problem of calibration.

#### EQUIPMENT AND METHODS

The neutron irradiation facility (Fig. 1) consists of a purposely-built shielded room housing a Philips sealed-tube neutron generator, which produces monoenergetic 14 MeV neutrons, and a couch mounted on wheels. The supine patient is irradiated laterally, with a horizontal beam of neutrons, then the couch is turned around and the other side of the patient irradiated. The period of irradiation depends upon the element being determined; for nitrogen the period is 40 s for each irradiation, for sodium 200 s. Neutron dose is monitored by counting the output pulses from an Anderson and Braun type neutron monitor<sup>5</sup> situated under the couch. The radiation dose when only neutron is being measured is approximately 50 mrem.

After irradiation the patient is transferred as quickly as possible to an eight detector whole-body radiation counter<sup>6</sup> and this usually takes about five minutes. The gamma-ray spectrum of the patient's induced activity is then accumulated for 30 min in the memory of a multi-channel analyser (Nuclear Data Inc. 50/50 system with an attached PDP8 computer). The analyser is adjusted to an energy calibration of 15 keV/channel and the spectrum of each detector is routed into a separate group of 256 analyser channels. At the end of the counting period the eight spectra are corrected

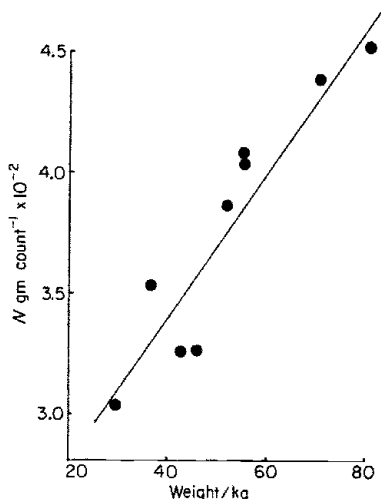


2. Patient spectrum with 50 mrem dose.

by computation to an exact energy calibration of 15.0 keV/channel and then summed together to form one spectrum (Fig. 2). This is then analysed to find the amounts of each of the induced radionuclides which, when their spectra are added together, give the observed complex spectrum. The mathematical analysis is carried out by a weighted least-squares procedure which uses as standards the separate spectra of the radiation products of each of the elements N, Na, Cl, P and Ca, together with the spectra of  $^{40}\text{K}$  and  $^{137}\text{Cs}$ . The spectra from each of the elements were obtained in initial experiments by performing the activation procedure on an anthropomorphic phantom containing a known amount of each element in turn, in solution. The amounts of each of the component activities as calculated by the analysis, are corrected for radioactive decay during the periods of irradiation, transfer and counting, and normalised to a standard neutron output.

Interfering nuclear reactions are also taken into account. For instance, the 0.51 MeV annihilation radiation spectrum is composed of radiation from radionuclides which produce positrons. Approximately 85% of the quanta come from  $^{13}\text{N}$ , the reaction product of the nitrogen which we are estimating. About 10-15% come from the same isotope generated in the reaction of oxygen with protons set in motion by neutrons colliding with hydrogen during moderation. To calculate this contribution, body water is estimated from the weight and height of each patient, and the amount of oxygen in this water multiplied by a factor of 1.15 to allow for other oxygen in the body. The counts from oxygen contributing to the annihilation spectrum are then calculated by proportion from those obtained from a phantom filled with a known amount of water. Small additional contributions from phosphorus-30 and chlorine-34 are taken into account by noting the magnitude of the other activities these elements produce; phosphorus also forms aluminium-28 which gives a very prominent peak at 1.78 MeV and chlorine gives two peaks at 1.60 MeV and 2.17 MeV.

The method is calibrated for nitrogen by determining the counts in the 0.51 MeV spectrum when the activation and counting procedure is carried out on a phantom filled with a known urea solution. The phantom consists of hollow plastic cylinders of circular or elliptical cross-section, representing different regions of the body. The effective size of an assembled phantom can be varied to a limited extent; for example, a small person is simulated by using only the thoracic section as the main trunk, instead of using both a thoracic and a pelvic section. The relationship of calibration factor (grams of nitrogen per nett count in the 0.51 MeV spectrum) to the effective size of the urea-filled phantom was studied, using various combinations of weight, height and lateral body width as measures of body size. The simplest measure was chosen, i.e. weight, and the regression of calibration factor on weight was calculated. This regression is used to obtain the calibration factor of each patient, Fig. 3.



### 3. Calibration factor against body weight for the determination of total-body nitrogen.

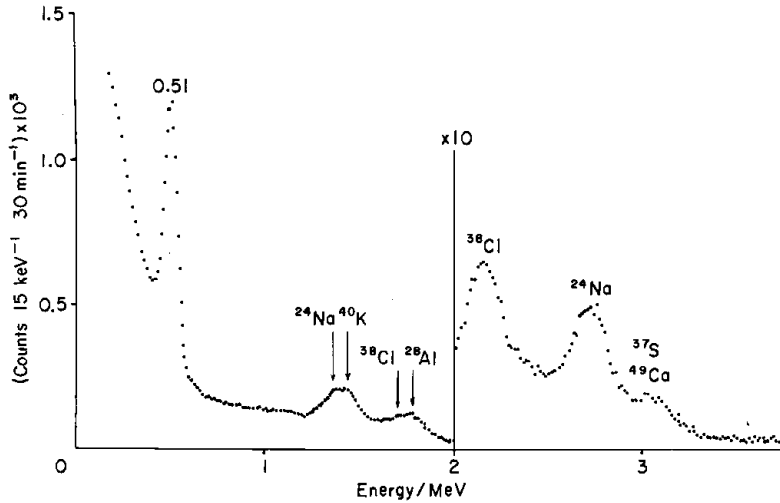
This method of calibrating, using a phantom filled with urea solution as a standard, presented a possible source of inaccuracy. The nitrogen is free to move around in each phantom part and the initial non-uniform distribution of the induced nitrogen-13 changes to a uniform distribution within each part by the commencement of counting. On the other hand, in the patient, the initial non-uniform distribution of the nitrogen-13 remains the same throughout the procedure because the nitrogen is unable to move from its tissue site. The non-uniform activation arises because the efficiency of activation of nitrogen in the centre of the trunk is approximately 40% of that at the surface due to the moderation of fast neutrons as they traverse the depth of the body. The efficiencies of detecting the nitrogen-13 induced in a patient, and in the similarly shaped standard phantom with which the patient's activity is compared to obtain the result, could therefore be expected to be different, giving an inaccuracy in the estimation of the subject's total body nitrogen.

We examined this point by irradiating and counting the section of the phantom having the largest cross-section — the thoracic section — in which this effect would be the greatest. In one experiment the urea solution was prevented from mixing by containing it in 64 small containers placed in the trunk and in a second experiment the solution was allowed to mix freely. There was little difference between the detected activities of the fixed and free nitrogen, the ratio between them being  $0.94 \pm 0.04$ . Consequently this effect was assumed to have negligible effect on the calibration.

A major part of the natural radioactivity of the human body is that from potassium-40. For the patient undergoing total-body nitrogen measurements, the detected radiation from potassium remains a prominent component amongst the activities induced by the neutron irradiation because of the low dose of 50 mrem. Consequently both potassium and nitrogen are determined from the complex patient spectrum following the irradiation. The patient is therefore not required to spend a prior period in the whole-body counter. We examined this point by measuring the total body potassium in five subjects before irradiation and again from the complex spectrum following irradiation. The two methods gave nearly equal results. The ratios of the two — TBK without activation:TBK following activation — are 0.995, 0.975, 1.032, 0.972 and 0.972.

We have used this facility to study nitrogen metabolism in critically ill surgical patients during the last twelve months (September 1976 - September 1977). Over 200 separate measurements have been performed and the Philips neutron generator has been out of operation for only five days.

The method is also being applied to the measurement of total-body sodium. Sodium-24 is produced by the thermal neutron reaction:  $^{23}\text{Na} (n, \gamma) ^{24}\text{Na}$ . It has a half-life of 15 h, which is long compared to those of the other induced activities, and emits two



4. Spectrum from a phantom containing a mixture of elements in physiological amounts, 0.5 rem.

gamma-rays at 1.37 MeV and 2.75 MeV (Fig. 4). The method has been calibrated in a similar manner to the nitrogen measurement, by using in the least-squares analysis a standard spectrum of sodium obtained by irradiating an anthropomorphic phantom having a known sodium content. The dependence on the body build of the subject is smaller than that of the nitrogen measurement. This is because the decrease in the thermal neutron fluence in the centre of the body is less than that of the fast neutron fluence, giving a more uniform activation of sodium across the width of the body. Furthermore, the gamma-rays from sodium are attenuated by tissue to a smaller degree than the annihilation radiation from nitrogen because of their higher energies.

As in the measurement of nitrogen, we have tried various combinations of the parameters of body size and we find that the calibrations based on weight, and on weight divided by height, gave the least standard error of estimate (Figs 5,6). The value of sodium obtained by the procedure, by reference to a standard sized phantom, is multiplied by the calibration factor, CF, to give total-body sodium corrected for body size.

$$\underline{CF} = 0.00074 \times \underline{W} + 0.939$$

$$\underline{CF} = 0.208 \times \underline{W/T} + 0.904$$

The change in the calibration factor over the range of phantom sizes used, although small, was found to be significant, and we use the regression on weight for patients.

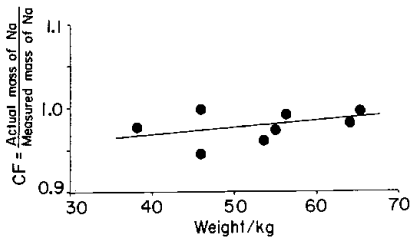


Fig. 5

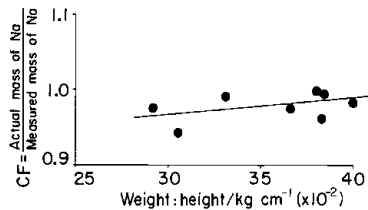
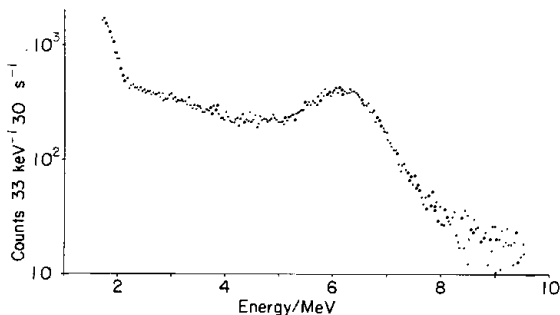


Fig. 6

5. Calibration factor against weight for the determination of total-body sodium.
6. Calibration factor against weight/height for the determination of total-body sodium.



Spectrum of a water-filled phantom immediately following neutron irradiation -- 0.75 rem.

We tried an additional test to demonstrate that the calibration has only a small dependence on body size. We performed the procedure on a phantom, firstly using the normal lateral irradiation and secondly by antero-posterior irradiation. There was no difference in the two sodium results within the error of measurement, 1%, in spite of the large change in the irradiation geometry.

A possible source of inaccuracy in measuring sodium is the contribution from magnesium. This produces sodium-24 by the fast neutron reaction  $^{24}\text{Mg} (n,p) ^{24}\text{Na}$ . We measured the magnitude of this interference by irradiating and counting the anthropomorphic phantom filled with 130 g of magnesium as magnesium acetate solution. The magnesium contribution to total-body sodium was calculated to be 0.06% which we accept as negligible.

It is necessary to deliver a larger dose, 0.5 rem, to patients for the measurement of sodium than that for nitrogen in order to obtain satisfactory precision in the counting statistics. There are two reasons for this. Firstly there is less sodium in the body than nitrogen, and secondly the disintegration constant for sodium-24 is approximately 1/100th of that of nitrogen-13.

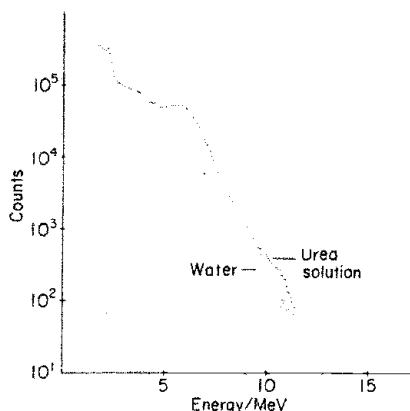
We intend to include total-body sodium measurement in our activation procedure in the immediate future in order to assess the volume of extra-cellular fluid in which the sodium is contained.

In addition to nitrogen and sodium, chlorine, phosphorus and calcium are estimated in the same irradiation, but as yet we have not applied the results to clinical problems.

Oxygen in the body is also activated by fast neutrons by the reaction  $^{16}\text{O} (n,p) ^{16}\text{N}$ ; the principle gamma-ray has a convenient energy of 6.13 MeV, Fig. 7, but the half-life is only 7.14 s. The induced activity has therefore to be measured immediately following the irradiation. This is done by placing radiation detectors adjacent to the patient in the neutron generator facility and switching on the counting system at the end of the irradiation. If only oxygen is to be determined then the procedure can be optimized for this. However we can apply the measurement following any period of irradiation and we plan to do this in Leeds by counting for 30 s following each of the two 40 s irradiation periods in the determination of nitrogen.

The patient's spectrum in this period is dominated by the induced activity from oxygen and we derive the body oxygen from this. The coefficient of variation given by counting statistics alone is 1% for a radiation dose of 0.5 rem. We are currently developing this technique for two reasons, firstly for a direct estimation of the oxygen interference in the measurement of total-body nitrogen and secondly as a measure of total-body water.

The major problem is the activation of the sodium iodide detector, mainly iodine-128, which causes a high counting-rate during the counting period and a corresponding large dead-time of the counting system, 70%. We are overcoming this problem by confining the neutron field by collimation so that only the subject is directly irradiated, and not the detector. In addition we surround the detector, apart from the aperture viewing the patient, by a massive shield of concrete, wax and lead<sup>10</sup>. The dead-time



8. Spectra from a 25L container, containing water and water plus 6.5 kg of nitrogen as urea.

is reduced to 10% by these techniques but the contribution from the oxygen in this shield is significant. We hope to develop the technique by improving the signal-to-background ratio, and to increase the sensitivity by using two detectors instead of the one.

Nitrogen can be measured by neutron activation using a different method from the fast neutron reaction described above. The gamma radiation from the patient is detected and analysed during the irradiation using the same detector as for the oxygen studies. Nitrogen undergoes a thermal neutron capture reaction in which one of its gamma rays emitted at the moment of capture has an energy which is unique and easily distinguishable amongst those from the other body elements. Its energy is 10.8 MeV, whilst the prompt gamma radiation from the other body elements is approximately 8 MeV or lower<sup>11</sup>. The response of our detector is composed from three main activities, the activity induced in the detector and its surroundings, the gamma radiation caused by the inelastic scattering of fast neutrons, and the prompt-gamma radiation<sup>12</sup>. The number of counts in the 10.8 MeV region additional to those from a non-nitrogenous phantom is a measure of the amount of nitrogen in the patient (Fig. 8).

The major problem is to reduce the unwanted contributions generated in the crystal itself by neutrons reaching the detector and causing inelastic scattering gamma-rays. The efficiencies of neutron and gamma ray shielding of both the neutron generator and detector shielding are therefore being improved.

In addition to the elements we have mentioned, we are calibrating the procedure for the determination of the two major elements in bone, calcium and phosphorus and we hope to measure some minor elements in local regions of the body using a solid-state detector.

#### ACKNOWLEDGEMENTS

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#### DISCUSSION

J.L. GOULD: What is the method of measuring the patient's neutron dose?

C.B. OXBY: We used four methods of measuring neutron dose, in fact.

- (a) By measuring neutron output by activation of copper and calculating dose for this using a conversion factor of  $6.9 \times 10^5$  rad for n per cm<sup>2</sup>, a QF of 8 and a 20% contribution for contralateral irradiation.
- (b) By neutron film badges attached to each patient -- supplied and read by NRPB.
- (c) By an Anderson and Braun type neutron monitor (Studsvik of Sweden) placed under the patient.
- (d) By a TE ionization chamber calibrated with caesium sources.

All four methods are consistent; they all lie in the range 45-55 mRem.

J.L. GOULD: Wouldn't anticoincidence methods improve the resolution of the 10 MeV  $N_{16}^+$  prompt  $\gamma$ -measurements?

C.B. OXBY: No, I do not believe so because the 'background' is very similar radiation to that of the 11 MeV prompt  $\gamma$ -radiation of nitrogen. In addition, we will be using two NaI detectors (diameter 6 in, thickness 5 in) and to provide an anticoincidence shield would be very bulky and expensive. These anticoincidence detectors will in turn require physical shielding, the bulk of this being very great.