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BODY COMPOSITION AS MEASURED BY IN VIVO NEUTRON ACTIVATION ANALYSIS

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The development of the in vivo neutron activation technique has made possible, in the last fifteen years, the direct determination of the absolute levels of certain elements in human beings (1). A technique has been developed for the measurement of absolute levels of calcium, phosphorus, sodium and chlorine in human subjects by means of delayed neutron activation analysis (2). With this technique, baseline studies on normal subjects have related body composition to the parameters of age, sex and body habitus (3). Numerous studies have also been conducted on the changes in body composition in various diseases and physiological disorders, and therapeutic regimens have been assessed through their effect on body composition (1).

Recently, by means of the newly developed prompt gamma neutron activation technique, in vivo measurements of total body nitrogen have been made (4). The mass of both muscle and non-muscle lean tissue, as well as the respective protein content (nitrogen) of these tissues, can be quantified and compartmental body composition established. Quantification of lean body mass and protein content are useful in a variety of investigations on the effects of various diseases and nutrition.

A large scale study is currently underway, conducted jointly by Brookhaven National Laboratory and Long Island Jewish-Hillside Medical Center, on the changes in body composition resulting from the cachexia of malignancy. The ultimate objective of the overall project is to assess the changes in body composition associated with hyperalimentation and other modes of nutritional support to cancer patients.

The first phase of this study is now in progress. In this phase, a study is being made of a control group of normal patients to provide baseline data against which data from cancer patients can be evaluated. Total

body nitrogen and potassium are measured in a group of normal men and women, and are analyzed as a function of age. Additionally, changes in skeletal mass (total body calcium) are also recorded, and body water is measured simultaneously with the use of tritiated water.

Methods

Each normal volunteer subject received a medical examination. The subjects selected were active persons in good health; none showed any history or clinical symptoms of metabolic renal or cardiovascular disease. None of the subjects selected were on any medication, either just prior to or at the time of the study. The cancer patients were selected from the cancer program of Long Island Jewish-Hillside Medical Center. These patients have various types of carcinoma, and are in varying stages of the disease.

The prompt gamma neutron activation facility measures total body nitrogen (TBN) with an accuracy and precision of $\pm$ 3% in the anthropomorphic phantom. A detailed description of the prompt gamma neutron activation technique for absolute measurement of whole body nitrogen has been presented (4). Briefly, the procedure is as follows: A rectangular beam of fast neutrons (60 x 30 cm) is used. The bed on which the patient rests is passed over the stationary neutron beam, so that the subject is irradiated in entirety. The gamma detection system is composed of two 6 x 6 in. NaI (Tl) detectors positioned above the subject, (Figure 1). The neutron source, 85 Ci of ^{238}Pu,Be, is collimated and shielded, as shown.

The detector geometry yields a quite uniform composite sensitivity (i.e., an equal number of counts per unit mass of nitrogen per unit dose). The use of an internal standard reduces the requirements for a highly uniform composite sensitivity for absolute measurements. The internal standard employed utilizes the measurement of total body hydrogen (4).

The advantage of this technique, over the conventional method of analysis, is that errors in counting resulting from differences in irradiation and detection conditions, as well as differences in the size and shape of the patients, are considerably reduced. This reduction in error makes sequential nitrogen measurements considerably more reliable, particularly when the weight of the patient has changed significantly, as occurs in cancer patients. In addition, requirements for reproducing the position of the patient or the geometry for counting are less exacting.

The present method of nitrogen measurement is reasonably comfortable, and requires only that the patient be scanned both in the prone and supine positions. With restricted beam size, a heavy water moderator and good collimation, the clinician or nurse may remain near the patient during the irradiation. The total radiation time is less than 20 minutes, and the dose delivered to the body in this procedure is 26mrem.

The neutron activation facility designed for performing the total body analysis of calcium (TBCa), phosphorus, sodium and chlorine has previously been described (2). The induced ^{49}Ca, ^{24}Na, ^{38}Cl and ^{28}Al (from P) are measured with a whole body counter. The accuracy and precision of this technique for calcium, as measured in an anthropomorphic phantom is $\pm 1\%$ (1 SD).

The unique 54 detector Brookhaven whole body counter is used for the absolute measurement of total body potassium (TBK) (5,6). With its on-line computer facility, the counter has a response which is relatively invariant with respect to both the size of the individual and the internal location of the radionuclide.

Other indices of body composition are also measured in this study: total body water (TBW) (via tritiated water) and 24 hour urinary creatinine excretion, which is also related to muscle mass. Nutrient intake data were obtained in order to relate the above parameters of body composition.

Measurement of total body nitrogen, potassium, calcium, sodium, chlorine, and phosphorus in a population of 280 normal black and white male and female subjects from 20 to 90 years of age is now underway. Analyses of preliminary data will be presented in this paper to illustrate the nature of the experimental and analytical approach utilized in the present study.

Analytical Methods

A mathematical model for the prediction of normal values of TBN for an individual will be developed, similar to the model developed for TBK (7). This algorithm will be used to ascertain relative deficits in individual cancer patients. A similar procedure is used for the evaluation of normal levels of TBCa in individuals as a function of their lean body mass (K) and height (3).

A three-compartment model for body composition has been adopted, similar to models developed over 30 years ago (8,9). A mathematical model for estimating muscle and non-muscle mass and their respective protein contents was developed recently by Burkinshaw (10). In that study, the errors of estimation were too large to allow for conclusions to be drawn on body composition of individuals, although the method was quite adequate for the determination of group means. With the high degree of accuracy of the TBN and TBK measurements available for the present study and with the use of total body nitrogen and potassium data, it is possible to determine, in vivo, the mass and the protein content of both the muscle and non-muscle lean tissue compartments. The essentials of the technique (which have been presented) demonstrate the simplicity with which these sophisticated analytic procedures can be applied (10,11).

Briefly, it is possible, if both K and N are found in the muscle and non-muscle lean tissue in different concentrations to determine the parameters of body composition. The calculations are based on the model developed and on the ratios of K and N concentrations in these compartments. The underlying assumptions are that the lipid from adipose tissue contains no K and N, and further, that the ratio of the concentration of [N] / [K] is different in muscle and non-muscle tissue. A further assumption is that these concentration ratios do not change with age or in disease. The mean values for the N/K ratios were taken from the literature and summarized by Burkinshaw (10). The values of these ratios were used in the equations to calculate the content of muscle and non-muscle lean tissue and their protein content (11).

Results

The total body nitrogen (TBN) and total body potassium (TBK) on 14 normal male subjects previously studied (by the underwater weighing technique) at the Null Laboratory at Penn State are presented in Table 1. The correlation coefficient relating TBN and TBK was 0.93, while the corresponding r values for the correlation of TBN to H_2O was 0.93, and that of TBK to H_2O was 0.94.

The lean body mass and body fat of these 14 normal male subjects are also presented in Table 1. It can be seen that values for the lean body mass calculated by three different techniques (a. potassium method; b. potassium and nitrogen method and c. body water method) are in good agreement, as are values for body fat. The mean LBM, as measured by underwater weighing at the Null Laboratory (62.3 $\pm$ 11.4%) is in close agreement with the above values. Further, the ratio was relatively constant in this normal group (13.42 $\pm$ 4.7%). The ratio of K/K_p (measured to predicted TBK) was high: 1.08. The high value is attributed to the fact that the men in this group are very athletic and thus have a higher than normal muscle mass.

Discussion

With the use of the predictor equation and the ratio of $[N]/[K]$ in muscle and non-muscle lean tissue (see refs. 10,11), the mass and protein content of both muscle and non-muscle lean tissue compartments were calculated for several groups of normal subjects and cancer patients (Table 2). The average muscle mass (M_m) of the normal males (20-49 years) was 21.37 kg, while their non-muscle lean tissue mass (M_n) was 38.07 kg. The sum of these two compartments is the lean body mass (LBM); a mean value of 59.44 kg was obtained (Table 2).

The protein content of the muscle compartment (N_m) was 4.01; the protein content of the non-muscle soft tissue (N_n) was 8.52. The mean total protein content in the body was 12.54 kg. The mean ratio of N/K was 13.71 for this group.

Comparable values for a group of normal females of the same age range are also shown in Table 2. The values of the muscle mass and its protein content (M_m and N_m) were 50% lower than those of the males, while the values of the non-muscle mass (M_n) and its protein content (N_n) were 18% lower than those of the age matched male mean. The female LBM and total protein content was 30% lower than that of the males.

When the normal males (20-49 years) were compared with a group of older male cancer patients (average age, 59 years), large differences in the mean value of all the above parameters were noted. In contrast, the differences between female cancer patients (50-70 years) and their female aged matched controls were considerably less than those of the corresponding male groups.

The female cancer population had 30% lower mean muscle mass and muscle protein than their age matched controls. The mean non-muscle tissue of female cancer patients and its protein content were not significantly

different from the age matched controls. The LBM of the cancer group was only 7% lower than the controls, and their mean total protein was 4% lower than the controls.

While these are only preliminary data, they do suggest that age and sex are very important parameters and must be used in the evaluation of the size of the soft tissue compartments and their protein content.

It is apparent that there is a marked difference in nitrogen and muscle mass with age and less of a difference with the non-muscle lean tissue mass and their protein content with age. As was the case for calcium and potassium, the absolute levels of nitrogen measured by neutron activation must be normalized for body size and habitus in order that individuals be intercompared. Clearly, the type of cancer, duration of the disease and modes of therapy used all have to be factored into the study.

At present, a large scale study is being pursued to obtain essential base line data required for the prediction of the normal values of the above parameter for each individual. In addition, different types of cancer patients are being studied by the above technique over a period of time in order to evaluate associated changes in body composition.

Conclusions

New techniques employed in research on body composition in normal and cancer patients are presented in this report. The technique of prompt gamma neutron activation (PGNAA) for the measurement of total body nitrogen along with the measurement of total body potassium is used to measure the mass of muscle and non-muscle lean tissue and their protein content. Additionally, both total body water and bone tissue (calcium) are measured. The measurements of mass and protein content of these compartments provide data not previously available. The higher accuracy of the prompt gamma neutron activation

technique as compared with other techniques (n,2n for example) and the highly developed whole body counter provide data which are sufficiently accurate to be used in the determination of whole body composition of individuals, and thus enable intercomparisons to be made. A considerable bank of data on the normal levels of total body calcium (skeletal mass) and total body potassium already exist, and are being supplemented by this new study.

With the completion of this study of 140 normal white men and women and an equal number of black men and women, it should be possible to derive predictory equations for total body nitrogen, as has already been accomplished for both total body calcium and potassium.

In future studies, these background data on normal changes in the mass of the lean body compartments and their protein concentrations should provide the necessary basis for the determination of abnormalities in body composition of cancer patients. Finally, the effects of hyperalimentation, in conjunction with therapy of cancer patients, should provide valuable information on the relation of diet and nutrition to body composition, and thus on the effectiveness of particular therapeutic nutritional regimes.

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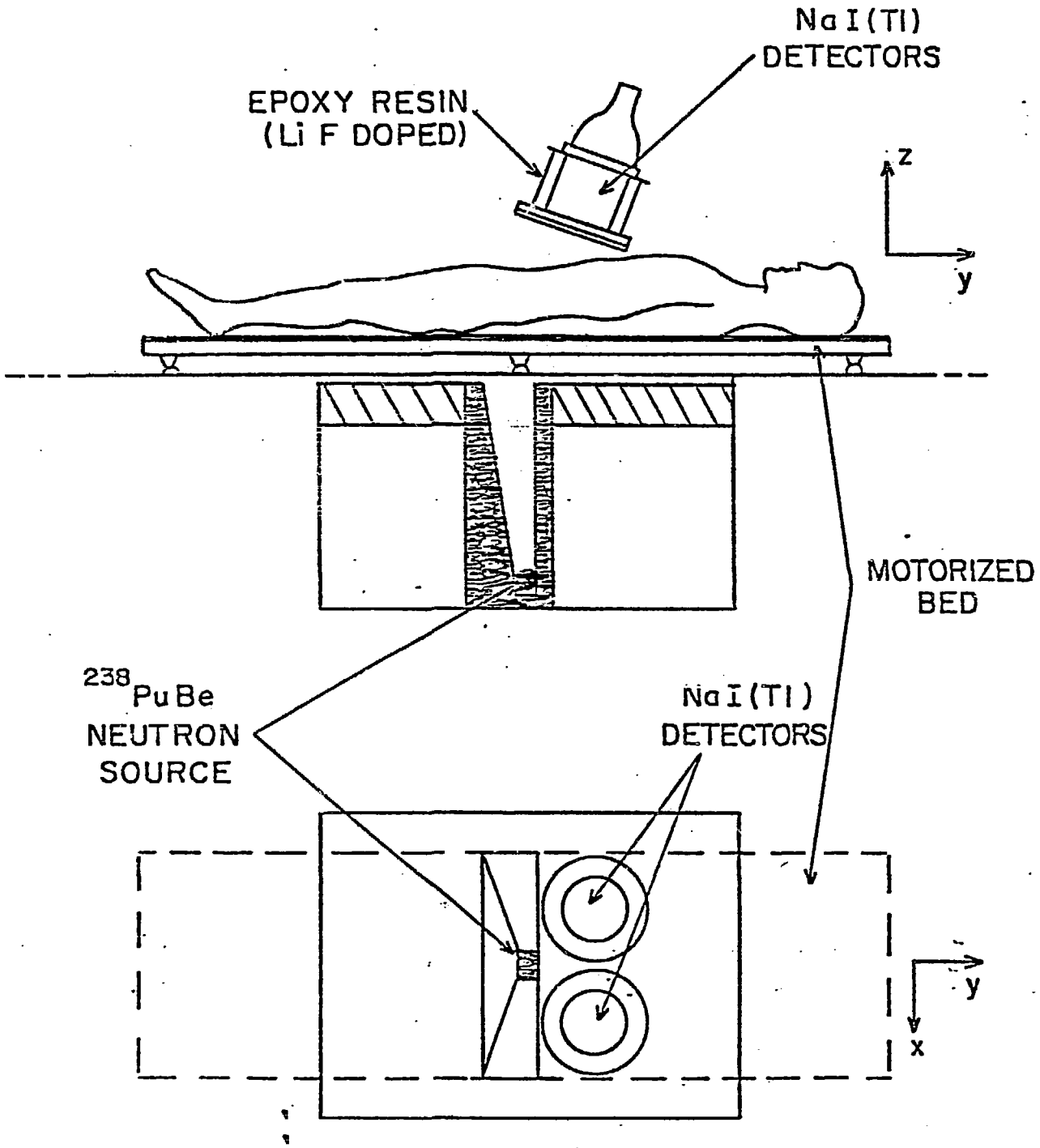

Fig. 1 Schematic diagram of Prompt-Gamma Neutron Activation Facility. The position of the neutron source, the sodium iodide detector and the patient are shown.

TABLE 1.

LEAN BODY MASS AND BODY FAT OF NORMAL MALES (20-30 Y) DETERMINED FROM NITROGEN, POTASSIUM AND BODY WATER

NO. SUBJECTS	AGE (Y)	WT (KG)	N (G)	N/K	K (G)	K/K_P	LEAN BODY MASS (KG) A	LEAN BODY MASS (KG) B	LEAN BODY MASS (KG) C	BODY FAT % WT A	BODY FAT % WT B	BODY FAT % WT C
14	24.6	75.2	2041	13.42	152.5	1.08	60.5	60.6	62.0	19.4	19.2	18.0
	cv(%)	±12.0	±11.2	±4.7	±12.9	±8.2	±12.9	±11.4	±12.8	±34.5	±30.0	±32.5

N = TOTAL BODY NITROGEN, MEASURED

K = TOTAL BODY POTASSIUM, MEASURED

K_P = TOTAL BODY POTASSIUM, PREDICTED

A. LBM - FROM K (64.5 MEQ/G K = 2.52 GK/KG LBM

B. LBM - FROM K + N (SEE EQUATIONS IN TABLE 2)

C. LBM - FROM H_2O $H_2O(L)/0.76$

A. BODY FAT = BW - LBM(A)

B. BODY FAT = BW - LBM(B)

C. BODY FAT = BW - LBM(C)

TABLE 2 - BODY COMPOSITION OF NORMAL SUBJECTS AND CANCER PATIENTS: SOFT TISSUE COMPARTMENTS & PROTEIN CONTENT

	N	M_M	M_N	LBM	N_M	N_N	Total Protein	N/K
	G	KG	KG	KG	KG	KG	KG	-
NORMAL MALES N = 20 (20-49 Y)	2013 ±10.5*	21.37 ±24.0	38.07 ±14.6	59.44 ±11.3	4.01 ±24.0	8.52 ±18.1	12.54 ±10.7	13.71 ±6.1
CANCER MALES N = 14 $\bar{A}GE$ - 59 Y	1562 ±12.4	17.04 ±39	29.21 ±15.4	46.3 ±13.3	3.21 ±39	6.56 ±15	9.77 ±12.4	13.76 ±9.9
NORMAL FEMALES N = 29 (20-49)	1432 ±11.1	10.50 ±39	31.04 ±19	41.52 ±10.6	1.98 ±39	6.98 ±19.3	8.96 ±11.1	15.09 ±9.3
NORMAL FEMALES N = 12 (50-70 Y)	1234 ±9.2	8.90 ±52	26.90 ±23	35.77 ±7.8	1.61 ±56	6.04 ±23	7.65 ±9.7	15.20 ±11.7
CANCER FEMALES N = 9 $\bar{A}GE$ - 59 Y	1155 ±15.9	6.04 ±88	27.08 ±23.9	33.24 ±16.4	1.14 ±88	6.24 ±25	7.37 ±15.8	15.48 ±12.4

N = Nitrogen

M_M = Mass of muscle tissue

M_N = Mass of non-muscle lean tissue

N_M = Protein content of muscle (nitrogen x 6.25)

N_N = Protein content of non-muscle lean tissue

LBM = Lean body mass ($M_M + M_N$)

TOTAL PROTEIN = $N_M + N_N$

N/K = Total body nitrogen/total body potassium

CV = SD/mean(%)