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ABSTRACT

The clinical usefulness of total body neutron activation analysis (TBNAA) was clearly established at an IAEA panel meeting in Vienna in 1972. It is best demonstrated by the studies involving the measurement of total-body calcium. This measurement provides data useful for the diagnosis and management of metabolic bone disorders. It should be emphasized, however, that while most of the applications to date have involved calcium and phosphorus, the measurement of sodium, chlorine and nitrogen also appear to be useful clinically.

Total-body calcium measurements utilizing TBNAA have been used in studies of osteoporosis to establish absolute and relative deficits of calcium in patients with this disease in comparison to a normal contrast population. Changes in total-body calcium (skeletal mass) have also been useful for quantitating the efficacy of various therapies in osteoporosis. Serial measurements over periods of years provide long-term balance data by direct measurement with a higher precision (± 2%) than is possible by the use of any other technique.

In the renal osteodystrophy observed in patients with renal failure, disorders of both calcium and phosphorus, as well as electrolyte disturbances, have been studied. The measure of total-body levels of these elements gives the clinician useful data upon which to design dialysis therapy.

The measurement of bone changes in endocrine dysfunction have been studied, particularly in patients with thyroid and parathyroid disorders. In parathyroidectomy, the measurement of total-body calcium, post-operatively, can indicate the degree of bone resorption. Skeletal metabolism and body composition in acromegaly and Cushing's disease have also been investigated by TBNAA.

Levels of cadmium in liver and kidney have also been measured in-vivo by prompt-gamma neutron activation and associated with hypertension, emphysema and cigarette smoking.

Total-body nitrogen and potassium measurements serve as indices of muscle mass and are useful in studies of the interrelation of cancer, diet and nutrition. An essential requirement in these studies is the in-vivo measurement of changes in body composition, primarily revealed by nitrogen content. Currently the optimal method for measurement of total-body nitrogen is prompt-gamma neutron activation.

These are some of the clinical applications involving in-vivo neutron activation that have been performed to date. Clearly these applications have only indicated the enormous potential of this technique. There can be little question that in-vivo neutron activation is a useful addition to the techniques for medical research which provides new and previously unavailable information.

INTRODUCTION

The development of the in-vivo neutron activation technique has opened an era of research into the elemental composition of human beings. Studies of body composition prior to this development by means of isotope dilution, radiography, fluoroscopy, photon absorptiometry, biopsy and whole-body counting yield data on relative change in level but not on absolute value of the level of the element. There is one exception - total body potassium can be measured directly by means of whole-body counting.

Until recently, remarkably few data had been recorded on the exact amounts of the elements of which the human body is composed. However, with the new technique of in-vivo total body neutron activation, (TBNAA), a number of elements have lately been measured: Ca, P, Na, Cl. With a refinement of TBNAA, total body levels of N can also be determined, Table I. Not all elements of biological interest, however, can be usefully detected by neutron activation. Analysis for Fe, Cu and Zn, for example, is better performed by other techniques.

Neutron activation is an analytical tool based on nuclear reactions rather than chemical reactions. The essential physical parameters involved include isotopic abundance, cross-section, half-lives of the product isotopes, and energy emission of the product.

A. Total-body delayed neutron activation techniques

TBNAA systems, designed for in-vivo studies, generate a moderated beam of fast neutrons to the total body of the subject [1-7]. Capture of the neutrons by atoms of the target elements creates unstable isotopes. The atoms revert to a stable condition by the emission of one or more gamma rays of characteristic energy. This energy level then identifies the element, and the level of activity indicates its abundance. Radiation from the subject is measured soon after irradiation, in a highly shielded whole-body counting facility and standard gamma spectrographic analysis is applied. Besides the reduced dose to the patient, there are numerous advantages derived from the use of α,n neutrons over neutrons produced by cyclotrons or neutron generators[2]. If total-body neutron activation analysis is eventually to become a part of the armamentarium of the medical profession, the most likely direction of development will be in the application of "portable" α,n neutron sources such as ^{238}Pu, Be [1], see Fig. 1.

B. Partial-body delayed neutron activation techniques

Intra-thyroidal iodine has been measured with a collimated beam of neutrons from a reactor [8,9]. Partial-body activation has also been used to measured Ca in localized areas of the body with the use of isotopic neutron sources (^{238}Pu, Be) and (^{241}Am, Be) [10-14]. ^{252}Cf has also been investigated as a neutron source for partial-body activation [14, 15].

C. Prompt-gamma neutron activation techniques

The excess energy released in the binding of the neutron can be emitted as a prompt-gamma (i.e., in $< 10^{-16}$s). Measurement of total-body hydrogen by prompt-gamma analysis was first demonstrated in 1966 by Rundo and Bunce [16]. More recently, Biggin et al., measured total-body nitro-

gen with the use of a pulsed neutron beam from a cyclotron [17, 18].

With the use of similar techniques, Harvey et al. [19] measured total body nitrogen. Vartsky [20] performed a comparative study between the $^{14}N(n, 2n)N^{13}$ and $^{14}N(n, \gamma)N^{15}$ reactions for the measurement of total body nitrogen.

Levels of cadmium in the liver were also measured after exposure of the subject to prompt-gamma irradiation [21]. In this study a semi-conducting detector (Ge, Li) was used for on-line analysis of Cd. Vartsky [22] further developed the technique, employing ^{238}Pu, Be neutron sources to measure Cd in both kidney and liver (Fig. 2).

CLINICAL APPLICATIONS

The clinical usefulness of TBNAA was first demonstrated at an IAEA panel meeting in Vienna in 1972 [23]. Its usefulness is best shown by the studies involving the measurement of total-body calcium. This measurement provides data useful for the diagnosis and management of metabolic bone disorders. It should be emphasized, however, that while most of the applications to date have involved calcium, the measurement of sodium, chlorine, phosphorus and nitrogen also appear to be useful clinically.

A. Total-body measurement of calcium

1. Normals: For the study of changes in skeletal calcium in metabolic bone disorders, it is first necessary to take into account the normal changes with age. The non-invasive nature of the TBNAA technique and the low levels of radiation dose employed have made possible the study of normal subjects [24-27]. A mathematical model for the prediction of normal total-body calcium levels in terms of age, sex and body habitus has been developed for use as reference [25]. It is also of physiological interest and clinical usefulness to relate skeletal mass (total calcium) to muscle mass (total potassium) [28].

2. Osteoporosis: Total-body calcium (TBCa) measurements utilizing TBNAA have been used in studies of osteoporosis to establish absolute and relative deficits of calcium in patients with this disease in comparison to a normal contrast population [29-34]. These studies have demonstrated that a decrease in total bone mass is a normal concomitant of the aging process. Further, this phenomenon is accelerated in certain individuals, particularly postmenopausal women. A diagnosis of osteoporosis is reasonably certain when compression fractures occur. Unfortunately, prior to the occurrence of these fractures, it is difficult to distinguish between an osteoporotic individual and a normal person matched for sex, age and body habitus on the basis of present criteria. Accurate quantification of bone mass is difficult to achieve with the present state of the art; small changes that occur in the early stages of osteoporosis do not manifest themselves with present methods of measurement.

Clearly the assumption is made that there is a definite relation between the level of bone mass (to which the degree of osteopenia is inversely proportional) and the occurrence of compression fractures. On this basis, accurate measurement of bone mass is highly desirable. If there exists a critical level of bone mass for an individual (in terms of height and weight), it is of great value to determine this threshold value below

which the risk of structural failure is sufficiently great as to warrant therapy.

Each of the various methods used to determine the nature and degree of changes in skeletal mass have significant limitations. Quantitative microradiographic changes observed from bone biopsy specimens are not readily quantified, and further, provide information only on localized areas of bone. Measurements made by radiographic technique can be applied to the entire skeleton, but these measurements lack the sensitivity required for quantifying levels of change associated with the development of pathological conditions. Quantitative bone roentgenography, particularly the measure of cortical thickness of the appendicular skeleton, is useful, but not always indicative of the state of the axial skeleton. Photon absorptiometric techniques, while highly quantitative and precise, provide information only on localized areas of the skeleton.

Most of the difficulties encountered in the application of other methods are resolved by the use of total-body neutron activation analysis (TBNAA), which permits the direct *in-vivo* measurement of total calcium content of the body, and hence skeletal mass, to be made with as high a degree of precision as $\pm$ 2%, 2 SD [7].

A number of clinical trials have been conducted with total body calcium (TBCa), measured by TBNAA, as the end point of efficacy [35-40]. For example, Wallach [37] reported that 50% or more of osteoporotic women, treated with porcine calcitonin (100 MRC units dose) showed clinical improvement along with a mean increase of 3% in TBCa. Five patients manifested a mean increase of 9% in TBCa, indicative of a significantly increased bone mass following calcitonin treatment.

In another recent study, the effect of therapy which utilizes growth hormone to stimulate bone formation [38], and simultaneously inhibits bone resorption with calcitonin, was evaluated in patients with primary osteoporosis [39]. The technique of TBNAA was again used to measure TBCa. No significant increase in skeletal mass (TBCa) occurred during the low dose human growth hormone regimen. An increase in skeletal mass, however, was observed in all patients following the high dose growth hormone regimen, except for one patient who developed secondary hyperparathyroidism. Although this study must be considered to be of preliminary nature, the magnitude of the response in calcium balance suggests that skeletal mass can be increased in osteoporosis if combination therapy is employed [39].

In another study, combined treatment of osteoporotic patients with salmon calcitonin, sodium fluoride and calcium, over a period of 24-33 months, significantly increased the mean TBCa ($p < 0.05$) [40]. This increase indicates that treatment prevented further development of osteopenia.

The efficacy of synthetic salmon calcitonin (sCT), in the treatment of senile male osteoporotics, was also studied in terms of TBCa and bone mineral content (BMC) at six month intervals [41]. Males, 50 or more years of age, with diffuse demineralization and collapse of one or more vertebrae, were studied. Thirty-one patients were randomly divided into three groups: (1) a control group receiving multivitamins, (2) a calcium supplemental group receiving 1 g Ca and multivitamins, and (3) a calcitonin

group receiving 100 MRC units sCT daily plus calcium and multivitamins. No significant changes in TBCa were observed among the three groups during the first year. However, the group which received sCT showed significant increases in TBCa (4-6%) at 18 and 24 months. These increases in TBCa were not reflected by BMC measurements.

3. Renal osteodystrophy: Renal osteodystrophy in patients with renal failure has been studied extensively [42-48]. Disorders of both calcium and phosphorus, as well as electrolyte disturbances are reported. Total-body levels of Ca and P give the clinician useful data upon which to base therapeutic regimes. Changes in the concentration of calcium and phosphorus in the dialysate are rapidly reflected in the total body Ca and P measurements of the body. The dialysate concentration can then be adjusted to reduce the loss of calcium associated with dialysis [49].

The effect of pharmacologic doses of 25-hydroxycholecalciferol (25-OHD) on TBCa and BMC of the distal radius was evaluated in renal osteodystrophy patients on hemodialysis [50]. Two groups were studied. Group I received oral 25-OHD for 100 weeks. Group II received supplemental oral calcium only. Both groups were hemodialyzed with a 6.5 mg percent dialysate Ca.

The TBCa increased significantly in members of Group I; the change in BMC was variable. No change in TBCa or BMC was observed in Group II patients. It was concluded that the observed TBCa reflected an increase either in bone or in soft tissue Ca, or both.

4. Paget's disease: Serial measurements of TBCa were made in twenty patients with generalized symptomatic Paget's disease while they received long-term calcitonin therapy [51]. Total-body calcium had increased by an average of 22% above predicted normal values prior to calcitonin therapy; it decreased significantly (4%) during long-term calcitonin therapy. Total-body phosphorus, nitrogen and sodium also decreased during therapy. These data confirm histologic evidence of disappearance of Pagetic bone, and radiographic evidence of a decrease in bone volume during calcitonin treatment.

5. Endocrine dysfunction

(a) Thyroid and parathyroid disorders: Changes in skeletal mass in patients with endocrine dysfunctions have been studied, particularly in those patients with disorders of thyroid [52] and parathyroid [53]. After parathyroidectomy, the level of TBCa is indicative of the degree of bone resorption. On thi basis, surgeons can gauge the effectiveness of the removal of the hypertrophic parathyroids.

(b) Cushing's syndrome: Skeletal metabolism and body composition were investigated in patients displaying Cushing's syndrome [54]. The technique of TBNAA was utilized to measure skeletal mass (TBCa) and body composition. Eight patients with Cushing's syndrome were studied. In addition, serum concentration of 25-hydroxycholecalciferol (25-OHD) was measured in four of these patients, and in an additional 17 patients who were receiving exogenous glucocorticoids.

Prior to therapy, skeletal mass (TBCa) and lean body mass (^{40}K) were considered to be decreased in five of seven patients. The osteopenia was generally not corrected as determined in follow-up activations subsequent

to treatment of the Cushing's syndrome. The only significant increases in total-body calcium occurred in two patients who presumably had not completed body growth. Serum levels of 25-OHD were in the normal range in the sponstaneous Cushing's, as well as the iatrogenic Cushing's syndrome patients.

(c) Acromegaly: The effect of hyper-somatotropism on skeletal metabolism was investigated in ten acromegalic individuals [55]. The mean TBCa was 9% higher than the predicted values calculated on the basis of height. The ratio of TBCa to lean body mass (^{40}K) was reduced in four subjects. Although this effect may be the result of a greater increase in soft tissue mass than in skeletal mass, only two patients had total-body Ca levels which were less than the values predicted on the basis of height. These two subjects could be considered to have osteopenia.

6. Rheumatoid arthritis: The evaluation of diffuse osteoporosis in rheumatoid arthritis (RA) remains controversial. An important problem associated with the disease is the role of long-term corticosteroid therapy in the development of osteopenia. In the present study, TBCa was evaluated in 19 women with RA, with and without corticosteroid treatment [56]. The skeletal mass, as measured by TBNAA, was within normal limits in seven patients with no steroid treatment; it decreased in the remaining patients on corticosteroid treatment. The decrease in TBCa was most marked in postmenopausal women. Thus age is a significant factor in the development of osteoporosis following prolonged corticosteroid therapy.

7. Alcoholism: Total skeletal mass was measured in two groups of chronic alcoholic subjects with and without Laennec's cirrhosis [57]. No loss of skeletal calcium was determined. However, there was a marked loss of lean body mass (total body potassium) in alcoholic subjects with cirrhosis.

8. Osteogenesis Imperfecta: Three postmenopausal women with osteogenesis imperfecta tarda (OI) were treated daily with salmon calcitonin and calcium supplements for 12 to 33 months [58]. TBNAA measurement of TBCa revealed a marked deficit in these patients, exceeding that found in severely osteoporotic women. In one patient, the rapid loss of TBCa was partially reversed after twelve months of treatment. The second patient showed an increased TBCa (9%) after 33 months of treatment. Inconclusive results were obtained for a third patient who was receiving treatment with corticosteroids for asthma. The results confirm the findings of previous studies that supplied calcitonin to children with OI, and suggest that calcitonin may also be of benefit to adults with OI.

9. Myotonic dystrophy: Muscular wasting and endocrine disturbance are marked in most patients with myotonic dystrophy (MD). Six of seven MD patients studied exhibited a marked deficit in total body potassium (TBK); calcium, phosphorus and chlorine levels remained normal [59]. MD appears to be one of the few metabolic disorders studied in which the constant relationship between TBK and TBCa is altered. These data suggest that low levels of circulating androgen in MD are not necessarily associated with a decreased skeletal mass.

10. Thalassemia: Long-term administration of calcitonin to five patients with thalassemic bone disease produced clinical improvement; however, a net gain in TBCa occurred in only one patient [60]. The total

body calcium levels ranged from 357 to 665 g, 12 to 54% below the normal levels. These patients exhibited the greatest calcium deficits seen in any of the subjects studied.

11. Post-Gastrectomy: The skeletal mass and serum levels of 25-hydroxy-vitamin D were studied in 18 post-gastrectomy patients [61]. The skeletal mass, measured by TBNAA, was decreased significantly in 3 men and 3 women, one-third of the total cases studied. In the remainder of the patients, the TBCa values were within normal limits. The presence of spinal osteoporosis was suspected in only two of the patients on the basis of radiological examination. The frequency of osteopenia, as evaluated by TBCa, was higher than the 10% previously reported. There was no correlation between time since gastrectomy and TBCa levels. In some patients, marked lowering of serum 25-OHD and elevated plasma alkaline phosphatase were observed. All patients with low TBCa had elevated alkaline phosphatase levels. There was no correlation between TBCa and serum 25-OHD.

B. Total-body sodium and chlorine

1. Total-body sodium and chlorine in normal adults: TBNAA was used to determine the absolute levels of total-body sodium (TBNa) and total body chlorine (TBCl) in 81 normal adults [62]. For the age span studied, (30 to 90 years), the mean values of TBNa and TBCl remained relatively constant for males, but decreased slightly for females beyond sixty years of age. The TBNa and TBCl values were normalized for body dimensions (weight, height, body surface area) as well as age and sex. In addition, TBNa was related to skeletal mass (TBCa) and lean body mass (TBK). The quantity of body sodium in excess of the chlorine space was determined. This value, defined as sodium excess, was significantly correlated with TBCa. The values for TBNa, TBCl and sodium excess obtained in the present study serve as normal baseline levels for other studies.

2. Total and exchangeable sodium in hypertension: The altered distribution of extracellular fluid (ECF) and intracellular (ICF) was studied in hypertensive uremic patients [63]. Both volume expansion and increased vasoconstrictor activity are alleged to influence blood pressure in dialysis patients. TBNAA, radioimmunoassay and radioisotopic techniques were used to measure the following parameters: TBNa, TBCl, exchangeable sodium (NaE), total body water (TBW), plasma renin activity (PRA) and lean body mass (TBK). The dialysis patients were divided into two groups, retrospectively, based on the distribution of the total body water.

Blood pressure was significantly elevated in patients in Group B. NaE/TBK and PRA were elevated above control levels in all patients, but there was no significant difference between the elevated levels of Group A and Group B individuals. Neither volume expansion nor increased vasoconstrictor activity appears sufficient to provide a basis for the hypertension. The members of Group A with normal percentage distribution of TBW between ECF and ICF have minimal hypertension, while those in Group B with an abnormal percentage distribution of TBW have significantly more severe hypertension.

C. Total-body nitrogen

Changes in body composition of cancer patients relative to their dietary and nutritional status are currently under study by the author.

Specifically, it is desired to determine whether various nutritional regimes can either prevent or minimize loss of total body nitrogen. The importance of maintaining positive nitrogen balance in cancer patients is obvious. Total body nitrogen (TBN) will be measured with the use of the most advanced technique of neutron activation [prompt-gamma, $^{14}N(n, \gamma)^{15}N$ reaction]. Quantitative measurement of TBN will be made in both normal subjects (for baseline data) and in cancer patients. Measurements of the latter will be related to nutritional support regimes and anti-neoplastic therapeutic programs. Total body nitrogen and TBK will be used as indices of total cellular mass.

D. Partial-body measurement of iodine, nitrogen and calcium

Several groups of investigators have applied partial body neutron activation techniques to clinical problems. A more detailed description of these clinical applications is presented in reference [20]. Boddy and Lenihan have measured intrathyroidal iodine, using intermediate-energy neutrons [8, 9]. Appleby [11] used partial-body activation to measure calcium in bone. Catto [13] used ^{241}Am, Be sources to measure calcium in the hand of normal subjects and patients with metabolic disorders. Maziere and Comar [14] have measured sodium and Ca/P ratio by local irradiation of the hand, using combined ^{238}Pu, Be and ^{252}Cf sources for both normal subjects and osteoporotic patients. McNeill [10, 12] irradiated the torso with neutrons from ^{238}Pu, Be sources to measure the calcium content in a study of osteoporosis and osteomalacia. More recently, Mernagh [64] has measured nitrogen in the torso by a prompt-gamma technique, using the same (α, n) sources.

E. Partial-body measurement of heavy metals

The internal deposition of cadmium is recognized as a potentially serious health problem. Cd accumulates in the liver and kidneys. For members of the general population, the chief hazard resides in kidney damage. Cd poisoning has also been proposed as a causative factor in human hypertension and emphysema.

Cd concentrations in kidney and liver are being measured by prompt-gamma neutron activation in a program currently underway [22]. Since prolonged industrial exposure to Cd is correlated with both kidney damage and incapacitating emphysema, a study is being initiated to determine the dose-effect relationship between the accumulation of Cd in occupationally exposed subjects. A portable prompt-gamma neutron activation facility is presently being constructed to enable these studies to be carried out at industrial sites.

Above are listed some of the many clinical applications of in-vivo neutron activation that have been carried out, or are currently underway. While these applications have been drawn chiefly from our own work, the enormous potential of the technique for medical research is clearly demonstrated. In-vivo neutron activation is a powerful technique for medical research, and is providing new and previously unavailable information.

TABLE I. MEASUREMENT OF BODY ELEMENTS BY IN VIVO NEUTRON ACTIVATION ANALYSIS

Stable element	Amount in 70 kg standard man (g)	Proportion by weight in 70 kg standard man (%)	Induced nuclide	Neutron reaction	Gamma or X-ray to be measured
Oxygen	42000	60	^{15}N	n, p (fast)	delayed γ (6-7 MeV)
Hydrogen	7000	10	^{2}H	n, γ (thermal)	prompt γ (2.2 MeV)
Nitrogen	2100	3	^{13}N	n, 2n (14 MeV) n, γ (thermal)	delayed γ (0.51 MeV) prompt γ (10.8 MeV)
Calcium	1050	1.5	^{49}Ca ^{37}A	n, γ (thermal) n, α (14 MeV)	prompt γ (many); delayed γ (3.10 MeV) delayed X-ray (2.6 keV)
Phosphorus	700	1	^{28}Al ^{32}P	n, α (fast) n, γ (thermal)	delayed γ (1.78 MeV) prompt γ (0.08 MeV)
Sodium	105	0.15	^{24}Na	n, γ (thermal)	prompt γ (many); delayed γ (2.75 MeV)
Chlorine	105	0.15	^{38}Cl ^{37}S	n, γ (thermal) n, p (fast)	prompt γ (many); delayed γ (1.6 and 2.2 MeV) delayed γ (3.10 MeV)
Magnesium	35	0.05	^{27}Mg ^{24}Na	n, γ (thermal) n, p (fast)	delayed γ (0.84 MeV) delayed γ (2.75 MeV)
Iron*	4.2	0.006	^{56}Mn	n, p (fast)	delayed γ (0.84 MeV)
Iodine*	0.01 (in thyroid)	0.03 (in thyroid)	^{128}I	n, γ (thermal)	delayed γ (0.45 MeV)
Manganese*	trace	trace	^{56}Mn	n, γ (thermal)	delayed γ (0.84 MeV)
Copper*	trace	trace	^{64}Cu	n, γ (thermal)	delayed γ (0.51 MeV)
Cadmium*	trace	trace	^{114}Cd	n, γ (thermal)	prompt γ (0.559 MeV)

* Partial-body activation.

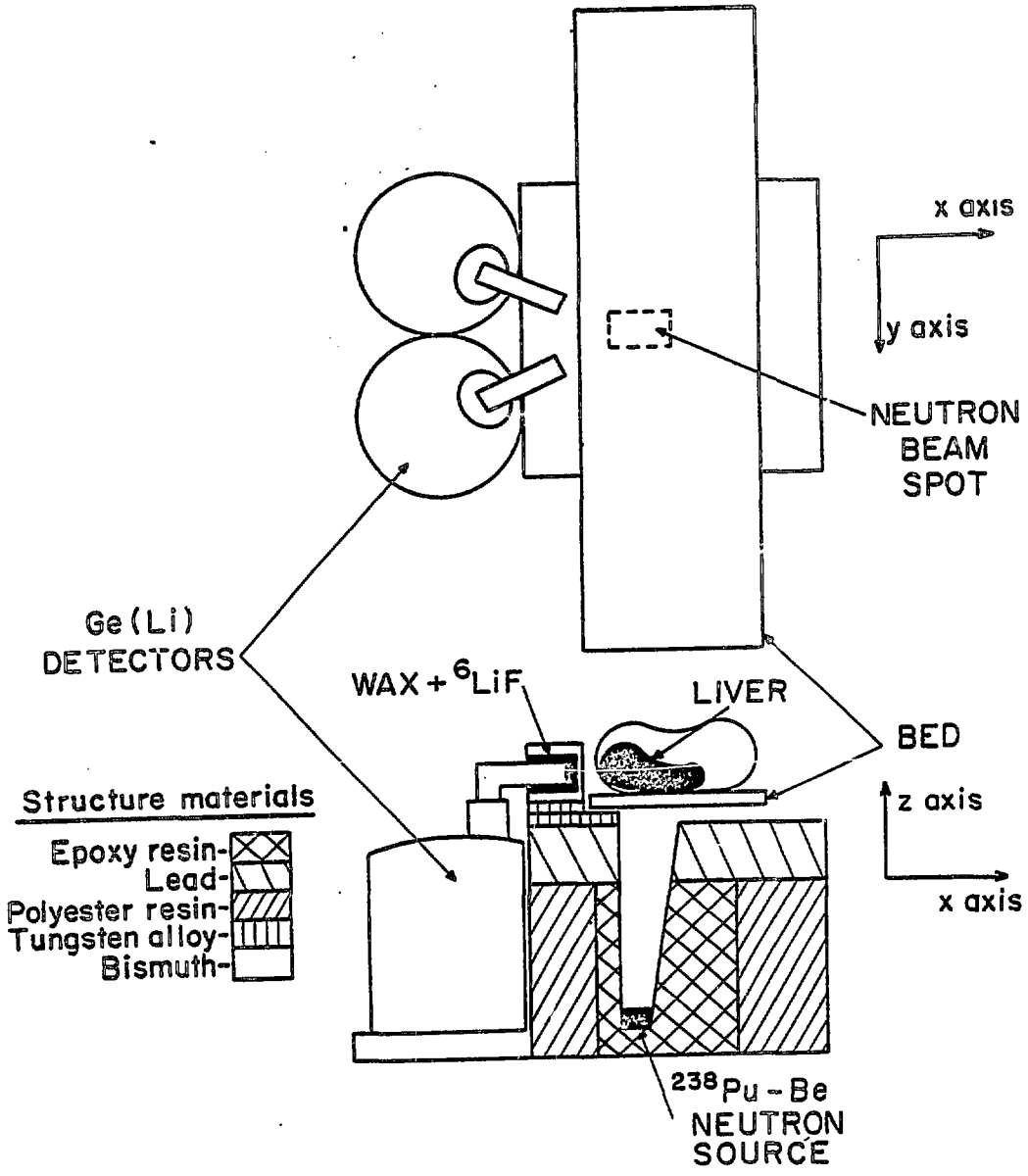
FIGURES

Fig. 1:

The Brookhaven ^{238}Pu, Be total-body neutron activation facility. The subject is covered with the polyethylene moderator and is positioned on the cot between the upper and lower guide tubes. The guide tubes are used to position the fourteen 50-Ci ^{238}Pu, Be sources.

Fig. 2:

The Brookhaven partial-body prompt-gamma neutron activation facility. The ^{238}Pu, Be neutron source (85-Ci) is shown schemiatically in the collimated shielding, in the lower diagram. The upper diagram is a top view of the patient bed. The neutron beam spot for irradiating liver or kidney is shown along with the position of the Ge(Li) detectors.


x axis
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SPOT
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WAX + ^{6}LiF
LIVER
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z axis
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Structure materials
Epoxy resin-
Lead-
Polyester resin-
Tungsten alloy-
Bismuth-
^{238}Pu - Be
NEUTRON
SOURCE

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