

APPLICATIONS OF NUCLEAR TECHNIQUES
FOR IN VIVO BODY COMPOSITION STUDIES
AT BROOKHAVEN NATIONAL LABORATORY

by

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ABSTRACT

The development and clinical application of a number of nuclear techniques for studying body composition is described. These techniques include delayed neutron activation for the analysis of calcium, phosphorus, sodium and chlorine and prompt-gamma activation for the measurement of nitrogen and cadmium. In addition, the measurement of in vivo iron by nuclear resonance scattering and lead by x-ray fluorescence is described.

1. HISTORICAL DEVELOPMENT

Brookhaven National Laboratory (BNL) has long been involved in research on calcium metabolism. When it became apparent that it was possible to measure total body calcium, BNL actively undertook the development of such a facility.

In 1967-1968, a research program was begun with the goal of developing an in vivo total body neutron activation system. The neutron source employed was a 14 Mev Texas Nuclear generator in use in the Physics Department. At the same time, a number of α, n sources: $^{238}\text{PuBe}$, $^{210}\text{PoBe}$, and $^{241}\text{AmBe}$, were investigated.

It was also necessary to determine the absolute calibration for the measurement of calcium with an Alderson phantom. The uniformity of the thermal neutron flux and the flux density were also measured in a variety of phantoms. The effects of polyethylene moderators were studied as part of the effort to achieve the highest possible uniformity in flux density in the phantoms. The results of these various studies were first reported at the Conference on Progress and Problems in Neutron Activation at SURRC in East Kilbride, in 1969.

It took approximately a year after the completion of the phantom studies to obtain permission from the BNL Human Studies Committee to activate the first human subject. The first paper on in vivo activation analysis of calcium in man at BNL was published in 1970. The results of the studies of 14 Mev neutrons and the lower energy neutrons from "portable" α, n sources were both reported at that time.

The studies were continued and broadened. Approximately one year later, in 1971, a report was published on the measurement of total body nitrogen, calcium, sodium, and chlorine in seventeen patients with conditions ranging from metastatic breast cancer to osteoporosis and chronic renal failure.

The neutron generator used for all of these studies was located in the Physics Building. Thus, it was necessary to transport the patients very quickly by ambulance to the whole-body counter situated in the Medical Center. A police escort was required to clear the way for the ambulance used for transport to ensure maximum road safety on the trip to the Medical Center.

The studies with neutron activation were continued with this neutron source for approximately two years. About two hundred activations were performed. During this period, a new 700 Ci $^{238}\text{PuBe}$ neutron activation facility was constructed in the BNL Medical Research Center. The distance of this new facility, from the whole body counter in the BNL hospital can be covered in approximately three minutes. The absolute calibration of the system for the measurement of total body levels of calcium, sodium, chlorine, and phosphorus, was developed.

To date, well over 2,500 activations have been carried out on both normal subjects and patients with a wide variety of diseases, particularly osteoporosis and renal osteodystrophy (see section 3). This was the first α, n neutron activation facility designed specifically for clinical use and constructed in a hospital environment. The radiation dose to the patient was reduced to 270 mrem, the smallest dose delivered by an existing neutron activation facility (1,2).

In 1977, BNL built the most sensitive and highly developed system for the in vivo measurement of cadmium in liver and kidney (3). It employed 85 Ci of $^{238}\text{PuBe}$ in a highly shielded collimated arrangement. The collimator was made of epoxy resin heavily doped with Li_2Co_3 and ^6LiF . The detection limits (2SD) for Cd were 2.2 mg for kidney and 1.0 $\mu\text{g/g}$ (wet weight) for the liver, with a localized dose of 470 mrem. This cadmium facility was installed in a specially designed 34-foot trailer. This transportable facility can be moved to various locations for use in epidemiological studies. It was used in one major field study to measure Cd in the kidney and liver of workers at a cadmium smelter. The $^{238}\text{Pu, Be}$ source and shielding have been replaced in the facility with a ^{252}Cf source and certified IAEA shipping cask. This alteration has achieved an improved sensitivity simultaneously with a significant lowering of the dose to the subject. It has also eliminated the regulatory problems of transporting plutonium through various localities. Transportation with the ^{252}Cf source presents far fewer problems.

BNL reported in 1971 on studies of total body nitrogen based on the $(n, 2n)$ reaction in both normal subjects and in a variety of patients. More recently (1978) an improved system was developed for the measurement of total body nitrogen with the prompt-gamma neutron activation technique (4). The body nitrogen counts are measured simultaneously with total body hydrogen. The latter measurement is then used as an internal standard for

determination of total body nitrogen. The radiation dose delivered to the skin for the bilateral scan geometry of the patient is less than 45 mrem. The precision of the body nitrogen measurement in a human subject is approximately 3-4%.

The prompt-gamma nitrogen measurement facility has been used extensively for the past three years. Cancer patients on various types of dietary supplementation and obese patients on protein-sparing diets have been studied. Data on a control group of normal individuals provide the requisite baseline information.

In the last two years, the BNL program has expanded to include a number of other nuclear technologies applied to medical problems. Iron is currently measured by nuclear resonance scattering (NRS) in patients with thalassemia. This technique holds promise for other elements as well. Presently, an x-ray fluorescence (XRF) technique is being developed for the measurement of L-x-rays from lead deposited in the tibiae of human subjects.

2. TECHNICAL DEVELOPMENTS

There has been a long series of technical developments in the various nuclear technologies at Brookhaven culminating in "state-of-the-art" techniques. The theoretical considerations that lead to these developments have been detailed in references (5). The factors involved in selecting the neutron sources for total body neutron activation, the type and positioning of the moderator and radiation dose to the subject have all been presented (4,5). Consideration of these factors indicated that 4.0 Mev neutrons have an overall advantage of 2 relative to 14 Mev neutrons in TBNA. Further, multiple (α, n) sources in a broad-beam geometry and simultaneous bilateral exposure have an advantage of 3.6 relative to 14 Mev neutrons from a continuous beam neutron generator. Portable (α, n) sources provide ease of operation and high precision from the constant output of neutrons.

A significant technological advance was the development of a portable (α, n) neutron activation facility for measuring cadmium *in vivo* in kidney and liver of the non-industrially exposed population. This facility was mounted in a 34 foot trailer. This mobile unit can easily be moved around the country for epidemiological studies as well as industrial exposure studies. Recently, the neutron source was changed from $^{238}\text{Pu, Be}$ to ^{252}Cf which decreased radiation dose without a loss in sensitivity but greatly increased the ease of moving the trailer. The present mobile system exceeds all IAEA regulation for the transportation, shielding and use of ^{252}Cf sources.

A technique for the measurement of body iron utilizing nuclear resonant scattering of gamma rays has been developed (6). 847 keV photons emitted from a gaseous $^{56}\text{MnCl}$ source are resonantly scattered from ^{56}Fe present in the body. Measurement is made using large volume Ge(Li) detectors. The spatial uniformity of activation, the sensitivity of the detection system and the limits of detection have been investigated. Measurements were made on a liver phantom. The resonance scattering technique permits determination of normal levels of Fe in the liver with a radiation dose of 2 rem.

A non-invasive measure of the skeletal levels of lead was developed by an x-ray fluorescence technique (XRF) as part of a toxicological study of lead in man. With this technique it will be possible to relate body burdens of lead to blood lead levels and to other indicators of biological effect from lead. The instrument will be calibrated and validated for the measurement of absolute levels of lead in the skeleton. When fully operational the system will be installed in an existing mobile facility designed for the field study of internally deposited cadmium.

The most recent applications development involved a pulsed Van de Graaff generator as a source of pulsed neutrons, for the feasibility measurement of lung silicon by inelastic scattering of fast neutrons.

3. CLINICAL APPLICATIONS

The clinical usefulness of the BNL total body neutron activation analysis (TBNA) program 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 TBNA 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 ($\pm 3\%$) 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 has given the clinician useful data upon which to evaluate 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. Changes in skeletal metabolism and body composition in acromegaly and Cushing's disease have also been investigated by TBNA.

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. These studies have demonstrated an increased body burden of Cd for cigarette smokers.

Total body nitrogen and potassium measurements serve as indices of protein and 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. A more detailed summary will be found in references (1,2). 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.

The object of the studies with the nuclear resonance scattering technique is to measure body deposits of iron in clinical studies involving chelation therapy of patients with Thalassemia major. The portable XRF system provides a rapid and accurate screening test to determine lead exposure in any population at risk. On the basis of in vivo measurement of lead body burdens and the above indicators of biological effect, it should be possible to set more precise criteria for permissible lead exposure in the occupationally exposed populations.

4. RESULTS

4.1. Total-body measurement of calcium

4.1.1. 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 TBNA technique and the low levels of radiation dose employed have made possible the study of normal subjects (7-9). 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 a reference (7). It is also of physiological interest and clinical usefulness to relate skeletal mass (total calcium) to muscle mass (total potassium) (10).

4.1.2. Osteoporosis: Total body calcium (TBCa) measurements utilizing TBNA 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 (11-16). 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. Total body neutron activation analysis (TBNA) 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 $\pm 2\%$ (2SD).

A number of clinical trials have been conducted with total body calcium (TBCa), measured by TBNA, as the end point of efficacy (17-22). For example, Wallach (19) 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 3-9% in TBCa.

In another recent study, the effect of therapy which utilizes growth hormone to stimulate bone formation (20), and simultaneously inhibits bone resorption with calcitonin, was evaluated in patients with primary osteoporosis (21). The technique of TBNA 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 almost all patients following the high dose growth hormone regimen. 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 (21).

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 ($p < 0.05$) (22). 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) of the radius at six month intervals (23). 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.

4.1.3. Renal osteodystrophy: Renal osteodystrophy in patients with renal failure has been studied extensively (24-29). Disorders of both calcium and phosphorus, as well as electrolyte disturbances were 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 (30).

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 (31). 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.

4.1.4. 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 (32). 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.

4.1.5. 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 (33) and parathyroid (34). After parathyroidectomy, the level of TBCa is indicative of the degree of bone resorption. On this basis, surgeons have gauged the effectiveness of the removal of the hypertrophic parathyroids.

b. Cushings's syndrome: Skeletal metabolism and body composition were investigated in patients displaying Cushing's syndrome (35). 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 (⁴⁰K) 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 spontaneous 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 (36). The mean TBCa

was 9% higher than the predicted normal values. 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 predicted values. These two subjects could be considered to have osteopenia.

4.1.6. 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 (37). The skeletal mass, as measured by TBNA, 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 post-menopausal women. Thus age is a significant factor in the development of osteoporosis following prolonged corticosteroid therapy.

4.1.7. Alcoholism: Total skeletal mass was measured in two groups of chronic alcoholic subjects with and without Laennec's cirrhosis (38). No significant loss of skeletal calcium was determined. However, there was a marked loss of lean body mass (total body potassium) in alcoholic subjects with cirrhosis.

4.1.8. Osteogenesis Imperfecta: Three post menopausal women with osteogenesis imperfecta tarda (OI) were treated daily with salmon calcitonin and calcium supplements for 12 to 33 months (39). TBNA measurements 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.

4.1.9. 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 (40). MD appears to be one of the few metabolic disorders studied in which the relatively 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.

4.1.10. 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 (41). 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.

4.1.11. Post-Gastrectomy: The skeletal mass and serum levels of 25-hydroxy-vitamin D were studied in 18 post-gastrectomy patients (42). The skeletal mass, measured by TBNA, 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 changes in TBCa levels. In some patients, marked lower serum 25-OH 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.

4.2. Total-body sodium and chlorine

4.2.1. Normal adults: TBNA was used to determine the absolute levels of total body sodium (TBNa) and total body chlorine (TBCl) in 81 normal adults (43). 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 normal population study have served as baseline levels for the clinical studies.

4.2.2. Total and exchangeable sodium in hypertension: The altered distribution of extracellular fluid (ECF) and intracellular fluid (ICF) was studied in hypertensive uremic patients (44). Both volume expansion and increased vasoconstrictor activity are alleged to influence blood pressure in dialysis patients. TBNA, 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. 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.

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.

4.3. Total body nitrogen

Changes in body composition of cancer patients relative to their dietary and nutritional status have been studied (45-47). Specifically, it was desired to determine whether various nutritional regimes can either pre-

vent or minimize loss of total body nitrogen. The importance of maintaining positive nitrogen balance in cancer patients is obvious. Total body nitrogen (TBN) was measured with the use of the current technique of neutron activation (prompt gamma, $^{14}\text{N}(n,\gamma)^{15}\text{N}$ reaction). Quantitative measurement of TBN was 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. TBN and TBK have been used as indices of protein and total cellular mass.

4.4. Cadmium in liver and kidney

The internal deposition of cadmium is recognized as a potentially serious health problem. Significant Cd accumulations occur in the liver and kidneys. For the general population, the major health hazard appears to be irreversible kidney damage. Cd deposition in the kidney has been proposed as a causative factor in human hypertension, while lung Cd has been associated with emphysema.

Cd concentrations in kidney and liver are being measured by prompt-gamma neutron activation in a program currently underway (48-50). Since prolonged industrial exposure to Cd is correlated with kidney damage a study is being conducted to determine the dose-effect relationship between the accumulation of Cd in occupationally exposed subjects. The portable prompt-gamma neutron activation facility was constructed to enable these studies to be carried out at industrial sites (50). An evaluation of the critical concentration for the kidney has demonstrated a value near 300 $\mu\text{g/g}$ for the renal cortex (50).

4.5 Iron in liver and heart

To date, five patients with Thalassemia have been measured by the nuclear resonance scattering technique. The limits of detection are adequate to measure the level of iron in the liver. However, for the measurement of iron in the heart greater sensitivity would be desirable. It is not possible yet to measure normal heart iron levels in normal subjects.

4.6 Lead in tibia

To assess the feasibility of measuring bone lead concentrations non-invasively in vivo, characteristic L x-rays were induced post mortem in the superficial tibial cortex of intact legs in five adults who had no history of occupational history to lead, using an external source of ^{125}I (51). Tibial lead concentrations found subsequently by flameless atomic absorption spectroscopy in the same bones varied from 15 to 35 $\mu\text{g Pb/g}$ wet weight, within the modern normal range. The linear correlation coefficient between x-ray fluorescence signals and lead concentration was $r = 0.92$.

Radiation dose of 1 rem to 1 cm^2 of skin yielded net lead peaks which ranged from one to seven times the standard deviation of background, while doses to the adjacent bone marrow were about 60 mrem.

Above are listed some of the many clinical applications of in vivo neutron activation that have been carried out, or are currently underway. 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.

5. PLANS FOR FUTURE

The Brookhaven group will continue to develop the above nuclear technologies for use in clinical research studies. Continued development has improved the sensitivity of measurements along with a reduction in radiation dose.

The most recent study evaluated the feasibility of quantitating the level of silicon in the lung by inelastic scattering of neutrons (52). This technique employed pulsed neutrons from a Van de Graaff generator. Further development should lead to clinical trials.

It is planned to continue the nuclear resonance studies for the measurement of iron body burdens by improving the collimation, shielding and the radiation sources. It is hoped to be able to measure normal levels of iron in the heart. The technique will then be used in clinical centers now studying Thalassemia Major utilizing chelation methods for reducing iron stores. These studies have, in the past, been hampered by a lack of sufficiently sensitive quantitative measurement of the heart concentration of iron.

The XRF instrument will be further developed to improve the sensitivity for the measurement of lead. The system will be calibrated and finally validated by the analysis of intact amputated legs, as described above. When fully operational, the final system will be installed in an already existing mobile facility, designed for the field measurement of cadmium. Thus, it will be possible to measure both elements in the same individual during field studies.

The whole range of pulsed neutron activation techniques (in-beam, prompt, and delayed) is being re-evaluated. Compact portable neutron generators (both (D,D) and (D,T)) are being developed for potential clinical applications. These compact devices (~ 8 cm length) are ideally suited for portable facilities.

New applications applying both old and new nuclear technologies to medical problems will continue to be explored.

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