PROGRESS IN CLINICAL USE OF PHOTON ABSORPTIOMETRY*

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Proc. Int. Symp. Clinical Aspects of Metabolic Bone
Disease (Detroit, June 1972) Excerpta Medica Press
(in press)

INTRODUCTION

Direct photon absorptiometry by low energy (20- to 100-keV) radionuclide transmission scanning provides a precise and accurate (less than 2% error) indication of bone mineral content. This method, since its introduction a decade ago, has achieved widespread acceptance by researchers and clinicians concerned with measurement of the skeleton. Details of the method, experimental results, and varied applications have been described in numerous publications, and have been dealt with in a recent symposium volume (Cameron, 1970). The essence of the absorptiometric method consists of passing a mono-energetic well-collimated beam of radiation, typically from a several hundred mCi source of ^{125}I (27.4keV) across a limb; the changes of beam attenuation due to the bone mineral are recorded and analyzed. In the past decade considerable sophistication has been gained relating to instrumentation, data interpretation, and biomedical application. This report describes some of the technical progress made in our laboratory, particularly those innovations with direct bearing on medical applications. In addition, some of the biomedical applications of absorptiometry and clinical findings are discussed.

TECHNICAL INNOVATIONS

(a) Direct Readout System: For the past decade most systems for photon absorptiometry have used scaler-timers and digital output. Over the past several years our laboratory has developed an analog system, using a precision linear-ratemeter and logarithmic conversion of the ratemeter signal, to provide immediate digital readout of bone mineral content and bone width (Mazess et al., in press). The direct readout system has several advantages over digital handling of scan data including: (1) lower operational and equipment costs, (2) immediate availability of results, and (3) smaller size and weight, allowing greater mobility. These advantages have lead one company (Norland Instruments) to produce a commercially-available direct readout system. Complete plans for construction of such a system are available from the University of Wisconsin Instrumentation System Center (Engineering Research Bldg.)

* Supported by NASA - Y - NGR - 50 - 002 - 051 and AEC-(11-1)-1422

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Table 1. Precision of measurement of a three-chambered standard over a 20-month period of clinical use; figures are coeff. of variation.

CHAMBER	AMONG MEASUREMENTS			AMONG 7 SOURCES	
	Mineral	Width	n	Mineral	Width
SMALL	1.91%	0.96%	275	1.58%	0.41%
MEDIUM	1.19%	0.96%	969	0.72%	0.30%
LARGE	1.04%	0.45%	275	0.84%	0.23%

The direct readout system is as accurate and precise as earlier digital systems. Over a 20-month period the coefficient of variation for hundreds of measurements on standards was about 1% (Table 1); the error in predicting the ash weight of bone sections was about 1.5%. Clinical measurements were done on about 100 patients using both digital and analog systems simultaneously; the results from both systems were highly correlated ($r=0.99$) and the standard error of estimate in predicting from one system to the other was about 3%.

(b) Analysis of Sources of Error: A variety of technical factors, excluding gross errors in setting-up instrumentation, can effect absorptiometric scans. These factors are associated chiefly with the nature of the photon beam; the source, its geometry and filtration, are quite important, as is detector geometry. P.F. Judy has investigated and evaluated the sources of error in his doctoral dissertation ("A Dichromatic Attenuation Technique for the In Vivo Determination of Bone Mineral Content") including:

- (1) finite counting intervals
- (2) beam profile
- (3) beam hardening and filtration
- (4) edge effects
- (5) scattered radiation
- (6) counting statistics
- (7) variation of bone mineral composition
- (8) variation in the composition of the soft-tissue surrounding the bone or in the marrow cavity.

These technical factors can be controlled so that precision and accuracy is maintained. Deviations can be ascertained by making determinations on suitable standards, or through other appropriate calibration procedures. R.M. Witt has developed standards consisting of annuli of dipotassium phosphate solution in a lucite block; these permit assessment of precision over time, and allow calibration. Variation among seven laboratories in values reported for these standards was within about 2% indicating the small errors involved in absorptiometry even in completely different laboratories.

The largest single source of error in making serial measurements on an individual, or in comparing individuals, does not involve the method itself but only the location of the correct scan site. The magnitude of this error is inversely proportional to the care taken in positioning the

subject. For linear scans in the clinic routine precision is on the order of 2%, but it can be improved to 1% by making individualized casts of the subject's limb. In field surveys the precision is reduced to about 5%.

(c) Area Scanning: One way to minimize repositioning and location errors is to scan a larger area of the limb in order to average out anatomical irregularities, or any peculiar local anomalies. J. Sandrick has developed a small light-weight scanner for rectilinear area scanning. Plans of this scanner, and its controls, are available from the AEC Technical Information Service.

We evaluated the increased precision achieved by area scanning over conventional linear scans by measuring 5 subjects, using both approaches, on 5 occasions over a 6-week period. The variation in mineral content is reduced by about 40% while the variation in width over time is reduced by only 10% on the forearm bones (Table 2). The absolute magnitude of the error, however, is quite important; area scanning on the radius gives a precision of 0.8% which permits sensitive assessment of changes in mineral content.

Table 2. Comparison of the precision of area scanning versus linear scanning on the forearm bones at midshaft. The data are averages from 5 subjects done on 5 occasions over a 6-week period; 10 repeat scans were done on each subject on each occasion.

		COEFF.	VARIAION	AREA/ LINEAR	AREA- LINEAR
		area	linear		
<u>ULNA</u>	MINERAL	1.58%	2.37%	0.67	0.79%
	WIDTH	2.08%	2.31%	0.90	0.23%
<u>RADIUS</u>	MINERAL	0.80%	1.46%	0.55	0.66%
	WIDTH	1.63%	1.90%	0.86	0.27%

(d) Dichromatic (Dual-Photon) Absorptiometry: In the past several years we have concentrated on developing absorption measurements at two energies, rather than at a single energy, in order to measure bone embedded in soft-tissue, or to measure the relative amounts of lean and lipid components of soft-tissue. A combination of radionuclides, such as ^{125}I and ^{241}Am (27- and 60-keV); are used, or a single source with two emissions, such as ^{109}Cd (22- and 88-keV) or ^{153}Gd (43- and 100-keV) may be used. New sources, such as $^{123\text{m}}\text{Te}$ and $^{125\text{m}}\text{Te}$ are being investigated. The dual photon approach permits measurements of bone without the necessity for a constant thickness of tissue-equivalent material surrounding the limb. In practical terms, this eliminates the need for limb immersion in water baths, or for preparation and use of Super-Stuff. More important, however, is the new potential for dichromatic scanning of locations impossible to measure with the single-photon method, such as the spine and hip.

Preliminary dual-photon scans of the spine have shown a long-term precision of 4.6% using ^{153}Gd on a spine phantom. Comparable precision can

be achieved on humans in vivo provided there is careful relocation. In a less controlled situation we have found variation from 7 to 20% over time depending on the subject. Area scanning is now being used to enhance reproducibility.

(e) Validation Studies: Over the past decade it has been shown that absorptiometry is a very accurate indicator of local bone mineral content. Under simulated in vivo conditions the ash weight of bone sections is predicted with an error of only 1 to 3%. The accuracy of measurement on uniform standards is even higher (less than 0.5% error). Absorptiometric determinations are related not only to the weight of the bone mineral in the scan path, but to the weight of the total long bone, and also to the total skeletal weight. In series of excised bones, both Wilson and Mazess (1971) have shown that a scan on any long bone is highly correlated with scans on any other long bone. Apparently there is relative uniformity in the mineral content, and in changes of mineral content, throughout the appendicular skeleton. This finding indicates the usefulness of scans in indicating mineral status. Recent results by C. Wilson, however, show that the mineral content on appendicular bones is only moderately correlated with spinal bone mineral strength ($r=0.7$). However, even scans on adjacent vertebra do not give much information about their neighbors ($r=0.8$). Scans on appendicular bones, however, are well-correlated ($r=0.87$) with the mineral content of the femoral neck; this important relationship indicates that a radius scan may be of diagnostic aid in relation to hip fractures.

SUBSTANTIVE APPLICATIONS

(a) Normative Data: We have measured the bones, typically the shaft of the radius and the ulna, on over 1000 U.S. white adults, and on over 400 white school-age children. In addition, measurements have been made, as part of the International Biological Program, on several hundred Eskimo children and adults from both northern Alaska and northern Canada. Similar normative data has been collected by other laboratories (Kaiser Research Foundation, Jefferson Medical Center, Mayo Clinic, Univ. of Rochester, Univ. of Indiana) and the pattern of bone growth and bone loss has been outlined in white, Negro, and Oriental populations. In the elderly whites, bone loss occurs earlier and to a greater extent in females at ages 40 to 50, and continues at about 10% per decade thereafter. Bone loss does not occur in males until age 50, and the loss amounts to only about 3% per decade. Even more rapid bone changes occur in children; their bones grow at a rate of about 8% per year. Accumulation of such data by different laboratories will not only better define the normal pattern of age changes, but will allow more exact discrimination and interpretation of skeletal deviancy.

(b) Patient Data Bank: We have measured the bones in over 1000 patients exhibiting a variety of diseases. J.M. Jurist has devised a standard medical history and coding system; uniform data is collected from all patients, then coded and put on magnetic tape. This clinical data bank is updated about every 6 months. Copies of this system are available on request.

Use of the data bank allows convenient sorting of clinical data with respect to any of the variables (subject description, disease diagnosis,

treatment). M. Mueller, who supervises clinical measurement of bone mineral, has studied several hundred patients with rheumatoid arthritis using the data bank. In 144 women it was found that the loss of bone mineral was associated with the severity and duration of the disease. In steroid-treated patients the mineral loss was seen after a shorter disease duration and lesser severity; the extent of demineralization seemed related to the total steroid dose received. Similar studies are being done in other disease categories.

• (c) Discrimination of Skeletal Abnormality: Mere deviancy of bone mineral content for a particular age-sex category does not necessarily indicate skeletal abnormality or pathology. Bone size and body size affect the amount of bone. On the other hand, there appear to be some minimal thresholds below which the bone is architecturally unsound regardless of other factors.

E. Smith and J. Jurist found that a bone mineral content of 0.68 g/cm on the radius shaft discriminated between 50 white females free of disease and 50 osteoporotic (defined by spontaneous fractures of the femoral neck, vertebrae, or radius) females. Bone mineral content below this value indicates osteoporosis and the danger of fracture regardless of the subject's body size or age. In a series of 24 cadavers examined by C. Wilson the femoral necks were broken in all cases where the radius mineral content was below 0.68 g/cm. Discrimination of abnormality might be improved by use of height, weight, limb circumferences and lengths, and biochemical information; we are examining this possibility.

In school-age children indices of skeletal abnormality are difficult to develop since bone grows at 8% per year and also varies with body size. We have used regression relationships observed in a sample of 322 white children to formulate indices of abnormality; deviancy from the expected bone mineral content is examined using prediction equations for age, bone width, and height and weight. In a sample of normal children about 5% fall more than two standard deviations below the mean, but it is not clear if these children really evidence marginal skeletal status or if this is merely the nature of the "normal" distribution. These deviant children average only 6% (7 months) retardation in skeletal age, and there is no association between degree of demineralization and maturational delay.

(d) Serial Observations of Skeletal Abnormality and Treatment: The high precision of absorptiometry makes it especially useful for observing the small changes occurring with skeletal disease, or measuring those small changes resulting from therapy or alterations of bone stress. P.F. Judy has collaborated with J. Vogel (U.S. P.H.S. Hospital, San Francisco) in monitoring changes during bed rest. Judy has also monitored bone mineral in 5 chronic hemodialysis patients using precise relocation made possible through casts. All patients were in end-stage renal failure with a creatinine clearance less than 3 ml/min; none received vitamin D and all were free from apparent skeletal involvement as seen radiographically. Over a period of from 20 to 72 weeks the coefficient of variation in the patients was less than 1%; the variation in the standard was only 0.2% and in the normal control subject it was 0.3%. Use of the ultra-precise method permitted confirmation of the absence of onset of renal osteodystrophy in these patients.

We have cooperated with Hugh Hickey (Marquette Medical School) in following the bone changes in elderly nuns receiving fluoride supplementation (75 mg/day). Both treated and untreated controls lost bone over the two-year follow-up period, but there were no apparent differences between the groups.

E. Smith followed bone changes in elderly subjects during an exercise program and also with physical rehabilitation. Control subjects lost 0.5% bone mineral over 9 months; the exercise group gained 1.7% over their control value of bone mineral, while the physical rehabilitation group, which apparently were demineralized as a result of previous bedrest, gained almost 8%. Studies of the effects of exercise on bone are in progress.

DISCUSSION AND CONCLUSIONS

The development of any novel biomedical method, such as absorptiometry, requires both technical and applied research efforts. Many laboratories and researchers are involved in this work, and the present report outlines some of the recent contributions of the Wisconsin laboratory. In order to aid communication in this expanding field we have tried to institute regular research meetings (in the fall of even-numbered years) and instructional workshops (in the fall of odd-numbered years). As the body of technical and substantive information dealing with absorptiometry increases we expect to find increasing clinical utilization and understanding of this method.

ACKNOWLEDGMENTS

We gratefully acknowledge the help of J. Jurst, M. Mueller, E. Smith, J. Sandrick, K. Kianian, and R.M. Witt in this research; J. Fischer and S. Kennedy have collected our clinical data with care and interest.

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