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Final Progress Report on NASA-Y-NGR-50-002-051 and NAG2-166 1968-1982

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Final Progress Report on NASA-Y-NGR-50-002-051 and NAG2-166 1968-1982

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prepared for
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From 1968 to 1982 this NASA project on skeletal and body composition evaluation was performed at the Bone Mineral Laboratory. The work done over that time included:

(a) analysis of errors affecting single-photon absorptiometry and development of instrumentation,

(b) analysis of errors affecting dual-photon absorptiometry and development of instrumentation,

(c) evaluation of skeletal uptakes of diphosphonates,

(d) comparison of other skeletal techniques,

(e) cooperation with NASA projects for skeletal evaluation in space flight (MO-78) and in immobilized animals,

(f) organization of scientific meetings on bone measurement methods and smaller workshops on absorptiometric measurement,

(g) monkeys,

(h) research on body composition and fluid shifts, and

(i) research on radiation detectors for absorptiometry.

As a consequence of that support measurement systems were developed that allowed accurate and very precise (1-2% error) measurement of both compact and trabecular bone <u>in vivo</u> and in fact systems were developed which allowed measurement of the total skeleton. It is now realized that the loss of trabecular bone with immobilization or space flight amounts to 1%/week and that this loss in adults is recovered very slowly if at all. As a consequence bone loss is the major biological impediment to prolonged space flight. Similarly fluid shifts in space flight can become large and have adverse consequences. The absorptiometric procedures we established allow measurement of such shifts.

A. SINGLE-PHOTON ABSORPTIOMETRY

Early in the project a direct readout instrument was developed for bone mineral measurement using ^{125}I. This became commercially implemented by both Norland Instruments (in the U.S.) and by Gammatec (in Denmark) with over 400 such instruments in clinical use. We defined various sources of error affecting measurements (scattered radiation, beam hardening, count losses due to deadtime, ^{125}I-contamination, beam profile effects, uneven tissue composition). These could not be corrected with earlier analog instruments but correction algorithms were implemented in latter direct readout instruments using microcomputers. A special linear scanner was built for possible use in space flight. Rectilinear scanning with ^{125}I was instituted to reduce the precision error by 30-50% and to allow measurement on bones with an irregular shape (such as the distal radius or os calcis). This reduced the precision error on the radius from 2% to 1.4%. The interrelationship of single-photon scans on the long bones was examined, and it was found that such scans were highly related with each other ($r>0.95$) and with total skeletal mineral. In normal subjects total body bone mineral could be predicted with an error (1 SEE) of only 8% but the prediction error was 12-18% on the femoral neck and 15% to 25% for the spine.

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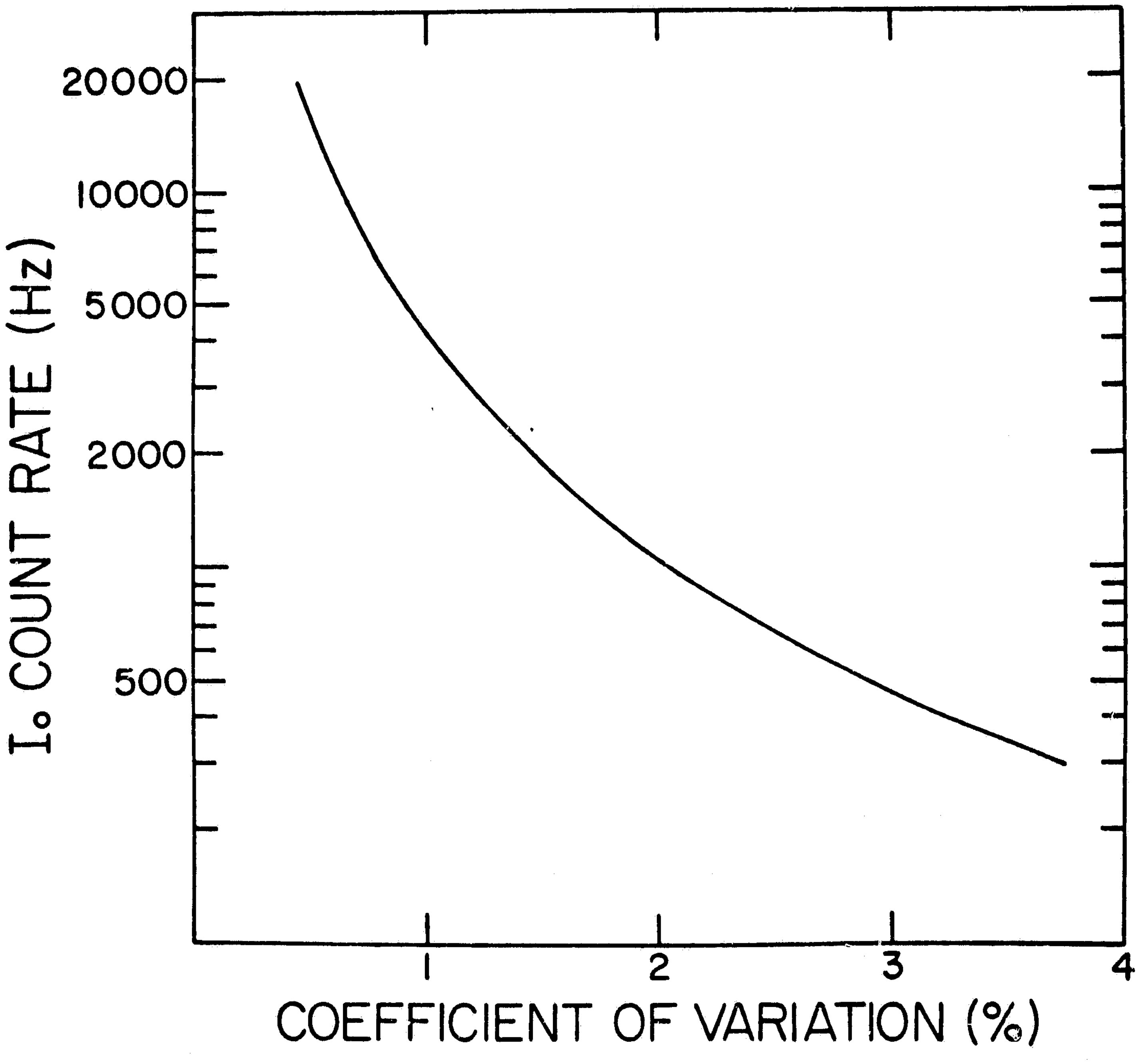
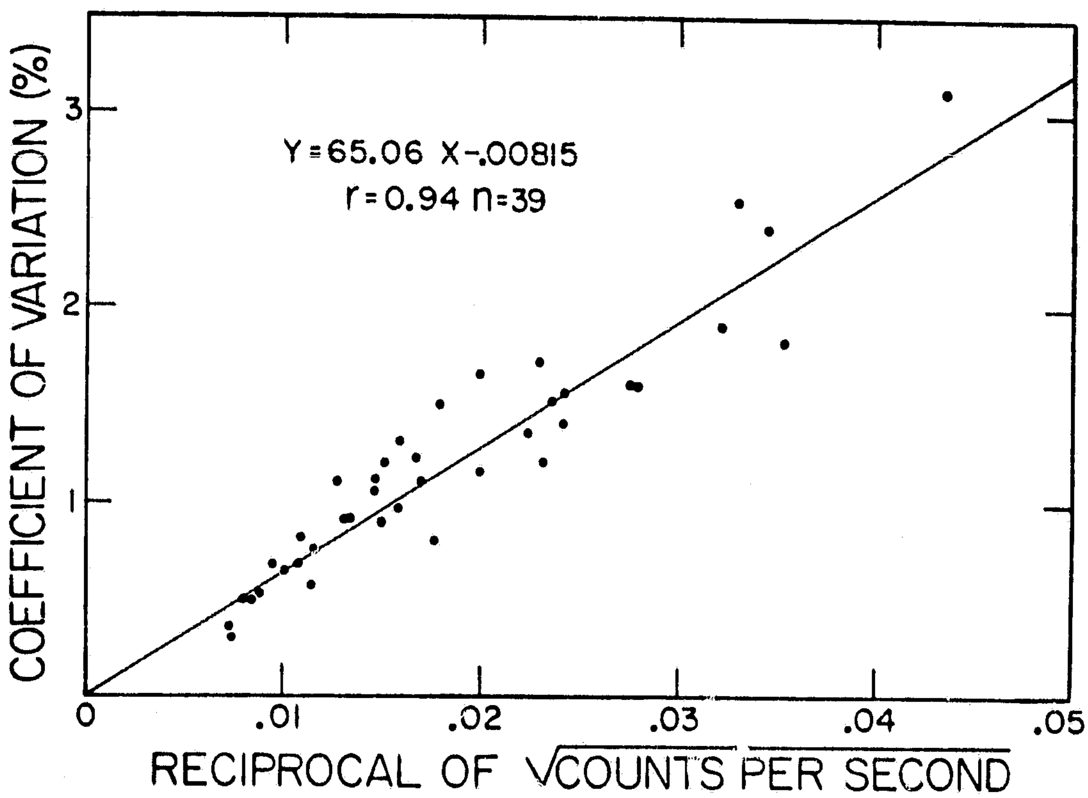
THE COEFFICIENT OF VARIATION IN SINGLE-PHOTON ABSORPTIOMETRY CAN BE REDUCED BY INCREASING THE COUNT RATE IN ADJACENT SOFT-TISSUE



AT HIGH COUNT RATES THE COEFFICIENT OF VARIATION CAN BE REDUCED TO BELOW 1%.

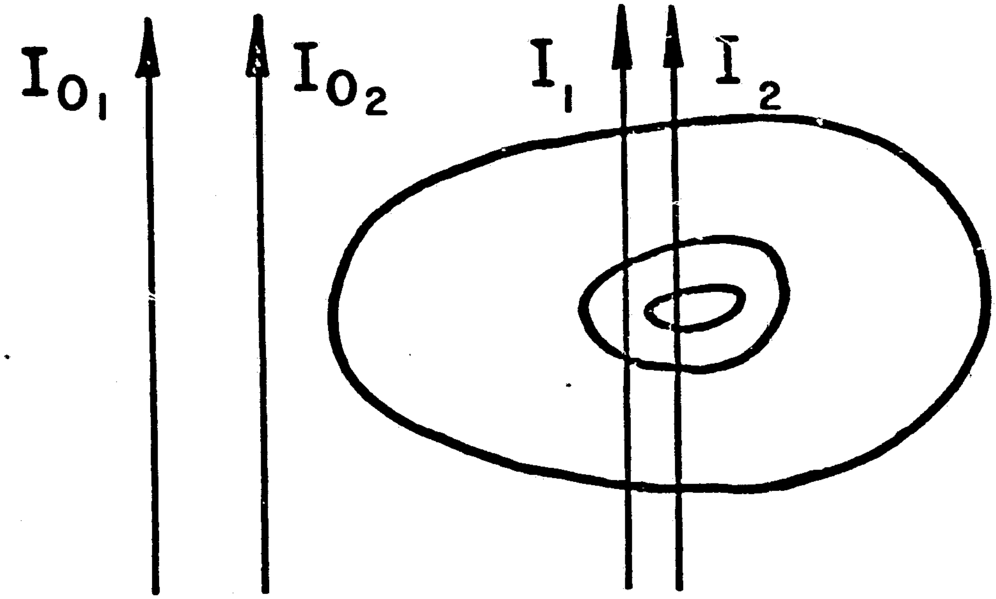


B. DUAL-PHOTON ABSORPTIOMETRY

Absorptiometry using two single-energy beams was developed early in the project in order to allow measurement of bone in vivo without the need for surrounding a limb in tissue equivalent material. In addition this allowed measurement of the tissue composition of that limb and evaluation of fluid shifts. A combination of ^{125}I and ^{241}Am sources (28 and 60keV) was used. With the availability of ^{153}Gd in 1970 it became possible to extend dual-photon measurements to the spine and to measurements of total body bone mineral. ^{153}Gd has nearly optimal energies (44 and 100keV) for measurement of thick body areas.

Sources of error in the dual-photon method were defined and a system was built and delivered to Ames Research Center to monitor bone mineral in immobilized monkeys. That system allowed precise long-term measurements (1.6% precision error on standards). The precision on monkeys was also good. Measurements of total body bone mineral content were made on normal subjects, patients and skeletons. The precision error in vitro was 1.5-2.0 and 2-3% in vivo. Recently the precision error in vitro was reduced to 0.7% without increase of the low dose (1 mrem). It has been possible to obtain measurements of regional bone mineral, including the spine, from the total body measurements.

DUAL PHOTON ABSORPTIOMETRY



$$I_1 = I_{O_1} \, EXP(-\mu_{BM1} \times BM - \mu_{ST1} \times ST)$$

$$I_2 = I_{O_2} \, EXP(-\mu_{BM2} \times BM - \mu_{ST2} \times ST)$$

DUAL-PHOTON ABSORPTIOMETRY USES MEASUREMENTS

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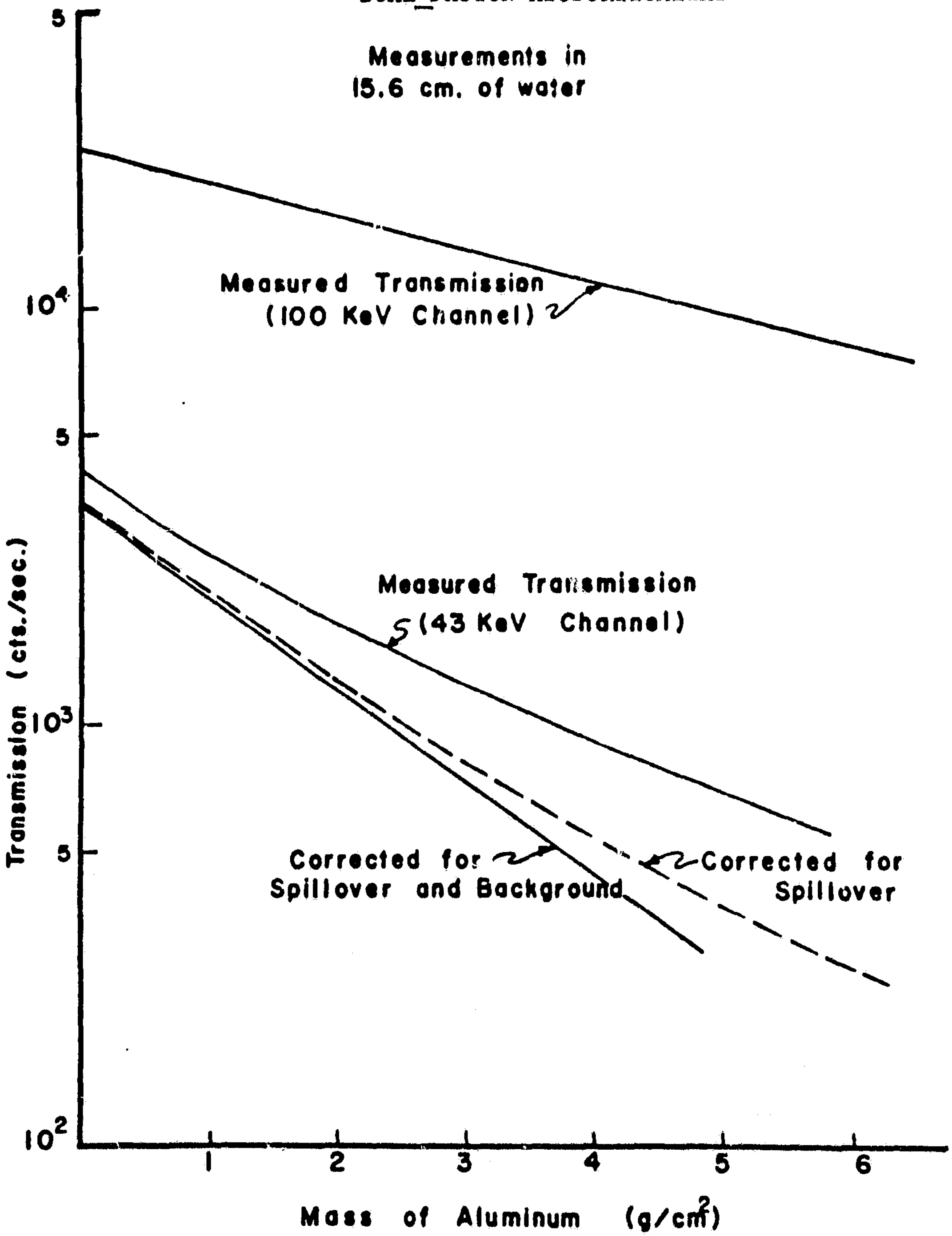
SUITABLE CORRECTIONS MUST BE APPLIED FOR
DUAL PHOTON ABOSORTIOMETRY



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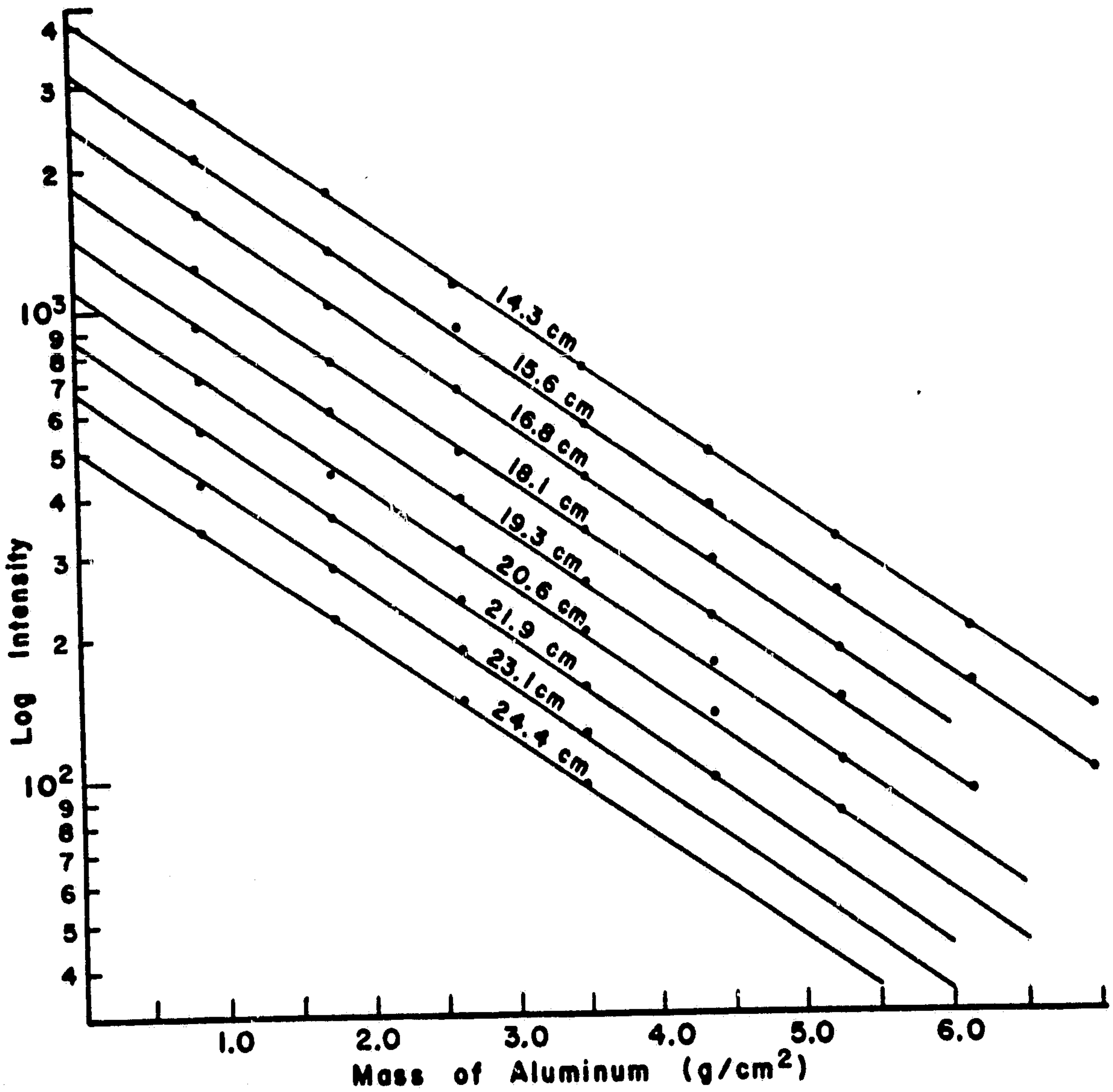
LINEAR ATTENUATION CAN BE ATTAINED AT ALL SOFT-TISSUE THICKNESSES



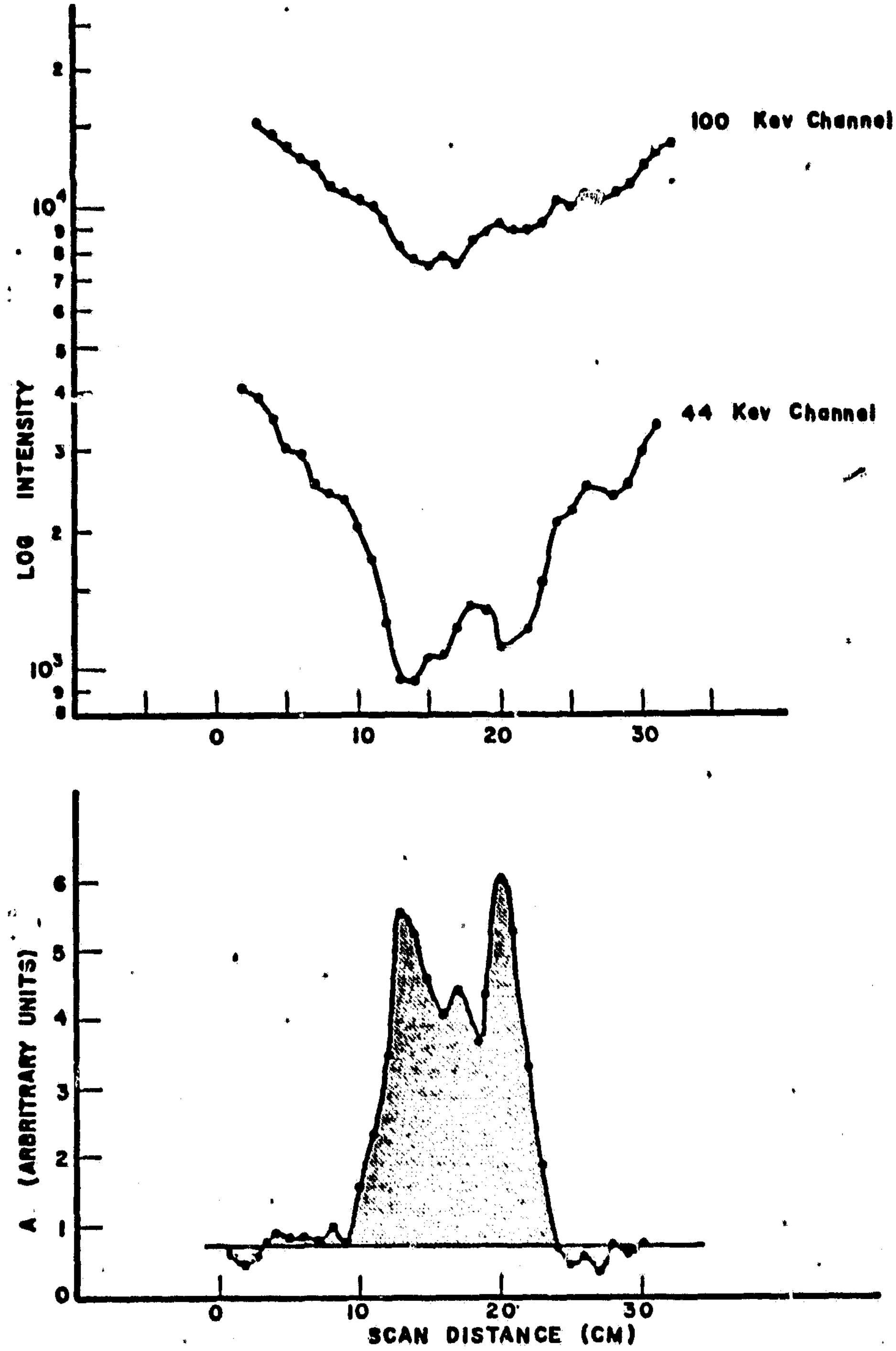


Figure 1. The transmitted intensities of the two photon beams and the value A versus scan distance.

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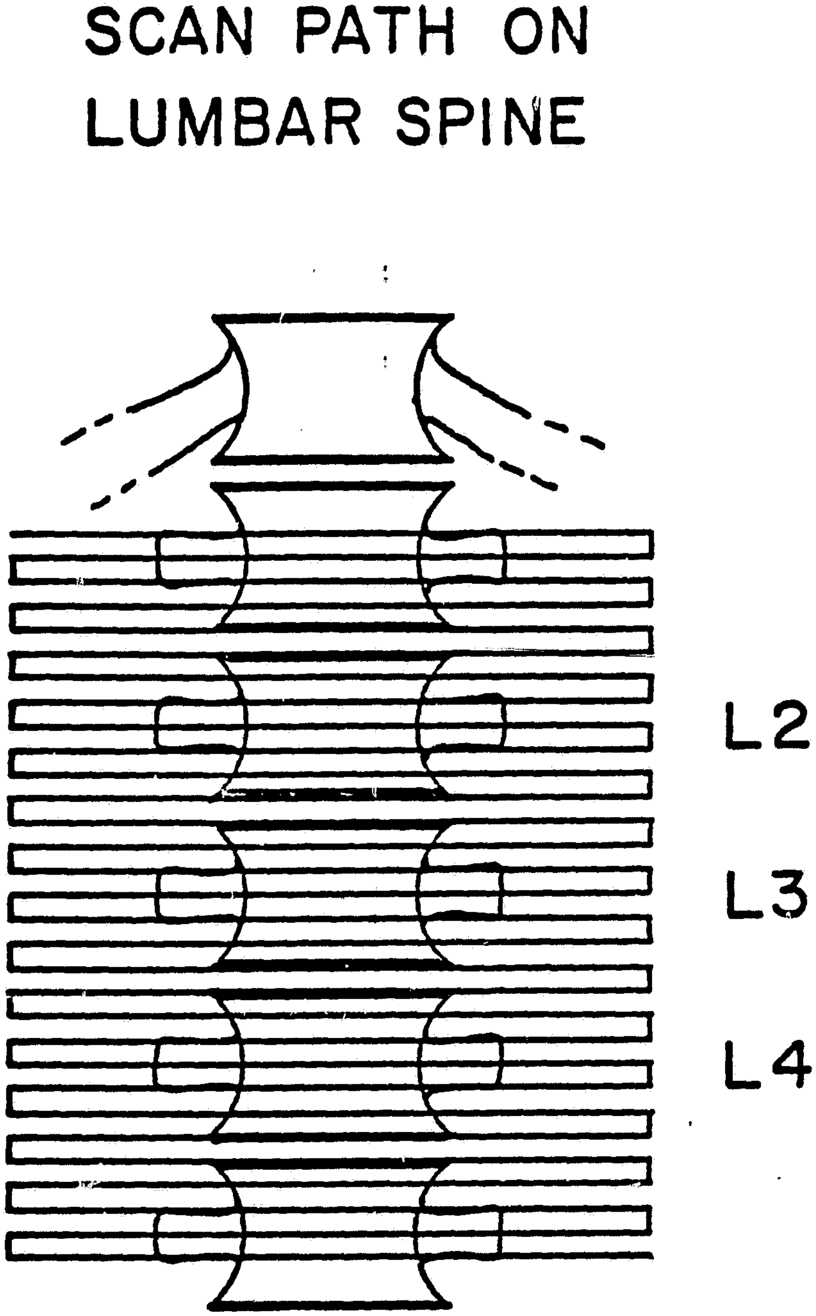

FIGURE 5
RECTILINEAR SCAN OF LUMBAR SPINE

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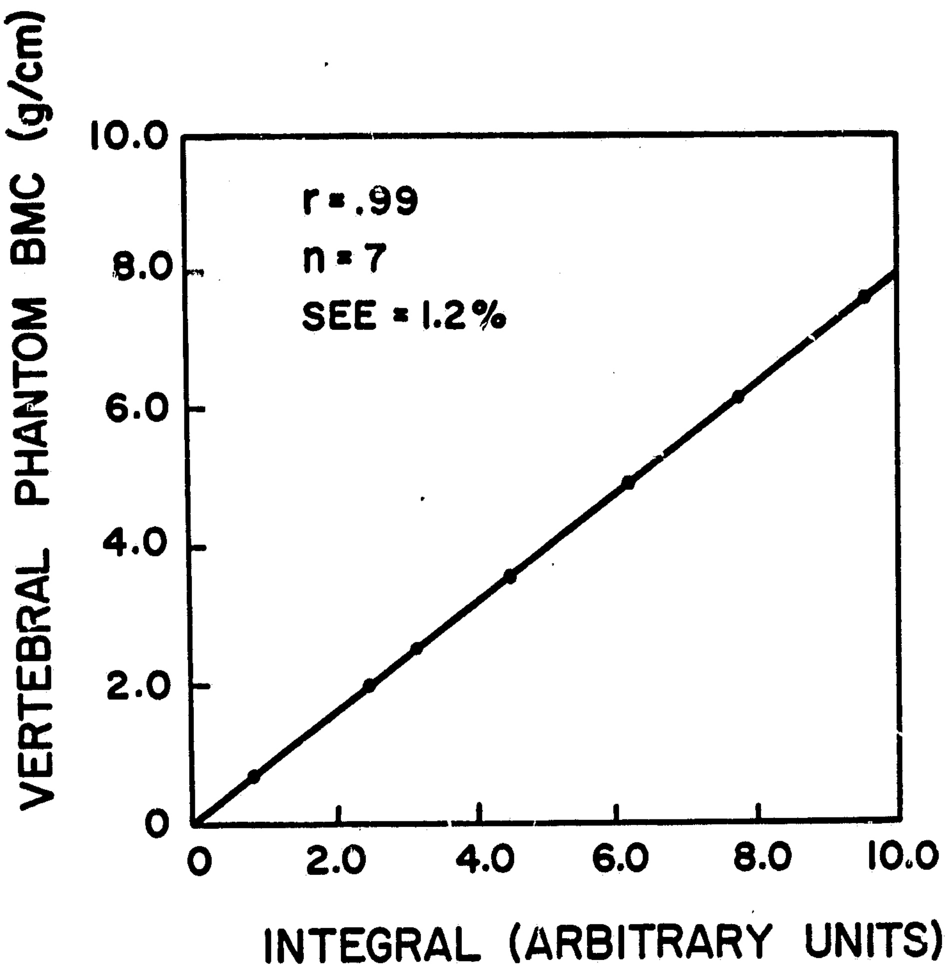
ACCURACY OFDUAL-PHOTON SCANS ON PHANTOMS



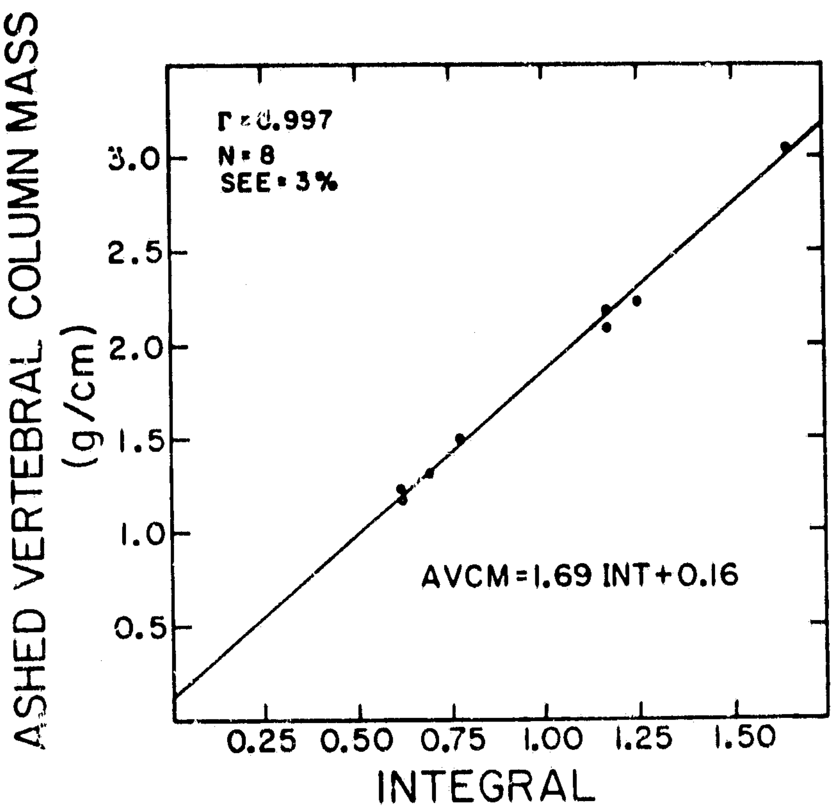
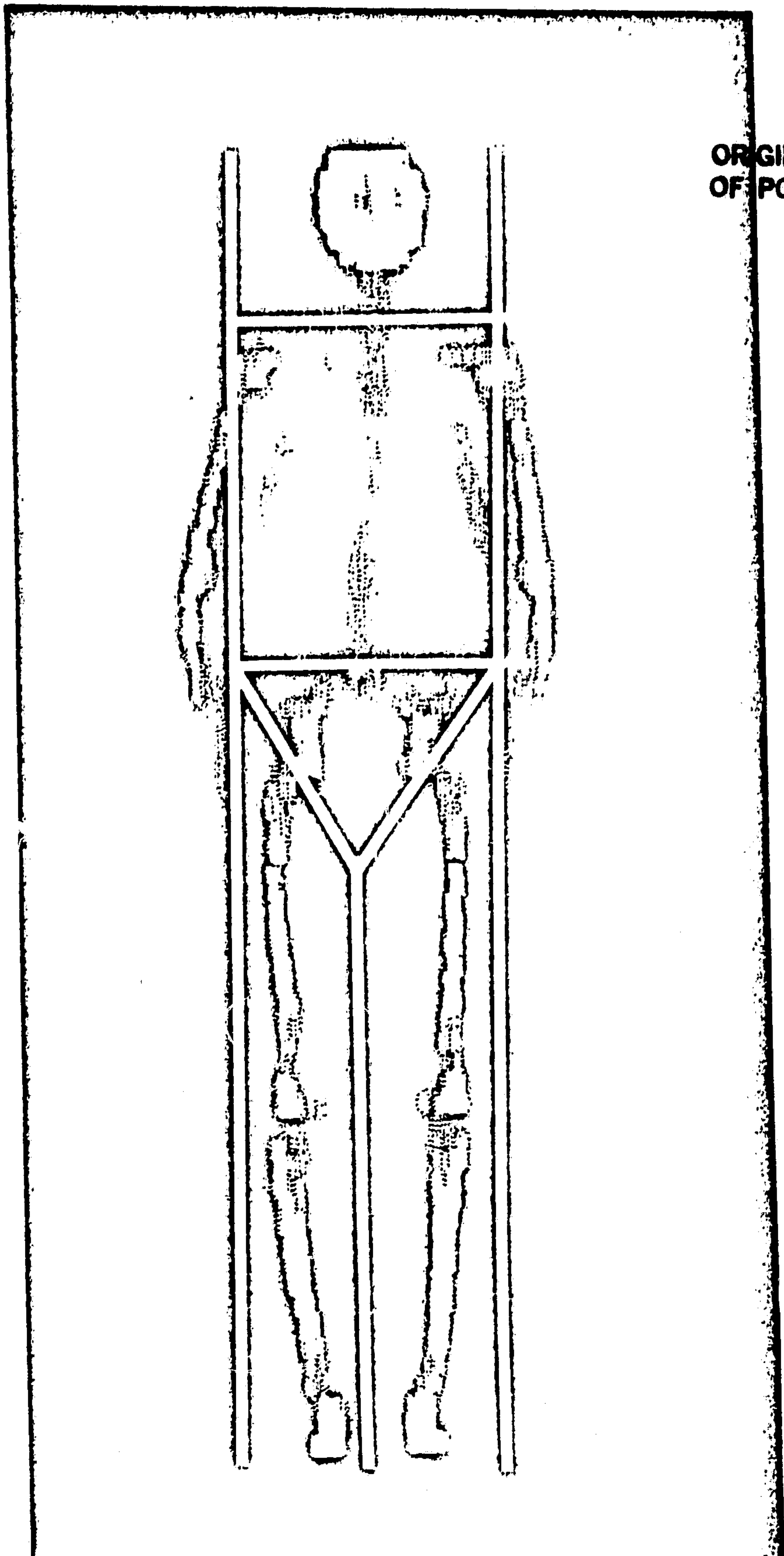


Figure 3
Regression of the absorptiometric estimate of bone mineral mass and the actual ashed vertebral bone mineral mass.

SCREEN APPEARANCE OF A TOTAL BODY BONE MINERAL SCAN SHOWING THE REGIONAL AREAS MEASURED



ACCURACY OF TBBM VERSUS TBCa (By neutron activation analysis)

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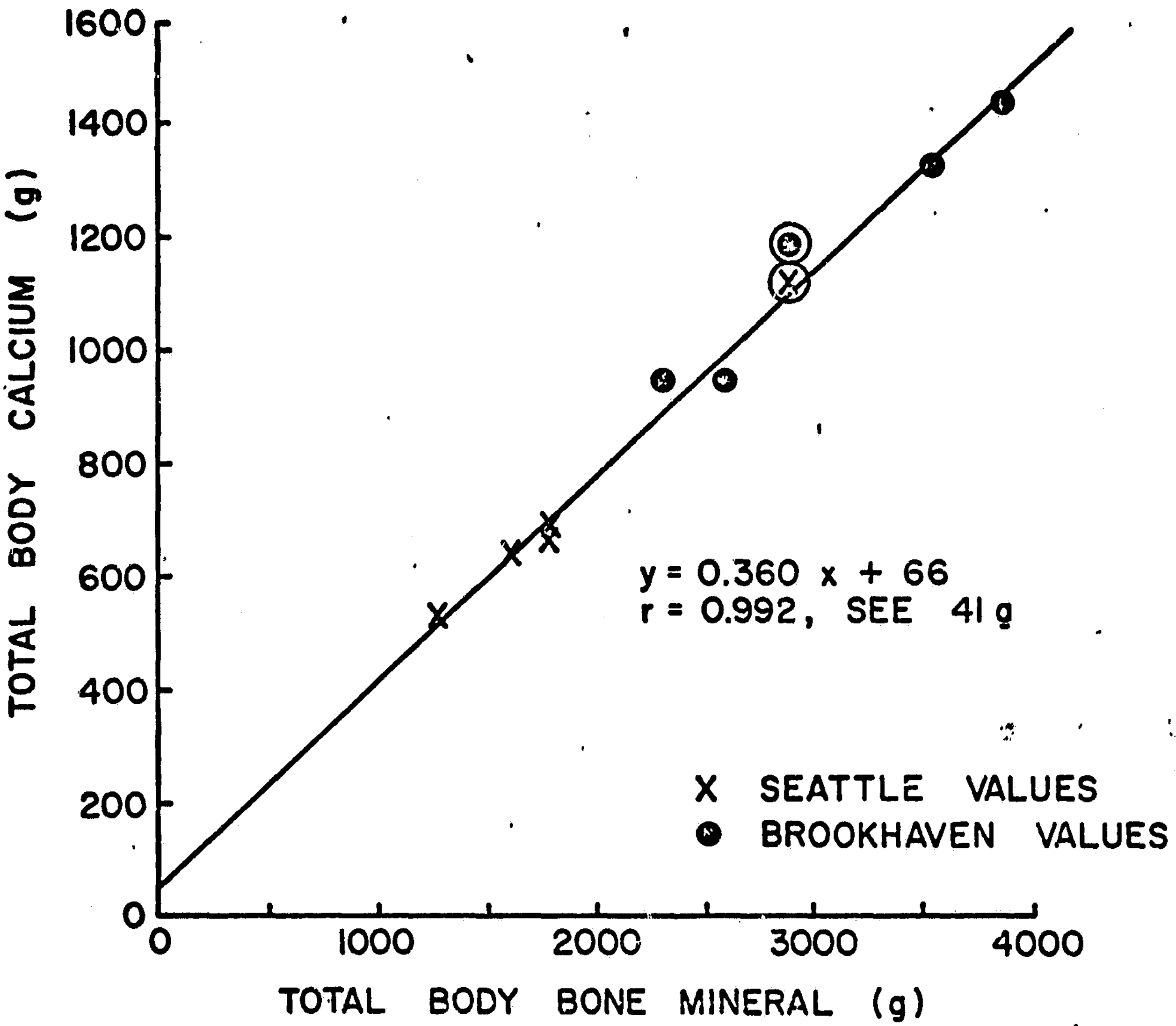


C. SKELETAL UPTAKE OF DIPHOSPHONATES

We have used a whole-body counter to monitor the uptake of ^{99m}Tc-labelled (50μsec) diphosphonates (HEDP and MDP) over a 24-hour period.

These uptakes were shown to be fairly uniform in normal young men but there were marked deviations in patients with bone disease. There was a 20% retention of HEDP and a 30% retention of MDP at 24 hours in normal subjects. The retention corresponded directly to the amount excreted in the urine. A two-component exponential equation fitted the data very well. This allowed evaluation of bone activity (rather than mass or density) using a low dose (6mrem) method.

PARAMETERIZATION OF THE RETENTION OF ^{99m}Tc-DIPHOSPHONATES

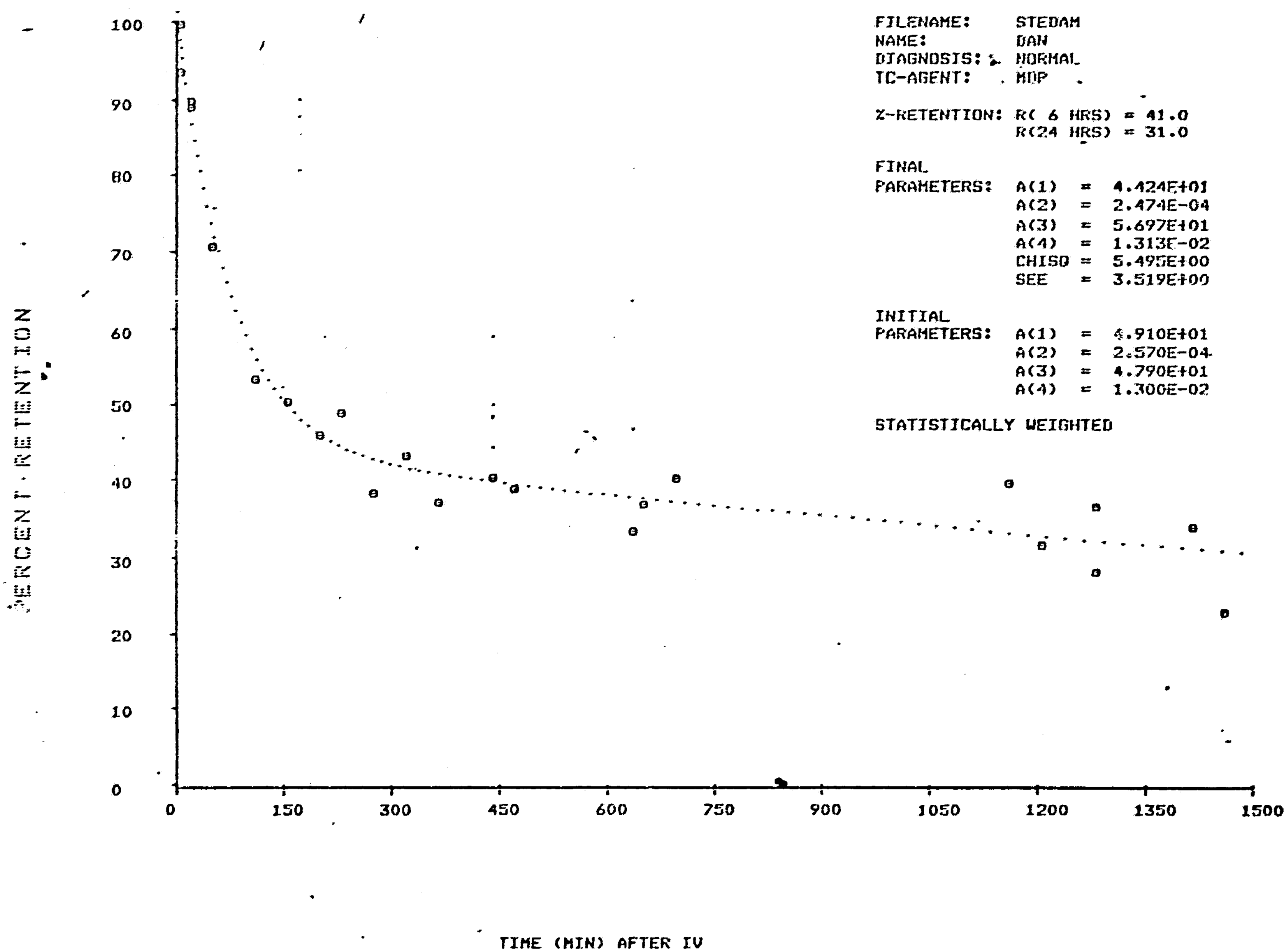
Retention curves were easily resolved using a two-phase model of exponential loss (see enclosed sheets). The first phase of rapidly decreasing activity represented clearance from soft-tissue. The intercept at T_o indicates the amount of clearance while the slope (A_4) indicates the rate. The slower second phase represents bone uptake; the intercept at T_o (A_1) indicates the projected bone uptake at T_o while the slope reflects long-term loss from bone (and soft-tissue). This model fit all areas (total body, head, chest, legs) quite well; X^2 was low and the standard error of estimate about each curve averaged 3%. For three normal adult males the values were:

		A1	A_2 (*10^{-4})	A_3	A_4
TOTAL BODY	HEDP	35.1	5.48	63.8	.0112
	MDP	38.2	2.58	63.3	.0120
HEAD	HEDP	42.6	4.28	57.4	.0084
	MDP	51.6	2.62	48.4	.0121
CHEST	HEDP	37.9	5.87	61.8	.0141
	MDP	42.7	2.05	57.3	.0183
LEGS	HEDP	24.1	3.03	75.0	.0054
	MDP	30.0	4.12	66.9	.0052

It is apparent from the table that the head had greater bone uptake (A_1) than the chest which in turn had greater uptake than the legs; in each case A_1 was greater for MDP than for HEDP. The bone avidity was usually greater for MDP as shown by the smaller slopes for A_2. As a consequence the whole body retention at 24-hours was 30% with MDP and only 19% with HEDP. Measurements in renal patients showed high retention due to a lack of clearance. In subjects with bone disease retention was high although renal clearance was normal. The results explain the clinical finding of greater contrast in bone scans with MDP than HEDP. They also show that 24-hour whole body ^{99m}Tc-diphosphonate retention studies used in metabolic bone disease will be influenced not only by renal clearance, but by variation in local bone retention.

% χ^2 change = 8E-3

RETENTION IN HEAD



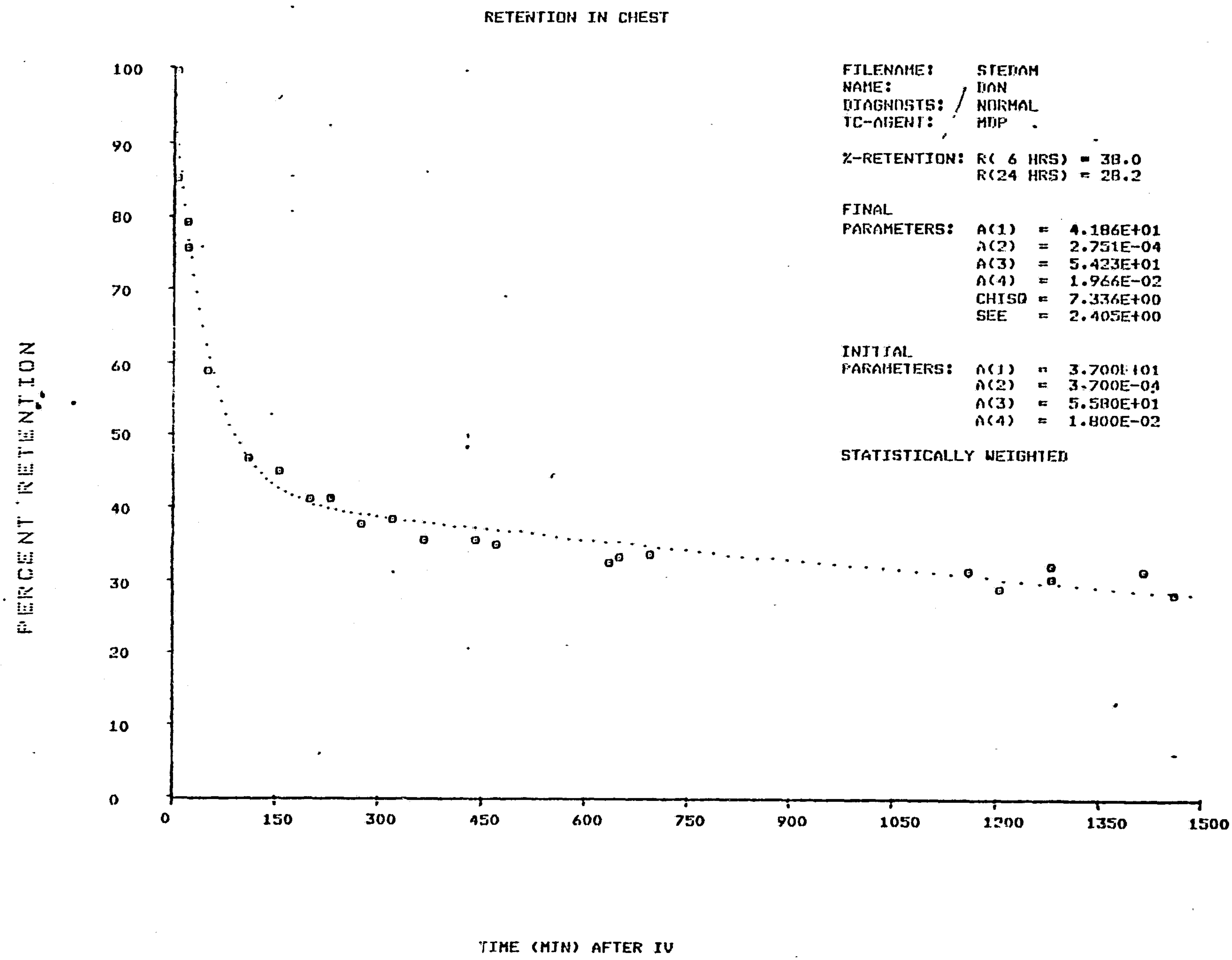
FILENAME: STEDAM
NAME: DAN
DIAGNOSIS: NORMAL
TC-AGENT: MDP

%-RETENTION: R(6 HRS) = 41.0
R(24 HRS) = 31.0

FINAL PARAMETERS:
A(1) = 4.424E+01
A(2) = 2.474E-04
A(3) = 5.697E+01
A(4) = 1.313E-02
CHISQ = 5.495E+00
SEE = 3.519E+00

INITIAL PARAMETERS:
A(1) = 4.910E+01
A(2) = 2.570E-04
A(3) = 4.790E+01
A(4) = 1.300E-02

STATISTICALLY WEIGHTED



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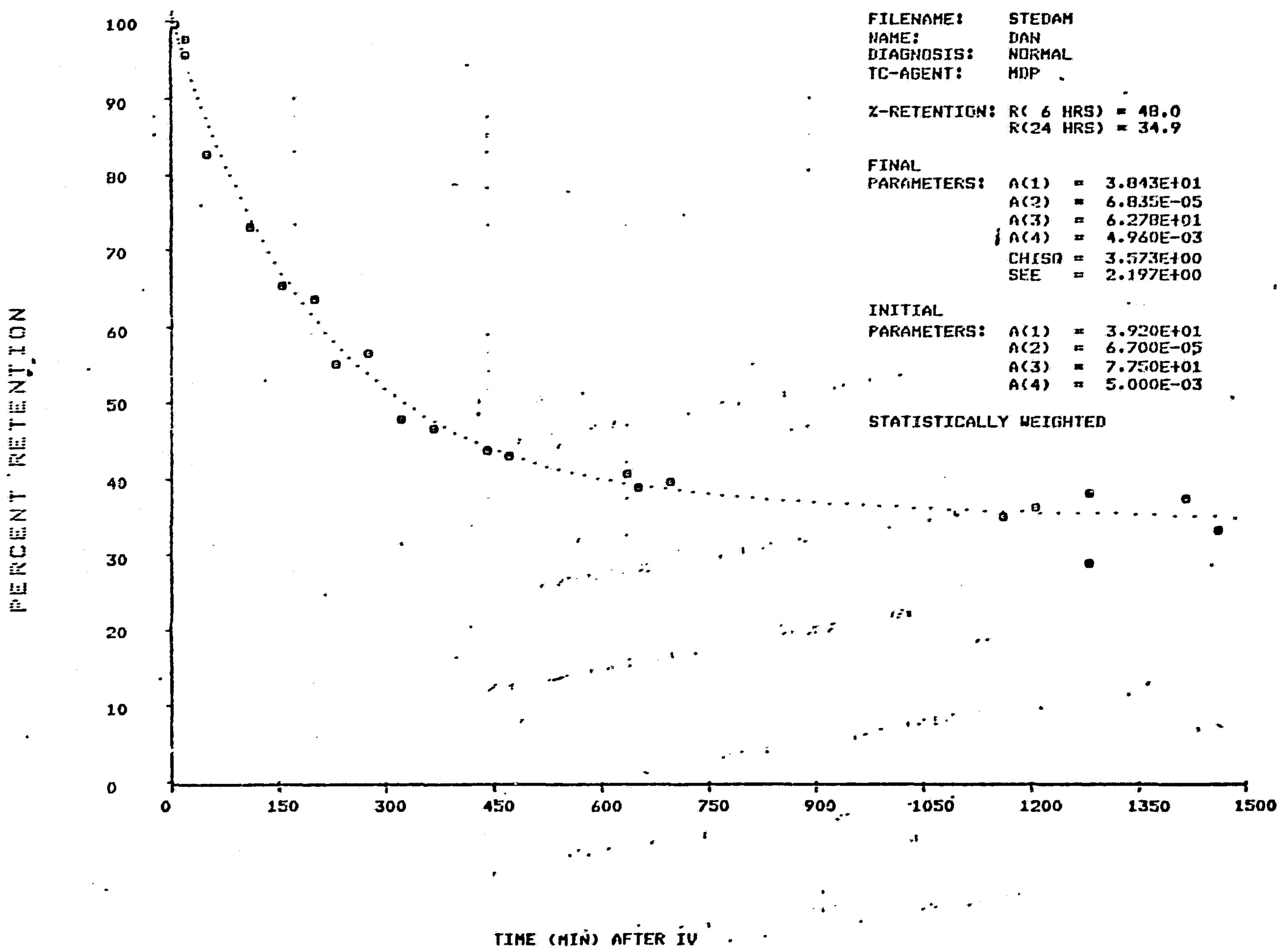
RETENTION IN LEGS



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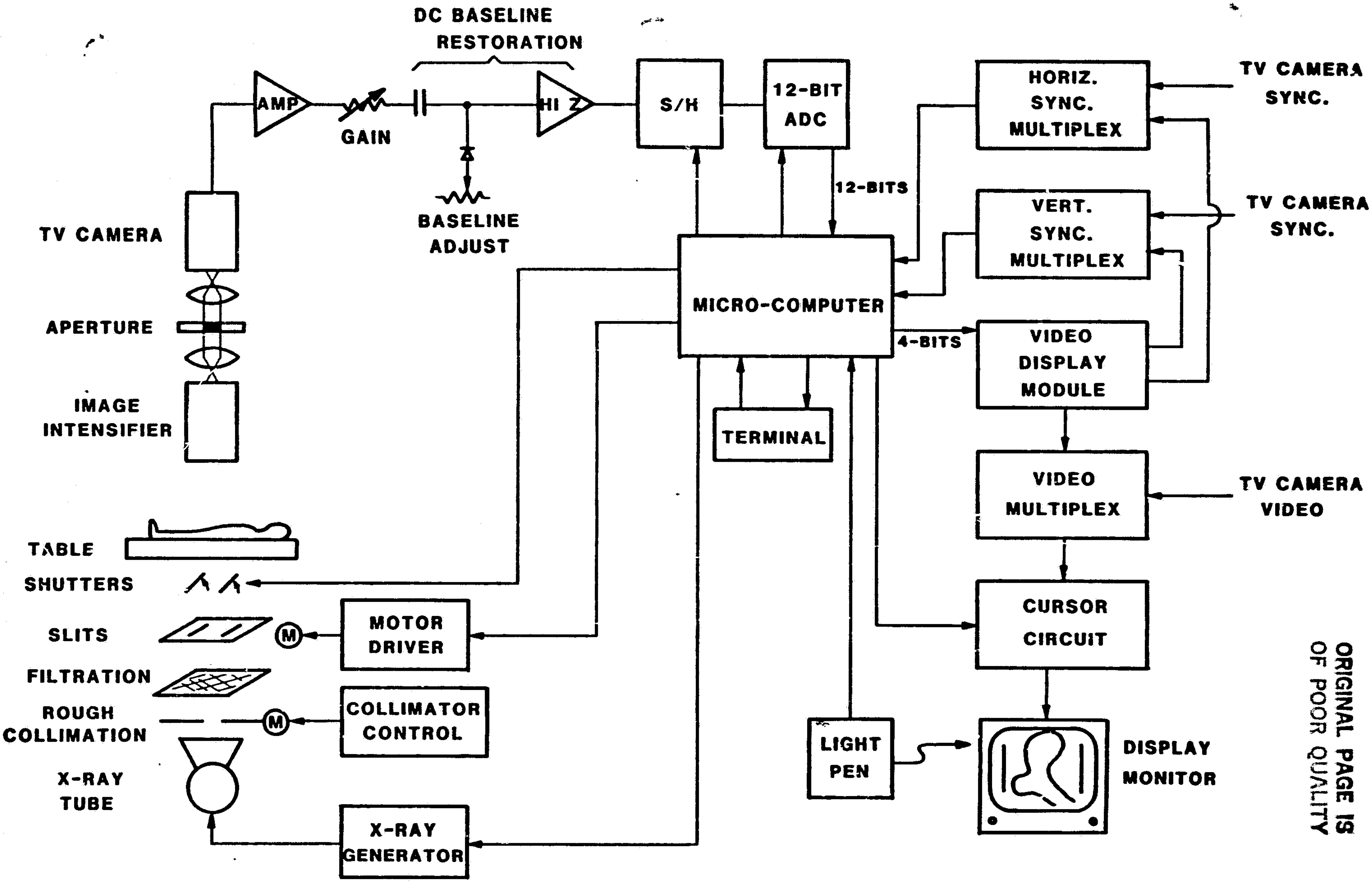
D. COMPARISON WITH OTHER TECHNIQUES

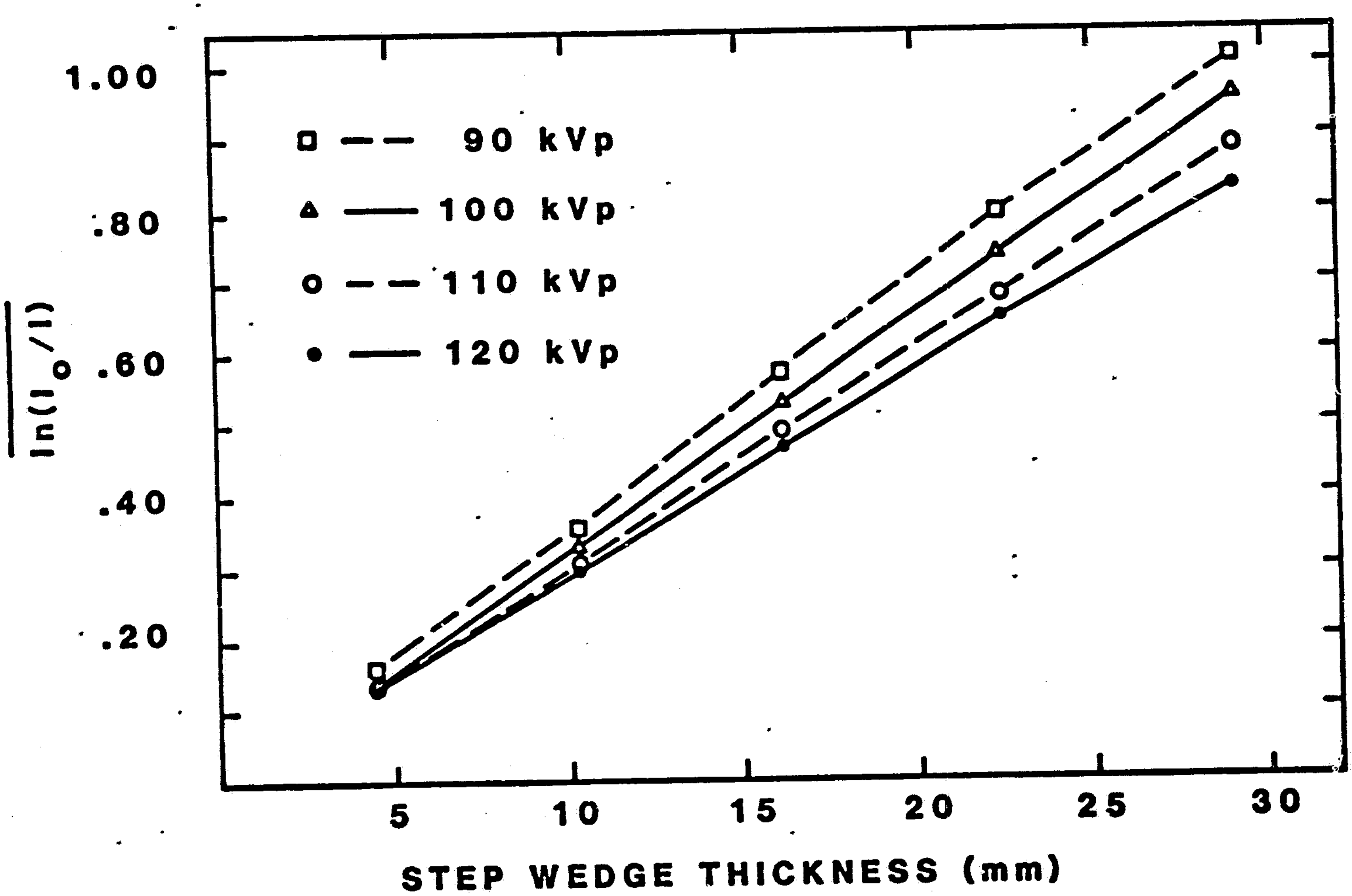
No one method provides all requisite information on bone quantity or quality. Consequently we have examined, and compared, several measurement approaches.

During the early part of the project extensive work was done on resonant frequency measurement in vivo (John Jurist). Comparisons were made between ^{125}I-absorptiometry and the various photodensitometric approaches (Vose and Mack at Texas Women's University and Colbert at Radiological Labs) which showed the latter to be faulty. An alternative radiological approach, videodensitometry, was developed. However, scattered radiation was minimized by using scanning slits. We have obtained good linearity ($\pm$3-5%) and high precision (0.7%) using this method. Compton scattering methods could provide a means for assessing trabecular bone so we developed a method using Compton-coherent scattering. This was fairly accurate and precise but the dose was very high (400mrem for 3% precision).

Finally we did studies using x-ray CT of the spine in monkeys and man. We showed that difficulties of repositioning led to very large errors (15%) in results (using a GE 7800 scanner). The results on the same spines were far more precise (2%) using dual-photon absorptiometry. It was also shown that x-ray CT of the spine was the most erroneous measurement method ever advocated for use in humans. The large potential errors (30%) of the method due to varying marrow fat make it totally unsuitable for monitoring bone in space flight.

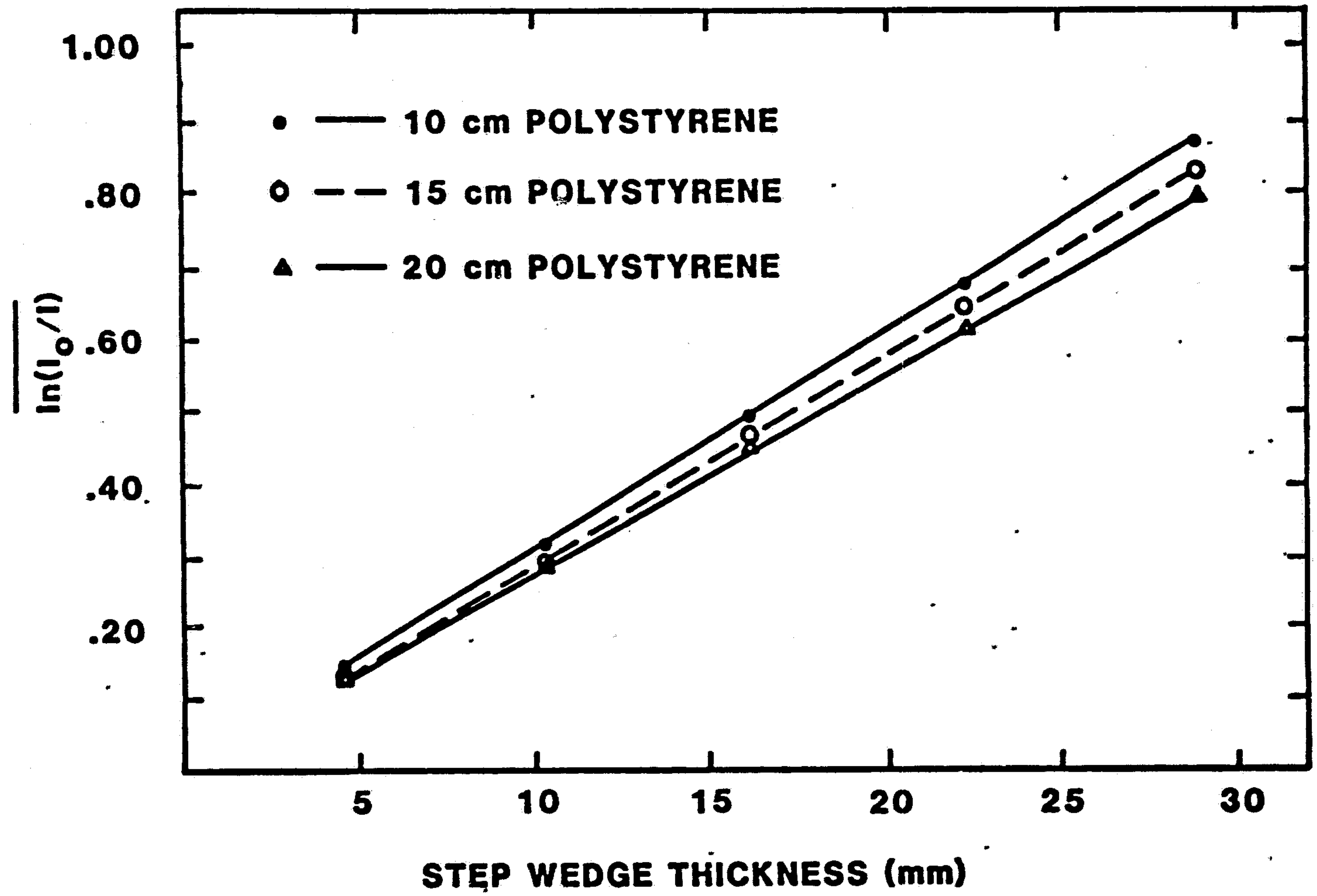


ROENTGEN VIDEOABSORPTIOMETRY SYSTEM



EFFECTS OF KVP ON ATTENUATION

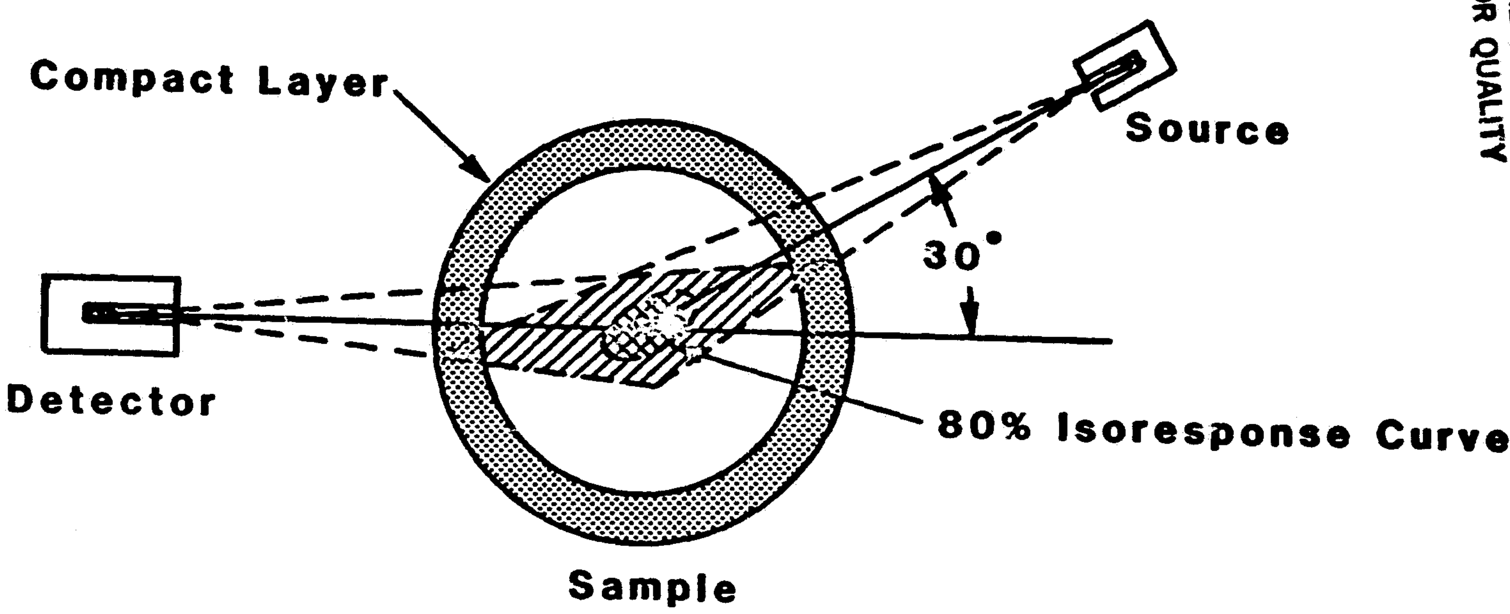
Fig. 4



EFFECTS OF SOFT TISSUE THICKNESS ON ATTENUATION

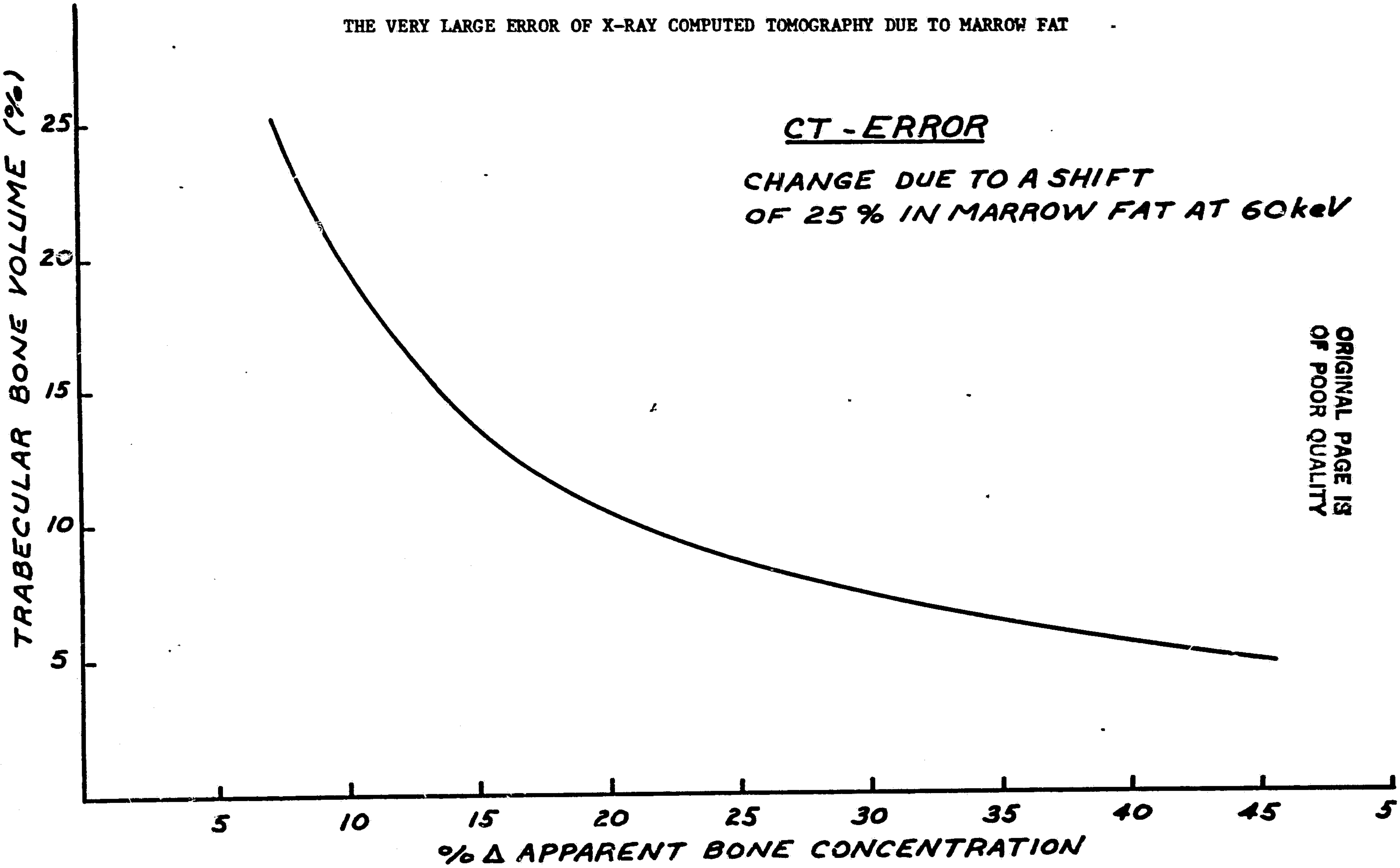
THERE WAS A VERY SLIGHT EFFECT OF HARDENING AND SCATTER

Fig. 5



COMPTON-COHERENT SCATTERING METHOD IS OPTIMAL AT THE LARGE ANGLE
SINGLE-SOURCE COMPTON SCATTERING CAN ALSO BE DONE AT THIS ANGLE.

THE VERY LARGE ERROR OF X-RAY COMPUTED TOMOGRAPHY DUE TO MARROW FAT



E. COOPERATION WITH NASA PROJECTS FOR SKELETAL EVALUATION IN SPACE FLIGHT (MO-78) AND IN IMMOBILIZED ANIMALS

Technical support was provided for investigators at U.S. Public Health Service hospital in San Francisco for absorptiometric studies (^{125}I scanning of limbs and os calcis). Studies were subsequently done on immobilized subjects, in flight simulation and in astronauts during space flight.

We have also provided technical support to investigators at Ames Research Center and provided them with a dual-photon scanner system for monitoring immobilized animals.

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F. MEETINGS AND WORKSHOPS

Since the inception of the project a series of scientific meetings have been organized in order to facilitate the interchange of information on bone measurement methods, and on specific applications (such as the 1982 meeting on immobilization outlined in Appendix C). This has permitted international input regarding problems of methodology as well as suggesting novel solutions to some of these problems. Published reports eminating from these meetings (1970, 1973, 1976 and 1978 specifically) have been widely disseminated.

1969 - Workshop on Absorptiometry - O'Hare

1970 - Bone Measurement Meeting - Chicago

1971 - Workshop on Absorptiometry - O'Hare

1973 - Bone Measurement Meeting - Chicago

1975 - Workshop on Absorptiometry - Madison

1976 - Bone Measurement Meeting - New Orleans

1978 - Bone Measurement Meeting - Toronto

1982 - Workshop on Immobilization - San Francisco

1982 - Workshop on Dual-Photon - San Francisco

G. ANIMAL STUDIES

Single-photon absorptiometry was used to measure the limbs (radius, ulna, humerus) on a series of 63 adult female monkeys. Sequential measurements (4 occasions) were made over two years to examine the influence of oophorectomy. The operated animals had a higher rate of aging bone loss than controls. This project allowed us to develop higher precision linear scans on small animals and gave familiarity with the animal model used for immobilization studies at Ames Research Center.

We cooperated with Ames Research Center in doing spinal and total body bone mineral measurement of monkeys used in experimental studies. A special spine scanner was built, documented, tested and delivered to ARC. That scanner has allowed high precision measurements of the lumbar spine in immobilized animals. About 55% of animals tested several times over 4 months showed less than a 3% variability. Spinal bone loss in two immobilized monkeys at ARC was 0.5%/week and 1.2%/week.

H. DETECTORS

There has been extensive research done over the past decade on detectors that could be used for bone and soft-tissue absorptiometry in space flight.

A variety of conventional scintillation detectors using photomultiplier tubes were examined with respect to size, sensitivity and stability. A special folding linear scanner was made that used an experimental RCA detector; this could allow scanning of the limbs in space. In addition we evaluated Cl Te and HgI detectors but these small, low power detectors were not suitable because of high background. A large project was undertaken, which later received NIH support, on position-sensitive proportional counters (PSPC). The PSPC's could allow local and area bone and soft-tissue determinations without the need for a motor-driven scanner mechanism. We examined single- and multi-wire detectors and developed a multi-anode detector that allowed use of high count rates. The various problems with PSPC detectors were analyzed, particularly in regard to energy versus spatial resolution, and reduction of scatter and parallex errors (see thesis by J. Hanson). Quantitative data in vivo was obtained with a PSPC that was loaned to our laboratory by Oak Ridge National Lab. The results on limbs correlated very well with results of ^{125}I absorptiometry (r=0.97) on the same subjects. Quantitative images also were obtained on the femoral neck and the spine. However, the PSPC we had could not provide dual-energy discrimination and so could not be used for ^{153}Gd scans of these area.

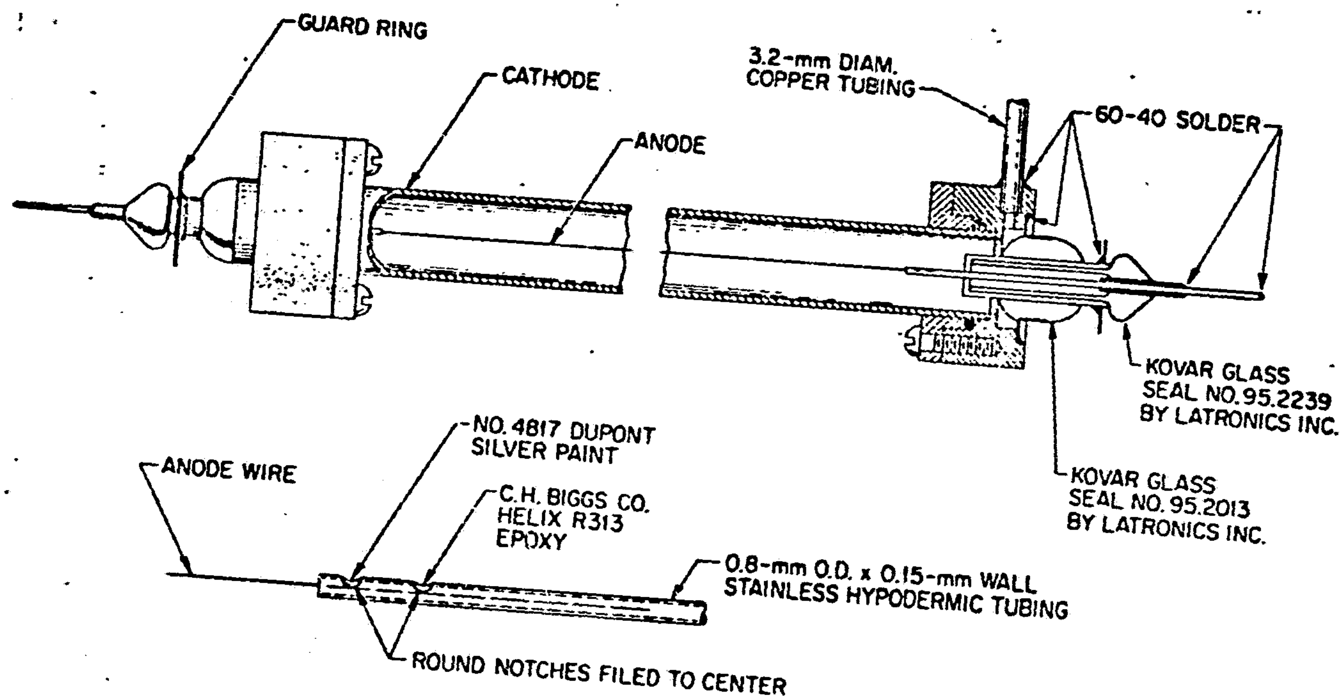


Figure ~~3.1~~ 1 Construction details of a linear PSPC (courstesy of M.K. Kopp).

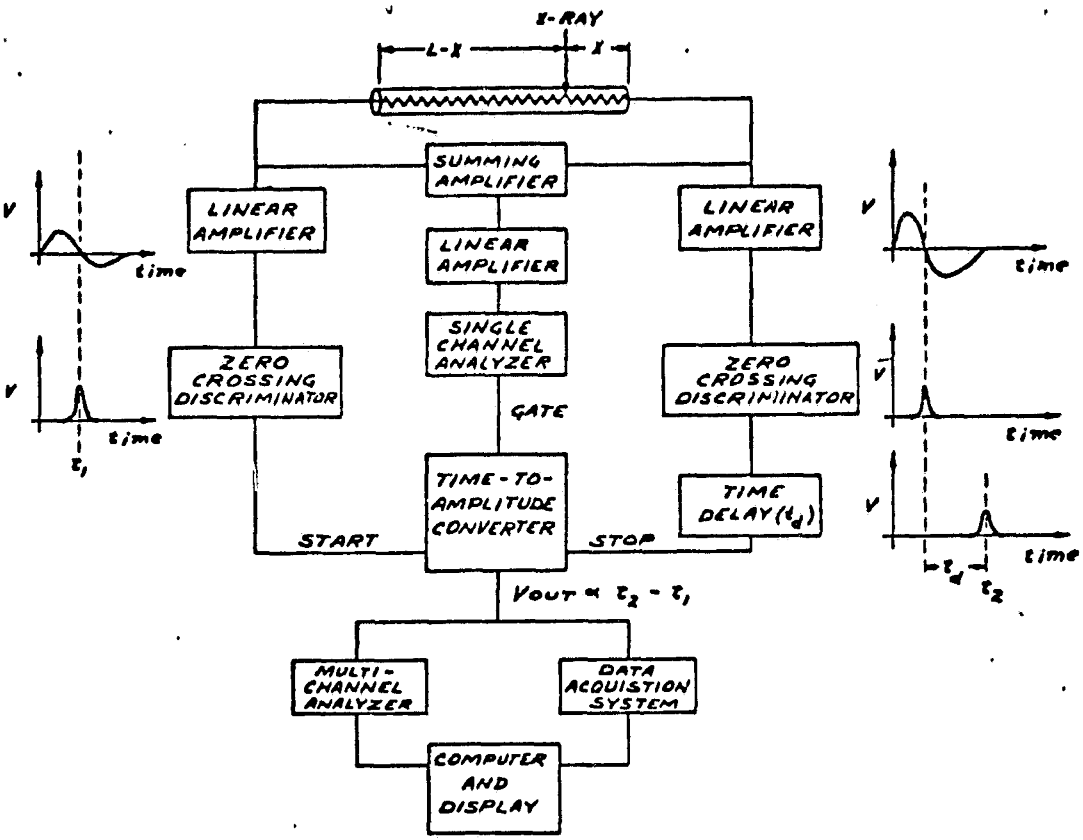
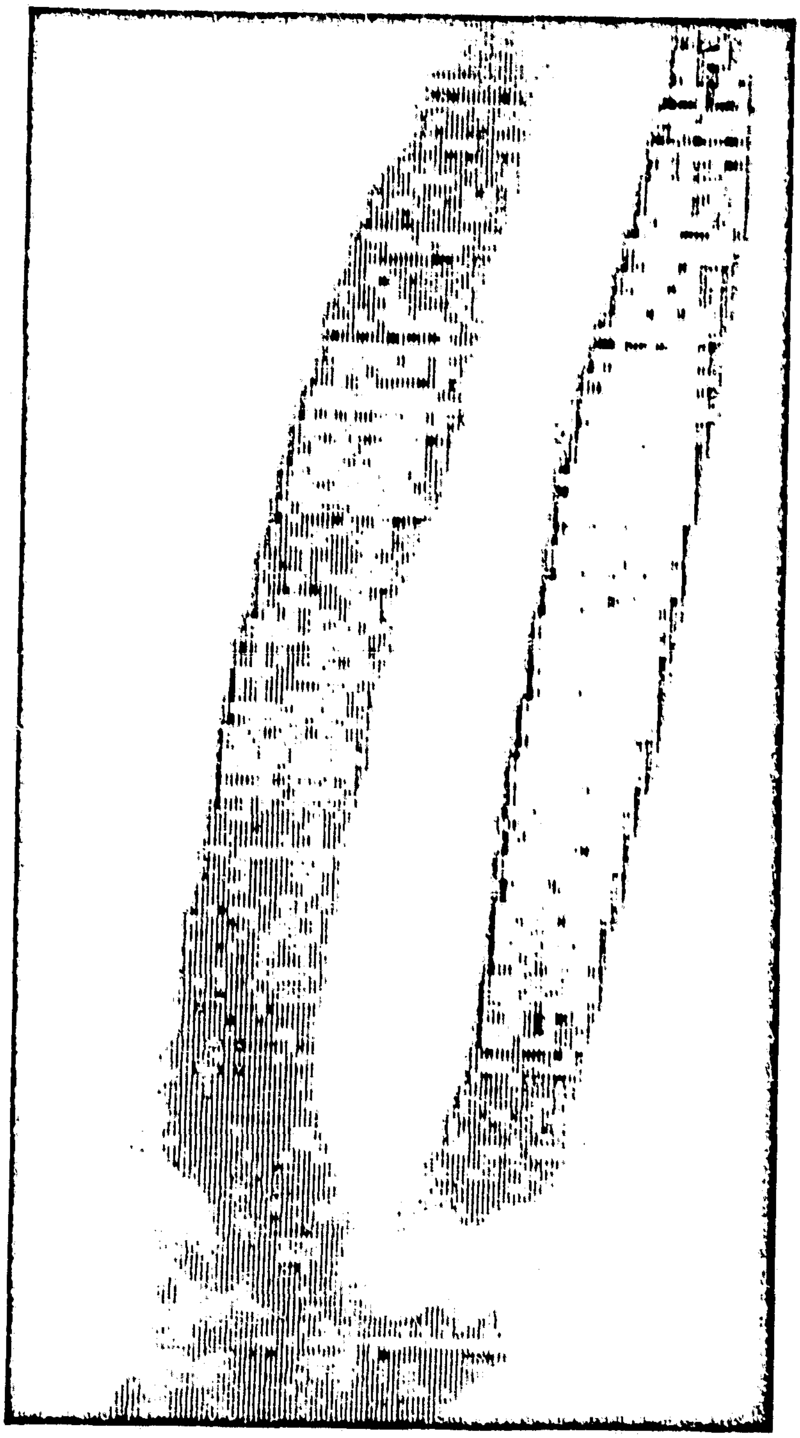


Figure A.2 Block diagram of PSPC system components.



PSPC IMAGE OF THE FOREARM *IN VIVO* (WITH ^{125}I).

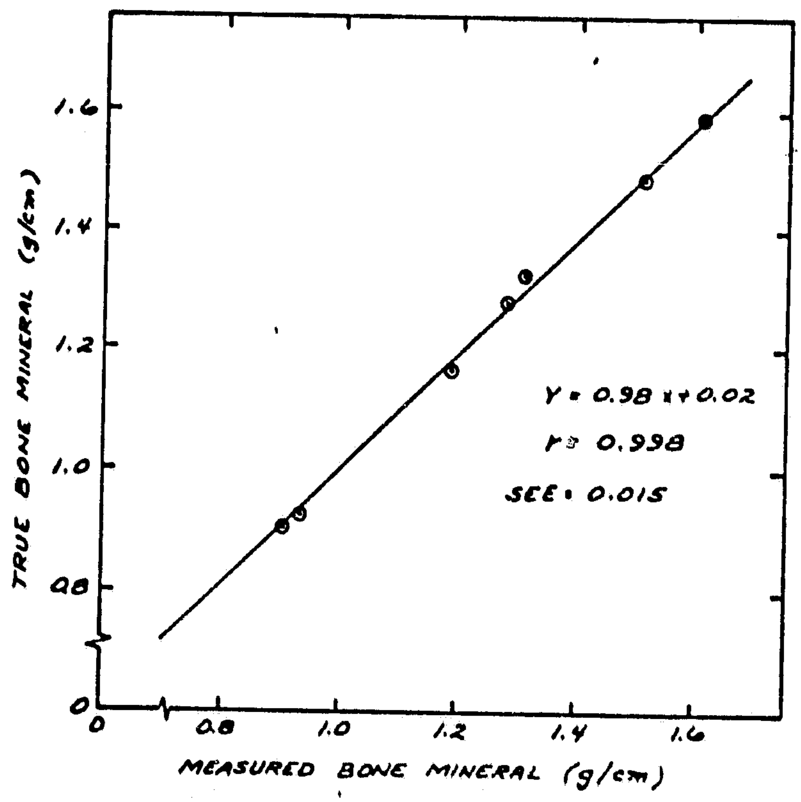


Figure ~~6.12~~ 9 The radius bone mineral of 7 normal subjects measured with the 2M1D linear PSPC compared to the true value determined from the conventional scanning method.

~~Figure 1~~

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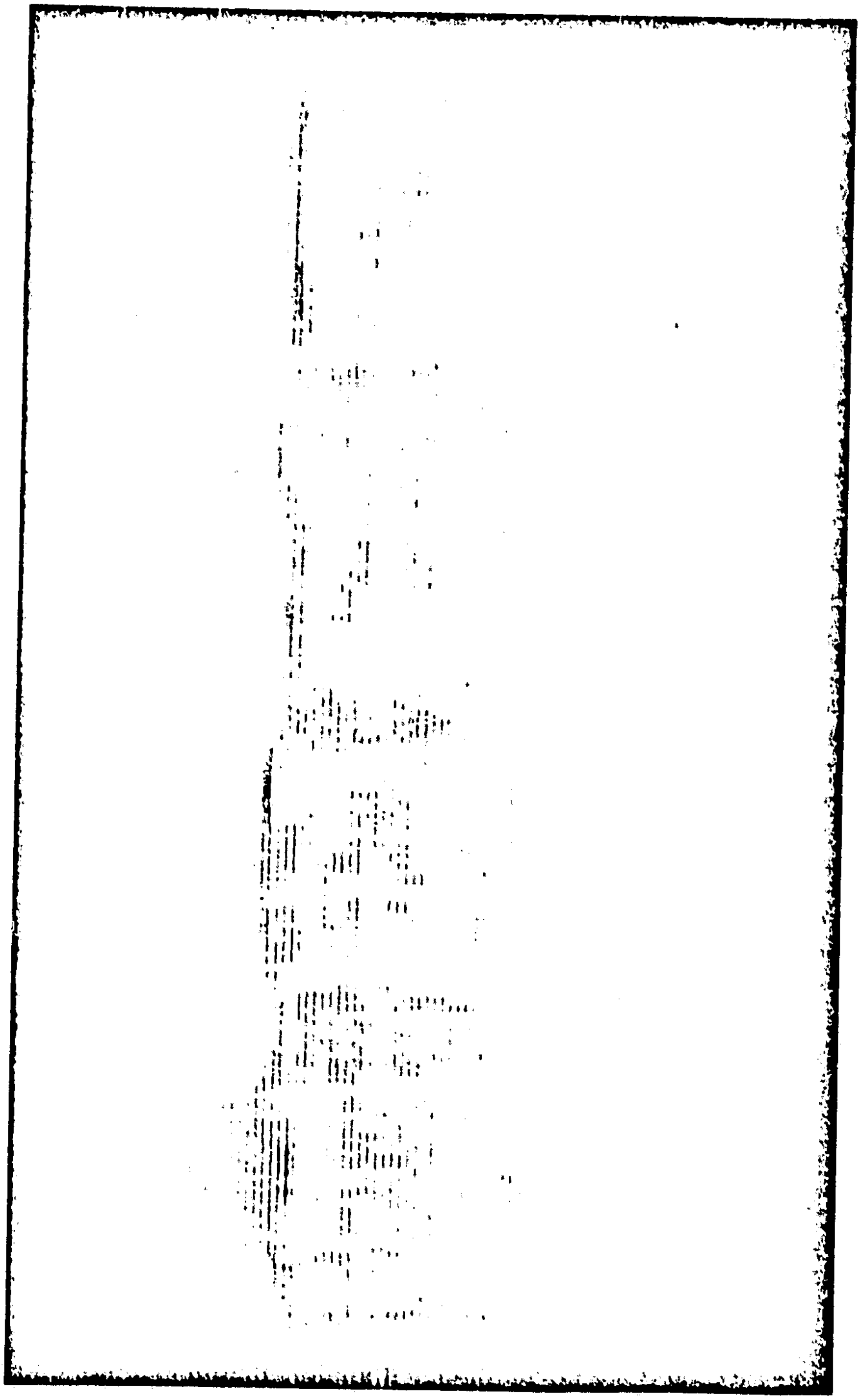


PSPC IMAGE OF THE LUMBAR SPINE (WITH ^{125}I) IN AIR.

A HIGHER ENERGY SOURCE IS NEEDED FOR WORK IN VIVO

I. BODY COMPOSITION AND FLUID SHIFTS

Pioneering work on measurement of body composition in the limbs was done during the first years of this project using a dual-photon absorptiometry approach. This initial research used ^{125}I (27keV) and ^{241}Am (60keV) sources to determine the amount and composition of soft-tissue on the forearms, legs, and upper arms of human subjects. We also showed that absorptiometry could be used to monitor fluid changes in the limbs by sequential monitoring of changes associated with venous occlusion. More detailed experiments were done to define sources of error of the method, to assess its use in monitoring fluid changes in patients, and to evaluate predictive accuracy of limb measurements in assessing total body composition. The fundamentals of the method were described in the Ph.D. thesis generated by Robert Witt and in the collaborative work done with physicians from the University of Wisconsin Department of Surgery (J. Maylan and Wm. Wolberg). It was shown that the time course of fluid changes could be very accurately monitored by limb measurements in dogs whose fluid volume was experimentally manipulated. However, there were differences between the magnitude of fluid changes in the limbs and the central body. Fluid changes were monitored in patients during and after surgery and in the couse of therapy for large area burns. The major difficulty with these measurements was their local specificity; in many cases central pooling could occur without being reflected in the limbs.

This was also a factor in predicting total body composition (from body density assessed by combined underwater weighing and deuterwim oxide dilution). Total body composition could be predicted with high accuracy from scans of the upperarm but not of the forearm in 10 young adult males. This was not affected by voluntary dehydration (loss of 2% body weight).

After 1976 our studies used dual-photon absorptiometry with ^{153}Gd (44 and 100keV) for measurement of body composition. In these studies body composition and soft-tissue were determined in scans of the entire body (time required 60-minutes; dose about 2mrem). Regional values also were determined from these studies (arms, legs, trunk) so that the central body and limbs could be separately evaluated. Body composition was evaluated from body density measurements in 18 women and compared to the absorptiometric results. There was a high correlation (r=0.90) between body fat derived from the two methods, and the degree of association was increased (r-0.94) when the influence of skeletal mass (determined by absorptiometry) on density was taken into account. These studies showed that total body absorptiometry was a highly reliable and accurate measure of regional and total body composition, providing a direct measurement which was independent of the "constancy" assumptions indulging most composition methods. The low-dose makes repeat measurements feasible. This method could be used to monitor the fluid shifts occuring during and after immobilization and space flight.

Figure 1: Relationship between a known mass of water and values obtained by D.A.

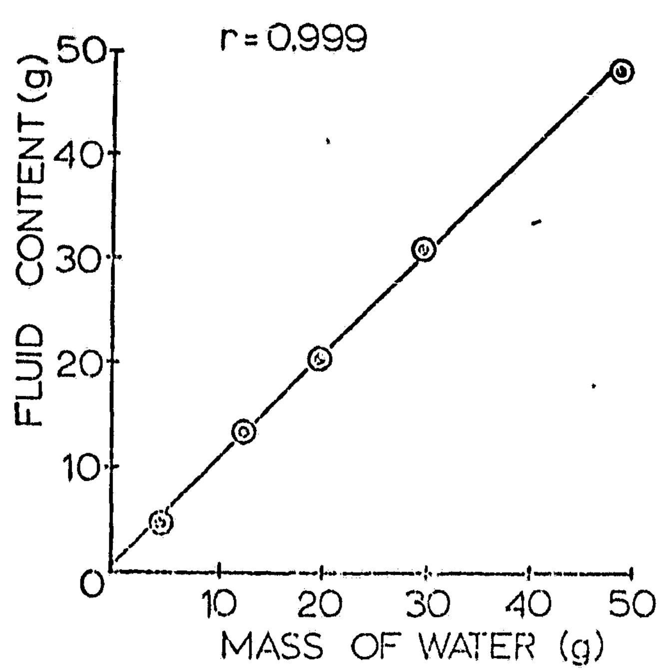
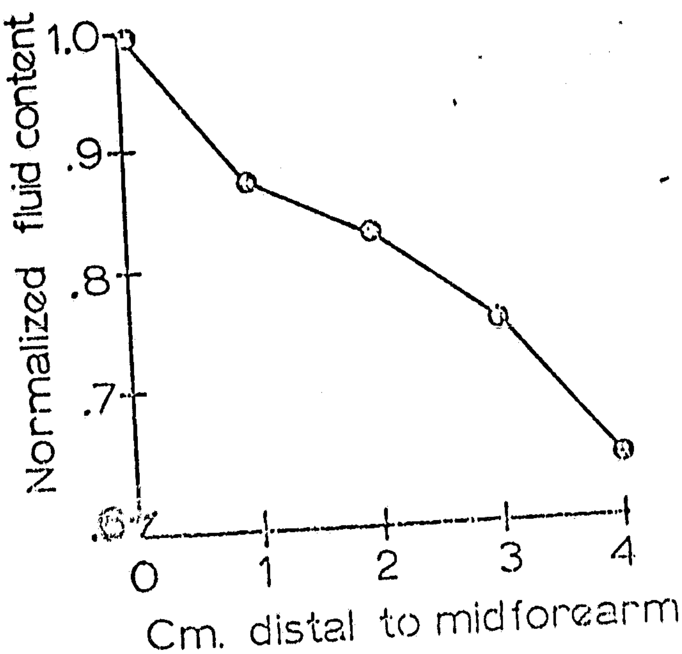


Figure 2: Fluid content of forearm determined by DA at 1 cm intervals distal to the midforearm.



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Figures 3-5: Dichromatic absorptiometry was used to determine changes in the fluid content in the thigh of a dog in which alterations in total body fuild were produced by exsanguination, transfusion and infusion. Data is presented as % change from baseline values.

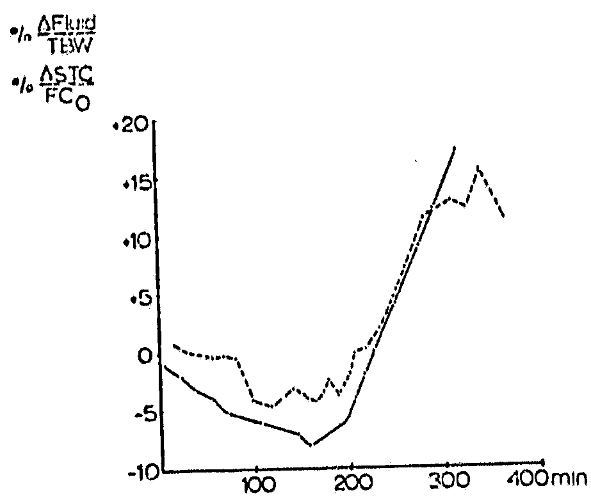
•——• $= \frac{\Delta fluid}{TBW}$

•------• $= \frac{\Delta STC}{FCo}$

TBW = Total body water

STC = Lipid-free soft tissue content

FCo = Fluid content at beginning of study.



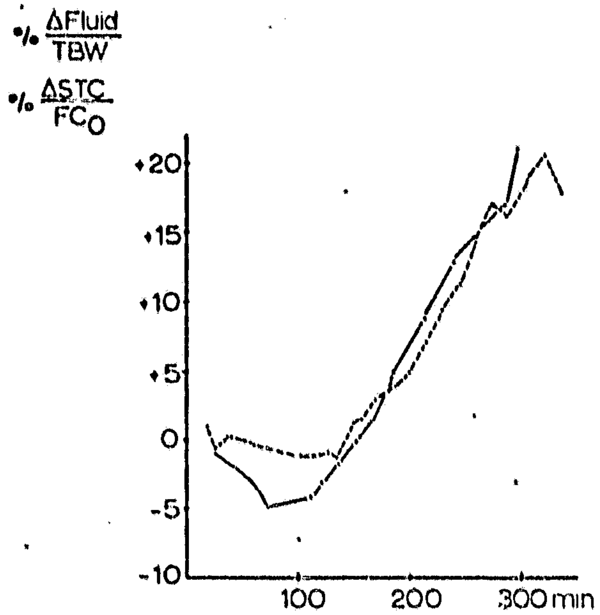
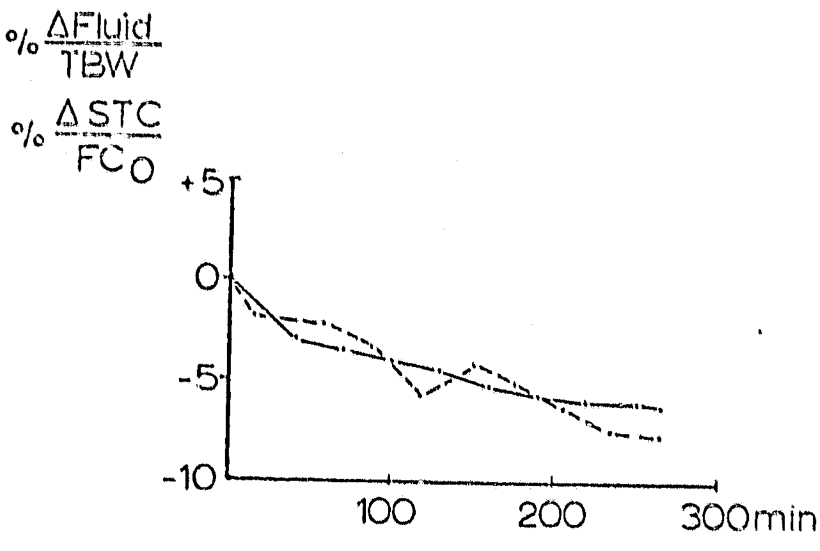

% ΔFluid / TBW
% ΔSTC / FCo
+20
+15
+10
+5
0
-5
-10
100
200
300 min

Figure 5


% ΔFluid / TBW
% ΔSTC / FCo
+5
0
-5
-10
100
200
300min

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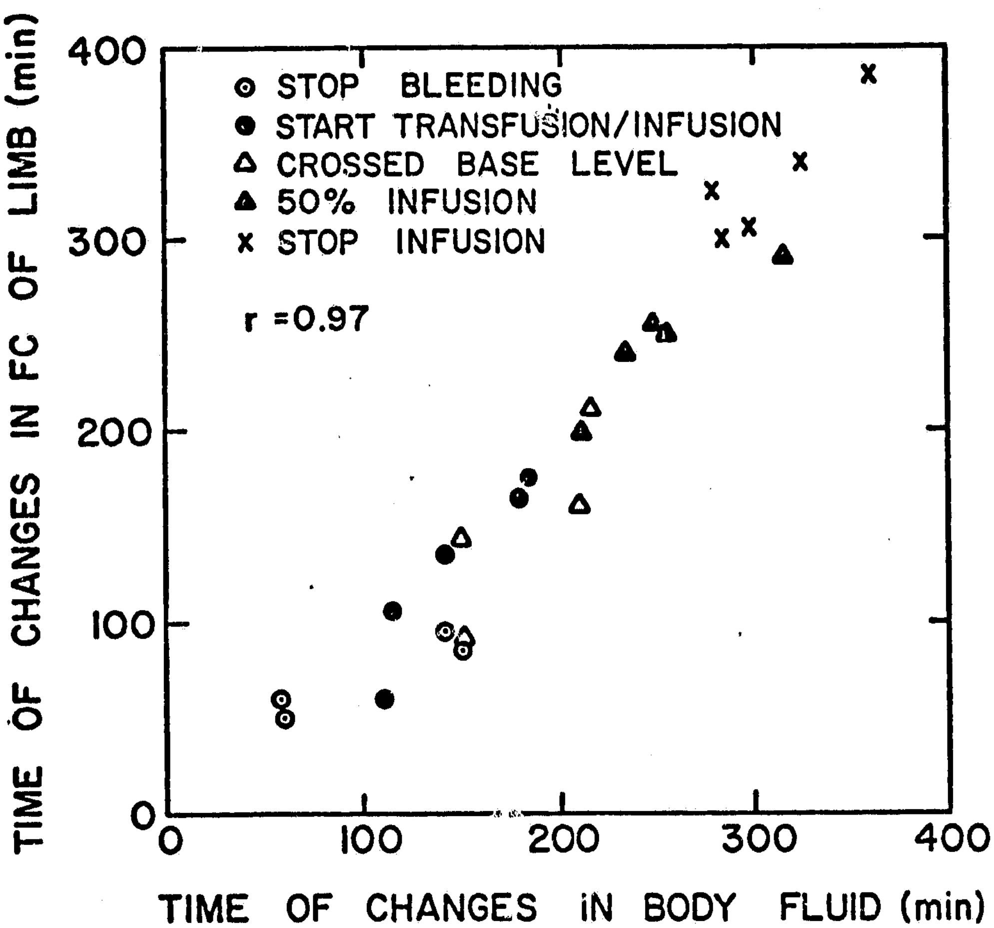

Figure 3. Temporal correspondence of absorptiometric changes in limb fluid content in dogs and actual body fluid changes.

Figure 6: D.A. was used to determine changes in the fluid content of patients undergoing a cholecystectomy and choledocholithotomy. Data is presented as % change from baseline values.

.------. = $\frac{\Delta fluid}{TBW}$

.______. = $\frac{\Delta STC}{FCo}$

TBW = Total body water

STC = Lipid free soft tissue content

FCo = Fluid content at beginning of study.

↑ Represents time of surgery.

Vertical divisions represent 24 hour midnight to midnight periods

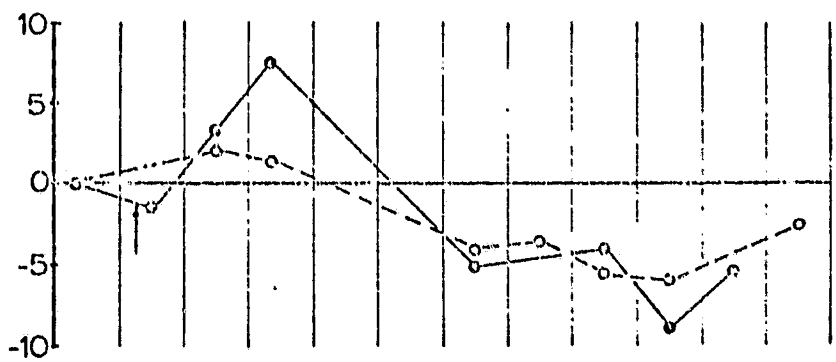

Figure 7: Same as figure 6 determined in patient undergoing splenectomy.

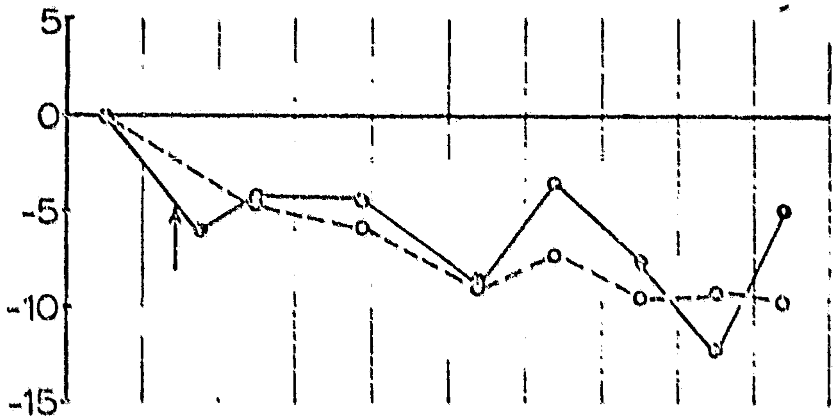

Figure 8: Relationship between changes in FC in the limbs relative to the baseline (FCo) and the changes in body water relative to the estimated TBW.

- ● Patient measurements of FC when there was a corresponding value for the body water.
- ◘ Animal measurements at the time of maximum decrease and increase in FC.

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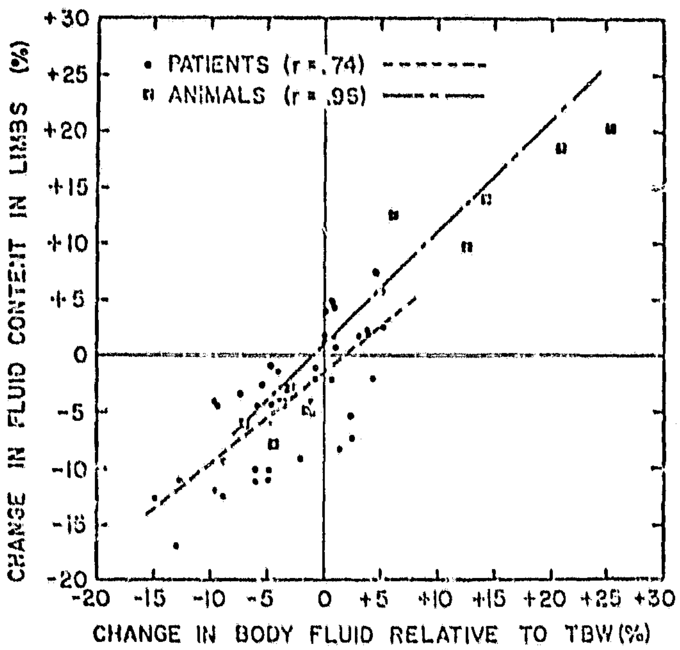

APPENDICES

A. Contents of Joint AEC-NASA Progress Reports (COO-1422-1 to COO-1422-184)

B. Bibliography of publications of R. B. Mazess from the Bone Mineral Lab

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2. C00-1422-2 Ash Weight vs Bone-Mineral Content by the Direct Photon Absorption Technique.

3. C00-1422-3 Longitudinal Studies of Bone-Mineral Content by the Photon Absorption Technique.

4. C00-1422-4 Factors Affecting the Measurement of Bone-Mineral Content by the Direct Photon Absorption Technique.

5. C00-1422-5 Improved Instrumentation for Bone-Mineral Measurement _In Vivo_**.

6. C00-1422-6 Bone-Mineral Measurement by Improved Photon Absorption Technique.***

7. Measurement of Bone-Mineral _In Vivo_: An Improved Method.

* Presented to the Symposium of Low-Energy X- and Gamma Sources, Ill. Inst. of Tech., Chicago, Illinois, Oct. 1964.

** Presented to the First International Conference on Medical Physics, Harrogate, England, September 1965.

*** Presented to the Conference on Progress in Development of Methods in Bone Densitometry (NASA), Washington, D.C. March 1965.

NOTE: Report No. 1 discusses work most of which was done prior to our obtaining our present AEC contract. Report No. 7 discusses work completed entirely before we obtained our present AEC contract. These reports are included for convenience.

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COO-1422-44	Some Physical Methods of Skeletal Evaluation, Proceedings of the Symposium on Hypogravic and Hypodynamic Environments, text of a paper delivered at the syposium, June 16, 1969, French Lick, Indiana, in press, by J.R. Cameron, J.M. Jurist, R.B. Mazess
COO-1422-45	A Coding System for Clinical and Normative Studies by J.M. Jurist, J.L. Fischer and K. Kianian
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COO-1422-47	In Vivo Determination of the Elastic Properties of Bone: I. Theory, Apparatus, and Method of Ulnar Resonant Frequency Determination, 1969, in press, by J.M. Jurist
COO-1422-48	In Vivo Determination of the Elastic Properties of Bone: II. Resolution and Precision of the Ulnar Resonant Frequency Determination, 1969, in press, by J.M. Jurist
COO-1422-49	In Vivo Determination of the Elastic Properties of Bone: III. Ulnar Resonant Frequency in Osteoporotic, Diabetic, and Normal Subjects, 1969, in press, by J.M. Jurist
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9. COO-1422-95 Bone Mineral Determination in Vitro by Radiographic Photodensitometry and Direct Photon Absorptiometry (abstract only; article available upon request).
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19. COO-1422-178 Dual Photon Absorptiometry Measuring Systems: Corrections to Detected Photon Counts

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. . . Philip F. Judy and John M. Vogel

22. COO-1422-181 An In Vivo Method for the Determination of Vertebral Bone Mineral Content Utilizing ^{153}Gd

. . . Mark Madsen

23. COO-1422-182 Precision and Accuracy of Photon Absorptiometry

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APPENDIX C. REPORT ON IMMOBILIZATION AND BONE MEETING, SAN FRANCISCO 1982

IMMOBILIZATION AND BONE

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The major advances of the past several years in bone measurement have direct applications for manned space missions, for paraplegics, for patients confined to bed by disease and for the large population of relatively hypodynamic elderly individuals. A meeting held in San Francisco (June 16, 1982) focussed on newer measurement methods and on major results obtained by both histological and non-invasive approaches. The specific aim was to provide NASA with information to help implement appropriate programs of research.

G. Donald Whedon (NIH) summarized the history of research on bone loss in immobilization and space flight. Negative calcium balance of 150-200mg/day continued for up to 20-30 weeks in young bed rest subjects; in the Skylab astronauts, the pattern and degree of calcium loss was similar to that in bed rest but with much inter-individual variation. Calcium losses in patients with spinal cord injuries appeared somewhat higher than in bed rest subjects, and higher losses were found in subjects with complete versus incomplete spinal cord lesions. Calciuria usually declined to the normal range by 30 weeks, but in some patients a modest elevation was evident even after one year (N. Eric Naftchi, New York University). Losses in paraplegic patients were evidenced histomorphometrically by a 33% reduction of trabecular bone volume in iliac crest biopsy over 25 weeks (P. Minaire and C. Alexandre, Hospital Regional, St. Etienne, France). There was both an increase in osteoclastic resorption and a decrease in bone formation. Cortical bone was affected slightly at first but to a greater extent after 2-3 months. There was a dramatic increase in yellow marrow (from 30-80%, or 1%/week) which later returned to normal.

Bone losses were also observed in 34 adults transiently (11-61 days) immobilized for prolapsed intervertebral disc. Dual-photon absorptiometry of the lumbar spine showed a mean bone decrease of 0.9%±0.3%/week (B. Krølner, Hillerød Hospital, Denmark). Reambulation led to recovery which was nearly complete in 15 weeks. In a group of 31 older women exercise 1 hour 2-5 times weekly produced an increase of lumbar bone of 3.5% over 8 months. T. Hansson (Goteborg University, Sweden) using dual-photon absorptiometry observed a decrease of 1-2%/week in spinal bone in 13 adolescent girls immobilized for 3-6 weeks for correction of scoliosis. Only 4 of the 13 (those least mature at time of operation) had regained all lost bone 5 years later; the remaining 9 showed variable recovery with 5 showing no restitution at all. The above losses in the spine were of the same magnitude as those observed in the trabecular bone of the os calcis (5%/month, using single-photon absorptiometry) during the prolonged bed rest studies sponsored by NASA at the PHS Hospital, San Francisco (J. Vogel, Dominican Hospital, Santa Cruz, CA). These same NASA-PHS studies suggested that diphosphonates may be able to inhibit some of this bone loss particularly if there is treatment prior to immobilization (J. Bevan, Proctor & Gamble, Cincinnati).

Experimental studies in animals also have shown bone losses during immobilization and space flight. Immobilized (body cast) monkeys lost spinal bone and the concomitant decrease of mechanical strength continued even after short-term (14 day) immobilization was terminated; the degree of reversibility may be age-related (L. Kazarian, Wright-Patterson AFB). Localized bone loss was evident (23-31% over 6 months) in compact bone of the proximal tibia at a site of muscular insertion even though there was not loss of compact bone in the radius and ulna (D. Young, NASA Ames Research Center). Recovery of the loss may take as much as 5-10 times longer than the period of immobilization. Growing rats observed after space flight (18-22 days - Kosmos) showed many of the changes noted in monkeys and man: decreased trabecular bone volume, increased marrow fat, decrease in bone formation (E.R. Morey, Holton, NASA Ames Research Center). All changes in flight returned to control levels within 25 days post-flight except for trabecular bone mass. D. Baylink (Loma Linda University) described a "coupling factor" (a high molecular weight protein with mitogenic activity specific to bone and cartilage) and speculated on the possible role it might have in the bone loss during immobilization.

Dual-photon absorptiometry for bone measurement _in vivo_ (with ^{153}Gd) was reviewed by R. B. Mazess. Long-term precision error in spinal measurements on man and monkeys has teen 2-3%. Accuracy on spinal samples was 2-4%. Total body bone mineral measurements also have acceptable precision and accuracy and though more complex than spinal measurements do indicate regional changes of both bone mineral and lean body mass. Quantitative computed tomography (QCT) using a conventional x-ray source provides a reproducible (1.6 - 2.3%) measure of spinal bone (H. Genant, C.E. Cann and D. Boyd, U.C., San Francisco). The measure could be more sensitive than dual-photon spine scans since QCT can measure the purely trabecular bone in the centrum whereas the total of spinal bone is measured with DPA. At the menopause, women lost twice as much bone in the anterior centrum as in the entire vertebra and 7 times more than in compact bone. However, conventional single-energy x-ray CT is subject to errors due to shifts in marrow fat (a 10% fat shift gave a 5% error). This error can be reduced greatly (to 1.4%) by making determinations at two energies, or by using a low-energy CT scanner in areas where marrow fat is invariant. A special dual-energy scanner using

^{153}Gd sources and a ring of semi-conductor detectors is under construction. Single-energy CT scanners (using ^{125}I or filtered x-ray tube sources) have been developed for measurement of trabecular bone in the limbs (P. Ruegsegger, Institute for Biomedical Engineering, Zurich). These devices provide very precise (<0.3%) values (yet with low x-ray dose). Trabecular bone measurements at peripheral sites (tibia and radius) were well correlated, with each other and with spinal mineral ($r \sim 0.9$). Trabecular bone loss in an immobilized limb was about 16% after ~16 weeks while compact bone loss was only 3%. Compton-scattering methods provide a totally different alternative for measurement at peripheral sites (M.A. Greenfield, UCLA). Investigators have obtained precise (4%) values at both the distal radius and the os calcis *in vivo*, but the accuracy is affected by multiple scattering and other factors.

The consensus of the group was that immobilization and space flight entail considerable losses of trabecular bone (averaging about 1%/week), but the degree of loss may vary greatly among individuals. It has been estimated that mechanical properties of the spine may be seriously compromised with a bone loss of 30%. Generally, loss of compact bone from the weightbearing skeleton occurs at slower rates (<1%/month) than trabecular bone loss but localized loss of compact bone at areas of muscle insertion also can occur at a high rate. In non-weightbearing bones there is apparently little loss of compact bone. Both increased bone resorption and decreased bone formation can be implicated in the bone loss of immobilized or weightless states but there was divided opinion on their relative roles which may reflect different mechanisms operative at different periods in the course of immobilization.

Reversibility of bone loss does occur but the period of recovery is several times longer than the period of loss. Again, there is wide individual variation in recovery with some individuals showing little, if any, response to reambulation, the slower bone turnover of increased age probably being an important factor. Evidence is not conclusive on prevention of immobilization bone loss through diet or drug treatment.

The influences of high calcium intake, disphosphonates, salmon thyrocalcitonin, and exercise on prevention or suppression of the calcium loss in bed rest have been studied recently but only preliminary reports have appeared; fluoride has yet to be tested in this area. Undoubtedly, further studies are merited in which newer methods are used for measurement of trabecular bone (dual-photon absorptiometry, computed tomography, Compton-scattering) as well as older methods (single-photon absorptiometry) for measurement of the os calcis or of long bones. Measurements at several locations, both axial and appendicular, are recommended because of the anatomical variability. Serial measurements of total body bone mineral could provide a noninvasive indicator of calcium balance as well as showing regional changes. Measurements need to be made at fairly frequent intervals in order to define the pattern of change in an individual; the lower radiation dose of absorptiometric approaches, and x-ray CT on the limbs, makes these methods attractive for sequential monitoring. The large changes of marrow composition which accompany immobilization must be recognized as a problem for non-invasive bone measurement. A 50% increase of marrow fat will appear to be a 25% bone loss to single-energy spinal CT, a 12% bone loss with Compton-scattering, a 7% bone loss to dual-energy CT and a 3% bone loss to dual-photon absorptiometry. These errors can be relatively large compared to an actual, localized bone loss of perhaps 25% after 6 months of immobilization; changes in marrow fat also can complicate assessment of recovery.

The new findings in animals and humans reported at the Workshop confirm the import of bone loss with immobilization. New methods are available which will permit non-invasive monitoring of loss and recovery, and which will facilitate studies related to prevention of and therapy for such loss. Immobilization bone loss occurs at a rate 5 to 20 times greater than those in other demineralizing conditions and hence may provide a useful model for examination of metabolic bone disease and its therapy.

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APPENDIX D. THESES

1971 Judy, P.F. A Dichromatic Attenuation Technique for the In Vivo Determination of Bone Mineral Content. (Ph.D.)

1971 Sorenson, J. Methods for Quantitating Radioactivity In Vivo by External Counting Measurements (Ph.D.)

1972 Wilson, C.R. The Use of In Vivo Bone Mineral Determination to Predict the Strength of Bone. (Ph.D.)

1975 Kan, W. Direct Readout of Bone Mineral Content with Dichromatic Absorptiometry. (M.S.)

1975 Witt, R.M. The Determination of Fluid Content by Dichromatic Absorptiometry. (Ph.D.)

1978 Sandrik, J. A Roentgen Video Absorptiometric System for the Measurement of Lung Tumor Mass. (Ph.D.)

1979 Hanson, J.A. Absorptiometry with a Linear Position-Sensitive Proportional Counter. (Ph.D.)

1981 Peppler, W.W. Combined Transmission-Emission Scanning Using Dual-Photon Absorptiometry. (Ph.D.)

APPENDIX E: Report for INTERN. SYMP. SPACE PHYSIOL. (Toulouse, France 1982)

MEASUREMENT OF SPINE AND TOTAL BODY MINERAL BY DUAL-PHOTON ABSORPTIOMETRY

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ABSTRACT

Dual-photon absorptiometry (^{153}Gd at 43 and 100 keV) was used to monitor the bone mineral content (BMC) in phantoms, vertebrae in vitro, the lumbar spine in humans and immobilized monkeys as well as total body bone mineral (TBBM). The accuracy of measurement was excellent on phantoms and on bone specimens (1 SEE 2%). Accuracy was only moderately affected by experimental alteration of "marrow fat". A 10% shift from red to yellow marrow caused only a 0.3% shift in BMC. In comparison such a compositional alteration causes a 3-4% error in single-energy X-ray computed tomography of the spine. Precision of measurement on spinal phantoms in vitro was 1.5%. The precision on human subjects and on monkeys averaged 2-3%. In 50 monkeys measured repeatedly (3-5 times) over 4 months 55% showed a precision error of under 3%. The precision of TBBM in vivo was about 2% but recent improvements have decreased the error to 1%.

The spinal bone loss in two restrained (4 weeks and 11 weeks) monkeys was about 1.2 and 0.5%/week respectively. This was similar to the loss shown in immobilized humans by both absorptiometry and histomorphometry (1%/week).

Dual-photon absorptiometry allows frequent monitoring (dose 20 mrem) during immobilization and remobilization without the great influence of the very large marrow composition shifts (2%/week) that accompany these events.

INTRODUCTION

Dual-photon absorptiometry with two radionuclides was developed during the late 1960's to provide a means of measuring the peripheral skeleton without the necessity of embedding the limb in a layer of tissue-equivalent material (West and Reed, 1968; Judy 1971). There was some attempt to use the method on the spine (Roos 1974) but it was not until the introduction of ^{153}Gd with emissions at two energies (44 and 100 keV) optimal for thick body sections that this became practical (Mazess et al 1970, 1974; Dunn et al 1980; Krolner and Pors Nielsen 1980; Price et al 1976). ^{153}Gd has a relatively long half-life (242 days) and the usual 1 Ci source can be used for at least one year. The initial work done with ^{153}Gd showed that accurate results could be obtained regardless of soft-tissue thickness or composition (Wilson and Madsen 1977). It also was shown that factors such as marrow composition would have a minor effect on bone determinations. A change of 10% from red to yellow marrow produces an artifact of only 0.3% in the dual-photon measure of bone. This contrast with an error that is 10 to 15 times larger (3.5 to 4.5%) for X-ray computed tomography.

Dual-photon measurements have been shown to accurately indicate the mass of bone specimens (Wilson and Madsen 1977; Dunn et al 1980). Measurements on entire skeletons indicated the total body bone mineral (TBBM) with a very small error (1.5% - Peppler and Mazess, 1981) and measurements <u>in vitro</u> were highly correlated with total body calcium determined in the same subjects by neutron activation (Mazess et al 1981). These studies have indicated that the method can be used for accurate determinations at limited local sites, over small areas, or even over the entire body. Spinal measurements have been shown to be extremely sensitive in detection of osteoporosis (Riggs et al 1981). Dual-photon absorptiometry is ideally suited for measurement of the bone changes seen with immobilization and for evaluation of preventive agents and of therapy.

METHODS

Local area measurements are usually done on the lumbar spine because of the high sensitivity of this zone to both disease processes and to therapeautic agents. The radionuclide source is coupled to a collimated scintillation detector on a rigid yoke which can be passed in a rectilinear raster pattern across the patient. Detector collimation must be relatively small (1 cm) to minimize the influences of scattered radiation. Corrections in the data must be made for:

(a) count loss due to amplifier deadtime
(b) background radiation
(c) Compton-scatter in the detector crystal
(d) scattered radiation from the subject
(e) beam-hardening by soft-tissue

For spine scans a transverse speed of 2 to 5mm/sec is used with longitudinal steps of 3 to 5mm. For total skeletal scans the transverse speed is 1 to 3cm/sec with step intervals of 1 to 3cm. Initially data was collated on magnetic tape for subsequent analysis but direct on-line calculations are now possible using microcomputers.

A special microcomputer-based dual-photon system has been used for scanning the spine of monkeys at Ames Research Center over the past three years. That system has been used in measuring adult male pigtail monkeys (8-15kg in body weight) as well as smaller (1.5-3.2kg) adult Cebus monkeys. The precision in measurement of standards was 1.6%. Spinal scans were performed on 50 monkeys (3-5 replications) to assess precision. In 55.4% of the animals the variability was under 3% and these monkeys were selected for later use in biological experiments.

A similar system is used for spinal scanning on humans at the University of Wisconsin. The precision on standards was about 1%.

HIGH PRECISION MEASUREMENT

It has been possible recently to diminish the precision error for remeasurement of both spinal and total body mineral without any increase of dose. Some improvement has been achieved by decreasing the usual step interval. At the same time the transverse speed was increased to keep the time of scanning (and dose) constant. For spine scans a step interval of about 3mm provides better resolution than the usual step interval of 4.5mm while the transverse scan speed can be increased to 4 or 5mm/sec. The precision on a 10 cm long area covering L4 through L2 is given in Table 1 at different speeds ans step intervals.

Table 1. Precision of remeasurement on a lumbar spine *in vitro*

SPEED	STEP	n	DENSITY (g/cm^2)	CV(%)
2.5 mm/sec	3.0	44	.934	.61
2.5 mm/sec	4.5	21	.929	.67
2.5 mm/sec	10.0	10	.953	1.35
5.0 mm/sec	3.0	33	.953	.52
5.0 mm/sec	4.5	10	.949	.74
5.0 mm/sec	10.0	30	.917	.80

The above results show that the area density of a series of vertebrae can be determined with a fairly low precision error even without precise relocation. The variation about the average value for the six different series was only 1.5%. This reflects the relative uniformity (3%) along the spine in area density compared to the variability in density of the body itself (about 10%).

Similarly, procedures for measurements of TBBM have been refined over the past years. The previous transverse scan speed of 2 cm/sec. has been doubled and the step interval has been reduced to 1.3 mm from 2.6 mm. With the previous procedure the precision of measurement on an isolated skeleton was 1.4% (n=142) over a 4-year period, but with the new procedure the precision error was 0.7%. This same low precision error was observed in one study on normal subjects while the error in osteoporotic patients was 1.2% (Chris Gallagher, personal communication). The precision error in spinal density from a total body scan was about 3% (n=12).

IMMOBILIZATION STUDIES

Studies have been carried out in several centers on immobilized patients and monkeys using dual-photon scanning. One of the first studies was done on the third lumbar vertebrae of 13 adolescent girls immobilized for 3 to 6 weeks for correction of scoliosis (Roos 1974). The average bone loss was 1 to 2% per week. The four least mature girls at the time of operation regained all lost bone 5 years later while nine others showed variable recovery and five did not regain the lost bone. The bone loss in 34 adults immobilized for 11 to 61 days was somewhat less than in the adolescents (0.9% 0.3% per week) but in these cases reambulation led to complete recovery in 15 weeks (Krolner and Toft 1982). In another study (Krolner et al 1982) exercise was shown to increase spinal bone mineral. In two monkeys immobilized for 4 weeks and 11 weeks the bone loss from the lumbar spine was 1.2% and 0.5% per week. Thus dual-photon results on the spine confirm the pattern of loss observed by histomorphometry of the pelvis (Minaire et al 1974). It is interesting that the rate of bone loss from the os calcis, observed with single-photon (^{125}I) absorptiometry, was very similar to that seen in the axial skeleton (Vogel and Whittle, 1976).

CONCLUSIONS

Low precision errors are essential for monitoring bone changes with immobilization and with space flight. The best precision seems to be obtained with gamma-ray CT of the extremities where errors of about 0.5% can be achieved (Ruegsegger et al 1981). However, changes in the extremites may not accurately reflect changes in other areas of trabecular bone, such as the spine. For example, there may be a latency of several weeks before bone loss occurs in the distal radius or os calcis when the body is immobilized, yet this delay does not occur in the spine or pelvis. In fact, trabecular bone of the adult radius does not decrease at all with immobilization (though that of adolescents does). Consequently, studies are needed to demonstrate if the precise gamma-ray CT results on lower limbs do in fact correlate with spinal results. Similarly, the studies done on astronauts using ^{125}I-absorptiometry of the os calcis suggest that a slightly more precise improvement of that method could prove valuable for evaluation of bone with immobilization and/or space flight. Conventional X-ray CT simply cannot be used to examine the spine even if its relatively poor precision (5%) can be overcome because the method is very inaccurate (30% error). The large changes of marrow fat (2%/week) that can occur with immobilization (and perhaps with reambulation) render this approach invalid. Dual-photon absorptiometry of the spine has a definite role to play in (a) providing a noninvasive criterion against which other techniques may be evaluated, and (b) providing an errorfree modality for precise assessment of bone changes during and after space flight. Dual-photon absorptiometry also can provide a measurement of TBBM and hence of total body calcium (which is about 37% of TBBM). Sequential observations of TBBM could eliminate the need for costly and time-consuming studies of calcium balance and thereby facilitate evaluation of dietary factors in the space environment. Adequate results can be achieved with instrumentation that is readily available in both Europe and the United States.

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