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BIOLOGICAL EFFECTS OF RADIATION AND RELATED BIOCHEMICAL
AND PHYSICAL STUDIES

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Investigators: John S. Laughlin, Ph.D., Member
W.P. Laird Myers, M.D., Member
Departments: Laboratory 5501
Laboratory 5604

Sloan-Kettering Institute for Cancer Research
410 East 68th Street, New York, New York 10021

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A. INSTRUMENTATION AND DATA HANDLING

1. The Total Organ Kinetic Imaging Monitor (TOKIM)

Objectives:

The proposed installation of a cyclotron at our Center stimulated the construction of a gamma camera system to be used for the detection of positron annihilation photons. Since the biologically important radionuclides carbon-11, nitrogen-13 and oxygen-15 have short half-lives and decay solely by positron emission, the Total Organ Kinetic Imaging Monitor (TOKIM) system was designed and built for obtaining both static images and performing dynamic organ function studies of distributions of compounds labeled with these isotopes.

Materials and Methods:

The TOKIM system consists of two Anger-type (1) scintillation camera detectors using 34.3 x 1.3 cm NaI(Tl) crystals; associated pulse height analysis, coincidence, positron and computer interface electronics; and an IBM-1800 computer. The purpose of this system is to provide a versatile imaging device for obtaining both tomographic and dynamic information for a source distribution and the use of an on-line computer for image processing and display. Three modes of operation have been explored with this system: (a) positron mode; (2) in which the opposed detector heads are used in coincidence; (b) 90°, for observing cascade gamma rays in coincidence; and (c) multi-probe detector mode with the heads used separately for dynamic studies.

Results:

The positron mode and other forms of tomography (3,4) are limited in application because of tomographic blurring of images from distributed sources. In the 90°-correlation mode, a different technique has been considered in which the x, y, and z coordinates of any activity distribution are obtained directly. This method depends on the detection of cascade gamma rays in coincidence by collimated gamma cameras. This technique has been used in a similar fashion in a scanning system (5) for individual planes. The detection of cascade gamma rays in coincidence by collimated gamma cameras has enabled the three-dimensional resolution of activity differentials and voids without interference from surrounding activity.

There are several nuclear decays in which two photons are emitted nearly simultaneously and isotropically. In the 90°-correlation mode, the camera heads are equipped with a multihole collimator and a slot collimator. The detection of one gamma

ray by the camera with the multihole collimator determines its line of propagation. The detection of another photon by the camera with the slotted collimator determines its plane of origin. Thus, the coincidence detection of two photons using these detectors determines the unique intersection between a line and a plane resulting in an (x, y, z) coordinate point in the source. This is illustrated in Fig. 1.

A conventional multihole collimator is used on one gamma camera head to obtain the x and y coordinates. Another collimator, consisting of a series of thirteen 1.2 cm wide slots separated by 1.2 x 7.5 cm lead septa, is used on the second head, placed at 90° to the first, to determine the z coordinate. The isotope used in these experiments was ⁷⁵Se which emits photons in cascade with energies of 136-265keV and 121-280keV. The pulse-height analyzers were set to accept the range from 110keV to 300keV, so that either cascade was observed in two combinations. The resolving time of the coincidence circuit was 30 nsec, so the 0.5 nsec or less life-times of the intermediate states did not affect the coincidence efficiency.

When a coincidence event is detected, the x, y, and z coordinates are digitized in 0-63 channels and recorded on magnetic tape. The channel calibration is 0.5 cm per channel. The data are processed on the computer to obtain a two-dimensional matrix (e.g., PLANE (x,y)) for a given increment of the third variable (e.g., Δz). These matrices are then displayed in an alphanumeric print-out. This technique differs from radionuclide tomography in which one plane is sharply in focus with the other planes present but unfocused. In this method information arising from activity outside the plane of interest does not appear in the output for that plane.

In order to simulate clinical scan conditions, phantom measurements were performed using a rectangular box filled with 2600 cm³ of water containing 50 μ Ci of ⁷⁵Se. Three cylinders made of Lucite, with diameters of 2.5 cm, 3.8 cm and 5.0 cm were placed diagonally across the phantom as shown in Fig. 2. The length of each cylinder is equal to its diameter. The box was located 5 cm above the slotted collimator and 12 cm from the face of the multihole collimator. In practice, it would be more advantageous to position a source in contact with the multihole collimator. This was not possible in these experiments because of the shielded, cylindrical camera heads. The count rates for this source activity and geometry are given in Table I.

TABLE I

Singles rate in x-y detector with multihole collimator	200cps
Singles rate in z detector with slotted collimator	20,000cps
Total coincidence rate	1cps
Random coincidence rate	0.1cps

Because the detectors are used with collimators, the singles rates are below the level where pulse pile-up becomes a problem. The desired real-to-random coincidence ratio directly determines the amount of activity which can be viewed by this system. A ratio of 10:1 was used throughout these experiments, so that accidental coincidence background contributed only 10% to the results. Coincidence data were accumulated over a period of 60 hours for a total of 200k coincidence counts.

Figure 3 shows line printer output in three-standard-deviation increments for the box containing the voids. The lower, left-hand picture shows the x-y plane for $0 < z < 63$ and contains 200k counts. This is similar to the single head picture one would obtain using the multihole collimator. In this output, it is not apparent that there are three separate voids. Figure 3B contains 21k counts and shows the x-y slab for $17 < z < 20$. The 3.8-cm void is clearly seen in this plane. It is the only void seen since events originating from all other planes have been omitted from this display. In Fig. 3D is shown the x-y slab for $35 < z < 38$ and contains 10k counts. The presence of the 5 cm void is clearly indicated. Figure 3A shows the output for a plane in between the 3.8-cm and 5-cm voids containing a uniform distribution of activity. Another method of viewing this data is shown in Fig. 4 with an x-y plane for $25 < y < 31$. The presence of the 2.5 cm void in the lower, right-hand corner of the box is just discernible. The effect on the image due to the slotted structure of the collimator and the decrease in counts with increasing z distance can be observed in this view.

Another important operating characteristic, which needs to be determined for any scanning system, is the detectability of a specific activity differential. This measurement was also made using the rectangular box phantom. The voids were removed and in their positions were placed three 4-cm³ counting vials containing concentrations of ⁷⁵Se which were 4, 8, and 10 times that of the phantom. The specific activity ratio increased with in-

creasing distance (z) from the multihole collimator. Data were accumulated for a total of 200k coincidence counts over a period of 60 hours. The computer print-outs in three-standard-deviation increments are shown in Fig. 5.

Figure 5C shows the x-y slab for $14 \leq z \leq 17$ and contains 26k counts. The vial containing the 4:1 concentration ratios, respectively. All three sources are clearly displayed in the x-y planes as well as in the x-z plane for $27 \leq y \leq 38$, shown in Fig. 5a. From these displays it is evident that three-dimensional localization is achieved with only a 10% interference, due to accidental coincidence counts.

Conclusion:

In summary, for simulating clinical conditions, with respect to geometry and total counts obtained, this method has proved feasible for detecting voids down to 12 cm^3 in volume and specific activity ratios of at least 4:1 in a volume of 4 cm^3 . The major problem with this technique is obviously its low coincidence counting efficiency. Since it took 60 hours to accumulate 200k counts, there is a need to increase the sensitivity by a factor of 60 to make a reasonably good three dimensional image of the source in one hour. A factor of 8 can be obtained by the use of multiple detectors and, since the coincidence resolving time was 30 nsec, a factor of 10 can be achieved by using faster detectors. It is hoped that future developments of this technique will increase its efficiency and lead to practical application of three-dimensional imaging of radionuclide distributions.

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Fig. 1. Principle of operation of the 90° correlation mode of the TOKIM system

Fig. 2. Phantom source showing the size and position of activity voids

Fig. 3. Three-standard-deviation output for phantom containing activity voids

- A. XY plane for $11 \leq z \leq 14$ showing uniform distribution in between two voids.
- B. XY plane for $17 \leq z \leq 20$ showing slab containing 3.8-cm void in center.
- C. XY plane for $0 \leq z \leq 63$ showing conventional output for a single head camera equipped with a multihole collimator.
- D. XY plane for $34 \leq z \leq 38$ showing slab containing 5-cm void at the left.

Fig. 5. Output planes in three-standard-deviation intervals for phantom containing activity differentials.

- XZ plane for $27 < Y < 38$ showing the positions of the three vials along a diagonal.
- XY plane for $26 < Z < 29$ showing slab with vial containing 8:1 concentration ratio in the center.
- XY plane for $14 < Z < 17$ showing slab with vial containing 4:1 concentration ratio at the right.
- XY plane for $43 < Z < 47$ showing slab with vial containing 10:1 concentration ratio at the left.

2. Application of the Modulation Transfer Function to the Reduction of Image Degradation

Objectives:

To develop and investigate the feasibility, practicality, and quality of results of the application of the Modulation Transfer Function (MTF) method for the reduction of image degradation.

Materials and Methods

Degradation reduction techniques formerly researched and developed have been extended in the form of variable digital filtering, in which several digital filters are derived directly from the modulation transfer function. These filters dictate varying amounts of degradation reduction (information retrieval) and data smoothing (noise reduction) and are transformed to the spatial domain and applied in a manner dependent upon the radioisotope distribution as indicated in the image distribution.

For purposes of simplicity, all activity is assumed to be in a plane parallel to that in which the γ -rays are detected, and further, the response of the system is translationally and rotationally invariant. The imaging system may then be expressed in polar coordinates as the convolution integral of the object radioisotope distribution $o(r, \theta)$ with the kernel point spread function (PSF):

$$I_u(r, \theta) = \int_0^\infty \int_0^{2\pi} o(r', \theta') PSF(|\vec{r} - \vec{r}'|) r' dr' d\theta'$$

Transforming to the spatial-frequency domain using Fourier transforms obtains

$$I_u(v, \phi) = O(v, \phi) MTF(v)$$

where

$$I_u(v, \phi) = \int_0^\infty \int_0^{2\pi} I_u(r, \theta) e^{-2\pi i r v \cos(\theta - \phi)} r dr d\theta$$

$$O(v, \phi) = \int_0^\infty \int_0^{2\pi} o(r, \theta) e^{-2\pi i r v \cos(\theta - \phi)} r dr d\theta$$

$$MTF(v) = 2\pi \int_0^\infty PSF(r) J_0(2\pi v r) r dr$$

The frequency representation of PSF is the modulation transfer function (MTF), and J_0 is the Bessel function of the first kind

and zero order.

In principle, the convolution integral in the frequency domain is trivially inverted resulting in the desired isolation of the object distribution, however, in reality this cannot be carried out because MTF crosses the frequency axis, leading to infinities in MTF^{-1} . To circumvent this problem MTF^{-1} is empirically cut off at a frequency ν_c close to which the MTF has its first zero value.

Generally at low spatial frequencies the signal-to-noise ratio is considerably higher than at high spatial frequencies, i.e., more information is lost at high frequencies (small details) than at low frequencies. Based on this, the cut-off frequency ν_c is varied over the spatial extent of the image, depending on the local signal-to-noise ratio. With successively lower signal-to-noise ratios, ν_c is diminished so that high frequency noise, which increases with respect to signal, is not amplified. In this way degradation reduction or information retrieval is achieved in areas of high signal-to-noise ratio, and data smoothing or noise reduction in areas of low signal-to-noise ratio.

In carrying out this procedure, the entire image is first scanned to determine local density fluctuations, i.e., a 5x5 matrix of interest is imposed upon each element and searched to determine the relationship of the central element to the rest of the matrix vis-a-vis signal-to-noise ratio. The element is then assigned one of the several correction functions for spatial convolution. In this way, the particular correction function defined for each point does not depend on the absolute count density but rather on its local variation. Only elements in the vicinity influence the choice of correction function.

Figure 6 indicates cross-sectional results of the application of variable digital filtering to computer simulated multiple-line source phantoms. A gaussian (e^{-r^2/σ^2} , $\sigma = 1.25ch$) was used to degrade the original image as shown, and the correction procedure applied to attempt to retrieve the original distribution. The original phantom consisted of simulated line sources of equal activity, each one channel wide, separated by one, two, three and four channels with a constant 10% background. Cross-sections of the degraded images indicate half-widths of the order of one channel, while the cross-section of the processed images indicates half-widths of only one half channel, with significant restoration in absolute count distribution. Of particular interest is the first and last sets of lines, separated by voids of only one channel. The original image had a specific activity ratio of 10:1, while the degraded curve indicates minimal detectability (a variation of only a few counts/channel). The processed image exhibits significant gain in detectability, with depression of some 30% over the voids.

Digital filtering was applied to the computer simulated phantom depicted in Figure 7. The display technique consists in writing density patterns on a Tektronix 611 Storage Display Unit, the choice of density pattern being related to the isotopic intensity at the point. The scale repeats itself after going through 16 levels of intensity, as demonstrated by the accompanying grey scale. This is particularly convenient since the approximate relative intensity of two areas can usually be obtained from this combination analog/digital display.

Figure 7a shows the original distribution as introduced into the computer. Background suppression has been utilized in the display, but the true background was ten counts/channel. The density within the phantom varied from 25 to 400 counts/channel. The smallest distribution was 1 channel, and the largest was 3 channels x 3 channels. The phantom was degraded (cf. Figure 7b) utilizing the gaussian point spread function described earlier. The analog/digital nature of the display makes comparison with the original distribution relatively simple. Most areas have been degraded to roughly half their values and the smaller, weak sources have fallen below back-ground level.

Figure 7c shows the results of filtration using a single filter/correction function derived from the MTF. The improvement is only minimal. Figure 7d shows the results of filtration using the techniques of variable digital filtering. There is almost complete restoration of the density level contours for both hot and cold sources, as verified by a numerical output (not shown here). The smaller, weak sources have been retrieved from below background level and both resolution and detectability have been demonstrably improved.

Fig. 6. Line source phantom showing cross-sections of:
 (1) original computer simulation of line sources
 with varying separations; (2) the phantom degraded
 by the Gaussian point spread function; and (3)
 the corrected version of the phantom, using five
 correction functions, with exponential damping
 given by $\exp(-ar^2)$, where $a = 0.975$.

COMPUTER SIMULATED PHANTOM

Fig. 7. Computer simulated phantom: (a) original distribution, (b) degraded with Gaussian point spread function, (c) corrected using non-variable filtering, (d) corrected using variable digital filtering.

3. Methodology of Absolute Quantitative Organ Scanning

Objective:

The main objective of this project has been to calibrate the Heg scanner for absolute organ activity measurement using the radionuclides Cr-51, Ga-67 and short lived cyclotron produced Fe-52, P-18 and $^{13}\text{NH}_3$. The basic problem is to establish scanning procedures and method of data analysis whereby the isocount contours, activity content and size of an organ can be resolved from radio-active tissue or marrow background in-vivo.

Materials and Methods

The high energy gamma system (HEG) employed is of dual head rectilinear type. The basic frame construction is that of an Ohio Nuclear Scanner model. The detectors are those originally used on an earlier high energy scanner and contained heavily shielded 4"x4 NaI(Tl) crystals. A schematic diagram of the electronics and interface to magnetic tape is shown in Fig. 8. Four single channel analyzers and scalars are available for each detector and allow for the summed and single response of the system. Positional encoders are used to determine the scan increment (0.4"x0.4") in the X and Y directions and the incremental recording time is measured by a precision pulser. The data accumulated on all eight scalars, the positional information and time elapsed are dumped sequentially for each scan increment on magnetic tape. The data are replayed and processed to obtain a line printer image and organ uptake calculation.

The detector designs developed for this system were a series of long dual focal length collimators F(14cm, 18cm) for the moderate energy of Cr-51(320 k.e.v.) and the positron annihilation radiation (511 k.e.v.). The dual response of these opposed detectors were optimized for uniformity with depth in an absorbing medium with emphasis placed on the low response off-axis region. Resolution F.W.H.M. for collimated systems was of the order of 2.5cm and a sharp cut-off in the off-axis response was achieved. Detector sensitivity was designed for whole body scan times of approximately 15 hours.

Calibration of the Heg scanner was achieved by scanning phantoms sources of known activity; simulating the in-vivo geometries of the liver and spleen and over a patient thickness range from 20 to 30 cm. Cylindrical spleen phantoms (60-1,000ml) and a wedge liver phantom (2,200ml) containing known microcurie quantities of Cr-51 (320 k.e.v., $\Delta E=100\text{k.e.v.}$) and Ge-68 (511 k.e.v., $\Delta E=100\text{k.e.v.}$) were scanned in 20, 25 and 30cm water tanks (cross section 20x20cm) and at detector separations of 25, 30, 35cm. respectively. Data were also taken in tanks containing radioactive water simulating active blood or tissue background in-vivo. The mean half layer thickness in water was measured for both nuclides under the same experimental conditions.

Since the method of scan data analysis is primarily directed at obtaining a quantitative measure of organ activity, the actual scan display was kept as simple as possible. For example, Fig. 9 shows a computer line printer image of the summed detector response to a 250cc cylindrical source closely resembling normal spleen size. The source was scanned at 10cm depth in a 20cm tank containing radioactive water. The scan data are displayed as a raw data matrix.

The method for resolving the scan elements within the organ isocount image contours is illustrated by the count profile along XX' shown in Fig. 9. Using the summed detector response, the maximum count/elements within the image matrix is obtained from the scan output. To determine the maximum cts./element (BKG) is determined at an area (A) adjacent to the image boundary. The image contour levels are then defined as (0-60%) of this adjusted maximum ($Y_{max} - BKG$). The scan characters representing these count levels are indicated. The scan analysis program then integrates all the elements whose counts are equal to or greater than the defined countour levels. The area of integration is limited to any localized region of a scan by the rows and columns surrounding the source scan image.

Table (II) illustrates the two integration methods generally used for uptake studies; the summed detector (S.D.) and the geometric mean (G.M.) response. Both these integration methods are used in this study but are applied only to those elements within the defined contour areas. Correction for tissue background is also applied to each element in a similar manner using the mean active back-ground/element previously calculated as in Fig. 9.

To derive a better approximation for background closer to the source boundary a second computation was made. The mean counts/element around the source image boundary (10% contour to integration limits) was calculated. This computation was particularly useful when correcting for active marrow within the rib-cage surrounding the liver and spleen in Fe-52 patient scan analysis.

Detector sensitivity was calibrated by deriving conversion factors (C.F.) that relate the integral counts within each image contour to the source activity. The phantom scanned above contained 153 μ c of Cr-51 and the computed C.F.'s were found to increase with the source area scanned. The value of each C.F. and their apread refer to the particular source size and geometry when scanned. The 30% contour area for this scanning geometry was found to correlate closely with the cross-sectional area of the source. Extensive calibration of the scanner system sensitivity and source size measurement for patient analysis was therefore required.

Results:

Fig. 9 gives an illustration of the resolution

and response characteristics of the HEG system for the phantom source volume range studied. The phantom source were well resolved at each depth and only a small dispersion between the source image contour areas (50% to 10%) was observed. Both collimated systems for Cr-51 (320 k.e.v.) and Ge-68 (511 k.e.v.) had very similar source resolution with the 30% image contour in each case closely correlating with the source cross sectional area. With the well defined image it was possible to relate the system response to source activity for each image contour as shown in the plot of conversion factors Vs source size. This is particularly useful in analysis of patient organ uptake where the organ is not quite quantitatively resolved from active tissue or other active organs.

Table III shows the system ability to resolve source size and activity content when positioned at different depths in a 30cm tank containing radioactive water uniformly distributed at 0.07 μ c Cr-51/ml. The wedge liver phantom was positioned 1" from the spleen phantom and the scan parameters used are shown on same table. Background correction (BKG. Corr.) for the surrounding radioactive water, above and below the source, is expressed as a percent of the system's response to the source alone. This correction therefore will depend on the source depth. Data for the active and non-active tanks, however, demonstrate rather clearly the resolution (30% contour area) and response (C.F.'s) characteristics are not impaired by the presence of the radioactive medium. The summed detector response was dependent on the source depth for the larger tank used. Table III shows how the geometric mean computation reduces the variability of the systems response with source depth for the above experimental data using Cr-51.

Fig. IV and Table IV show the resolution characteristics for resolving two adjacent sources containing Ge-68 and positioned at 0.4" separation in a 25cm tank. Experimental data demonstrate the small off-axis penetration experienced for the more energetic photons of 511 k.e.v. In the scan output of raw data 30% suppression was used to outline each source resolution achieved. The measured source size for the spleen phantom as shown correlated well with the earlier calibration data and the activity content was well resolved from the adjacent liver phantom activity by integrating the higher image contours.

Conclusion:

The HEG scanner system is presently being used to derive an absolute in-vivo measure of:

- (a) Splenic sequestration of A.C.D. damaged red cells
- (b) Measurement of tumour uptake using $^{13}\text{NH}_3$ and absolute serial measurement of undamaged red cells and Fe-52 uptake in the erythropoietic system.

The resolution characteristics of this system were designed for whole organ or organ activity resolution and is not suitable for small tumor or lesion detection. The data analysis program is automated and includes integration and background

computation, correction for isotope decay and determination of the percent of injected dose in an organ. Correction is also made for the difference in thickness of the subject being scanned and the nearest tank size used for scanner calibration using the mean half layer thickness for each isotope energy. Processing time to obtain final organ activity is short, about 5 minutes and allows the physician to be informed of the result shortly after the scanning procedure is complete.

Phantom data indicate that this system is reliable and has generally an error range of $\pm 10\%$ but this range is dependent on the degree of radioisotope uptake in the organ being evaluated.

The experimental procedures discussed are not possible with conventional detector systems since their response is dependent on the particular scanning geometry of each patient and the location and size of the organ in-vivo. Their variability of the off-axis response and the extent of septal penetration makes both organ activity resolution and tissue background correction extremely difficult.

BLOCK DIAGRAM OF DIGITAL INTERFACE		
SLOAN-KETTERING INST.	JOHN CONTI	8/69

Fig. 8. Schematic diagram of HEG electronics and interface to magnetic tape.

Source Size and Activity Resolution with HEG System

Fig. 9. Method for resolving source activity and size from a radioactive medium using HEG system.

Fig. 10. Source resolution and response characteristics for HEG system using Cr-51 (320 k.e.v.) and Ge-68 (511 k.e.v.).

Resolution of Adjacent Sources with HEG System

Fig. 11. Resolution characteristics of HEG system for resolving activity and size of two adjacent sources containing Ge-68.

	<u>Image Contour</u>	<u>Level No.</u>	<u>Element No. (Ele)</u>	<u>Int. Cts.</u>	<u>Int. Cts. Corr. Bkg.</u>	<u>C.F. Cts/μCi</u>
S.D.	50%	11	51	6962	5192	33.9
	30%	10	70	8579	6150	40.2
	10%	8	102	10445	6905	45.1
	0%	7	446	23278	7799	51.0
G.M.	50%	11	51	6867	5166	33.8
	30%	10	70	8453	6106	39.9
	10%	8	102	10257	6837	44.7
	0%	7	446	22943	7988	52.2

$$S.D. = \sum_{2=1}^{Ele.} (U_1 + L_1)$$

$$U_1 = Cts./Ele$$

CORR. BKG. upper
detector

$$G.M. = 2 \times \sum_{2=1}^{Ele.} \sqrt{(U_1 \times L_1)}$$

$$L_1 = Cts./Ele$$

CORR. BKG. lower
detector

Source Act. = 153 μ Ci Cr-51

Table II.

Method for Resolving Source Activity and Size from a Radioactive Medium
Using HEG System.

Spleen Phantom Vol. = 250 ml₂
 Cross Section Area = 60 cm²
 $\mu\text{Ci } ^{51}\text{Cr/ml}$ = 4.34

Liver Phantom Vol. = 2.2 litres
 Cross Section Area = 138 cm²
 $\mu\text{Ci } ^{51}\text{Cr/ml}$ = 0.49

Tank Vol. = 32.7 litres
 $\mu\text{Ci } ^{51}\text{Cr/ml}$ = 0.07

Spleen Phantom Position (cm)	BKG. CORR.	50%	C.F. 30%	Source Area (30% Contour)	Liver Phantom Position (cm)	BKG. CORR.	50%	C.F. 30%	Source Area (30% Contour)
5	20%	23	30	67 cm ²	15	60%	16	19	162 cm ²
10	26%	19	22	68 cm ²	15	60%	17	19	163 cm ²
15	30%	17	21	71 cm ²	15	60%	17	21	151 cm ²
20	26%	20	23	69 cm ²	15	60%	17	19	153 cm ²
25	20%	28	32	62 cm ²	15	60%	16	19	161 cm ²
Non-active tank									
15	0%	17	22	63 cm ²					

30 CM TANK

Table III

Resolution of a phantom source positioned at different depths in a radioactive water tank.

Spleen Phantom Vol. = 250 ml
 $\mu\text{Ci } ^{51}\text{Cr/ml}$ = 4.34
 Tank Vol. = 32.7 litres
 $\mu\text{Ci } ^{51}\text{Cr/ml}$ = 0.07

Spleen Phantom Position (cm)	Summed Detector Response C.F.		Geometric Mean Response C.F.	
	50%	30%	50%	30%
5	28	30	14	22
10	19	22	17	22
15	17	21	18	26
20	20	23	17	24
25	28	32	16	23

30 CM TANK

Table IV

Comparison of the summed detector and geometric mean response to a phantom source positioned at different depths in a radioactive water tank.

Spleen Phantom Vol.	= 250 ml
Cross Sectional Area	= 60 cm ²
Activity μ Ci Ge-68/ml	= 0.255
Liver Phantom Vol.	= 2.2 litres
Cross Sectional Area	= 138 cm ²
Activity μ Ci Ge-68/ml	= 0.02
Tank	= 25 cm

	<u>Image Contour</u>	<u>Level No.</u>	<u>Element No.</u>	<u>C.F. (Cts/μCi)</u>	
				<u>S.D.</u>	<u>G.M.</u>
Liver Phantom	50%	9	134	245	240
	30%	7	165	271	266
	10%	4	262	306	300
Spleen Phantom	50%	13	46	184	183
	30%	10	67	227	226
	10%	6	99	256	255

Table V

Resolution Characteristics of HEG System for Resolving Activity and Size of Two Adjacent Sources Containing Ge-68.

4. Parallel Hole Collimator Design

Objectives

The determination of collimator penetration for all parallel hole collimators of a given hole shape could theoretically be computed in one comprehensive tabulation. The only additional specifications necessary to select a particular design would be the penetration fraction, the resolution and the depth at which it was specified, and the absorption coefficient of the collimator material at the gamma energy desired. This approach is most valuable at gamma energies over several hundred keV, where collimator design of sufficiently low penetration without undue loss of efficiency is far from simple.

This approach can be efficient only if the parameters chosen, which must adequately describe both the collimator's physical properties and its imaging properties, constitutes the minimum possible sized set.

The final objective was to map the collimator characteristics in a format to enable rapid determinations of efficiency, and resolution at desired penetration for both synthesis and analysis.

Materials and Methods

This work, with some reformulation and overlap, continues that of the previous report. The computer program was rewritten to compute a more exact approximation to the integral. To enable intercomparison of characteristics between collimators of different hole shapes (round, square, etc.), the resolution was redefined in terms of area spread of an imaged point or its root rather than a particular linear dimension. Thus, the collimator is described in terms of its hole area, its element area, i.e., the area of the polygon following the septal midline around the hole, the ratio of these areas and its square root, and the hole's solid angle or its square root. The usual parameters D, L, T and μ representing hole diameter, hole length, septal thickness and linear absorption coefficient are then derivable.

The area resolution $(R')^2$ is $\frac{1}{4}$ of the imaged area of a point source at a distance A in front of the collimator onto a detector at distance C behind it. The following relations apply:

- 1) Angle Resolution = $\left(\frac{1}{L} \right) \sqrt{\text{Hole Area}}$
- 2) Linear Space Efficiency = $\sqrt{\text{Hole Area}} / \sqrt{\text{Element Area}}$
- 3) Absorption Length: μL (product)

- 4) Effective Resolution $R' = \alpha (A + C + L)$
- 5) Normalized Resolution $\mu R' = \alpha (\mu(A + C) + L)$
- 6) Geo.Effic/Unit Area $E = \alpha^2 \beta^2 / 4 \pi$

The penetration fraction for a parallel hole collimator is

- 7) P.F. = $\frac{\text{Penetration Aperture/element area}}{\text{Geometric Aperture/element area}}$

Aperture is the integral of the solid angle times transmission factor $\exp(-\mu \ell_1)$ integrated over the element area and over the bottom surface, for flux originating from a uniform planar source parallel to the collimator. The geometric aperture flux is confined to the hole and the penetration aperture flux excludes all corner flux from the integral. Fig. 12 shows the geometry. We rewrite 6):

- 8) P.F. = $4\pi L^2 / (\text{Hole Area})^2 \iint dS_1 dS_2 \exp(-\mu \ell_1) / 4\pi R^2$
- 9) P.F. = $12 \cdot L^2 / (\text{Hole Area})^2 \int_0^{30^\circ} d\phi \int dy \int P dP \int dx \exp(-\mu \ell_1)$

The summed septal transmission length along R is ℓ_1 . Equation 8) refers to a rotating X,Y coordinate system such that the $dS_1 = dx dy$ integration is evaluated for each value of ϕ , where ϕ is the direction of the X axis as well as P on the bottom. We integrate dS_2 as $P dP d\phi$ on the bottom, but note the integration from 0 to 30° is simply repeated 12 times by the geometry.

We define hole spacing as unity for convenience in integrating P in which case $L^2 = \sqrt{3} \beta / 2\alpha^2$. Since both α^2 and β^2 are efficiency factors in solid angle and area packing respectively, we may increment these parameters in simple steps which preserve the efficiency/unit area E, at preselected values. The values are one decibel steps such that every 10 steps the efficiency changes by a factor of 10. The normalized equation which we integrate is:

$$10) \text{ P.F. } = 24/\sqrt{3} \alpha^2 \beta^2 \int_0^{30^\circ} d\phi \int dy \int P dP / (\sqrt{3} \beta^2 / 2\alpha^2 + P^2) \int \exp(-\mu \ell_1) dx$$

The X integral is solvable analytically into 4 forms of integrand so that triple integrals are left.

Most of the program is devoted to finding boundaries of holes at the top or bottom and incrementing the integration stepwise from the region closest to the origin hole outward. The ϕ and the P

integrals are evaluated by gaussian quadrature but for the y integration, hole intersections occur during the incrementing causing derivative discontinuities so that trapezoidal integration was desirable.

Results and Conclusions:

For any constant penetration fraction, the tabulated values are reverse interpolated at constant efficiency to find α , β and μL values which are plotted on a α vs μL chart. Fig. 13 shows a round hole chart for 1% penetration fraction. Note that iso- β trajectories are shown. This chart should be properly considered as a collimator characteristics chart - one of a family of such charts for the given hole shape and penetration fraction.

To use this, one needs a second chart of the imaging equation (5). Lines of constant $\mu R'$ are plotted vs α and $\mu L + \mu(A + C)$ to the same scale on a transparency. The abscissa includes $\mu(B + C)$ representing the additional distance from source depth to detector to project the image. The charts are overlaid with the origin of the characteristic chart at the required $\mu(B + C)$ value on the resolution chart. To the right, μL values track on both charts as shown in Fig. 14. The functional interrelations are completely visible and one essentially has a collimator slide rule.

An experimental check based upon the total transmission is shown in Fig. 15 for a lead collimator. The calculated values of geometric efficiency plus corner penetration and penetration fraction were compared and found in reasonable agreement.

However, data similarly obtained for a tungsten collimator yields excessive measured penetration over calculated. The data fits reasonably, if the μL values are multiplied by 0.8. This problem has not been resolved but a possible explanation is that the buildup of quasi-forward scatter which tends to be collimated and falls in the photopeak of the detector should be larger in the case of tungsten because it depends more heavily on compton absorption than lead in the energy region below 661 keV. Certain geometries may also enhance this effect, and additional investigation seems desirable.

Fig. 12. Top view shows X,Y coordinate system which rotates 0 to 30° at angle ϕ . The hexagon is the element area. Penetration flux is integrated from all points within the hexagon to all points outside the hexagon projected to the lower surface. The side view shows septal intersection lengths along R which are summed to compute transmission probability $\exp(-\nu l l_1)$.

Fig. 13. Collimator characteristics chart for round holes at 1% penetration fraction.

Fig. 14. Collimator characteristics chart overlaid on Resolution chart for $\mu(A + C) = 31$. The relations between the four variables μL , α , β and E (expressed in decibels, DB) are given for any 1% penetration fraction design.

Fig. 15. Lead collimator total transmission compared to calculated values, showing separate contributing parts. Tot. Effic. = $E(1 + P.F. + \text{Corner Pen. Fract.})$.

B. METABOLIC AND IMPROVED ORGAN SCANNING STUDIES

1. ^{13}N -Labeled Ammonium Chloride for Tumor Studies

Objectives:

Ammonia metabolism is especially noted for its central role in organ physiology of the kidney, liver and brain and in the biochemical pathways related to amino acids, purines and urea. Function of these organs and the related metabolic pathways are involved to some extent in virtually all human disease. The objective of this work is part of an overall research goal to produce new radiopharmaceuticals which will have useful applications in medicine. Since higher animals use ammonia as a nitrogen source for synthesis of nonessential amino acids, injected N-13 labeled ammonium might be expected to show up in tumors with high metabolic activity.

Materials and Methods:

Ten-minute nitrogen-13 is the longest lived of the radioisotopes of nitrogen and the only practicable tracer for medical studies. Its 100% decay by positron emission coupled with its short physical half life offers an optimum ratio of clinical information to modest radiation dose. In a cooperative study with The Animal Medical Center, (AMC), we have recently investigated animals with spontaneous neoplasms. We are studying qualitative uptake of $^{13}\text{NH}_4^+$ in tumors using the TOKIM system and, by scanning with the HEG system, are able to calculate the percent of injected dose incorporated.

Results:

At this time in this work we have studied three dogs and one cat with spontaneous tumors. These are listed in Table I.

TABLE I

		<u>Tumor Type</u>
AMC (1)	Dog	Thyroid carcinoma
AMC (2)	Dog	Mammary carcinoma
AMC (3)	Cat	Fibrosarcoma
AMC (4)	Dog	Round cell sarcoma

All of these animals showed definite uptake of ^{13}N activity in their primary tumors and metastatic lesions. The shape and size of these tumors obtained from the TOKIM output compares favorably with the known tumor structure. The only exception to this last statement has been the cat with the large fibrosarcoma. However, at sacrifice this tumor was highly necrotic.

In Fig. 16 is shown a comparison of $^{13}\text{NH}_3$ and ^{67}Ga right, lateral chest scans for AMC (2). The primary tumor and metastatic lesions are clearly seen in both scans. However, the metastases inside the chest wall are only seen in the ^{67}Ga scan. The high uptake of $^{13}\text{NH}_3$ in heart and liver obscures these tumors. This animal has not been sacrificed, so the presence of metastases has only been confirmed by x-ray examination. In fact, the uptake in the shoulder area is not seen on the radiographs.

Figure 17 shows a ventral-dorsal scan of the abdomen and thighs of AMC (3) obtained 33 min. after injection of 10 mCi of $^{13}\text{NH}_4^+$. The bladder contains much activity due to washout through the kidneys. The crescent-shaped area to the right of the bladder shows uptake in the tumor. The overall geometry of the tumor is just visible.

The uptake of ^{13}N -labeled ammonium was well defined in the round cell sarcoma case, AMC (4). Figure 18 shows a left-lateral and a dorsal-ventral scintiphoto of the head of the dog. These pictures were made at 5 and 15 minutes after intravenous administration of 14 mCi of $^{13}\text{NH}_4^+$. The primary tumor is shown on the right side of the jaw. There is also a region of increased uptake below and to the right of the brain. This is possibly metastatic disease in the lymph system.

Fig. 16 Right lateral chest scans of AMC (2). The $^{13}\text{NH}_3$ scan, on the top shows uptake in the heart, liver, shoulder area and the primary mammary tumor. The ^{67}Ga scan, below clearly displays the primary tumor and lesions in the chest and shoulder areas.

Fig. 17. Ventral-dorsal scan of abdomen and thighs of AMC (3).
The gray scale has been recycled, so that the tumor
uptake is seen to the right of the urinary bladder.

Fig. 18 Left-lateral (top) and dorsal-ventral (bottom) scans of the head of AMC (4). Uptake of ^{13}N activity is seen in the primary tumor in the jaw, the mandibular lymph nodes, and the brain.

2. Pulmonary Function Studies with Gaseous Tracers to Demonstrate Acute Pulmonary Radiation Reaction

Objectives:

(1) To try to identify physiologic abnormalities which may be diagnostic of acute pulmonary radiation reaction, and to follow these changes serially after.

(2) To evaluate the alveolo-capillary membrane transfer of ^{15}O -labeled oxygen, carbon monoxide, and carbon dioxide.

Materials and Methods:

Eleven healthy, mongrel dogs, weighing between 15 and 23 kilograms, were evaluated prior to a single dose of radiation therapy to one lung, and at regular intervals following this treatment.

The baseline studies consisted of determination of rate of uptake of ^{15}O -labeled oxygen, carbon monoxide, and carbon dioxide; of the distribution of the inspired isotope mixture to each lung field; of the relative distribution of ^{133}Xe by perfusion to each lung field; chest X-ray; and hemoglobin. After a single dose of ^{60}Co therapy to one lung field through opposing anterior and posterior portals, follow-up measurements of the distribution of ventilation, perfusion, and of the rate of uptake of the ^{15}O -labeled gases were performed at 10-day intervals.

The mixtures of radioactive gases were prepared on the SKI small medical cyclotron, with calibration and analysis of each sample. The isotope mixture was administered via a cuffed endotracheal tube in a single inspiration of 450 ml to the anesthetized animal. Inspiration was sustained by means of a piston-driven animal respirator for a period of one minute. The activity was recorded on the TOKIM system and the rate of disappearance of the ^{15}O -labeled gases was plotted at two second intervals. The distribution of the single breath was determined by the sum of counts of inspired gas in each lung field for the initial four seconds. The distribution of perfusion was determined by summation of the counts ^{133}Xe delivered by blood flow to each lung field. In one animal, after radiation, the distribution of ventilation was also assessed by distribution of inhaled xenon. Five animals were studied until their spontaneous death and five animals were sacrificed when their physical condition began to deteriorate.

Results:

The baseline half-time for clearance of ^{15}O -labeled oxygen was 17.6 seconds; of carbon dioxide, 6.5 seconds; and of carbon monoxide, 7.4 seconds.

One animal died before administration of the radiation therapy; a second animal died an anesthetic death the first day after therapy; the third animal died 61 days after receiving 2250 rads to the left lung with no discernible change in pulmonary function; and the fourth animal died 18 days after receiving 2750 rads to the right lung without evidence of change.

Symmetrical Deterioration:

Three animals showed decline symmetrically in the rate of clearance of ^{15}O -labeled gases with mean clearance times increasing from 5 seconds to 12 seconds in one animal; from 8 seconds to 24 seconds in a second animal; and from 10 seconds to 20 seconds in the non-irradiated lung and 25 seconds in the irradiated lung in the third animal. In these three animals, the distribution of ventilation and perfusion to the irradiated lung were stable at 90 to 110% of the values obtained in the non-irradiated lung.

Asymmetrical Deterioration:

In three animals the rate of clearance half-time of ^{15}O -labeled gases from the irradiated lung increased considerably over the clearance half-time from the control lung. In one animal, the mean clearance half-time for carbon monoxide prior to irradiation was 8 seconds in both lung and 80 days after 2750 rads remained 6 seconds in the control lung and 10 seconds in the irradiated lung.

In a second animal the baseline clearance half-time was 5 to 8 seconds and remained 5 seconds in the control lung and 10-12 seconds in the irradiated lung. Finally, in a third animal, the baseline clearance half-time was 7 to 8 seconds, remaining stable in the control lung, but increasing to 23 seconds in the irradiated lung, approximately 160 days after 2000 rads to the right lung. In all three of these animals, there was marked decrease in the distribution of inspired air and of perfused xenon to the irradiated lung.

Deterioration:

In one animal, there was decline in clearance half-time from baseline values of 8 or 9 seconds to 24 seconds in the irradiated lung and 14 seconds in the control lung. In this animal, there was preferential distribution of inspired ^{15}O -labeled carbon monoxide and of xenon perfusion to the irradiated lung.

Histologic Examination:

As of the time of this report, the histologic analysis of autopsy specimens of lung, heart, and other pertinent organs is pending.

Conclusion:

The interpretation of these discrepancies and abnormalities after unilateral pulmonary radiation will depend in part on the histologic finding. However, the physiologic data alone do permit these two conclusions:

- (1) There is a considerable time lag between administration of unilateral pulmonary irradiation and the apparent pulmonary dysfunction. This varied from 120 days for a dog receiving 2000 rads, to 60 days for dogs receiving 2750 rads, to 20 days for two dogs receiving 3000 rads.
- (2) In all animals to which oxygen, carbon monoxide and carbon dioxide were administered-the changes in clearance half-time of any one gas were accompanied by comparable parallel changes in the clearance half-time of the other two gases. This may suggest that the effect of radiation on the clearance of radio-labeled gases is mediated by pulmonary blood flow and is limited by changes in pulmonary blood flow.

3. Erythropoietic and Phagocytic Function Studies Utilizing Absolute Quantitative Organ Scanning

Objective:

To quantitate erythropoiesis in patients with aberrant hematologic dyscrasias by measuring ^{52}Fe uptake in the reticuloendothelial system and, to assess splenic sequestration of ^{51}Cr labeled erythrocytes as an aid in clinical diagnosis.

Materials and Methods:

When patient diagnosis and treatment are dependent upon the functioning of the reticuloendothelial system, accurate assessment of organ sequestration and erythrogenesis is mandatory. In the continuing project of absolute quantitative organ scanning, we have previously developed and verified a method ascertaining

the amount of ^{51}Cr labeled autologous erythrocytes sequestered by the spleen. Patients in whom splenectomy was planned were injected with ^{51}Cr labeled acid citrate dextrose (A.C.D.) damaged red blood cells. Each patient was scanned within three hours prior to splenectomy on the High Energy Gamma (HEG) scanner using the depth independent dual foci collimators designed for the quantitation of ^{51}Cr . A program specifically developed for quantitative analysis was used to process all patient data. The methodology of absolute quantitative organ scanning can be found in section A-3 of this report.

We have devised an analogous method for quantifying liver and spleen erythropoiesis as shown by ^{52}Fe ferrous citrate concentration. Dual foci collimators with "constant resolution" designed for the 511 KeV of cyclotron produced ^{52}Fe were used for the phantom measurements and correlative patient studies. Each patient was scanned 13-28 hours post intravenous injection of 140 to 365 Ci ^{52}Fe . In the last four cases the ^{52}Fe was labeled to the patient's plasma before being injected and plasma iron clearance half-time values were ascertained. The tagging procedure consists of adding the calculated amount of ^{52}Fe to approximately 20 cc of patient plasma and incubating for 20 minutes at 23°C .

Results:

Patients studied to date include: 18 with Hodgkin's Disease (H.D.), 7 with chronic myelogenous leukemia (C.M.L.), 2 with systemic lupus erythematosus (S.L.E.), 3 with lymphosarcoma, 2 with Gaucher's Disease, and one each with Waldenstrom's macroglobulinemia, reticulum cell sarcoma and acute leukemia. The mean of the ratio of in-vivo to in-vitro measurements was found to be $0.99 \pm 20\%$ S.D. A summary of patients results can be found in Table VI. In patients with Hodgkin's Disease splenic weights range from 100 to 450 grams with two extremely large spleens of 873 and 1469 grams. In C.M.L. patients the spleens evidencing disease weighted more than those diagnosed as histologically normal with a range of 175 to 1620 grams. It is of interest to note the relatively high radioactive uptake in C.M.L. patients with histologic evidence of C.M.L. in their spleens. The largest and heaviest spleens, 2000 and 2300 grams, were found in the two patients with Gaucher's Disease. Table VII labeled "Sequestration of ^{51}Cr Labeled A.C.D. Damaged Autologous RBC's in Various Disease States" attempts to show correlation among diagnosis, spleen pathology and percent uptake of injected radioactive chromium approximately one day post-injection. Cr-51 data, Table VIII, correlates uptake weight and spleen size in disease states. The patient data clearly indicates that absolute splenic sequestration of ^{51}Cr labeled erythrocytes can be determined independent of spleen size, location, uptake, or geometry.

Eleven patients have undergone study with cyclotron produced Fe-52 to determine quantitative results of their erythropoietic activity. In two patients with marrow aplasia, one of whom had myeloma, splenic uptake was below 3% of injected dose. In three patients with histologically confirmed myelofibrosis with myeloid metaplasia, the splenic uptake was 12%, 36% and 76%. Patients with chronic granulocytic leukemia in two cases had uptakes of 35% and 5% while two other cases were found to be less than 1%. An 8% uptake was found in an erythroleukemic patient and a recently diagnosed Hodgkin's patient had a 3% uptake. Table IX contains a summary of patient data. Scan in-vivo values refer to those obtained using the total summed counts of the 50% scan image contour. In order to verify our method it was decided to chose a number of patients scheduled for splenectomy. In these cases in-vitro uptake values can be compared with their in-vivo counterparts. This information is vital in the differential diagnosis of splenic pathophysiology especially when related to data for splenic sequestration and destruction.

Conclusion:

The amount of iron uptake in the spleen is a composite of that used for erythropoiesis and the deposition of iron stores. Differentiation of these is based on clinical judgment. With absolute determinations it has been possible to ascertain the extent of extramedullary erythropoiesis. Our method of absolute quantitative uptake will aid in the choice of patients who may be benefited by splenectomy.

Table VI

Summary of Patient Splenic Sequestration

<u>Name</u>	<u>Diagnosis</u>	$\mu\text{Ci } ^{51}\text{Cr}$ <u>Injected</u>	<u>% Injected Dose in Spleen</u>	
			<u>In-Vivo</u>	<u>In-Vitro</u>
A.G.	CML	348	53	50
A.A.	CML	360	16	17
R.M.	HD	420	27	21
J.L.	HD	310	9	11
D.F.	HD	311	7	8
V.Z.	HD	294	8	11
B.G.	Lymphosarcoma	377	19	17
C.L.	HD	360	4	3
L.V.	SLE	434	3	3
C.B.	SLE	331	7	5
S.P.	HD	307	5	5
D.C.	HD	344	4	4
E.B.	HD	345	7	7
R.W.	HD	300	15	26
V.W.	CML	310	41	40

Table VI continued

<u>Name</u>	<u>Diagnosis</u>	$\mu\text{Ci } ^{51}\text{Cr}$	<u>% Injected Dose in Spleen</u>	
		<u>Injected</u>	<u>In-Vivo</u>	<u>In-Vitro</u>
A.C.	CML	340	45	38
D.G.	HD	302	14	12
B.K.	CML	388	16	14
K.C.	RCS	374	35	46
E.O.	HD	331	11	10
J.K.	Lymphosarcoma	300	2	2
T.S.	HD	375	6	8
E.D.	HD	319	13	11
E.P.	Gaucher's Disease	387	36	44
J.M.	CML	308	56	53
I.W.	HD	397	26	26
R.W.	Acute Leukemia	319	4	5
C.F.L.	HD	352	2	2
F.M.	HD	243	15	11
F.O.	HD	229	33	24
F.C.	Gaucher's Disease	308	23	36
J.V.	CML	267	5	4
M.C.	Lymphosarcoma	274	10	9

Table VI continued

<u>Name</u>	<u>Diagnosis</u>	$\mu\text{Ci } ^{51}\text{Cr}$ <u>Injected</u>	<u>% Injected Dose in Spleen</u>	
			<u>In-Vivo</u>	<u>In-Vitro</u>
J.D.	HD	349	7	10
P.D.	Waldenstrom's Macroglobulinemia	*	92 μCi	84 μCi

* Patient received previous injection of ^{51}Cr therefore cannot be expressed as % of dose

CML: Chronic Myelogenous Leukemia
 HD: Hodgkin's Disease
 SLE: Systemic Lupus Erythematosus
 RCS: Reticulum Cell Sarcoma

Table VII

Sequestration of ^{51}Cr Labeled ACD Damaged Autologous RBC'S in Various Disease States

<u>Diagnosis</u>	<u>Pathology Report</u>	<u>Patients</u>	<u>Uptake Range</u>	<u>Mean</u>
HD	Normal	12	3 - 26%	9.7%
	HD	6	2 - 33%	14.0%
CML	Normal	3	4 - 17%	11.8%
	CML	4	38 - 56%	46.1%
Lymphosarcoma	Normal	2	2 - 9%	5.2%
	CLL	1	17.4%	17.4%
Gaucher's Disease	Normal	0	---	---
	Gaucher's Disease	2	36 - 44%	40.1%
SLE with Thrombocytopenia	Normal	2	3 - 5%	4.3%
	SLE	0	---	---
Waldenstrom's Macroglobulinemia	Normal	0	---	---
	Waldenstrom's Macroglobulinemia	1	23.9%	23.9%
RCS	Normal	0	---	---
	Interstitial Fibrosis	1	45.6%	45.6%
Acute Leukemia	Normal	0	---	---
	Hyperplasia	1	4.5%	4.5%

Table VIII
⁵¹Cr Splenic Data Regarding Comparisons of
 Uptake, Weight and Size in Disease States

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<u>Patient Name</u>	<u>Spleen Weight(gm)</u>	<u>Length (cm)</u>	<u>Width (cm)</u>	<u>Depth (cm)</u>	<u>% Uptake</u>
<u>Hodgkin's Disease:</u>					
F.O.	450	15.0	9.0	3.0	33.0
I.W.	1469	20.5	15.0	9.0	25.9
R. We.	372	14.0	10.0	6.0	25.5
R.M.	160	12.0	7.0	8.0	21.0
E.D.	873	15.5	14.0	8.0	13.3
I.R.	310	13.0	12.0	6.0	12.1
D.G.	150	14.0	8.0	3.0	11.7
J.L.	150	15.0	8.0	2.0	11.3
F.M.	260	15.0	9.0	2.0	11.2
V.Z.	178	12.0	9.0	4.0	10.5
J.P.	332	16.0	10.0	12.0	10.1
E.O.	190	12.0	8.0	4.5	9.8
L.E.	410	23.5	10.5	5.5	9.8
D.F.	160	12.0	9.0	5.0	7.7
E.B.	100	10.0	6.0	3.0	7.2
T.S.	180	10.0	9.0	4.0	5.8
S.P.	270	12.0	8.0	8.0	4.6
D.C.	135	12.0	6.0	4.0	4.4
C.L.	125	11.0	6.5	2.5	2.8
C.F.L.	120	14.0	8.0	3.0	2.0

Chronic Myelogenous Leukemia:

J.M.	225	14.5	8.7	5.0	56.1
A.G.	1620	28.0	22.0	5.0	50.0
V.W.	291	15.5	8.5	4.5	40.4
A.C.	430	17.5	10.0	4.0	37.7
A.A.	175	12.0	9.0	5.5	17.0
K.B.	270	15.5	9.0	4.0	14.4
J.V.	320	14.5	7.0	2.0	4.1

Lymphosarcoma:

B.G.	1530	25.0	19.0	6.0	17.4
M.C.	230	13.0	9.0	6.0	8.8
J.K.	105	9.5	7.0	2.6	1.6

Table VIII continued

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<u>Patient</u> <u>Name</u>	<u>Spleen</u> <u>Weight(gm)</u>	<u>Length</u> <u>(cm)</u>	<u>Width</u> <u>(cm)</u>	<u>Depth</u> <u>(cm)</u>	<u>%</u> <u>Uptake</u>
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Systemic Lupus Erythematosus:

C.B.	95	11.0	8.0	6.0	5.4
L.V.	167	9.0	7.0	3.0	3.1

Gaucher's Disease:

E.P.	2000	35.0	14.0	14.0	44.3
F.C.	2300	26.0	18.0	10.5	35.8

Waldenstrom's Macroglobulinemia:

P.D.	280	12.0	8.0	5.0	---
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Reticulum Cell Sarcoma:

K.C.	462	12.0	11.0	4.0	45.6
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Idiopathic Thrombocytopenic Purpura:

L.R.	120	10.0	5.5	3.5	4.1
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Acute Leukemia:

R.W.	592	18.0	15.0	5.0	4.5
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Table IX

SUMMARY OF Fe-52 PATIENT DATA

<u>Patient</u>	<u>Diagnosis</u>	<u>Organ</u>	<u>Grams</u>	<u>% Uptake In-Vitro</u>	<u>% Uptake In-Vivo</u>	<u>Organ Activity (μCi)</u>	<u>Non-Organ Tissue Activity NOA (μCi)</u>
M.S.	Myelofibro- sis	Spleen	-	-	11.7	3.9	3.4
		Liver	-	-	6.7	2.2	2.7
R.T.	CML*	Spleen	-	-	3.8	0.6	0.8
		Liver	-	-	10.5	1.6	0.9
M.T.	Myelofibro- sis	Spleen	-	-	76.2	38.8	20.7
		Liver	-	-	-	-	-
L.H.	Myelofibro- sis	Spleen	-	-	35.8	14.2	5.6
		Liver	-	-	56.0	22.1	7.1
J.H.	Myeloma	Spleen	-	-	3.1	0.8	1.5
		Liver	-	-	10.0	2.6	4.6
R.S.	CML	Spleen	-	-	31.6	18.7	13.8
		Liver	-	-	53.5	31.6	11.7
W.M.	Erythro- Leukemia	Spleen	-	-	7.9	2.2	0.9
		Liver	-	-	10.3	2.8	1.5
W.S.	Aplasia	Spleen	-	-	3.1	1.8	7.5
		Liver	-	-	6.1	3.5	6.8
M.T.	CML	Spleen	232	<1.0	1.6	0.9	1.2
		Liver	-	-	8.3	4.5	0.1
R.R.	CML	Spleen	143	<1.0	<1.0	0.3	0.4
		Liver	-	-	3.0	1.7	2.1
D.S.	HD**	Spleen	185	2.9	2.3	1.6	0.9
		Liver	-	-	5.5	3.7	0.4

* Chronic Myelogenous Leukemia

** Hodgkin's Disease

4. Carbon-11 Labeled Cyanide as a Red Cell Tag for Spleen Visualization in Animals

Objectives:

To develop a new method of spleen visualization using C-11 labeled sodium cyanide.

Materials and Methods:

It is well known that heat damaging of autogenous red cells will lower intracellular pH and result in cell swelling (1). These cells are sufficiently damaged to be sequestered in the animals spleen with one hour after reinjection.

Radioisotopic labeling of the red cells is achieved by first treating them with sodium nitrite to oxidize hemoglobin into methemoglobin (2). In this form the red cells affinity for cyanide is very high.

A mixture of whole blood, acid citrate dextrose (ACD) and 2-3 mg NaNO_2 per 4 ml blood was incubated at 50° C for 20 minutes. Carbon-11 labeled sodium cyanide at pH 6.6 was then added.

Results:

Preliminary animal studies have developed no observable adverse reactions in 2 dogs and 3 rabbits. Distribution of the tracer at several time intervals up to 46 minutes post intravenous administration was visualized on the TOKIM oscilloscope using a pin hole collimator. Activity initially appeared in the heart only and in from 5-15 minutes entered the liver and spleen. A 7 minute post-injection picture demonstrates excellent spleen localization. These uptake regions then disappeared and kidney activity increased. At 30 minutes they were no longer visible but the urinary bladder was prominent.

Conclusions:

A new method of tagging the red cell utilizing C-11 labeled sodium cyanide has been developed. The short physical half life of C-11 and its mode of decay provide an advantage over other spleen scanning methods.

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5. Evaluation of ^{18}F as Scanning Agent

During 1972 the number of ^{18}F sodium fluoride bone examinations rose to 676 per year, as compared with 654 in 1971 and 110 in a one year period from June 1969 through June, 1970. To March 29, 1973 an additional 178 scans have been performed. This agent has essentially become routine for bone scanning, with only rare use of ^{85}Sr or $^{87\text{m}}\text{Sr}$ for bone examination since 1969. During the same interval the dose permissible for patients with malignant disease has increased from 0.014 mCi/kg to 0.086 mCi/kg. The dose calculations indicate bone irradiation of 1.2 rads from the higher dose. The amount administered to patients with benign disease has remained at the 0.014 mCi/kg for an estimated 0.2 rads to bone.

The rapid clearance of ^{18}F from non-osseous tissue has made it preferable to $^{87\text{m}}\text{Sr}$, and the lower radiation dose is the reason for selecting it instead of ^{85}Sr . The larger amount has shortened scanning time, permitted increased information density in the scans and, at the highest dose level, permitted use of a collimator with a higher resolution. Preliminary data from the 6 mCi dose (per 70 kg) and the 45-hole (0.8 cm FWHM) collimator suggest this may improve detection.

During the two years we have detected many lesions which were not visualized on radiographs in all types of malignant disease. This has enabled the clinician to select appropriate therapy and to match radiation portals to the disease in numerous cases. Data has routinely been recorded in magnetic tape for computer analysis, which materially aids in the interpretation, especially in determining the statistical significance of differences from the contralateral side when only one side is involved. A comparison of the computer analysis with the photoscan was made for the first 50 bone scans of 1972. We evaluated 116 sites or scans (counted as scans if no lesions). The computer data were superior in 57, the photoscan in 17 and the 2 were of equip worth in making a diagnosis in 42 sites or scans. No lesion was detected on the computer analysis which could not be visualized on the photoscan, but the significance of changes was more readily apparent from the computer print.

6. Studies of Radionuclides for Soft Tissue Tumor Localization

a. Gallium-67 citrate in patients

To the end of 1972 we have prepared 189 injections of ^{67}Ga citrate for the evaluation of non-osseous malignant disease. These studies conformed to the protocol of the Oak Ridge Associated Universities (ORAU), who furnished the ^{67}Ga . The patients received 0.035 mCi/kg and were scanned at 48 to 96 hours after injection. At the outset patients with lung masses scheduled for excision and patients with lymphoma or Hodgkin's disease were selected for the study. During the past eight months the protocol was broadened to include all other types of histologically proven malignant disease.

Review of the results has been accomplished by the recall of patients' records and the coding of data onto the ORAU forms for entry into their computer. The data submitted on 120 cases were received at ORAU on 3/2/73. Data are stored and analyzed by patient as well as by site. Review of data at triennial meetings of the ORAU group is producing preliminary evaluation. One of us (Dr. Richard S. Benua) is serving on the committee to review the data on Hodgkin's disease and to prepare the preliminary publication. This data shows that about 25% of the histologically proven sites of Hodgkin's disease fail to show on the scans. There are approximately 5% of false positive sites. The data are more accurate in the neck, axillae and chest, and less accurate in the abdomen and groin.

Digital data recorded during the scans has been analyzed by the computer in terms of standard deviations of difference to assist in the interpretation of scans at Memorial Sloan-Kettering Cancer Center. Evaluation of the role of the computer in the diagnosis of soft tissue tumors is at present incomplete.

As an adjunct to the ORAU protocol we have been obtaining tissues at surgery in selected cases. These are counted, together with blood and appropriate standards, to determine the percent of dose/kg. Preliminary results show that tumors containing 1.5 times the concentration of normal adjacent tissue may be strongly positive in hepatomas. Analysis of the tissue data is unfinished business for the next project year.

No ^{73}Se has been administered to patients, but the following section reports on work done using mice.

b. Distribution of injected Se-73 in mice

Objectives:

To study the distribution of injected selenium in mouse tissue, and to evaluate the localization of the nuclide in transplantable mouse tumors as an indication of its potential utility as a tumor scanning agent.

Materials and Methods:

Selenium-73 (7.1 hour half-life) was produced in the Institute cyclotron by ^3He irradiation of germanium targets. (For details see this Progress Report, Proposal #4, pages 11 through 13.) Two hour irradiation with a 20 μA beam current resulted in a yield of four to eight millicuries, after chemical separation.

After washing the surface of the germanium target with HCl, it was placed in a mixture of 2ml of concentrated HNO_3 and 2ml of HF, sufficient to dissolve the surface layer of the target containing the bulk of the activity. 20 ml of concentrated HCl was added to this solution and it was boiled under reflux to eliminate the nitric acid. The solution was washed twice with 20 ml of benzene, and after adding 2 ml of concentrated HBr, the ^{73}Se and germanium were extracted with benzene, leaving the arsenic contaminants in the aqueous phase. The benzene fraction was washed with 20ml of concentrated HBr-HCl (10:1) twice, then with 1/10 its volume of distilled water twice. Se-73 was then extracted into 10ml of 2M NaOH, in the form of selenite. Recovery was 90%. The selenate form was prepared by adding an equal volume of HNO_3 and heating to dryness in a sulfuric acid bath at 135°C under air stream. The dried residue was dissolved in isotonic saline of neutral pH. For the carrier-containing injections, stable sodium selenate or selenite was added in a dose of 0.1mg Se/kg body weight.

Tissue distribution studies were carried out in normal female CD-1 mice (28-30g), in female Swiss albino mice (20-22g) bearing Ehrlich carcinoma or Crocker sarcoma 180, in female AKR/J mice (20-22g) bearing Mecca lymphosarcoma, and in female BDF-1 mice with P815/VLB mast cell tumor. The tumors were implanted on the right lower abdomen by subcutaneous injections of ascites or homogenized tumor. Radionuclide injection was in the tail vein, and the animals were sacrificed at one and 24 hours in groups of four or five.

Results:

At one hour after injection, the highest tracer concentrations were in liver and kidney for all types of injections. Blood levels for carrier-free injections were 3.6 and 4.8 times that for carrier-added, for selenate and selenite respectively. The valence state of selenium did not greatly affect distribution in general, except in heart, where carrier-free selenite concentration was significantly greater than the other types. Femur and cartilage showed a preference for carrier-free selenite, and skin for carrier-containing selenite. In lung and spleen, carrier-free levels were higher, regardless of valence, and in liver, carrier-added levels were higher.

At 24 hours, the pattern changed considerably. Carrier-free activity cleared more rapidly from the blood than carrier-containing. Liver concentrations of carrier-added activity declined much more rapidly than carrier-free, falling well below the latter at 24 hours. Kidney retained carrier-free selenate, but diminished concentrations of the other three types. In most tissues, carrier-free activity was higher than carrier-containing, at 24 hours, with little valence dependence. The only normal tissues to show significant increases in activity from one to 24 hours were femur, cartilage and skin, and that only for carrier-free selenate.

Tumor concentration of ^{73}Se was generally low at one hour after injection, and in Ehrlich carcinoma, Crocker sarcoma 180 and Mecca lymphosarcoma, was little dependent on valence or carrier. The tumor/liver ratio was 0.04 to 0.16 for all types. At 24 hours, however, carrier-free concentrations increased by factors of 1.9 to 3.6 over the one hour values. Although no such increase occurred with carrier, loss of activity was far slower in tumor than in liver, yielding 24 hour tumor/liver ratios of from 0.28 to 0.60 for all tumor types and all forms of injections.

Mast cell tumor exhibited a preference for selenate uptake at one hour, both with and without carrier, but no valence effect at 24 hours. Carrier-free concentrations at 24 hours in mast cell tumor were significantly higher than for the other tumor types.

Conclusions:

Both a rapid (liver, kidney) and a slow (bone, cartilage, skin, tumor) rate of concentration of ^{73}Se were observed, the former suggesting chemical binding of selenium on -SH groups of various proteins, the latter, a substitution of selenate for sulfate in chondromucoprotein. Although mast cell tumor is rich in the chondromucoprotein heparin, the preferential uptake of selenate in this tumor was not great.

In general, the tumors studied showed a selective increase in concentration of inorganic selenium from one to 24 hours, but the differential developed too slowly for ^{75}Se to be of practical value as a tumor scanning agent, considering the half-life of 7.1 hours.

7. Fluorine-18 Metabolism in the Acutely Uremic Rat

This is a final report, the project having been initiated and completed in 1972.

The scientific background, which has not been given previously, is contained in the submitted bibliography.

Objectives:

Clinical observations have suggested that the metabolism of inorganic fluoride is impaired in the renal failure resulting from methoxyfluorane anesthesia. The object of this work was to study the effect of acute renal failure on the kinetics of the metabolism of carrier-free ^{18}F in the absence of disturbance of total fluoride burdens.

Materials and Methods:

Male albino rats weighing 200 to 300 gm were made uremic by intramuscular injection of 50% glycerol in water. Forty-eight hours later the uremic rats and matched controls were injected intra-cardially with about 0.1 $\mu\text{Ci/gm}$ body weight of carrier-free ^{18}F dissolved in neutral isotonic saline. At intervals from 15 minutes to 5 hours later the rats were killed by exsanguination from the exposed abdominal aorta. Radioactivity and urea nitrogen were determined in the blood samples, and the radioactivity in specimens of muscle, kidneys, ends and shafts of tibias separately, testes, liver and urine was measured in a well-type scintillation counter. The curves for ^{18}F concentration in the blood of control and uremic rats vs. time were corrected for urinary excretion and the resulting differential retentions (D.R.) were computer analyzed and correlated with concentrations in various tissues. The relative radiation doses in control and uremic rats were computed and compared.

Results:

In the 13 control rats (C), the previously known kinetics of ^{18}F in blood, bone, kidney, liver and muscle were confirmed and amplified. A new finding was that there was progressive storage of ^{18}F in the testes, the concentration increasing from about 1/4 the blood level at 15 minutes post injection to 3 times that in blood at 5 hours. This is in contrast to other normal soft tissues where the kinetics parallel those in blood quite closely. Because of the short half life of ^{18}F the late storage in the testes did not contribute much to the radiation dose.

The experimental rats fell into 2 groups of 9 mildly uremic animals with a blood urea nitrogen (BUN) of 17 to 47 mg/100 ml and 8 highly uremic ones (HU) with BUN of 130 to 270 mg/100 ml. In MU various parameters were significantly different from the controls, but the differences were less marked than in HU. Urinary excretion of ^{18}F was greatly impaired in HU, being near zero in some rats. Data for HU were analyzed in detail. The blood curves for D.R. in C and HU were computer-analyzed and 2 exponential components were fitted to the experimental points. Clearance of ^{18}F from the blood of HU was much slower than from C. As the marked differences in urinary excretion had been allowed for, the most probable cause for slower clearance from blood is slower uptake by bone. There was no significant difference in the net storage of ^{18}F in bone between C and HU, but analysis of the ratios of the concentrations in bone and blood showed that the bones of HU stored a much smaller fraction of the available ^{18}F than the bones of C. This is probably due to competition with the other anions which are retained in the acidosis of uremia.

In C the ratio: concentration of ^{18}F in kidney to concentration in blood was constant at 2.53 ± 0.33 from 15 min. to 300 min. after injection. In HU this ratio was greatly increased, reaching values of 10 to 19 in individual rats at 2 to 5 hours post injection.

The infinity radiation dose was computed for the various tissues examined. Relative to blood the doses for C were: bone, 24.6; testes, 0.3; muscle, 0.4; liver, 0.8; kidney, 2.5. In HU the radiation doses were increased above normal by only 5% to 40% except in the kidneys, where the dose was 2.4 times that in the controls.

Conclusions:

In acute uremia both the urinary excretion of ^{18}F and its clearance from the blood by bone are decreased. Both these diminished rates result in an increased retention of ^{18}F in the blood. Although the uremic kidney excretes little ^{18}F it maintains a tissue concentration relative to the blood up to 8 times the normal ratio. The normal testis shows a small selective storage of ^{18}F .

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C. METABOLIC AND SCANNING STUDIES ON PATIENTS WITH BONE AND
PARATHYROID DISEASE

1. Effect of Antitumor Therapy on the Local Kinetics of ^{47}Ca
and ^{85}Sr in Tumor-Invaded Bone

Objective:

To evaluate the effect of antitumor therapy on mineral deposition and removal in tumor-invaded bone using ^{47}Ca and ^{85}Sr .

Material & Methods:

Patients with tumor invaded bone have received a single labeling tracer dose of ^{85}Sr prior to starting local radiation therapy and the removal rate of this radionuclide has been followed in diseased and uninvolved parts of the skeleton.

^{47}Ca uptake in the same parts of the skeleton was also measured prior to treatment and repeatedly using additional tracer doses after treatment.

It has thus been possible to measure both the changes in the deposition phase of bone mineral and its removal phase in relation to local radiation therapy.

Results & Conclusions:

Studies previously carried out in ten patients have revealed that in the majority there was an increase in the local uptake of ^{47}Ca in the tumor invaded bone 30 to 45 days after the onset of radiation therapy. At the same time there was a relative increase in the ^{85}Sr retention in the bone lesions compared to normal bone which persisted for several months. Both processes led to a recalcification of the lesions and this was associated with clinical improvement in one patient so treated.

An additional patient was studied during the past year both after radiation therapy and later after treatment with an androgen and prednisone for metastatic breast cancer.

The effect of radiation therapy was essentially as described above. The effect of treatment with an androgen and prednisone is still under study. The control period data has been obtained and the patient is now to be reevaluated after 6 months treatment with these agents.

Future Plans:

More limited studies will be carried out on ambulatory patients receiving hormonal or non hormonal chemotherapy for metastatic breast cancer if they are included in a protocol involving the administration of ^{47}Ca such as during the course of bone mineralization measurements.

2. Studies of the Effect of Phosphate on Mineral Metabolism

(a) Studies in Man

Objectives:

To study the effect of phosphate therapy on calcium metabolism and calcium kinetics in patients with primary hyperparathyroidism and patients with cancer.

Materials and Methods:

The effect of oral phosphate administration has been studied in a total of six patients to date; four patients with hypercalcemia due to primary hyperparathyroidism and one patient with mild hypocalcemia (serum calcium 8.7 mg%) associated with carcinoma of the breast with metastases to bone and one patient with carcinoma of the penis, bone metastases and hypercalcemia. Techniques employed have included metabolic balance, radiocalcium kinetics, and urinary hydroxyproline excretion. Patients were hospitalized on the metabolic ward under conditions of complete metabolic balance (Ca, P, N). A control period of two weeks was followed by four weeks of treatment with a 2-3 grams phosphate supplement. A fourteen day ^{47}Ca kinetic study (50 μCi IV) was performed during the control phase and repeated during the last two weeks of therapy. Total body retention and point counts were measured by external scanning.

Results:

Phosphate led to a sustained reduction in serum and urinary calcium in all four hypercalcemic patients with primary hyperparathyroidism, but did not change the serum calcium in the patients with cancer, although the urinary calcium significantly decreased in both patients. Metabolic balance studies in the hypercalcemic patients showed a shift to a more positive calcium balance the change from pretreatment balance being in the range of +60 to +280 mg calcium per day. However, in the patient with breast cancer there was a shift towards a less positive calcium balance. Phosphorus balance became markedly positive in all patients. Nitrogen balance remained positive without significant change.

Calcium-47 kinetic studies demonstrated a fall in bone resorption rate during treatment in all five hypercalcemic patients and an increase in the bone resorption rate in the hypocalcemic patient with cancer.

Conclusions:

The data indicate that oral phosphate given to patients with hypercalcemia due to primary hyperparathyroidism causes a sustained reduction in serum calcium, a positive calcium balance, a fall in urinary hydroxyproline and reduction in bone resorption rate. The significance of these studies is that the mechanism of action of phosphate on hypercalcemia appears to reflect its inhibition of bone resorption.

The hypercalcemic patient with cancer did not show any change in serum calcium during phosphate therapy despite significant decrease in urinary calcium excretion, and increase in calcium balance and a decrease in bone resorption rate. His very active progressive disease possibly explains his resistance to the serum calcium lowering effect of phosphate. Alternatively, the mechanism of hypercalcemia in malignant disease may differ from that in hyperparathyroidism.

The findings in the patient with breast cancer in the preliminary study suggest that at least in this mildly hypocalcemic patient with bone metastases the effect of phosphate on bone resorption rate was different. It is possible that the effect of phosphate is different in normocalcemic, and hypocalcemic patients.

(b) Animal Studies

Objectives:

To evaluate the effect of phosphate on calcium exchange in rat tissues, to aid in defining the mechanism of action of oral phosphate in man.

Results:

Following six weeks of 150-190 mg/day of phosphate supplement, tissues of treated and control rats were analyzed for ^{47}Ca content at 24 hours after injection. Significant increases in ^{47}Ca uptake were found in both kidney ($16 \pm 7\%$) and stomach ($18 \pm 9\%$) of phosphate-treated rats. No significant differences were observed in other soft tissues or bone. The effect of supplemental phosphate on the resorptive mechanisms of bone was studied by prelabelling rat skeletons with ^{85}Sr in bone and kidney was measured upon sacrifice. The tibias of the phosphate-treated rats were significantly heavier than those of the controls, both for wet weights ($19 \pm 5\%$) and ash weights ($13 \pm 4\%$). Total calcium and phosphorus content in these bones were increased in proportion to the weight increase. There was no significant difference in the weights of either the kidneys or total body between the two groups. Phosphate-treated rats had significantly higher retention of ^{85}Sr in tibias and kidneys.

Conclusions:

The data suggest that treatment with oral phosphate in the rat leads to increased bone mass, most likely by inhibition of bone resorption, and is associated with deposition of calcium in the kidney and stomach. Phosphate treatment did not enhance bone accretion of ^{47}Ca .

3. Effect of Calcitonin on the Hypercalcemia of Cancer

Objectives:

To ascertain whether calcitonin is capable of controlling hypercalcemia associated with neoplastic diseases by in-

hibiting the pathologic bone resorption of cancer.

Materials and Methods:

The possible effectiveness of exogenously administered calcitonin (synthetic salmon calcitonin-AL0977) was investigated in ten patients with cancer and hypercalcemia. Eight of them had proven bone metastases. None of the patients received concomitant chemotherapy. All patients were initially skin tested for sensitivity and were not eligible for inclusion in the study if the skin test was positive. Levels of serum calcium, phosphorus, magnesium, creatinine, alkaline phosphatase activity and electrolytes and urinary excretion of calcium, phosphorus, creatinine were determined during pre-treatment, treatment and post treatment periods.

Results

The initial concentration of serum calcium ranged between 12.0-15.0 mg/100 ml. Of the ten patients treated, seven received synthetic salmon calcitonin (SCT) intramuscularly (im) in doses of 16-32 MRC units/kg/day for four to twenty days, and three patients received SCT intravenously (iv) in doses of 16 MRC units/kg/day (in 5% D/W administered at a rate not exceeding 4 MRC units/kg/hour)

Of the seven patients, six were treated with 8 MRC units/kg im bid and five of these showed a maximum decrease in serum calcium concentration of only 0.4-0.6 mg/100 ml and the sixth patient showed a decrease of 2.5 mg/100ml. The seventh patient had a decrease in serum calcium concentration of 1.7 mg/100ml (15.2 mg/100 ml — 13.5 mg/100 ml) following nine days treatment with 32 MRC units/kg/day (8 MRC u/kg every six hours).

The three patients who received seven intravenous infusions of SCT showed a fall in serum calcium of 0.3 to 1.3 mg/100 ml at the end of infusion with a return to pre-treatment levels within twenty-four hours.

All patients tolerated SCT therapy well except the patient treated with the highest dose of SCT (8 units/kg im every six hours) who had several episodes of vomiting during the first two days of therapy. SCT did not cause changes in blood urea nitrogen, serum phosphorus concentration, or serum electrolytes.

Conclusions:

These data indicate that SCT in these doses is not particularly effective in reducing serum calcium levels in patients with cancer hypercalcemia. Further studies in ectopic hyperparathyroidism might yield different results. Trials with an increased dose of calcitonin are required. The study is still in progress.

4. Distribution of Injected Sc-47 in Mice

Objectives:

To study the distribution of injected ^{47}Sc in mouse tissue, and in particular, to determine its localization in transplantable mouse tumor as an indication of its potential utility as a tumor scanning agent.

Materials and Methods:

Carrier-free ^{47}Sc was chemically separated from mixtures of ^{47}Sc and parent ^{47}Ca activities obtained from commercial suppliers. The ^{47}Sc was coprecipitated with $\text{Fe}(\text{OH})_3$, and the ferric ion removed by washing a 6N HCl solution with ether. Injection solutions were prepared by evaporating the washed acid to dryness and dissolving the residue in isotonic saline containing 0.1% sodium citrate as a chelating agent. For the carrier-containing injections, 1 mg stable scandium per kg body weight was added.

Female Swiss albino mice, weight 23 to 26 gram, implanted with Ehrlich carcinoma in the subcutaneous tissue of the lower abdomen, were injected in the tail vein, and sacrificed at one hour, 12 hours, one, two or three days post injection. Tracer content was measured in blood, brain, heart, lung, stomach, intestines (both with contents), pancreas, liver, kidney, spleen, muscle, femur and tumor.

A 4 kg female rabbit was injected with 100 μCi of the carrier-free solution and sacrificed at 18 hours. Both femurs were removed, mounted in wax, cut longitudinally and placed on x-ray film for 4 days.

Results:

Addition of carrier increased the rate of clearance from blood and decreased the concentration of activity in most tissues, except for kidney and stomach between one and 12 hours, and liver at 12 hours.

In blood, heart, lung, muscle, skin and brain, carrier-free concentrations were significantly greater than carrier-added at three days post injection, whereas no strong carrier effect was observed in pancreas, spleen, stomach, intestine, kidney, liver tumor and femur at this time.

Femur, liver, kidney, spleen and tumor showed a peak concentration at 12 hours followed by slow clearance, while other tissues had generally lower concentrations and cleared more rapidly. Femur showed marked uptake, particularly in the carrier-free injections. Concentration in brain was markedly lower than in all other tissues measured.

The autoradiography of rabbit femur indicated a distinctive concentration of activity in the marrow.

Conclusion:

A potential utility of radioisotopes of scandium for tumor detection is suggested by the preferential incorporation of carrier-free ^{47}Sc in at least one type of mouse tumor. Further work is necessary to determine the relative concentrations of injected scandium in marrow as against bone tissue.

5. Bone Mineralization Studies

Objectives:

To further evaluate the possibility of changing our present single-photon absorptiometric bone mineral analyzer to a dual-photon instrument. Theoretically, the dual-photon approach should overcome the inaccuracy of the bone mineral content measurement which results from the presence of subcutaneous fat.

To combine quantitative measurements of bone mineralization and ^{45}Ca kinetic studies to improve our understanding of the pathophysiology of disturbances of skeletal tissue structure and function.

To obtain relatively precise data by direct photon absorptiometry measurements of the bone mineral content of the radius and ulna of patients at different stages of renal failure. Correlation of this data will be made with the following to be obtained at the Bronx Veterans Administration Hospital: (a) radiographs of the forearms, (b) calcium determinations from iliac crest bone biopsies, (c) serum calcium and phosphate and serum alkaline phosphatase and (d) parathormone immunoassays. It is expected that such a study could lead to a simple safe method for early detection of renal osteodystrophy and allow for a sensitive approach to study the effect of different therapies.

To modify the present single-photon instrument to permit measurement of bone mineral content of the humerus and phalanges in addition to the radius and ulna. The ability to measure the humerus will permit a collaborative study with the Radiotherapy Department of Memorial Hospital to determine the effectiveness of radiation treatment of solitary metastatic lesions sometimes found there. Measurement of the phalanges will allow for the study of bone mineral content changes in a different type of bone, i.e., a mixture of cortical and trabecular as opposed to pure cortical in the radius and ulna.

To continue to accrue data on the mineral content of the forearm bones of normal individuals and patients with demineralizing bone conditions. In addition consideration will be given to obtaining data on the humerus and the phalanges.

To determine the proportionality factor (regression equation) which relates the measurement obtained from the osteodensitometer (integral value) to grams of bone mineral per centimeter of bone length by direct measurements of calcium and dry weight in the ashed material. Determinations of bone mineral content based on this proportionality factor is then to be compared to that obtained in other laboratories using a direct photon absorptiometry technique.

Materials and Methods:

It has been shown that the dual-photon approach can be readily engineered into the present SKI bone mineral analyzer

by (a) obtaining a single dual-isotope source with ^{241}Am above ^{125}I , (b) the use of two single channel pulse height analyzers and scalars and (c) the addition of an interface to allow the data to be sent directly into the IBM-1800 computer. A vendor has produced the required dual-isotope source at a reasonable cost. A post-doctoral fellow joined our staff in August 1972 and has developed a program to be used for the dualenergy bone mineral analysis.

The state of bone mineralization was determined by direct photon absorptiometry. This gives bone mineral content in either grams of bone mineral per unit length of bone or as grams of bone mineral per cm^2 in the scanned region. The ^{47}Ca kinetics were measured by the usual method consisting in the intravenous administration of a trace dose of ^{47}Ca , measuring its specific activity serially in the serum, and its excretion in the urine and feces serially. The exchanged calcium pool and accretion rate are then calculated from this data.

Bone mineral content measurements of patients with renal dysfunction have been started in collaboration with Dr. Ackad of the Renal Section of the Bronx Veterans Administration Hospital. Three classes of patients are participating in this study (1) end-stage kidney disease on maintenance hemodialytic therapy (2) end-stage kidney disease on chronic peritoneal dialysis and (3) chronic kidney disease at intermediate degrees of renal failure and not receiving any form of dialytic therapy.

Results:

A dual-photon method employing scans of forearms maintained in constant thickness of tissue equivalent material has been shown to give determinations of forearm bone mineral content which are not effected by the presence of subcutaneous fat. It has also been estimated that the precision and accuracy of this measurement with a dual $^{125}\text{I}/^{241}\text{Am}$ photon source presently under construction should be about $\pm 3\%$.

Patients in whom both bone mineralization measurements and ^{47}Ca kinetics were obtained revealed the following: Two patients with osteoporosis and a low accretion rate of calcium were found to have a normal value when expressed relatively to their low bone mineralization measurements. One patient with osteomalacia and low accretion rate was found to have a high accretion rate relatively to the markedly low bone mineralization.

One patient with cancer hypercalcemia had a normal accretion rate and a normal bone mineralization when anatomical bone was considered but low bone tissue mineralization when that value was corrected for the width of the radius. The exchangeable pool was elevated and this was probably in part due to the elevated serum calcium level and in part probably to increase bone mineral exchange surface related to his malignant metabolic disorder.

One patient with hemangiomatosis had elevated bone mineralization measurements both for anatomical bone and bone tissue,

normal accretion rate and a moderately elevated exchangeable pool probably due to increased surface exchange of mineral at the sites of the hemangiomatosis involving bones.

One patient with Cushin's syndrome had a normal accretion rate and exchangeable calcium pool and normal bone mineralization values. One patient with extensive bone metastases from breast cancer had a high accretion rate related to her extensive osteoblastic lesions and normal levels of mineralization of her uninvolved radius. It appeared in this case that an excessive rate of deposition of calcium in osteoblastic lesions was not associated with any loss of this element from normal bone tissue.

Another woman with limited bone metastases from breast cancer had a normal state of mineralization of the radius according to all parameters but had a very low accretion rate. When this was expressed relatively to the mineralization values it remained low. There was no ready explanation for this other than possibly the aging process in this woman of 72. The exchangeable pool which was elevated in this patient may have been due to increased bone surface available for exchange at the site of the metastases.

Bone mineral measurements have been carried out on 49 patients who were at various stages of renal failure. Serial measurements will be made on as many of these patients as possible over a two year period to determine the effect of therapeutic intervention on the course of renal osteodystrophy. The data obtained do show (a) a general agreement between the estimates of bone mineralization obtained from forearm radiographs and the more precise measurements obtained with the bone mineral analyzer and (b) the calcium analysis made available as the result of a single iliac crest biopsy and the bone mineral content measurement of the radius and ulna of a patient with severe osteomalacia both show a value of about 1/3 of normal.

Bone mineral content measurements on the forearm bones of 163 normal individuals have been obtained to date. This data will be used to determine the range of bone mineral content expected in the normal population available to us. Exclusive of the renal dysfunction patients from the Bronx VA Hospital, measurements on the radius and ulna have been carried out on 114 patients with the following diagnoses: Postmenopausal and senile osteoporosis, hyperparathyroidism, pseudohyperparathyroidism associated with malignancy, osteomalacia, metastatic breast cancer with normal serum calcium, metastatic breast cancer with hypocalcemia and osteolytic lesions of undetermined etiology.

Reproducibility studies show a precision of between 2 and 3% standard deviation for the measurements of the bone mineral content of the humerus and phalanges. A study of the effectiveness of radiation treatment on reducing the bone mineral content of solitary metastatic lesions found on the humerus awaits the availability of patients with this condition.

A regression equation was developed in our laboratory based on integral values determined with our digital instrument and measurements of calcium of ashed bones. Calculations of gr of bone mineral per centimeter bone length obtained from this regression equation and our integral values were compared to those obtained in the Radiology Department of the University of Wisconsin, where they calculated the bone mineral content based on an independently obtained regression equation and integral values. Their measurements were done on an analog osteodensitometer. The comparisons were made on similar bone reference standards and on the forearm bones of two individuals measured in both labs. The calculated values of the two labs in grams per centimeter for the radius and ulna bones of these two individuals gave an average deviation of 1.5%.

Conclusions:

The availability of a single dual-isotope source makes it possible to convert our present single-photon to a dual-photon instrument. It has been shown by work with excised bone in our laboratory that this modification will overcome the error inherent in single-photon absorptiometry due to the presence of subcutaneous fat and permit determinations of mineral content of forearm bones with a precision and accuracy of $\pm 3\%$.

The correlation between the accretion rate and the various bone mineralization studies has expanded our interpretation of these results. Since bone is the major reservoir of calcium in the body, movements of this elements in and out of the skeleton are better expressed in relation to its mineral content. While the mineral content of a portion of one bone is a limited sampling of the whole skeleton it reflects nevertheless the trend in the mineralization state of this tissue quantitatively and reproducibly. It will remain the only practical method giving such a quantitation until direct measurements of calcium contents of part or all of the body are developed enough to become applicable for this purpose.

The study recently started on bone mineral measurements of patients with renal failure has already shown (a) a general agreement between forearm radiographic information and bone mineral content measurements made with photon absorptiometry (b) for the only patient where we have both measurements there is agreement determination for an iliac crest biopsy specimen and a photon absorptiometry measurement, (c) this population of patients under chronic dialysis shows a distribution much more skewed toward low bone mineral values than does a normal population, Fig. 19, (d) a marked increase in bone mineralization in one patient who had a parathyroidectomy (see Fig. 20). This patient showed a 40% increase in bone mineral content, from 0.79 gr/cm² (48% of normal) to 1.09 gr/cm² (66% of Normal) in 12 months. If the rate of increase were uniform over the twelve month period, the sensitivity of the osteodensitometry technique would have made it possible to recognize a significant change in bone mineralization one month after the operation.

The forearm bone mineral content determinations on two individuals taking in two different laboratories using different types of direct photon absorptiometry instruments, and each laboratory using their own regression equation, shows agreement to better than 2%.

Fig. 19. Comparison of dialysis patient and normal populations; number of subjects versus number of standard deviations from the normal mean

Fig. 20. Forearm scans of a normal individual, separated in time by two years, and scans done on a hyperparathyroid patient one month before and 12 months after a parathyroidectomy.

6. Neutron Activation of Calcium and Other Elements

Objectives:

During the course of the past year a paper was presented (1) by H.E. Palmer, wherein, the feasibility of determining total body calcium in rats and dogs by measuring ^{37}Ar was shown. The subject is irradiated with fast neutrons. Thereby, a small quantity of calcium is converted into ^{37}Ar via the $^{40}\text{Ca}(n,\alpha)^{37}\text{Ar}$ reaction. This argon diffuses out of the bone and is vented from the subject through the lungs. The respiratory product gases are then separated from the argon and it is placed in a small proportional counter where it is quantitatively assayed. It was decided at this point to place a human total body in-vivo analogue to this study on a first priority basis. The in-vivo study of calcium, sodium and chlorine in limited volumes of lower limb bones, proposed in 1972, although in no way discredited, will now take second priority. Basically, this is for two reasons, it appears feasible to measure total body calcium with less than .001 rad on a research basis and quite practically with less than .010 rad dose, putting much less limit to the scope of patient studies than with the other higher dose methods, and the whole body counter required for the ^{49}Ca assay is replaced by a small comparatively inexpensive proportional counter for the ^{37}Ar assay. Fortunately, much of the equipment needed for our proposed whole body and partial body studies are compatible, so that, work on both projects is proceeding simultaneously. Clinical rationale for whole body and partial body studies are contained, respectively, in the Proposals for 1971 and 1972.

Our objective is to establish methods whereby changes in the mineral composition of the whole body may be compared with changes in the kinetics of bone as studied by conventional means, and to measure the calcium content of the whole body or a part of it and correlate such measurements with other parameters of the activity of bone tissue.

Material and Methods:

(a) ^{37}Ar Feasibility Study

The first step in a human evaluation of the ^{37}Ar method has been carried out. It was designed to determine if a reasonable quantity of ^{37}Ar could be quantitatively measured, after a reasonable respiratory gas collection period, and following a very low dose of fast neutron irradiation (0.59 millirad). Further requirements for this study were the following, fast neutron source with well known dose and flux characteristics (1.04×10^7 neutron/sec. $^{238}\text{Pu-Be}$ calibrated source), neutron dosimeters (fast neutron sensitive film badges and a moderating sphere neutron rem dosimeter), respiratory gas separation apparatus and low level ^{37}Ar counting apparatus. Gas separation and counting apparatus were set up for this feasibility study at Brookhaven National Laboratory (BNL). Mutual discussions lead to arrangement of a collaborative effort between ourselves, Dr. Raymond Davis, Jr. and Dr. John C. Evans in the Chemistry Division of BNL.

1. Gas collection and storage:

The respiratory gas collection and storage apparatus

was mounted on a portable cart. This allows easy control over subject gas supply and collection prior to, during and post irradiation. The subject can be moved to various convenient locations during these periods. Figure 21 shows the basic components of the system. The 20% oxygen-80% helium tank provides the breathing gas used through the entire procedure. Helium is substituted for the usual nitrogen component in air because it is more readily removed than nitrogen. This supply also eliminates the nearly 1% of natural argon in the atmosphere, which greatly reduces the blank quantity collected. The only blank argon that will remain will come from that which is washed out of the subjects tissues and a very small trace in the breathing gas. A leak tight face mask with inlet and outlet one-way valves is provided to control intake of breathing gas and exit of exhaled gas. The exhaled gas passes through indicator NaOH, for CO₂ removal, and indicator silica gel, for water vapor removal. These are removed at this stage because there is no hazard associated with placing them near the subject and the devices do not interfere with exhaling. The collected gas volume is reduced and moisture condensing in various parts of the system is avoided. A 30 liter Douglas bag provides a buffer volume. This variable system volume is necessary because expiratory air rates vary, making intermittent operation of the high pressure pump convenient. The pump is rated 1500 PSI at 11.3 liters/minute, which compares to a ventilatory response in the resting basal state of 5.8-10.3 liters/min.

2. Gas Separation and Counting

The very low dose achieved in this experiment depended primarily upon reducing background in the ³⁷Ar counting apparatus to on the order of 5 counts per day. A pure argon fraction must be obtained to keep the gas proportional counter volume as small as possible and to eliminate trace radioactive gases such as ⁸⁵Kr, ²²²Rn and tritium. The counter must be made of the most radiochemically pure materials available (Quartz envelope and zone refined metals). A volume must be provided for the counters that is surrounded by an anticoincidence ring of gas proportional counters, which in turn is surrounded by at least eight inches of lead shielding. Data from each counter is stored in a 256 channel portion of a multichannel analyzer.

Figure 22 illustrates the first steps in the gas separation procedure. The high pressure cylinder is attached to the system and allowed to leak in through the copper tube furnace (450°C.) to remove oxygen. A buffer tank is provided to keep the system from reaching too high an internal pressure. The gas is then passed through a titanium gettering furnace (950°C.), where nitrogen and other non-inert gases are removed. An activated charcoal trap, held at liquid nitrogen temperature, collects all remaining gases except helium, which passes through and is vented from the system. The trap is warmed to release the inert gases and quantitatively transferred into a titanium gettering cleanup bulb and then put into a transfer bulb.

The gas transfer bulb is attached to the system shown in Figure 23, where inert gas separation and transfer of the argon sample into a proportional counter occurs. A column gas chromatograph, consisting of a charcoal column and a thermal conductivity cell, is used to separate the Xe, and Ar components. Separate traps are provided for each fraction as they come off the column. A toepler pump transfers the argon from its trap into a final titanium bulb. The calibrated stem allows volumetric determination. The sample is then transferred into the proportional counter for counting. A representative counter spectrum is shown in Figure 24.

3. Irradiation procedure:

Subject was seated one meter from a $^{238}\text{Pu-Be}$ neutron source. He was connected to the breathing mixture gas 15 minutes prior to irradiation. His exhaled product was vented from the collection tanks. This prebreathing procedure was carried out in order to reduce the argon blank collected in the following periods. Three separate tanks were connected to the system in a manner allowing them to be filled sequentially with out interruption. A moderating sphere type LiI(Eu) scintillation detector served to authenticate the expected neutron dose rate. Film badge dosimeters were attached at various anatomical positions on the subject. As was expected there was no observable exposure from fast neutrons, because their minimum quantity measurable is 20 millirems. The calculated exposure for the $\frac{1}{2}$ hour irradiation period was 0.59 millirad or 5.9 millirem (10 quality factor). This dose amounts to 1/500th of the NRC's recommended maximum whole body dose during any 13 week period (3).

The first tank (100cu. in.) was filled during the irradiation period. A second tank (100cu. in.) collected the gas in the first $\frac{1}{2}$ hour following the irradiation period and a scuba tank (72 cu. ft. at 2250 PSI) was used during the immediately following two hour period. This three sample collection was designed to tell us something about the rate of release of ^{37}Ar produced in bone calcium.

(b) Neutron source study

The choice of neutron source for continuing these studies is based upon two considerations. First, it is desirable that the dose be delivered within a short term interval. Second, the neutron energy spectrum should be such that the most effective use is made of each source neutron. A $^{238}\text{Pu-Be}$ source was used in our initial study because its characteristics are well known and the average neutron energy is much higher for the $^9\text{Be}(\alpha, n)$ sources than for the fission type sources. However, the effective cross-section for producing ^{37}Ar in a calcium tank (11kg. calcium in the form of calcium nitrate dissolved in water 2'x3'x4') is only 96 mb using the $^{238}\text{Pu-Be}$ source. 4) Whereas, excitation function measurements 5,6, 7,8,9) show the cross-section for the $^{40}\text{Ca}(n,\alpha)^{37}\text{Ar}$ reaction starts out near zero at 2 MeV, rises sharply to 200mb at 3.8 MeV and subsequently falls off very slowly reaching 120 mb at 15 MeV. Approximately 25% of the neutrons from the $^{238}\text{Pu-Be}$ source are below 1 MeV10).

Two different reactions have been investigated using our CS-15 cyclotron. They are the $^9\text{Be}(^3\text{He}, n)$ using 23.3 MeV ^3He

ions and the ${}^6,{}^7\text{Li}(p,n)$ reaction using 14.7 MeV protons. The neutron energy spectrum arising from the ${}^9\text{Be}$ reaction at this energy has been measured ¹¹). In this case virtually 100% of the source neutrons are above 1 MeV and 85% are above 4 MeV, making it look like an excellent source for our purposes, with a potentially much higher effective cross-section. The Li target has not been investigated at our energy but studies at 10.3 MeV indicate it too has strong potential ¹²). All measurements made concerning these reactions were repeated in an identical manner for both of them. Dosimetry for the ${}^9\text{Be}$ reaction has been carried out in this laboratory¹³). The cyclotron provides ample neutron flux rates to perform the required irradiations in very short intervals (even a fraction of a second, if that were desirable). Another source possibility would be a relatively modest D-T generator (10^{11} neutrons/sec.)

TABLE X

<u>Sample</u>	<u>Argon(c.c.)</u>	<u>Krypton(c.c.)</u>	<u>${}^{37}\text{Ar}$ (Atoms EOB)</u>	<u>${}^{37}\text{Ar}$ (dpm EOB)</u>
RBO	135	0.25	-----	-----
RB1	4.7	0.19	4600	0.063
RB2	-----	0.028	9900	0.14
RB3	-----	0.6	42500	0.58
RB4	15.7	0.78	-----	-----
		Total	63400	0.78

Results and Conclusions:

(a) ${}^{37}\text{Ar}$ feasibility study

Listed in Table X are the results of the initial human ${}^{37}\text{Ar}$ study. The RBO sample was taken without any prebreathing by the subject. RB4 was a two hour sample taken 24 hours following the start of irradiation. ${}^{37}\text{Ar}$ content in that sample has not as yet been determined (counting facilities were not available).

Calculations, based upon the calcium tank data mentioned earlier, caused us to expect production of 220,000 atoms in the human subject or 3 dpm at end of bombardment. Due to nonequivalence of the calcium tank and the human body with regard to calcium distribution, tissue equivalence of the medium, and shape, this is, of course, only a rough estimate. As can be seen in Figure 25, the argon in the whole body comes out slowly, and from the data taken over the first 3 hours it appears to be ventilated linearly with time, with an average rate of release of 0.26 dpm per hour. Until we do longer time release studies and take measurements using realistic phantoms, it will not be clear what our production and extraction efficiencies are. Palmer's study using 15 MeV neutrons on rats resulted in

5.7 dpm/g-Ca/rad and 3.9 dpm/g-Ca/rad for dogs. The calcium tank data presented in this manner is 5dpm/g-Ca/rad and the total we collected in the human study corresponds to 1.3 dpm/g-Ca/rad.

Assuming our measured 1.3 dpm/gm-Ca/rad is shown to be reproducible and proportional to total body calcium content, what sort of exposures and counting times would be required to obtain 1% counting statistics. The sample counting period and exposure are related. Decay half time for ^{37}Ar is 35.1 days, so that, longer counting periods would lead to a substantial decrease in dose requirements. For example, using a counting period of 1000 minutes (overnight) leads to a 10 millirad exposure requirement, whereas, a 10,000 minute (week) count would reduce exposure to 1.2 millirads. It is safe to assume that a cyclotron short pulse dose and greater useful neutron production efficiency will lead to even lower dose requirements.

Noting that RB1 and RB4 each correspond to collections following a prebreathing period of 15 minutes, we see that approximately 5 scc of argon per $\frac{1}{2}$ hour are collected. Certainly part of this is coming from a trace quantity in the breathing gas mixture. The 135 scc result of RB0, which is a $\frac{1}{2}$ hour sample without any prebreathing, suggests argon is washed from the system very rapidly and that 15 minutes or less are sufficient to reduce the blank argon volume to a reasonable level for low level counting considerations.

The krypton volumetric and ^{85}Kr counting measurements on the same samples indicate krypton is released slowly and linearly with time from the body. Clearly, longer term time studies of the release from the body of inert gases are indicated.

(b) Neutron source study

Fast flux uniformity throughout a patients body is of primary importance in establishing a quantitative measure of whole body calcium. Even in comparative studies of the same patient to determine the calcium changes due to disease progress and, or therapy regimens, inhomogenities will lead to error in the quantity of loss or gain determinations. The direction of change will, of course, be known, but not absolute amounts of change. A number of factors contribute to these flux variations. The primary beam is attenuated with depth in tissue leading to lower fast flux levels in interior regions. Each neutron producing reaction has its own particular laboratory angular distribution, which is not necessarily isotropic and most often is not.

Fast neutron activation threshold detectors based upon the reactions $^{27}\text{Al}(n,\alpha)^{24}\text{Na}$ and $^{115}\text{In}(n,n')^{115\text{m}}\text{In}$ were utilized to map out both the lateral with respect to the beam axis, fast flux variations and the variations as a function of depth in a H_2O tank (30cm x 30cm x 35cm on axis). The two threshold detectors were irradiated simultaneously in cadmium cases. The aluminum reaction has roughly a 6 MeV threshold whereas the indium one has a threshold of about 1 MeV. Ratios of the flux determined using these two types of detectors allowed a comparison to be made between the relative pro-

portion of neutrons above these thresholds produced by different neutron sources.

The two reactions studied were the $^9\text{Be}(^3\text{He},n)$ and $\text{Li}(p,n)$ (lithium natural isotopic abundance) reactions. Our preliminary results indicate, as shown in Table XI, that the beryllium reaction has the highest ratio and therefore is the best choice from this standpoint for reasons already discussed.

TABLE XI

Reaction	Flux ($n/\text{cm}^2/\text{sec}/\mu\text{A}$ at 200 cm.)		Ratio
	Aluminum Foil	Indium Foil	
$\text{Li}(p,n)$	0.3×10^4	6.3×10^4	0.05
$^9\text{Be}(^3\text{He},n)$	1.27×10^4	4.9×10^4	0.259

The aluminum foil flux map for the beryllium reaction is shown in Figure 26, together with a diagrammatic representation of the irradiation set up. Figure 27 includes these results for the lithium reaction, but includes both the Al and In foil maps. These results show the lithium reaction to be considerably less variable with lateral position.

Figure 28 compares depth flux measurements in a H_2O tank, using both foils. These results indicate the depth variations in flux attenuation for the two reactions do not differ substantially.

In Figure 29, the beryllium reaction aluminum assay data has been used to construct curves showing the depth variations encountered using bilateral irradiations for three different thicknesses.

Both lateral and depth variations of these magnitudes will require careful phantom calibrations and placement of moderator materials at some locations in order to achieve quantitative calcium determinations.

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Figure 21. RESPIRATORY GAS COLLECTION
AND STORAGE APPARATUS

Figure 22. RESPIRATORY GAS SEPARATION TO INERT GAS

Figure 23. Inert gas separation apparatus

³⁷Ar PROPORTIONAL COUNTER SPECTRUM

2/20-2/25

Volume 10 cc

Corrected Yield 10,000 Atoms

$0.078 \pm .0042$ cpm

Calibration ⁵⁵Fe (0.028 keV/ch)

Figure 24. ³⁷Ar proportional counter spectrum

³⁷Ar VENTILATED THROUGH HUMAN LUNG FOLLOWING FAST NEUTRON IRRADIATION

Figure 25. Rate of release of ³⁷Ar from a human subject

NEUTRON FAST FLUX RELATIVE DISTRIBUTION PERPENDICULAR TO BEAM AXIS

Figure 26. Lateral neutron fast flux measurement of the ${}^9\text{Be}({}^3\text{He}, n)$ reaction using aluminum threshold activation foils

NEUTRON FAST FLUX RELATIVE DISTRIBUTION PERPENDICULAR TO BEAM AXIS

Figure 27. Lateral neutron fast flux measurement of the $6,7\text{Li}(p,n)$ reaction by aluminum and indium threshold activation foils

COMPARATIVE DEPTH NEUTRON FAST FLUX MEASUREMENTS

Figure 28. Depth fast neutron flux variation in a H₂O tank using aluminum and indium threshold activation foils

FAST NEUTRON FLUX DEPTH DISTRIBUTION

NEUTRON SOURCE:
 $^9\text{Be}(^3\text{He},n)$

ASSAY METHOD:
 $\text{Al}(n,\alpha)^{24}\text{Na}$
Threshold
Detector

Figure 29. Depth fast neutron flux variations for three thicknesses using bilateral irradiation

7. Treatment of Chondrosarcoma and Chordoma with S-35 Sodium Sulfate

Objectives:

To evaluate the usefulness of S-35 sulfate in the treatment of advanced chondrosarcoma and chordoma and to study the metabolism of sulfur in these tumors.

Materials and Methods:

Patients were chosen who had histologically proved diagnoses of chondrosarcoma or chordoma and in whom the tumors could not be completely removed surgically. Cases were excluded who had had recent treatment with cytotoxic drugs or who had evidence of significant bone marrow depression from other causes. A test dose of about 0.2 mCi/kg body weight of S-35 sodium sulfate was given by i.v. injection; within the next few days a biopsy of the tumor and one or more marrow aspirations were performed for microscopic examination and measurement of radioactivity. If the diagnosis was confirmed and a good selective uptake of S-35 by the tumor was found, the patient was given a therapeutic dose of 5 to 6 mCi/kg body weight. The treatment was repeated at intervals of weeks or months as indicated by the clinical and hematological status. The effect of therapy was evaluated by serial radiographs, by measurement of superficial tumors, and by repeated biopsies whenever the location of the tumor and the condition of the patient permitted.

Results:

Ten patients with chordoma were studied. It was found that, although the initial uptake of S-35 in chordoma tissue was similar to that in chondrosarcoma, the isotope was lost or diluted by subsequent growth in chordoma so rapidly that an effective radiation dose could not be accumulated. Hence treatment of this disease was discontinued, and the present report will deal with results in chondrosarcoma.

Eleven patients with chondrosarcoma were given test doses of S-35 sodium sulfate. The initial tumor uptake ranged from about 0.2 to 3.0 μ Ci/gm tumor per μ Ci injected / gm body weight, but in most cases the uptake in viable tumor was between 0.8 and 1.2 μ Ci/gm per μ Ci/gm injected. Six patients in whom the results of the test dose indicated that the uptake of S-35 by the tumor was satisfactory were given therapeutic doses, usually of 6 mCi/kg at each treatment. The treatment schedules are summarized in Table XI. Each patient had follow-up surgical biopsies, bone marrow aspirations or marrow biopsies at intervals which depended on the clinical and personal situation of the patient. In the patients who died numerous specimens of tissue were obtained at necropsy whenever possible. From 70% to 90% of the S-35 injected i.v. was usually excreted in the urine within 72 hours. Hence, after this time, a tissue concentration of 1 μ Ci/gm per μ Ci injected / gm body weight indicates a differential retention in that tissue of 3 to 10 above that of the body as a whole.

It was found that the radioactivity of the red bone marrow was high initially, averaging 1.2 μ Ci/gm per μ Ci gm injected, but fell rapidly. The mean initial biological H.L. was about 10 days, followed by a slower component of about 60 days H.L. The radiation exposure of the marrow was estimated to be 230 rads during the first 50 days and an additional 25 rads later, after an administered dose of 6 mCi/kg body weight. Similar estimates indicate a tumor dose of 800 to 1200 rads; muscle, 20 rads; fibrous tissue 40 to 200 rads; and normal cartilage in the same range as tumor.

Clinical results:

Effects on tumor. Two patients, JA and D. O., were boys aged 13 whose clinical course was rapid. There was minimal very short lived regression of visible tumor but both died very promptly and were considered to be clinical failures. Several biopsies and necropsy finding in J.A. showed progressively less cartilaginous elements in the tumor tissue so that the diagnoses were considered to be more consistent with osteogenic sarcoma with cartilaginous elements rather than true chondrosarcoma. C.F. was a terminally ill patient with chondrosarcoma involving pleura and lungs who died after only 2 treatments. The effect of therapy could not be judged in this case.

W.M. was a 57 year old male carpenter with extensive pelvic chondrosarcoma. He received 8 treatments with a total of 48 mCi/kg over a period of 17 months. He was asymptomatic during the course of treatment but developed a clinical picture of acute erythroleukemia from which he died 23 months after his first therapy dose. Serial biopsies showed necrosis of the tumor and at necropsy only a localized tumor mass about 3 x 7cm was found.

C.K. was a 55 year old female with a chondrosarcoma of the sacral area which had recurred after numerous resections during 14 years and had produced a visible and palpable mass at the beginning of therapy. The patient received a total of 45 mCi/kg in 8 doses over a period of 20 months. Twice the mass regressed following treatment with S-35 and serial biopsies showed evidence of considerable tumor necrosis. Another recurrence proved uncontrollable and the patient died 26 months after the start of S-35 therapy with pulmonary emboli and embolic metastases of chondrosarcoma.

R.T. is a 23 year old male with a chondrosarcoma of the upper left ribs posteriorly which was not controlled by surgery, external irradiation and hypophysectomy over a 5 year period and was showing secondary paraplegia. He received 5 treatments with S-35 in 15 months totalling 28 mg/kg. Follow-up shows clinical control.

Toxic effects:

All patients who received more than about 12 mCi/kg developed some reduction in marrow cellularity and in circulating platelets and granulocytes. With higher doses there was also some reduction in erythrocytes. There was considerable variation in the

counts as in shown in the data for C.K. (fig. 30). As stated above W.M. developed a picture indistinguishable from fatal erythroleukemia although his marrow was initially very resistant. Although all of the patients had some evidence of marrow toxicity the platelet counts remained at levels where clinical bleeding was not a problem, nor were neutropenia and anemia sufficient to cause serious symptoms. Marrow toxicity is thus not sufficient to prevent the therapeutic use of S-35 although it is a limiting factor in the dose that can be used.

Conclusions:

It is concluded that the administration of large doses of S-35 sodium sulfate is an effective method of slowing the growth of chondrosarcoma. The estimated radiation dose to the tumor is about 1000 rads per treatment of 6 mCi/kg body weight. The treatment was not found effective in controlling chordoma despite a significant selective uptake of S-35 in the tumor tissue.

Marrow toxicity is the limiting factor in this mode of therapy. The estimated radiation dose to marrow is about 250 rads per 6 mCi/kg body weight. Plans for the future include an attempt to develop a technique which will significantly reduce the marrow uptake of S-35 without a corresponding reduction in uptake by tumor tissue.

TABLE XI

Treatment Schedule, Patients with Chondrosarcoma.

Patient	Age Sex	# therapy doses	Treatment time, days	Cumula- tive dose, mCi/kg	Remarks
J.A.	M 13	4	153	21.6	Clinical failure. Probably a pleo- morphic osteo- genic sarcoma
C.F.	F 72	2	64	10.0	Clinical failure
C.K.	F 55	8	615	45.1	Two objective remissions followed by relapse
W.M.	M 57	8	524	48.3	Sustained control
D.O.	M 13	2	37	10.7	Clinical failure. Probably a pleo- morphic Osteo- genic sarcoma
R.T.	M 23	5	459	28.3	Sustained control

Fig. 30. S-35-Chondrosarcoma; Serial blood counts on Case C.K.

D. FEASIBILITY OF CHEMICAL BONDING STUDIES WITH X-RAY SPECTRA

Objectives:

To compare the sensitivity for the detection of the k-alpha lines of the lighter elements ($Z < 23$), by means of an x-ray crystal spectrometer, produced by a beam of cyclotron accelerated α -particles (15 MeV) to that obtained with electrons (25 KeV).

Materials and Methods:

Preliminary evaluation shows that the potential increase in sensitivity expected with 15 MeV α -particle excitation has not been achieved because of extraneous background present in the exit port room and particularly because of the high background produced in the collimators required to define the beam at the sample position. The cyclotron group at SKI has recently made it possible to focus the beam down to our required dimension ($\leq \frac{1}{4}$ ") by use of a slit system before the quadrupole lens (See report of Proposal #4) thus eliminating the use of physical collimation close to the target. This should eliminate a large fraction of the extraneous background and permit us to continue studies aimed at further decreasing the background by use of coincidence shielding.

Conclusion:

Ion optical focusing of the α -particle beams should eliminate a large fraction of the background which previously was produced in the physical collimators employed to define the beam. This will make it possible to evaluate techniques e.g., coincidence shielding, for further decreasing extraneous background thus increasing the sensitivity of this approach.

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