Progress Report To
Proposal #3

MASTER

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PROGRESS REPORT
TO
THE UNITED STATES ATOMIC ENERGY COMMISSION
CONTRACT AT(30-1)910
BIOLOGICAL EFFECTS OF RADIATION AND RELATED BIOCHEMICAL
AND PHYSICAL STUDIES

Proposal #3: Metabolic Studies in Cancer with Radioactive Isotopes

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September 30, 1971

MASTER

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A. INSTRUMENTATION AND DATA HANDLING

1. The Total Organ Kinetic Imaging Monitor (TOKIM)

Objectives:

The main objective for this project has been the use of the TOKIM system in a variety of metabolic isotope studies using radionuclides produced by the Institute's cyclotron. The TOKIM has been used for both visualization of static whole body distributions of new radiopharmaceuticals and the determination of rates of uptake and washout in dynamic studies. In addition the TOKIM has been used in lung function studies using oxygen-15 labeled O_2 , CO_2 and CO , and a liver blood flow study using Tc-99m labeled sulfur colloid.

Materials and Methods:

The TOKIM system consists of two 13 $\frac{1}{2}$ in. diameter Anger-type scintillation cameras interfaced to an IBM 1800 computer. The two detectors can be used in coincidence to obtain three dimensional resolution or separately for dynamic function studies. The coordinates of each scintillation event are packed into twelve bits of a sixteen bit computer word and presented along with an external synchronization pulse to a digital input of the 1800. The input program, operating in 4K words of core, stores data words in two 1050-word buffers. The buffers are chained, so as one becomes full it is dumped to magnetic tape while data input continues uninterrupted to the other one. The IBM multi-programming system provides for background processing of jobs during data input. With data rates of 1000 counts per second the central processing unit is available 95% of the time for batch processing.

The only problem with this method of data collection is the dead time for operation of the digital input. There is a 15 microsecond dead time between the occurrence of a sync pulse and the return of a ready signal. Also, the analog to digital converters have a rundown time of 10 microseconds plus 1/8 microsecond/channel. Both of these dead times are compensated for by using the buffer store capability of the ADC. This permits analog holding of a pulse which occurs during the dead time following an event.

A simple experiment was performed to measure the effect of pulse pile-up on data rate. A sample of oxygen-15 was placed under the detector and its decay was followed with time. Since pile-up has very little effect at low data rates the measured rate at the end of this run was assumed to be equal to the true rate. Indeed the half-time measured from the latter portion of the curve was 125 seconds. Extrapolating the curve backwards yields the true count rate. Figure 1 shows a plot

Fig. 1. Experiment to determine singles pile-up dead time for entire TOKIM system. Count rate versus time for a sample of $^{150}\text{O}_2$.

of these data. According to Poisson statistics, the measured rate is related to the true rate by: $C_M = C_T e^{-C_T \tau}$, where C_M and C_T are the measured and true rates respectively and τ is the "effective dead time" of the system. Figure 2 shows a semilogarithmic plot of the ratio C_M/C_T as a function of C_T . From this curve the effective dead time for the system of 22 microseconds was obtained. There is an unexplained "break" in the curve at 4000 cps; below this level no counts are lost. We have been able to collect reliable dynamic function data with this system at rates of 10,000 counts per second.

Results:

Data handling for this system can be separated into two categories: pictorial display and dynamic function studies. The data records on magnetic tape are replayed and accumulated in a 64 x 64 matrix array. This matrix can be displayed in a variety of ways: (1) an alphanumeric printout using standard deviation intervals, (2) density displays similar to scintiphotos and (3) an isometric plot. The latter two are presented on an 8" x 10" storage oscilloscope and photographed using 4" x 5" Polaroid film. The alphanumeric printouts are used most frequently for viewing scans; however, some clinicians find the isometric output potentially useful. Figures 3a and 3b show isometric plots for a Xenon-133 ventilation study on a 9 year old boy. The right lung had been collapsed to reduce damage during radiation therapy and was only about 80% re-inflated at the time of this study. Figure 3b is a 180° rotation of Figure 3a.

For dynamic function studies the matrices are first printed out in two standard deviation increments so that areas can be selected. The exact contours of the areas of interest are selected by entering the row number and the minimum and maximum for each row on cards. These area parameters are stored on disk and then retrieved when the data is replayed and counts inside these boundaries are integrated for a preset time increment. Figure 4 shows the general pattern for these data. The area corresponding to the lung field is indicated in the diagram. Counts over this area were accumulated for 1 second increments and a least-squares fit to a single exponential function was performed to a pre-selected set of points.

Conclusions:

In summary, the concepts of the TOKIM system are most relevant to research in Nuclear Medicine using cyclotron-produced radionuclides. Each new compound synthesized presents us with new problems to be solved in terms of its metabolic activity. The TOKIM system provides us with both static and dynamic scans of in-vivo radioisotope distributions. Data analysis is accomplished with a basic set of programs which can be tailored to meet the needs of a specific experiment.

Fig. 2. Curve used to determine "effective dead time" of 22 μ sec for the TOKIM system.

P.F, 3/17/71 Xe equil. from base

P.F, 3/17/71 Xe equil. apex

Fig. 3a & 3b. Xenon-133 posterior-anterior view ventilation study on a 9 year old boy (P.F.).

Fig. 4. Washout of a single breath of $C^{15}O_2$ from the lungs of a normal dog.

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:

a) Point Spread Function - The coupled TOKIM-IBM 1800 system, operating in the multiprobe mode, was used to obtain point spread function data for the 140 KeV γ of technetium-99m at various distances from the face of the collimator. The random nature of radioactivity presented some problems for the subsequent computer analysis of these functions. To determine the mathematical point spread function (initially assumed radially symmetric), the data, accumulated in a square 64x64 configuration, was parameterized by a series of 3-point parabolic sections, which were shifted both horizontally and vertically to determine properly averaged point spread functions from all four quadrants, which were finally combined into a single radially symmetric function.

b) Modulation Transfer Function - The modulation transfer functions of the data discussed above were obtained by integration of the radial point spread function multiplied by the spherical Bessel function of order zero. For subsequent analysis it was necessary to take the reciprocal of this function. This introduces infinities into the calculation since the MTF itself tends toward zero. These infinities were treated by imposing an empirical cut-off frequency, and assuming that the reciprocal simply goes to zero at this value.

c) Correction of Radiographic Images - Digital radiographic information representing various phantom and in vivo configurations have been convoluted with the appropriate "correction functions" derived from the calculations discussed above. Computational time considerations necessitated the ad-hoc introduction of an exponential damping (proportional to r^2), limiting the influence of a theoretical point source to a few channels, rather than its extension over the full 64x64 configuration.

Results:

a) The MTF method of image retrieval has been applied to the Multi-Function Scanner of Memorial Hospital. A 1mm diameter point source of ^{131}I was used as the original radionuclidic distribution.

The scanning speed was 5.8"/min. and counts were taken over 0.1" increments.

Figure 5 shows the observed distribution of the scan. Each symbol represents a 20% interval. The corrected distribution is shown in Figure 6. The maximum counts were 954 and 1393 in the original and corrected distributions, respectively. The periphery of the phantom became clear and the hot spot appeared on the corrected distribution in the left lobe.

b) The method was chiefly employed on radiographic images from the TOKIM digital Anger camera system. Figure 7 shows respectively: a) an "original" picture of the Picker thyroid phantom, with data accumulated in channels approximately $1/2$ cm x $1/2$ cm; b) an "average" picture obtained by 4 element averaging; and c) a "corrected" picture obtained by applying the above MTF methods to the original data. The pictures are colored for easy visualization (brown = 25%-50%; blue = 50%-65%; green = 65%-90%; red = 90%-100%). Examination and comparison of these three pictures shows:

1) The general outline of the phantom, as given by the 25% contour, is approximately the same for both the original and averaged pictures. That of the corrected image is more true as compared to the phantom. In particular, the isthmus between the left and right lobes is much narrower and true to the phantom in the corrected version than in either the original or the averaged.

2) It is readily seen that averaging has smeared the data in the region between the right lobe and the hot spot in the left lobe, i.e. within the isthmus. This is evident by the shape of the 65% contour. This smearing effect is not manifested in the corrected version.

3) The hot area in the center of the right lobe is artificially reduced in extent. The entire lobe should demonstrate uniform activity, but cold spots on top and bottom, although not distinctly visible, make the center of the lobe appear hotter than the ends. This is true on all three images.

4) The 1cm cold spot in the upper right lobe is not visible in any of the three pictures. The visualization of this spot was just beyond the capability of the TOKIM system, which has a resolution for Tc-99m of approximately 1.2 cm.

5) The 2.5 cm cold spot in the lower right lobe is observed, in both the original and corrected images, as an invagination of the 50% contour. This area is completely washed out in the averaged image.

The observed scintigram of the thyroid

Y. OKUMURA : INT. J. A.R.I., 22, 49-52 (1971)

Fig. 5. Observed scan of the Picker thyroid phantom filled with I-131. Each symbol represents a 20% interval.

Fig. 7. TOKIM image of a Picker thyroid phantom showing the original, averaged and corrected displays. The latter was obtained by applying MTF methods to the original data.

ORIGINAL

THYROID PHANTOM

Tc (99m)

% Spaced Levels

5	10%	O 55%	V 80%
10	15%	R 60%	W 85%
15	20%	S 65%	X 90%
20	25%	T 70%	Z 95%
25	30%	U 75%	*100%

AVERAGED

CORRECTED

6) The 1.5 cm cold spot in the upper left lobe can be clearly seen in both the original and corrected images, but not in the averaged version. In addition it results in the 50% contour being abnormally low, as compared to the 50% contour in the right lobe. This can be observed in all three pictures.

7) The appearance of the hot spot in the lower left lobe is significantly spread out in the averaged picture, and its shape is more true (with respect to the phantom) in the corrected version than in the original.

8) The maximum number of counts is approximately 10% higher in the corrected image than in the original. This is due to redistribution, by the correction technique, from outlying areas. This generally increases the statistical validity of the scan. It should be noted that all three images contain the same number (55,000) of counts.

c) Figure 8 shows the TOKIM image of the Picker liver phantom in the form of raw data, averaged image, and corrected image, respectively, as discussed above. Once again the pictures have been colored for easy visibility (black = 25%-40%; blue = 40%-60%; green = 60%-70%; yellow = 70%-80%; orange = 80%-90%; red = 90%-100%). Careful examination and comparison of these images shows:

1) It is obviously very difficult to draw meaningful contours in the unprocessed data. This condition is greatly alleviated for both averaged and corrected images.

2) The outer contours (from ~40% and lower) are approximately the same in all three images.

3) The quadrate and caudate lobes, which are thinner than their neighboring left and right lobes, (and therefore appear colder) may be seen in the original within the 60%-70% contour, but are artificially increased to the 70%-80% contour in the averaged picture. The area is properly retrieved in the corrected image and stands out prominently, enclosed within a 60% contour.

4) Both the left and right lobes are more readily visualized in the averaged and corrected images than in the original data. Both processed images depict the lobes as being enclosed within well defined 80% contours, while the original image depicts somewhat irregular shapes enclosed by 70% contours containing irregularly shaped 80% areas.

5) The original picture has the hottest point in the left side of the right lobe. Examination of the phantom reveals that the thickest area, and therefore the hottest, is actually located near

Fig. 8 & 9. TOKIM images of a normal Picker liver phantom and one with lesions. The original, averaged and corrected displays follow vertically for each figure.

PICKER LIVER PHANTOM

ORIGINAL

AVERAGED

CORRECTED

PICKER LIVER PHANTOM WITH LESIONS

ORIGINAL

AVERAGED

CORRECTED

the right periphery of the right lobe, as correctly shown in the processed images.

6) The averaged image demonstrates a cold area (80%) imbedded within the 90% area of the right lobe. The corrected picture more realistically depicts the shape profile of the phantom, and clearly shows this cold area as being a separation of the 90% areas, which was smeared out in the average picture. None of this was visible in the original data.

d) Lesions were introduced into the Picker liver phantom. The radiographic image and the subsequently processed images are shown in Figure 9. The lesions were placed 1) between the quadrate and caudate lobes; 2) at the superior aspect of the right lobe; and 3) centrally in the right lobe. Examination and comparison of the original and processed image shows:

1) The normally cold quadrate and caudate lobes are seen to be grossly colder than in the previous images of the phantom with no lesions (Fig. 8). However, the size and shape is somewhat exaggerated in the original image. The averaged picture clearly shows the lesion, but incorrectly depicts its size. The corrected image shows the lesion more true to its actual size.

2) Again, as above, both the left and right lobes are shown to be represented mainly by 80% contours by the processed images, whereas the original data shows these as 70% regions containing smaller irregularly shaped 80% areas.

3) The lesion at the superior aspect of the right lobe is clearly visible in both the original and processed images. However, the original data does not show a clearly separated cold area, as seen in the averaged image. The combination of the thickness contour of the phantom, and the lesion, produced an invagination in the 60% contour in original picture, which was smeared out in the averaged image, but retrieved by correction.

4) The third lesion can only be realized through a comparison of Figures 8 and 9. The lesion was placed in the thickest part of the right lobe, and therefore one effect negated the other.

Conclusions:

From an examination of the images of these phantoms, it has been demonstrated that the correction procedure employed generally increases the visualization of the organ structure and diminishes the artificial spread of activity to outlying areas. In addition, it has the advantage over averaging of not smearing out the important structures.

3. Methodology of Absolute Quantitative Organ Scanning

Objectives:

To establish a method whereby a specific organ activity and organ size can be determined absolutely on the basis of the organ's digital scan image, irrespective of the particular in-vivo activity distribution and measuring geometries involved.

This is a continuing project with the basic objectives of establishing a simple method for the determination of the activity in a given organ. The accurate determination of the extent of splenic sequestration could provide a criterion upon which the need for splenectomy could be based.

Materials and Methods:

The major limitation with conventional instruments arises since they are primarily designed for visualizing radioactive tracer distributions in a particular plane in-vivo. The measured maximum external count rate or the total integrated count rate over the organ scan image is therefore inherently dependent on the particular in-vivo tracer activity distribution and counting geometry employed. In the previous work on this project, substantial progress was made in the development of a scanning methodology and correction procedure. This included the design of a depth response independent dual foci collimator system F (14 cm., 18 cm.) suitable for organ uptake measurement employing ^{51}Cr (320keV). This isotope is generally used for tagging the red cell. The response of this dual system in a water medium for the 320 keV energy, expressed in terms of resolution (F.W.H.M.) of a line spread function varied within $\pm 11.57\%$ and plane sensitivity varied within $\pm 4.5\%$ over the detector separation of 22.5 cm. This separation was expected to be equivalent to the normal patient thickness. Perhaps more important in this study was the fact that the line spread functions measured over this equivalent patient thickness remained very similar in the low response regions off the detector axis. Further evaluation was made in determining the $2\pi\text{r}\Delta\text{r}$ x point sensitivity response, a more critical measure of the "beam like" response of the system. The "quantitative" resolution diameter, defined as that ring diameter within which 80%, arbitrarily chosen, of the total count rate of a plane source, was obtained. This resolution diameter was found to be 1.8 cm and varied within $\pm 7\%$ over the detector separation of 22.5 cm. Results quoted above were determined with an optimized energy window of 100 keV for ^{51}Cr .

Since the essential requirement of this dual detector system was both to resolve organ outline and predict its accumulated tracer content in-vivo, phantom studies of simulated organ geometries

in a water tank were emphasized in the evaluation of this organ activity scanning method. Phantom assemblies were scanned in a 20 cm water tank and the dual detector image was obtained using the general scan analysis program for the HEG scanner. Spleens of varying sizes were originally simulated with four cylindrical containers uniformly filled with a known amount of chromium and scanned at 5, 10, 15 cm locations measured from the base of the tank. At the central location these sources were scanned at different orientations with respect to the dual detector axis and the rectilinear scan direction. Conversion factors were then computed which related the total summed counts to the microcuries of ^{51}Cr present for each measuring geometry and source size. The integration of the counts were computed within the source image contours from a level of 10% to 50%. The image contours were expressed as a percentage of the maximum count-rate and the integration was obtained within X, Y coordinates of the scan matrix enclosing these contours. The extent of these calibrations allowed a graphical means of determining the appropriate conversion factor for any organ size and in the limiting situation where summation over the total organ image is not feasible.

Although this scanning development has successfully been applied in evaluating splenic activity in a limited number of patients (see Section B3b) who later underwent splenectomy, this progress was essentially preliminary. The original data were acquired on the old HEG scanner which had a different handling capacity and storage system with information being obtained on a $3/8$ " scan increment. This increment size was not reproducible on the new scanner. However, the primary objective in this work has to cover a comprehensive series of phantom calibrations, programmed in a efficient manner, such that organ activity can be determined irrespective of:

- (a) Patient thickness, which can vary from 20 cm to the extreme thickness of 30 cm;
- (b) Location or orientation of the organ;
- (c) The extent of activity surrounding the organ;
- (d) The possible Compton scatter contribution from active adjacent organs.

In considering the number of variable parameters that must be considered in the phantom calibrations, the need for a comprehensive revision of the scanner programs with emphasis on rapid data analysis was clearly evident. The revised programs were generated to achieve:

- (a) A computer scan output in the form of a raw data matrix, each element of the matrix corresponding to a 0.4 " scan increment. Since no smoothing of

the acquired data is involved, the scan data can be read and displayed immediately on a line for line basis from the magnetic tape.

- (b) Computer scan displays with any number of standard deviations between the mean of each level.
- (c) A means of identifying the maximum standard deviation level and computing the total summed counts within calculated image contours from 10% to 50% simultaneously and to define further any limits to this area summation by the rows and columns of the matrix.
- (d) Sum the output of any combination of all eight scalers (with multiplication factors) for the new HEG scanner.
- (e) A means of determining scan speed accurately from the scan data listing.

Five cylindrical containers representing an extended splenic size range were then taken, i.e., from 1 1/2" dia. x 3" to 3 1/2" dia. x 7" and filled with a minimum of 2 mCi of Cr-51. The millicurie content was accurately measured by comparison to a standard in an ion chamber under the same geometrical conditions. These phantoms were scanned at the following locations as measured from the base of each tank.

For a 20 cm tank: 5, 10, 15 cm

For a 25 cm tank: 7.5, 12.5, 17.5 cm

For a 30 cm tank: 5, 10, 15, 20, 25 cm

For locations of each source, the summed and single detector output of the F (14cm, 18cm) dual detector system was obtained with a 100 keV discriminator setting. Conversion factors (C.F.) were then obtained by normalizing the total summed counts for each image contour to a unit scan speed of 1 sec/0.4" increment and then dividing by the amount of activity within the source. Units of the C.F. were then counts/ μ Ci/unit scan speed.

In determining organ activity in-vivo, a subtraction procedure must, in general, be considered to correct for surrounding active tissue above and below the organ. The depth response-independent dual collimator system, previously described, was designed to simplify this correction. The response was measured over the full range between the detectors in a (water) scattering medium; separated at 20, 25, 30 cm. The beam like response measured as ($2\pi r dr$ x point sensitivity) was observed in each instance close to the collimator face (3cm distant). In clinical evaluation, this means that this response is experienced throughout the full patient

thickness range. To determine a correction procedure, each tank employed above was uniformly filled with a known amount of active water and scanned under the same conditions. The computed counts per unit area were then representative of that column of active water. Conversion factors were then derived, relating, in this case, measured counts per unit area for a given column height of active medium. From the scan image a given anatomical position over the abdomen, well resolved from any active organ is chosen, and the counts per unit area then are representative of a column of active tissue approximately in height to the actual patient thickness. The appropriate conversion factor will then give the representative microcuries distributed in-vivo and subtracted from the original value of organ uptake.

Results:

An example of the F (14 cm, 18 cm) summed detector image is shown in Figure 10 for the phantom size #3 (2 1/4" dia. x 5") corresponding to that of the normal spleen and positioned in the 20 and 30 cm tanks. The computer scan output is a raw data matrix, displayed by character levels, the mean of which are 2 standard deviations apart. In the rectilinear scan direction one character represents the Y increment, and in the scan direction across the source diameters two identical characters represent the X increment. This simplified manner of display, without any smoothing, is perhaps not pictorially pleasing but the emphasis here is in integrating the accumulated counts. The maximum level in each image is encircled and hence by re-running the magnetic tape, the integrated counts for each image contour can immediately be determined. Good source resolution was indicated with the intermediate count rate contours remaining close to the actual source dimensions. Source resolution is shown in Figure 10 by the small shaded area between the 50% and 10% contours. Though this included area is greater for sources in the larger tank, where more Compton scattering is experienced, its dimensions remained similar over the location range shown. A good illustration of the small off-axis penetration of this detector system is the sharp reduction in the counts just beyond the source, i.e., the lowest character level 'D' shown corresponds in this case to less than 0.5% of the maximum count rate for each image. This result is important in obtaining quantitative resolution of a source.

The necessity of identifying source or organ size in-vivo becomes more apparent in the selection of the C.F. to obtain μCi content. This is clearly illustrated in Figure 11, where the conversion factor for each source is plotted against source area for the 20 cm. tank. In integrating within the higher image contours the magnitude of the conversion factor becomes more dependent on source size. When integrating the total count rate over the full source image, i.e., the dimensions of the area scanned, the conversion factor is independent of source size to within experimental error. However, in analyses of these results, one must realize that in actual patient studies the spleen may not be completely isolated from active adjacent organs and large tissue background correction should be avoided to achieve a reliable result.

Fig. 10. Summed detector scan image of phantom source #3 positioned in the 20 and 30cm water tanks. The unsmoothed scan data is displayed at 2 standard deviations between the mean of each level.

Fig. 11. Plot of the variation of the computed conversion factors with source size for each image contour. This variation is plotted for two source locations in the 20 cm tank.

VARIATION OF CONVERSION FACTOR WITH SOURCE
SIZE AND LOCATION FOR EACH IMAGE CONTOUR

Fig. 12. Plot of the variation of the computed conversion factors with source size for each image contour. This variation is plotted for three source locations in the 30 cm tank for the 50% image contour and total scan area.

The data plotted in the same figure illustrate clearly that the dependence of the C.F. with location of each source was small; remaining within the range of $\pm 10\%$. Source activity, and as earlier shown, source size, can be accurately determined irrespective of its location in-vivo for this normal patient thickness.

Figure 12 shows the same data for the 30 cm depth. A striking change is seen in the considerable variance of the conversion factor with the off-center 5 to 25 cm positions. This marked change was expected since the dual response of the detectors was just balanced for depth independence at 20 cm separation and 320 keV energy of Cr-51. However, the C.F. dependence on source size was reduced at this greater detector separation.

The requirement of identifying the location of the source was therefore necessary. This was simply achieved by obtaining the ratio of the measured count rate of the upper and lower detectors within each image contour. Table I, shows how this ratio consistently indicated the location of the source, and the appropriate value for the C.F. shown could then be used.

In patient studies, analysis of splenic uptake is simplified by this approach. The summed detector image of the spleen is obtained with a slow scan speed chosen to obtain the maximum integral count-rate over the organ. With the patient thickness lying close to 20, 25 or 30 cm, the appropriate C.F. for each image contour can be determined from the plots as shown in Figures 11 and 12. The tissue background correction procedure has already been described. The C.F.'s for this background correction were determined to be 92.8, 79 and 73.1 cts/ μ Ci for active tissue column heights of 20, 25 and 30 cm.

In an endeavor to achieve greater depth independence for greater detector separations of 30 cm or more, a longer focal length dual foci collimator set was constructed from the same F (14 cm, 18 cm) mold. The iso-response curves of this revised system in air were significantly better than the original but data in an absorbing medium were not too different. However, the plane sensitivity measurements in water with a detector separation of 30 cm showed a smaller variation of $\pm 12.5\%$ for the new F (16 cm, 20 cm) set as compared to $\pm 15\%$ for the previous set.

Conclusions:

Quantitative organ activity scanning, where an absolute rather than a relative measure of organ function is obtained, remains a relatively undeveloped field in nuclear medicine. The completion of its development is important in order that nuclear medicine achieve its research and diagnostic potential. As an example, the specific application discussed here has been directed primarily at a measure of red cell sequestration by the

TABLE I

CONVERSION FACTORS FOR EACH SOURCE LOCATION FOR THE 30 CM TANK

Image contour	Position	S#1 C.F. Ratio ($\frac{U}{L}$)		S#2 C.F. Ratio ($\frac{U}{L}$)		S#3 C.F. Ratio ($\frac{U}{L}$)		S#4 C.F. Ratio ($\frac{U}{L}$)		S#5 C.F. Ratio ($\frac{U}{L}$)	
50%	15cm.	14.5	1.0	15.0	1.0	17.4	1.0	19.8	1.0	20.0	1.0
	(10,20)cm.	18.4	4.8	20.6	3.8	22.5	3.6	23.5	3.1	24.0	3.3
	(5,25) cm.	21.2	12.6	24.0	11.0	28.0	10.0	30.8	11.0	31.2	8.0
30%	15cm.	19.4	1.0	20.2	1.0	22.0	1.0	23.8	1.0	24.4	1.0
	(10,20)cm.	23.0	3.6	24.0	3.2	26.0	3.2	27.6	2.9	28.0	2.9
	(5,25)cm.	32	9.5	33	9.8	35	8.5	36.8	8.5	36.8	6.8
10%	15cm.	24.2	1.0	25	1.0	26.4	1.0	28.2	1.0	28.2	1.0
	(10,20)cm.	27.7	2.9	28.7	2.9	31.0	3.0	31.5	2.6	31.9	3.1
	(5,25)cm.	39.1	7.3	40.1	8.3	39.9	7.7	41.6	6.5	40.4	6.1
T.S.C.	15cm.	32.2	1.0	32.2	1.0	32.2	1.0	32.2	1.0	32.2	1.0
	(10,20)cm.	35.8	2.4	35.8	2.6	35.8	2.5	35.8	2.4	35.8	2.5
	(5,25)cm.	45.0	5.8	45.0	6.8	45.0	6.4	45.0	6.3	45.0	5.5

spleen but the methodology developed can realistically be applied to any organ. The simplicity of approach, both in the relatively inexpensive detector design and analysis of results was adhered to so that this general system could be incorporated with any standard commercial dual detector scanner.

Results of the phantom measurements taken have shown that although a suitable collimation and correction system has been developed, further measurements are necessary to improve the accuracy of the system for clinical application. To obtain an absolute or μCi content in an organ, consideration must necessarily be given to the size of the source and in extreme circumstances to its location and correction for the extent of the active surrounding medium. Evaluation of these measurements must include the probability that the organ image may not be isolated, as frequently occurs in viewing the spleen. Estimation of μCi content would, therefore, be made by integrating counts within a smaller limiting image contour which would in turn reduce the correction for tissue background. It should be realized that tissue background, in the clinical application considered, can vary both longitudinally and laterally across the patient's abdomen and, in particular, in the region of the spleen.

This project will be developed further by applying the correction for the collimator response using the inverse of the M.T.F. (section A2). This correction is ideally suited for this work, since the dual collimator response and hence the correction does not change with depth. All phantom work have been stored on a master magnetic tape such that corrected images can be evaluated to determine the relation between corrected total summed counts and the microcurie content in-vivo. This approach will be particularly useful in quantitatively resolving an organ and improve methods of determining tissue background in clinical situations where the organ is not quantitatively resolved.

4. Collimator Design

Objectives:

The object of this project was to find a method, applicable to parallel hole collimators for gamma cameras, which would relate the overall performance characteristics of resolution, efficiency and penetration fraction, as functionally interrelated, to the physical factors of collimator dimensions, absorption coefficient and source depth. A form of data presentation was sought which, with minimal trial and error, could indicate the results so that rapid synthesis and analysis of collimators could be obtained.

Materials and Methods:

The methods were mathematical, with an experimental check and a graphical final result.

The variables defining the geometric efficiency E , the resolution R (full width at half maximum) and the penetration fraction $P.F.$ were separated into the following four, based upon the geometric relationships of Fig. 13, applicable to uniform cross section holes. Quantities having the dimensions of distance have been normalized by multiplication by the linear absorption coefficient μ .

- 1) Angle of Resolution = (D/A) (conventionally for round holes)
which is $\frac{4}{\pi} \frac{\sqrt{\text{Hole Area}}}{A^2}$ for hex or other sections
- 2) Area Efficiency = Fraction of collimator area which is hole area

$$= (D/D+T)^2 \text{ for hexagon}$$

$$= \pi/2\sqrt{3} (D/D+T)^2 \text{ for circles}$$

$$= .906 (D/D+T)^2$$
- 3) Absorption length μA = collimator length in units of mean absorption length
- 4) Source depth $\mu (B+C)$ source depths in units of the mean absorption length

These follow from the definitions of resolution (relative) and efficiency:

$$\mu R = D/A (\mu A + \mu (B + C))$$

$$E = (\text{Hole Area}/4\pi A^2) \cdot (\text{Hole Area}/\text{Hole element area to septa midline})$$

The first term is the solid angle efficiency and the second the area efficiency. For round and hex holes, these are respectively

$$E = 0.711 (1/4\pi) (D/A)^2 (D/D+T)^2$$

$$E = 0.866 (1/4\pi) (D/A)^2 (D/D+T)^2$$

For simplification of this analysis we will use:

$$E = K (1/4\pi) (D/A)^2 (D/D+T)^2 \text{ and assume } K = 1.$$

The important point is that the angular resolution (D/A) is a factor of the efficiency expression.

The penetration factor is the ratio of the undesired photons arriving at the detector relative to the desired ones.

Fig. 13. Geometric relations of a point source as imaged by a parallel hole collimator.

P.F. = $\frac{\Sigma \text{ uncollimated flux}}{\Sigma \text{ collimated flux}}$ and is computable using the first three variables.

From this one may see that constraining the penetration fraction to some constant value would result in only two of the first three variables being independent, i.e., D/A, D/D+T, μA . Choosing these to be D/A and μA as cartesian coordinates, one could plot iso-efficiency lines with D/D+T varying along each line. Then, using an offset of $\mu(B+C)$ on the μA axis, the lines of constant μR , the resolution, could be superimposed. This is the format desired to present the results.

A computer program was written to compute the penetration fraction of a quasi-infinite parallel-hexagon hole collimator in terms of D/A, D/D+T and μA . The bulk of the penetrating rays, for thick septa collimators, are confined to the six "rays" of the width of the side of a hole, which radiate perpendicular to the hexagon sides (in a top surface projection of the picture). Since the septa are of constant thickness for all rays of the same angle of incidence, the computation is appreciably simplified.

The D/D+T and D/A variables, were incremented by the same factor throughout the computation, so that the penetration fraction values returned were at specific values of the geometric efficiency. This was essential to eliminate double interpolation.

The efficiency was incremented in steps of the 10th root of 10, a factor of 1.26, which is one decibel (db). The required increments of D/A and D/D+T become $\sqrt[10]{1.26}$. The usage of decibels, it may be noted, leads to many nearly round number values, since 3 db is a factor of 2 and 4 π is 11 db. The values of μR become incremented by the same logarithmic scale factors. The penetration fraction was also printed in decibel format, considerably compacting the data sheet.

It is informative to note that decibel usage originated in electrical engineering where its application to totalize the losses of cascade elements, such as filters, in the signal path is well grounded. A collimator is in effect a cascade filter, having separate losses in solid angle and in cross section area, the geometric efficiency being the product of the two. Thus both, $1/4\pi (D/A)^2$ and $(D/D+T)^2$, are expressible in decibel losses (and in fact the crystal efficiency and the internal absorption in the source may also be so expressed) so that overall efficiency is simply a sum of the contributing decibel losses.

The computed values of the total transmission efficiency of the collimator were compared to three measured values on a given collimator. The total transmission efficiency may be considered the total fraction of the source flux which is incident on the crystal, provided the source is small enough to be totally imaged.

Total Transmission Efficiency = Geometrical Efficiency
($1 + P.F. + C.P.F.$). C.P.F. is the corner penetration factor
from Mather (1) and is due to the enhanced solid angle efficiency
(and coarsened resolution) obtained for small values of μA .
For reason of its origin, the corner penetration flux has not
been considered part of the penetration fraction in this work.

Results:

The measured total transmission efficiency of the given round
hole collimator is plotted in Figure 14 with computed values ex-
pected for hexagon holes having the same values for diameter
across flats, D , septal thickness, T , and absorption length, μA .
The excess aperture over that of the geometric efficiency due to
corner penetration is indicated. The disparity between the ex-
perimental and computed values may be considered due to the thinner
septa with equal area round holes.

The graph of iso-efficiency lines with $D/D+T$ values in 1 db
steps is plotted for 10% (-10 db) penetration fraction in Figure 15.
The iso-resolution family is given in Figure 16 and should be a
transparency so that the origin on the μA scale aligns with the $\mu(B+C)$,
i.e., source and crystal normalized distances, when the plots are
overlaid, so the abscissa of the μR lines is $\mu(A + B + C)$.
Thus aligned, all iso-parametric lines are observable in correct
relation. The maximal efficiency points occur where the iso-
resolution lines are tangent to the iso-efficiency lines.

The μA and $\mu(B+C)$ scales of course must be linear but D/A is
arbitrary. Here negative reciprocal distances are used to obtain
straight μR lines. However, logarithmic (uniform decibel) spacing
leads to a uniformly spaced set of μR lines which are not straight,
and a maximum range of the variable at constant relative accuracy
on any one set of graphs.

Conclusion:

At least for the parallel hole class of collimators, a graphical
slide rule can be produced to predict all relevant parameters with
their proper interfunctional relationships maintained and dis-
played. It depends necessarily upon a computation algorithm to
solve the penetration fraction computation over the range of the
parameters desired. Since normalized variables are used, the
results are non specific as to gamma energy or collimator material
with only the absorption coefficient needed.

References:

1. Mather, R.L. Gamma-ray collimator penetration and scattering
effects. J. Appl. Physics 28: 1200-1207, 1957.

Fig. 14. A plot of the computed values of the transmission efficiency and its components for a hexagon hole collimator. The measured values of the transmission efficiency for a similar round hole unit are plotted at their respective absorption, μA , values for three gamma energies.

Fig. 15. Iso-efficiency lines for 10% penetration fraction versus collimator physical dimensions.

Fig. 16. Iso-resolution lines versus collimator dimensions. To be used with Fig. 15, overlaid, with origin of A scale aligned with value of $\mu(B + C)$ to show all parameters (as normalized to $1/\mu$) at once.

B. METABOLIC AND IMPROVED ORGAN SCANNING STUDIES

1. ^{13}N -Ammonia: A Physiologic Tracer for Molecular Medicine 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. This can only be considered as a preliminary report since much of our early work has been in the nature of a "fishing expedition." The findings, based on a small number of dog studies, indicate that N-13 labeled ammonia has several potential uses: (1) as a short-lived tumor scanning agent, (2) as a kidney function test and (3) for static imaging of myocardium and liver. These studies suggest that $^{13}\text{NH}_3$ will prove valuable in organ scanning and function studies of clinical patients.

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. We have been able to produce millicurie quantities of N-13 labeled ammonia from the relatively simple reaction of deuterons on methane gas. The $^{13}\text{NH}_3$, dissolved in saline, is of high purity (>99%) and good specific activity (up to 10mCi/cc). The large photon flux has made possible dynamic studies in normal dogs and dogs with malignant neoplasms for periods of more than 30 minutes with the Total Organ Kinetic Imaging Monitor (TOKIM) and the High Energy Gamma (HEG) scanner systems.

Results:

Figure 17 shows two whole-body scans, ventral and lateral aspects, of a normal dog 5 minutes after intravenous injections of 13 mCi and 10 mCi of N-13 labeled ammonium chloride respectively. The scans were performed from head to tail using the 19-hole tungsten collimator, and the outputs were not corrected for physical decay of the N-13. The scans show uptake in the brain, possibly the salivary glands, the heart, liver and bladder. The kidneys are not visualized very well in this scan since the radioactive ammonia is taken up immediately in the kidney and washes out with a halftime of about 10 minutes.

Fig. 17. Whole body scans of normal dog following intravenous injection of N-13 labeled ammonium chloride.

Figure 18 shows a similar scan of the heart and liver of the same normal dog taken 10 minutes after a 10 mCi I.V. administration of $^{13}\text{NH}_4^+$ in saline.

The myocardium is clearly visualized in all of these scans. This was a serendipitous result since there seems to be no preferred mechanism for ammonia to be accumulated in the myocardium. Two possible mechanisms are: (1) by ionic exchange for K^+ and (2) by means of glutamine synthesis it is incorporated in myocardial cells. Since an intravenous injection should promote the first case, a subcutaneous injection was performed to see if any enhancement of the myocardial image could be obtained. In the intracellular spaces the $^{13}\text{NH}_4^+$ will be converted, with the aid of glutamine synthesis, to glutamine. Any increased uptake of N-13 in myocardium after subcutaneous injection would therefore favor the second mechanism.

The comparison of intravenous and subcutaneous injections of $^{13}\text{NH}_4^+$ is shown in Figure 19. This figure shows scintiphotos, produced with the TOKIM, of the ventral chest of a normal dog. The picture on the left was taken 15 minutes after a 10 mCi I.V. injection and the picture on the right was taken 30 minutes after an 8 mCi subcutaneous injection in the right flank. The I.V. injection shows considerably more clearance of N-13 from the blood background. This indicates that ionic exchange for K^+ is probably the dominant mechanism for uptake of $^{13}\text{NH}_4^+$ in myocardium.

Approximately 10-20% of the injected ammonium chloride activity is removed quickly from the blood stream by the kidneys and collected in the urinary bladder. The mean halftimes for clearance from the kidneys of the three dogs studied are 10.6 min. and 7.7 min. for the right and left kidneys respectively. The right kidney is adjacent to the liver, which is accumulating N-13 and contributing to the count rate for the selected area. Figure 20 shows a plot of the washout of N-13 from the kidneys and the accumulation in the urinary bladder and liver for a normal dog. The computer printout shows the areas selected for the dynamic study. Note that the rate of uptake of N-13 in the kidneys is the same as the rate of accumulation in the bladder. This is indicated by the slopes of the washout curves and the curve produced by subtracting the saturation value in the bladder area.

The final application of $^{13}\text{NH}_4^+$ which we have explored is its use in detecting neoplasms. This work has been limited to scanning three dogs which had suspected spontaneous tumors. Of the three only one had a tumor - a thyroid carcinoma - which was confirmed at necropsy. Figure 21 shows a ventral view of the neck of this dog, obtained with the TOKIM, 10 minutes after an I.V. injection of N-13 labeled ammonium chloride. The tumor mass is clearly indicated in this scan.

Fig. 18. Heart-liver scan of a normal dog 10 minutes after an intravenous injection of 10 mCi of N-13 labeled ammonium chloride.

$^{13}\text{NH}_4^+$ VENTRAL CHEST SCANS OF NORMAL DOG

Fig. 19. Comparison of intravenous and subcutaneous injection of N-13 labeled ammonium chloride in a normal dog.

$^{13}\text{NH}_4^+$ CLEARANCE FROM KIDNEYS OF NORMAL DOG

I.D.: AMC-2 Run no. 95-26
AmI. Inj.: 2mCi Time A.I.: 1.0 min.
Vol. Cls.: 250K Scan time: 1.0 min.

Date: 3/24/71

View: DORSAL KIDNEYS

Output: 20"

Fig. 20. Washout of N-13 labeled ammonium chloride from the kidneys of a normal dog and the accumulation in the urinary bladder. The scan shows the areas selected in the dorsal aspect.

Fig. 21. Ventral scan of the neck of a dog with a thyroid carcinoma following injection of N-13 labeled ammonium chloride.

Conclusions:

Of the three applications presented here, the myocardium scans are the most striking. Although the mechanism for uptake is not understood, N-13 labeled ammonia provides us with a myocardial scanning agent which has an excellent information to radiation dose ratio. For kidney and liver function studies $^{13}\text{NH}_4^+$ is a new physiologic tracer. And finally, we might speculate that $^{13}\text{NH}_4^+$ will become a useful soft-tissue tumor scanning agent.

2. Pulmonary Function Studies with Gaseous Tracers

- (a) Assessment of pulmonary function in dogs using $^{15}\text{O}_2$, C^{15}O_2 and C^{15}O

Objective:

To establish rates of clearance of gases labeled with O-15, namely oxygen, carbon dioxide and carbon monoxide in normal dogs.

Materials and Methods:

Using our cyclotron oxygen-15 was produced by a d-n reaction on nitrogen gas. The isotope produced was suitably filtered and purified to administer as oxygen $^{15}\text{O}_2$; passed over charcoal at 500 degrees centigrade and cupric oxide at 850 degrees centigrade to produce C^{15}O_2 ; or passed over charcoal at 850 degrees and through Baralyme to yield C^{15}O .

These gases were administered to normal mongrel dogs weighing approximately 20 kg., anesthetized with intravenous pentobarbital positioned beneath the straight hole collimator of the Total Organ Kinetic Imaging Monitor (TOKIM) for a ventral scan. In every instance a 450 ml tidal volume was delivered by a Harvard animal respirator through a cuffed endotracheal tube with the breath held in inspiration for greater than 30 seconds. Digital dynamic data were stored on magnetic tape as described in Section A1 of this report.

A two standard deviation alphabetic print-out of the 64 x 64 matrix array accumulated for the entire breath holding period was obtained in order to select the areas of interest for summation over serial pre-set time increments. A least squares fit to a single exponential function was then performed to a pre-selected set of points from these data which had already been corrected for physical decay. It was important, especially for the studies utilizing carbon monoxide, to exclude the vascular pool from the area over which the counts were summed to obtain lung clearance rates. To accomplish this the vascular structures were identified by means of a xenon-133 perfusion study. However, consistent patterns in the carbon dioxide and carbon monoxide scans were correlated to the Xe-133 study and obviated the necessity of performing the latter every day the gaseous tests were done.

Results:

Figure 22 shows an example of a typical run utilizing oxygen-15 and indicates the image which is obtained in the quantitative data print-out. Two letters in the X and one in the Y direction represent the cumulative counts over one element in the 64 x 64 matrix for the entire breath holding period. Each letter signifies a count range whose mean is two standard deviations from the mean of the next higher level in the alphabet code. The code increases from A to Z although some letters are discarded to permit visual contrast between levels. The shaded portion indicates the area of summation. The lung fields are clearly seen with the mediastinum diaphragm and trachea as shown. Figure 23 presents a typical plot from which the $^{15}\text{O}_2$ clearance rate is derived. Points with error bars are those for which a linear least squares fit was done. As seen in this study the half time for oxygen was 17.6 seconds. Similar illustrations for C^{15}O are shown in figures 24 and 25. The pattern of uptake between oxygen and carbon monoxide are strikingly different. In the oxygen scan the most active areas are within the lungs while in the carbon monoxide scan it appears in the excluded vascular pool location. The carbon dioxide pattern is quite similar to that of carbon monoxide as seen in figure 26. The associated clearance plot may be found in Section A1. Six to thirteen total lung baseline clearance rates for each of these gases have been obtained on 5 dogs measured over a period of 3 weeks. Tables II, III and IV list the dog number, total number of runs, mean clearance half time in seconds, the standard deviation in seconds and the standard deviation expressed as percent of the mean clearance time for $^{15}\text{O}_2$, C^{15}O_2 , and C^{15}O respectively. The last line in each table is a statement of the mean clearance rate for all dogs and the associated standard deviation weighted by $1/\sigma^2$.

TABLE II

O_2 Labeled with ^{15}O Rate of Disappearance from the Lungs of Normal Dogs

Dog	Number of runs	Mean clearance $t_{1/2}$ in sec.	Standard deviation in sec.	% Standard deviation
499	11	25.55	6.41	24.1
566	10	24.22	8.86	36.9
567	10	14.75	2.22	15.0
613	10	18.56	2.85	15.3
614	8	19.77	5.40	27.3
MEAN		17.39	1.59	9.1

$^{15}\text{O}_2$ DYNAMIC LUNG FUNCTION STUDY OF NORMAL DOG

I.D. L-567 Run No 78-3 Date 1/26/71
Aml Inj 2.5 mCi Time A 1 0 sec View VENTRAL CHEST
Tot Cts 163840 Scan Time 30.05 sec Output 20

Fig. 22. TOKIM image of the ventral chest of a dog after a single breath of 2.5 mCi $^{15}\text{O}_2$. Shaded portion indicates area of integration for dynamic study.

Fig. 23. Graph showing disappearance of $^{15}\text{O}_2$ from the lungs pictured in Fig. 22.

Fig. 24. TOKIM display of the lungs of a normal dog after inhalation of 2.5 mCi $C^{15}O$.

Fig. 25. Clearance of $C^{15}O$ from the lungs shown in Fig. 24.

Fig. 26. TOKIM image of the lungs of a normal dog after a single breath of C¹⁵ O₂.

TABLE III

CO₂ Labeled with ¹⁵O Rate of Disappearance from the Lungs of Normal Dogs

Dog	Number of runs	Mean clearance $t_{1/2}$ in sec.	Standard deviation in sec.	% Standard deviation
499	12	10.50	1.56	14.8
566	9	7.08	2.32	32.8
567	9	5.42	0.76	14.0
613	8	6.40	0.85	13.3
614	6	6.62	1.16	17.6
MEAN		6.46	0.47	7.3

TABLE IV

CO Labeled with ¹⁵O Rate of Disappearance from the Lungs of Normal Dogs

Dog	Number of runs	Mean clearance $t_{1/2}$ in sec.	Standard deviation in sec.	% Standard deviation
499	13	11.13	1.48	13.3
566	8	6.68	1.31	19.6
567	8	6.11	1.13	18.5
613	7	7.80	1.13	16.1
614	6	6.99	1.41	18.1
MEAN		7.45	0.57	7.6

The range of mean clearance half time was 14.75 seconds to 25.55 seconds with a weighted mean of 17.39 seconds for ¹⁵O₂; 5.42 seconds to 10.50 seconds with a weighted mean of 6.46 seconds for C¹⁵O₂ and 6.11 seconds to 11.13 seconds with a weighted mean of 7.45 seconds for C¹⁵O. It is of interest to note that oxygen has the longest clearance half time and highest variability while there is no significant differential between carbon dioxide and carbon monoxide.

Conclusions:

These preliminary studies are the first step in a series of experiments to measure and evaluate respiratory dynamics. An

attempt will be made to identify regional blood flow, ventilation and membrane characteristics. Since the early work in London (1) in the late 50's and early 60's the rate of pulmonary clearance of O-15 labeled oxygen has been considered an index of regional oxygen consumption; the clearance of carbon dioxide, a measure of regional pulmonary blood flow; and the clearance of carbon monoxide, a parameter of the regional membrane diffusion capacity. The results of this study have given us a baseline of normal clearance half times for these physiologic gases labeled with O-15 but their variability, particularly for $^{15}\text{O}_2$ seems too large.

Oxygen-15 is administered in a mixture of 5% $^{16}\text{O}_2$ and 95% N_2 . It was hypothesized that this low oxygen tension might alter the rate of transfer from that under normal conditions of 20% oxygen in atmospheric air. Different O-15 specific activities created by diluting the inhaled gas with varying amounts of $^{16}\text{O}_2$ may be the cause of the troublesome variability in the oxygen clearance rates. Preliminary results indicate that the half time is increased with the greater amount of $^{16}\text{O}_2$ present. In addition, the effect of introducing different $^{16}\text{O}_2$ venous concentrations by pre-breathing the dog on the respirator with room air or a more highly concentrated $^{16}\text{O}_2$ mixture is also being investigated.

References

1. West, J.B., The use of radioactive materials in the study of lung function, Medical Monogram #1, Radiochemical Centre, Amersham, England, 1967.

- (b) Evaluation of pulmonary irradiation reaction using gases containing oxygen-15

Objectives:

To document changes in the regional pulmonary function of dogs after a single dose of high energy radiation administered unilaterally by performing serial dynamic studies using O-15 labeled oxygen, carbon dioxide and carbon monoxide.

Materials and Methods:

Gas production, administration, and visualization were outlined in the previous section. Digital dynamic data analysis was also the same except that the liver activity as well as the vascular blood pool was subtracted from the area of lung activity summation. The liver was localized by a Tc-99m sulfur colloid scan and a general technique was developed such that the upper edge of the liver was assumed to be a standard arc above the lower edge of the lungs for all subsequent gas runs. Percent difference in mean clearance half

time between left and right lungs i.e. (irradiated-normal)/normal was calculated.

All of the five dogs whose baseline clearance rates were reported on in the previous section received a single unilateral dose of Co-60 gamma-rays. The right lung of dog #566 received 2000 rads; left lung of #567, 2250 rads; left lung of #613, 3000 rads; right lung of #614, 3000 rads; and the left lung of #499 also 3000 rads. Chest radiographs were obtained prior to Co-60 irradiations, one month later and periodically thereafter in the longest survivor. Lab tests included hemoglobin, hematocrit and white count. Two to three dynamic studies of each gas were performed at least once and frequently twice a week until death. The one remaining dog is 24 weeks post irradiation and is now studied bi-monthly.

Results:

Of the five dogs studied, three died before changes in regional pulmonary function were reflected in the percent difference between irradiated and normal lung clearance half times. One death (#613) was due to an overdose of pentobarbital on the first gas study after radiation. Fluid and electrolyte depletion were credited with the death of #567. There was denudation of the mucosa with at least three superficial non-penetrating ulcerations. The irradiated left lung was congested and had decreased crepitation. There was erythema and a homogeneous increased vascularity throughout. The right lung was normal. This dog died 61 days after 2250 rads.

A perforated gastric ulcer with peritonitis was determined to be the cause of death of #499 at 60 days after 3000 rads. The irradiated left lung was firm, not collapsed, non crepitant but meaty and inelastic throughout. No exudate was found in either lung. Again the standard deviation of the percent difference in clearance half time between irradiated and normal lungs was large enough to include the mean percent difference from the baseline studies.

However, radiation changes were evident at necropsy in dog #614. The $^{15}\text{O}_2$ percent difference minus its standard deviation was at least 1-1.5 times greater than the mean baseline percent difference from 25-43 days post radiation. Factors of 3-8 for C^{15}O_2 and 3-14 for C^{13}O were also observed for this time span. Necropsy showed both lungs to be erythematous with a very prominent vascular pattern. On the untreated side there was an area of deep dependent post-mortem congestion. Decreased crepitation of both lungs appeared symmetrical. In summary, the animal seemed to have bilateral acute pulmonary radiation changes.

Our last interesting survivor is #566 who received the lowest dose of 2000 rads and did not show significant dynamic abnormality until 100 days after radiation. At 167 days, percent differences were +120%, +198% and +260% for $^{15}\text{O}_2$, C^{15}O_2 and C^{13}O respectively. We plan

to continue measuring the dog as long as his condition permits. In fact he was and remains the most lively of the 5 dogs.

Conclusions:

The physiologic course of acute pulmonary changes following irradiation has received sporadic attention, but has not been carefully documented to date because of the difficulty and discomfort of conventional studies of pulmonary function. Preliminary determinations on dogs have revealed the efficacy of this method as an index of pulmonary irradiation reaction. However, 3 out of 5 dogs died from extra pulmonary difficulties before the 0-15 labeled gas dynamic studies indicated lung malfunction. Results from the other two dogs showed a wide time-dose effect difference between 2000 and 3000 rads. Further studies are necessary before more definitive conclusions can be drawn.

- (c) Application of scintiscanning with xenon-133 to thoracic surgical problems

Objectives:

- (1) To assess the value of regional physiologic studies in planning and performing pulmonary resection.
- (2) To assess the response of regional pulmonary abnormality e.g. interstitial Hodgkin's infiltrates, to appropriate therapy.

Materials and Methods:

In 106 patients evaluation of the regional distribution of alveolar volume, ventilation, and perfusion has been performed on the six probe data acquisition system previously described in the 1968 progress report of Proposal #3. The digital output of this Hewlett Packard computer has been utilized to evaluate the symmetry and homogeneity of distribution of the isotope and to follow the dynamic processes of perfusion and ventilation with particular reference to the correspondence of perfusion and ventilation.

Results:

The results of these clinical studies have been of distinct value in three general areas.

- (1) Among patients being evaluated for pulmonary resection, regional studies utilizing xenon-133 in many instances have shown that pulmonary resection not only might be tolerated but might in fact be helpful because of the localization of major pulmonary abnormality to the area being considered for resection. In 10 to 15 patients clinical evaluation and conventional pulmonary function studies would have suggested that the patient would be unable to tolerate thoracotomy and significant pulmonary resection. However,

further studies by means of xenon-133 established the fact that the disability was due primarily to the pathology which would be resected. An example may be helpful.

A 76-year-old white male (R.F.) had experienced severe dyspnea after mild exertion for three weeks. Chest x-ray revealed a 4 centimeter mass in the right lower lung field. Conventional pulmonary function studies disclosed a total lung capacity 58 percent of predicted with vital capacity 59%, residual volume 57%. There was no airway obstruction. The arterial oxygen tension was 69 mm at rest, 54 mm after exertion, and 366 mm with the patient breathing 100% oxygen. The corresponding saturations were 94%, 89% and 100%. The high oxygen tension allowed an estimate of venous to arterial shunting about 20% of the cardiac output.

Figures 27-30 summarize the Xe-133 dynamic regional pulmonary function data in this patient. As can be seen from Figures 27 and 28, equilibration of the inhaled isotope suggests a moderately reduced alveolar volume in all areas of the right lung. From the distribution of isotope in a single breath (Figure 29) it is quite clear that there is marked hypoventilation of the entire right lung much beyond what could be accounted for by the reduced alveolar volume in that area. The perfusion study (Figure 30) with an injected solution of xenon-133 discloses only a mild reduction in the perfusion of the right lung and from the wash-out curves of perfused and equilibrated xenon the hypoventilation of the right lung is confirmed. Interpretation of these data was that the pulmonary restriction and arterial hypoxemia were due to the non-ventilated, perfused right lung. The patient underwent right radical pneumonectomy with good results.

(2) In approximately six cases the response of Hodgkin's infiltrates to chemotherapy has been documented. Prior to treatment regional studies have disclosed both reduced ventilation and reduced perfusion of the infiltrated areas. Following successful treatment there has been improvement in the ventilation of the affected areas without corresponding improvement in the perfusion of these areas.

(3) There are miscellaneous problems of respiratory physiology and pulmonary hemodynamics which have been partially clarified through the use of xenon-133 studies. The number of cases are few but the evaluation of regional ventilation and perfusion has assisted in the differential assessment of pulmonary hypertension, chronic pulmonary congestion, the ventilation-perfusion imbalance associated with chronic obstructive pulmonary disease, and other clinical problems.

Conclusions:

Evaluation of regional alveolar volume, ventilation, and perfusion by means of inhaled and intravenously injected xenon-133 has been helpful in the clinical management of neoplastic disease involving the lungs. This benefit is appreciated not only in the preoperative assessment of patients with bronchogenic carcinoma, but also in a variety of patients with infiltrative pulmonary disorders.

Fig. 27. Graphs showing the distribution of activity after a single breath containing 1.0 mCi of Xe-133 and during rebreathing of the isotope in a closed spirometer system.

Fig. 28. These graphs are a continuation of the equilibration study, although the ordinate scale is different. After rebreathing the isotope mixture at functional residual capacity, the subject took a single breath of the same magnitude as the initial breath. This allows comparison of the initial distribution of inspired air with the total, potential alveolar volume indicated by the distribution of the equilibrated isotope.

Fig. 29. Graphs showing the distribution and pattern of wash-out of a second single breath containing 1.0 mCi of Xe-133.

Fig. 30. The graphs indicate the pattern of alveolar-capillary perfusion after intravenous injection of a solution of 1.0 mCi of Xe-133, with subject in the sitting position. The curve of washout of the isotope delivered to the alveoli by perfusion is compared with the washout after the single breath and equilibration ventilation studies.

3. Erythropoietic and Phagocytic Function Studies

- (a) Quantitative evaluation of ^{52}Fe ferrous citrate and $^{99\text{m}}\text{Tc}$ sulfur colloid as indicators of hemotopoietic and phagocytic functional areas

Objective:

To quantify reticuloendothelial organ function following tracer doses of Fe-52 ferrous citrate and Tc-99m sulfur colloid in order to achieve a valid indication of the body's erythropoietic and phagocytic processes.

Material and Methods:

A variety of clinical entities such as polycythemia vera, chronic myelogenous leukemia, primary hemochromatosis and lymphosarcoma were evaluated after intravenous administration of Fe-52 tracer supplied by the SKI cyclotron.

All patients received 85-120 μCi of this positron emitter which has an 8.2 hour half-life and were scanned 12-18 hours after injection. A rapid exponential transfer of radioactive iron from the plasma to the bone marrow where it remains about one day has been shown by iron kinetic studies. (1)

Examinations on patients who received 10 mCi of Tc-99m sulfur colloid to determine sites of phagocytosis were initiated 15-30 minutes post-injection while the two patients who were injected with 50 μCi of Fe-59 were scanned the day following administration.

Approximately 300 μCi of Cr-51 labeled undamaged autologous erythrocytes were administered in an attempt to assay red cell sequestration and destruction. Scans were performed 30 minutes after injection and serially thereafter 2 or 3 times per week depending on the activity of the hemolytic process and as scheduling permitted.

Pulse height analyzers were set for both the 165 keV and 511 keV gamma peaks of Fe-52. Computer analysis of upper and lower detectors as well as the summed detector output for each energy level were obtained.

Results:

The results of patients studied with both Fe-52 and Tc-99m sulfur colloid were collated to attain a more precise hematologic picture. One case of chronic myelogenous leukemia exhibited inadequate phagocytic marrow activity with increased colloid phagocytosis by liver and spleen. Considerable iron uptake is seen in the vertebrae, pelvis, distal ends of both femora and proximal

ends of both tibiae. These changes indicate greater red cell activity on the basis of iron uptake in the marrow with a decrease in functioning granulocytic activity. The red cell survival study showed a striking decrease which was essentially exponential and therefore not related to cell age. Summation of counts from quantitative scans indicated a greater splenic sequestration than normal. Results therefore were indicative of marrow aplasia with reduced "myeloid:erythroid" ratio.

The clinical situation of polycythemia rubra vera of 18 years duration was investigated with iron, technetium and chromium isotopes. Previous evidence had suggested that a conversion to myeloid metaplasia had transpired. The expansion of marrow as a cause of the severe migratory bone pain was also considered. Results of the iron and technetium scans indicated an absence of erythropoiesis and phagocytosis. An increase in red cell destruction was shown in the serial scans done with undamaged Cr-51 labeled erythrocytes.

A patient with lymphosarcoma was studied with Fe-52 and Tc-99m sulfur colloid to determine his hematologic status following massive radiation therapy. Both parameters indicated decreased uptake in irradiated areas with an unexpected area of activity in the chest. These studies were of significant help in his clinical management. A patient with advanced hemochromatosis was studied in cooperation with the division of chemotherapy. Iron absorption, turnover and the amount of liver uptake were determined.

Conclusion:

Informative conclusions with respect to the reticuloendothelial system in hematologic diseases have been reached. The techniques employing Fe-52 and Tc-99m sulfur colloid as tracers in following the course of hemolytic disease and in the various leukemias have proven to be of consequence. It is planned to investigate further erythropoietic and phagocytic distribution in more patients in order to quantify reticuloendothelial organ function.

References:

1. Pollycove, M., and Mortimer, R., The quantitative determination of iron kinetics and hemoglobin synthesis in human subjects. J. Clin. Invest. 40: 753, 1961.

- (b) Clinical applications of absolute quantitative organ scanning

Objectives:

To employ procedures developed for absolute organ quanti-

tation in the investigation of patients with aberrant hematologic conditions such as systemic lupus erythematosus, Hodgkin's disease and various leukemias and anemias.

Materials and Methods:

Patients in whom splenectomy was planned were injected with a weighed amount of Cr-51 labeled ACD damaged autologous erythrocytes according to the method previously described by us (1). The number of microcuries injected was accurately determined by counting the syringe containing approximately 10 ml of labeled red cells in an ionization chamber before injection. Correction was made for any residual activity remaining in the syringe after injection. Approximately 1cc of the labeled red cells was held in reserve for use as a standard in the homogenization procedure. All patients were scanned within three hours prior to splenectomy on the day following injection. The HEG scanner, a dual headed rectilinear scanner with 4" x 4" NaI crystals, containing the depth independent response F (14 cm, 18 cm) collimators was used in all instances. The capabilities of these collimators and the results of phantom studies using several spleen sizes immersed in water filled tanks of different depths have previously been described under section A3. These data were collected on magnetic tapes and processed through the IBM 1800 computer using the HEGS program which was specifically designed for quantitation. Localization of the labeled erythrocytes in the spleen, liver and bone marrow is depicted in the scan printout by consecutive letters signifying count ranges whose midpoints are two standard deviations apart. Coordinates corresponding to the splenic area were selected and the magnetic tapes re-run through the computer to integrate the count above a certain count rate or, in other words, within a specified contour. Summed counts within 6 different contours i.e. 10% to 60%, were obtained for both upper and lower detector images as well as for the summed detector image. These counts were then normalized for scan speed to obtain counts per second.

The determination of the conversion factor (C.F.) depends on the patient thickness measured at the scan time and the size of the spleen as determined by the splenic scan image. The water tank (20, 25 or 30 cm) which most closely approximated their thickness was used in the calculations. The majority of patients were found to be close to the phantom tank of 20 cm although some corresponded to the 25 cm and one to the 30 cm water tank. The 50% contour from the in-vivo summed detector scan image was used as the boundary for splenic count rate integration which will henceforth be called total summed counts (T.S.C.) per second. The area within this contour therefore defined the spleen size. Appropriate conversion factors (C.F.) were determined from phantom study graphs relating source area to T.S.C./ μ Ci/second. In-vivo uptake was then calculated according to the following:
$$(T.S.C./sec) \div (C.F.) = \mu Ci \text{ uncorrected for surrounding tissue}$$

background. This background subtraction was achieved by multiplying the number of elements (alphabetic characters) within the spleen area by background counts per second chosen from the in-vivo scan but in a location distant from areas of concentrated activity. Division by another correction factor i.e. counts/ μ Ci/scan increment, obtained by scanning tanks containing only a water solution of uniform radioactivity gave the required microcuries of background activity which must be subtracted from the previously determined splenic uptake. The tissue background correction factors are 92.8, 79, and 73.1 counts/ μ Ci/scan increment for the 20, 25 and 30 cm depth tanks respectively. Finally, the percent splenic uptake was calculated and is based on the injected microcuries corrected for one days decay.

The true chromium content was determined by homogenization of the excised spleen. A few samples of known weight were assayed for radioactivity content in a Hewlett-Packard well scintillation counter. The results were multiplied by the total weight of the intact spleen and expressed as percent of injected red cell activity likewise corrected for one days decay.

Results:

Table V represents a summary of the patients studied thus far. In-vivo determinations of splenic uptake have been corrected for surrounding tissue activity. Background correction is expressed as a percent of the splenic uptake in μ Ci before background was subtracted. The first three patients were done on the HEG scanner before it was updated. Therefore a different series of conversion factors were used. In 10 patients studied, using the summed counts within the 50% patient contour and the 50% in-vivo contour for estimation of spleen size, the mean of the ratios of in-vivo to in-vitro measurements was 1.043 ± 0.27 .

The average spleen weight was 190 grams with a range of 95 to 372 grams. The splenic length as determined by the Pathology Department ranged from 8 to 15 cm with an average of 11.5cm. Widths ranged from 6 to 10 cm with an average of 7.7 cm. It is interesting to note that two patients had two accessory spleens each; the largest of which weighed 5 grams. All patients were between the ages of 15 and 38 years.

Of all the Hodgkin's disease (HD) patients, R.M. was the only one in whom a histologic diagnosis of HD in the spleen could be made, although the spleen was of normal size and weighed 160 grams. R.W.'s spleen was histologically normal but was enlarged and weighed 372 grams. The spleen as seen on the scan printout (Figure 31) appears well delineated from the liver and bone marrow. The percent of injected dose, as determined in-vitro was one of the highest. However, the closest percent uptake in-vivo

R.W. ♂ 300 μ Ci ⁵¹Cr ACD RBC's Summed Detector Image
Level Spacing 2 σ in vitro: 26% in vivo: 28%

Fig. 31. Spleen scan of R.W. following injection of 300 μ Ci of Cr-51 ACD damaged erythrocytes. Letters are separated by two sigma intervals.

Patient Summary of Absolute Quantitation of Splenic Uptake

<u>Name</u>	<u>Diagnosis</u>	<u>CI ⁵¹Cr Injected</u>	<u>C.F.</u>	<u>Background Correction</u>	<u>Splenic % of Injected Dose</u>	
					<u>In Vivo</u>	<u>In Vitro</u>
A.G.*	CML	348	1.12		43%	50%
A.A.*	CML	360	1.14		16%	17%
R.M.*	HD	420	1.05		26%	21%
J.L.**	HD	310	27/31.5	2.8%	10%	12%
D.F.	HD	311	22.3	2.2%	7%	8%
V.Z.	HD	294	34	9.3%	9%	11%
L.V.	SLE	434	30.5	17.9%	4%	3%
P.D.***	Waldenstrom's macroglobulinemia	352	22.0	7.5 CI	100µCi	84µCi
C.B.	SLE	331	21.9	4.4%	7%	5%
S.P.	HD	307	29.4	12.3%	5%	5%
D.C.	HD	344	30.5	8.6%	5%	4%
E.B.	HD	345	31.0	6.5%	7%	7%
R.W.	HD	300	32.0	4.1%	16%	26%

*Patients done under old system

**Anterior and posterior scans were obtained separately and were averaged to obtain % dose, therefore, C.F.'s represent Ant./Post.

***Results in microcuries since patient had residual ⁵¹Cr from previous injections

Table V

remains 44% lower than the true value. The explanation for this discrepancy remains obscure. Upon review, the summed counts obtained from the lower detector computer output are significantly increased when compared to the summed counts obtained from the upper detector. The count ratios of lower/upper for the 50% and 30% contours are 1.73 and 1.43 respectively. Comparing these ratios with three other patients, L.V., D.C. and S.P., who also had a "thickness" comparable to the 20 cm water tank, one finds count ratios of lower/upper for the 50% contour of 1.52, 1.47 and 0.87 respectively. In the same manner, the ratios of lower/upper for the 30% contour were 1.13, 1.12 and 0.86. The last three patients mentioned were found to have excellent agreement between in-vivo and in-vitro results. The significance of these ratios, if there is one, remains under consideration. Additional patients with increased splenic sequestration are desirable and would assist in the clarification of this matter. All HD patients, except one, underwent splenectomy within two months after being diagnosed. The other patient had a two and one half year history of HD. Perhaps this explains the normal pathological findings. The two patients with chronic myelogenous leukemia had a relatively high uptake.

The spleen of P.D., who had Waldenstrom's macroglobulinemia, weighed 280 grams and exhibited a lush parenchyma with faintly discernable germinal centers. Comparison between in-vivo and in-vitro uptake cannot be expressed as percent of administered dose since the patient had undergone a red cell survival study 3 weeks before splenectomy. A pre-scan was done before the injection for our study was given. This showed 27-34 microcuries to be present. From this we can assume that approximately 80 more microcuries were sequestered by the spleen in the 24 hours prior to splenectomy. Based on the number of microcuries injected this would be an uptake of 23%. The computer display of this scan with the area of summation outlined is shown in Figure 32.

Conclusion:

The patient data clearly indicates that it is possible to obtain absolute quantification of organ radioactivity. The technique is essential for determining the relative contribution made by an organ such as the spleen to red cell production and destruction. This permits a rational judgement with respect to splenectomy. Problems relating to organ area selection still bear consideration. It is hoped that a number of future patients will have an increased splenic sequestration so that our method can be certified for the full range of possible splenic activities.

References:

1. Mayer, K., Dwyer, A., and Laughlin, J., Spleen scanning using ACD-damaged red cells tagged with Cr-51. J. Nuc. Med. 11: 455-458, 1970.

P.D. of 350 μ Ci 51 Cr ACD RBC's Summed Detector Image
Level spacing 2 σ

Fig. 32. Spleen scan of P.D. following injection of 352 μ Ci of Cr-51 ACD damaged erythrocytes. Letters are separated by two sigma intervals.

(c) Blood flow concepts in heterotopic liver allografts based on kinetic studies using the TOKIM system

Objectives:

An auxiliary liver graft may be an attractive mode of therapy for various types of end-stage liver disease, such as hepatic cirrhosis. Also, it might function as a means of temporary hepatic support in acute hepatic failure when recovery of the host liver is expected to occur. The purpose of this study was to monitor auxiliary liver graft function, or rejection, and to measure liver blood flow without involving complicated vascular catheterizations. It was also possible in these experiments to evaluate different vascular circuits.

Materials and Methods:

Figure 33 illustrates the position of the auxiliary liver graft in the right flank of the dog and the parallel blood hook-up by means of end to side portal vein anastomosis. When rejection occurs, increased vascular resistance causes shunting of blood flow to the host liver. In this study we evaluated sixty dogs, divided into three groups according to their blood flow hook-ups. Group 1 was connected as in the figure in a simple parallel circuit. Group 2 was similar except that a silastic cuff was placed around the host's portal vein to reduce the cross-sectional area by one half. Group 3 was provided with a separate blood supply from the left renal vein so as to receive all the venous effluent of the left kidney. Post-operative care involved administration of intravenous fluids for two to four days after which these dogs could usually take regular kennel rations. Broad spectrum antibiotics were given for three days. Immunosuppression for mongrel recipients consisted of azathioprine, 8 mg per kg on day 1, 4 mg or less per kg subsequently, and prednisolone 3 mg per kg on day 1, gradually diminishing to a maintenance dose of 0.5 mg per kg by the seventh day.

The procedure used to evaluate these dogs was the measurement of the uptake of 0.5 mCi of intravenously administered Tc-99m labeled sulfur colloid. The apparatus was the TOKIM system. The TOKIM consists of an Anger-type scintillation camera interfaced to an IBM 1800 computer. Each head is equipped with a 13 1/2" x 1/2" sodium iodide crystal and a 1000-hole tungsten collimator. Each scintillation event is digitally converted and buffered to magnetic tape. These are later recalled and accumulated in thirty second increments for the areas of interest. Figure 34 shows the alphanumeric printout of the 64 x 64 matrix accumulated over 5 min. This output is used to select the areas over the heart, host liver and auxiliary liver. A linear, least-squares fit to a single exponential was performed to the uptake and disappearance curves.

Fig. 33. Technique of auxiliary liver transplantation in experimental groups.

Fig. 34. Alpha numeric printout for the 5.0 min. accumulation of Tc-99m labeled sulphur colloid in auxiliary, liver-transplanted dogs.

Results:

In order to evaluate our technique we performed sixty trials in five different normal dogs over a period of three months. The results of these studies are shown in Table VI.

TABLE VI

Radiocolloid Uptake Halftimes for Normal Dogs

<u>DOG</u>	<u>MEAN HALFTIME</u>	<u>STD. DEV.</u>	<u>% STD. DEV.</u>
L-313	1.09	0.12	11.3%
L-399	1.04	0.12	11.7%
L-431	1.07	0.16	14.7%
L-460	1.14	0.05	4.6%
L-425	1.14	0.14	12.0%

The weighted mean doubling time for all of these runs was 1.12 ± 0.04 min. This 3.6% standard deviation indicates a remarkable degree of reproducibility, considering that the uptake doubling time is affected by (1) the particle size spectrum of the colloid and (2) the cardiac output of the dogs.

Figure 35 shows a typical fit to the original data for the areas over the heart, host liver and auxiliary liver. Note that the slopes are all nearly the same. In the diagram on the right side it is to be noted that the error bars, for the subtracted count rate over the auxiliary liver, become very large. The reason for this is that a smaller amount of colloid is taken up by the auxiliary liver as it approaches rejection yielding low count rates, and the statistics depend on the sum of the saturation value and the count rate at any arbitrary time.

Some of the dogs previously had a host bile duct ligation so that their serum bilirubin levels could be correlated with the half-times. Figure 36 shows the results for serum bilirubin level plotted as a function of days after transplantation and the corresponding measured doubling time for uptake of the colloid in the auxiliary liver. We were able in most cases to predict rejection, as indicated by the increase in serum bilirubin level, from the change in the uptake doubling time. This change is preceded by an increase in the error of the least-squares fit to the data.

The next phase of our experiment was to provide a measure of blood flow to the two livers. Figure 37 shows a proposed compartmental model for this system. The two livers are assumed to be in parallel with the blood compartment.

Fig. 35. Least-squares fit to dynamic function data for the redistribution of Tc-99m labeled sulphur colloid in auxiliary liver-transplanted dogs.

Fig. 36. Serum bilirubin concentration and radio-celloid doubling time plotted as a function of days after transplantation. The increase in bilirubin concentration indicates refection of the auxiliary liver.

Figure 37. Compartmental model for auxiliary and host liver system.

Definitions:

- f = blood flow rate in cm^3/min .
 A = specific activity in $\mu\text{Ci}/\text{cm}^3$
 Ω = geometric factor (solid angle) and crystal photopeak efficiency
 E = efficiency of liver for removing colloid from the blood
 C = measured counts over a particular region of interest
 V = total volume of compartment

Subscripts: B (blood), H (host) and A (auxiliary)

The rate of change of total activity from the blood is given by:

$$V_B \frac{dA_B}{dt} = -f_1 A_B + (1 - E_H) f_2 A_B - f_3 A_B + (1 - E_A) f_4 A_B$$

Assuming that $f_1 = f_2$ and $f_3 = f_4$ yields

$$\frac{dA_B}{dt} = \left[\frac{-(E_H f_1 + E_A f_3)}{V_B} \right] A_B$$

The general form of this equation is

$$(1) \quad \frac{dA_B}{dt} = \lambda A_B \quad \text{where } \lambda = \frac{-(E_H f_1 + E_A f_3)}{V_B}$$

The boundary conditions are

$$t = 0, V_B A_B = I \text{ (0 amount injected, } \mu\text{Ci)}$$

$$t \rightarrow \infty, A_B = 0.$$

The solution is

$$A_B = \frac{I}{V_B} e^{-\lambda t}.$$

Similarly for the host and auxiliary livers:

$$(2) \quad \frac{dC_H}{dt} = f_1 E_H \Omega_H A_B(t)$$

$$(3) \quad \frac{dC_A}{dt} = f_3 E_A \Omega_A A_B(t)$$

with the boundary conditions:

$$t = 0, C_H = C_A = 0$$

$$t \rightarrow \infty, C_H = C_H(\text{max}) \text{ and } C_A = C_A(\text{max})$$

The solutions for equations (2) and (3) are

$$(4) \quad C_H = \frac{f_1 E_H \Omega_H I}{V_B \lambda} (e^{-\lambda t} - 1)$$

$$(5) \quad C_A = \frac{f_3 E_A \Omega_A I}{V_B \lambda} (e^{-\lambda t} - 1).$$

For a multihole collimator with both livers in the field of view $\Omega_A = \Omega_H$. We have shown this to be a good assumption ($\pm 5\%$) for phantoms at distances up to 25 cm from the collimator face.

Therefore, we have

$$(6) \quad \frac{C_H(\text{max})}{C_A(\text{max})} = \frac{f_1 E_H}{f_3 E_A}.$$

The two predictions for this model are (1) the measured half-time or doubling time should be the same, no matter which compartment is monitored, and (2) the ratio of the saturation values for colloid uptake over the two livers should be the same as the ratio of the efficiency flow product. Figure 38 shows a plot of these results for a long-term survival dog.

Conclusions:

In these experiments, we were able to predict the onset of rejection from the increase in the uncertainty of the measured doubling time for Tc-99m sulfur colloid uptake in the auxiliary liver. Also, the ratio of the saturation value for the total uptake of colloid over the two livers seems to be a measure of their relative blood flow. This ratio was used as a comparison in a rank sum test and it was found that groups 2 and 3 had a higher blood flow ratio than group 1 with respective confidence values of 90% and 95%. An unexpected result was the large variability, of the order of 10%-30%, in the uptake doubling times for the host and auxiliary liver.

These relatively large changes in the radiocolloid uptake half times might indicate that these measurements are more sensitive to physiologic changes than are the serum bilirubin levels. On the other hand, the uptake halftimes indicated rejection before the increased bilirubin levels in only 30% of the dogs studied.

4. Investigation of the Importance of Phosphorus Metabolism in Post-Transplant Liver Patients

Objectives:

To investigate a possible increase in inorganic phosphorus uptake in the liver in dogs having undergone ischemic damage or partial hepatectomy.

Materials and Methods:

Below normal serum inorganic phosphorus levels have been observed in post liver transplant patients as well as dogs in which ischemic injury to the liver had been caused by temporary occlusion of the hepatic circulation (see section B3). With a very severe injury this increase was seen as early as ten minutes. However, with a more moderate injury the phosphorus level was shown to initially rise, then decrease below normal from 1 to 4 days after injury and then increase to the norm at from 4 to 7 days. It was theorized that ATP, AMP and ADP are lost from degenerating liver cells and, in order to regenerate, the liver utilizes the blood phosphate. In an attempt to verify this hypothesis, serial measurement of radioactive phosphorus uptake was proposed in both normal and ischemic damaged livers. It was expected that an increased uptake of inorganic phosphate would be observed at 2-4 days after ischemic damage.

Fig. 38. Ratio of auxiliary liver host liver half times and saturation values for Tc-99m sulphur colloid uptake.

Unfortunately, the only radioactive isotope of phosphorus with a sufficiently long half life for this study is phosphorus-32 (β -decay at 1.7 MeV). This was administered as Na_3PO_4 . The detection of the bremsstrahlung emission is not an ideal scanning method. The problems of measurement are particularly complicated since only a small change in uptake was expected (normal liver uptake is about 10% of injected inorganic phosphorus). The residual activity in the blood is gradually taken up in the bone, bone marrow and tissue compartments. The small angle Compton scattering of the soft bremsstrahlung photons degrades the resolution of the organ's scan image. Results of any uptake measurements at two to three days after ischemic damage would therefore be difficult to interpret. In an endeavor to achieve a significant statistical difference between the counts over liver and adjacent tissue or bone background, large doses of P-32 (10 mCi - 20 mCi) were injected. The HEG scanner was employed to scan the liver with an energy window from 80 keV - 400 keV which included most of the bremsstrahlung spectrum. The F (16,20) cm dual focal length collimators were used to achieve a limited degree of depth independence for the P-32 activity distribution (See section A3).

In the initial protocol, both ischemic and normal control dogs were studied. Ischemic damage to the liver was performed approximately six hours before injection of P-32. Point counts over the liver and heart were taken for the first hour, followed by a whole body scan at the end of this interval and then later at 1, 2, 3, 4 days after injection (D.A.I.). Each dog was measured in the same geometry and positioned with their side on the scanner table. In the alphanumeric computer printout, produced from the summed counts from the upper and lower detectors, the positions of the liver, heart and shoulder bones could be found. A control for tissue background surrounding the liver was determined from the integrated counts over the dog's neck. The total summed counts over the whole dog at one hour after injection were taken as approximately representative of the injected dose administered in each case. Blood samples were taken every 10 minutes for the first hour and then every 12 hours. Urine was collected on a 24 hour basis. Both the amount of phosphorus in the blood and that in the excreted urine were determined as a percentage of the injected dose.

This protocol was later revised to include both dogs with ischemic and partially resected livers. Both partial hepatectomy and ischemic damage were performed at 3 days before isotope injection. The dogs were again scanned at 1 hour and at 1 D.A.I. but were then sacrificed and the liver activity determined in-vitro. The liver or the partial liver remaining in the dog was homogenized and the microcuries of P-32 in an aliquot of the homogenate measured in an ion chamber and compared with a standard in the same geometry. With each ischemic and resection dog a normal dog was sacrificed as a control. An attempt was made on

a number of occasions to derive the absolute liver activity at one hour after injection, knowing the integrated counts over the liver at both scan times. Samples of urine and blood were again taken as in the original protocol.

Results:

Upon injection, the phosphate was found to almost immediately accumulate in the liver and remain unchanged over the first hour for both normal and ischemic dogs. This result was demonstrated by the nearly constant point count measurements over that period. However, at 1 D.A.I. the phosphorus uptake in the damaged liver was observed to fall below the normal as shown in Table VII for 3 ischemic and 3 normal dogs. In general, the ischemic dog had a 50% drop in liver phosphorus activity 1 D.A.I. compared to a relatively small change in the normal dog. The expected increase in liver uptake for the ischemic dog at 2-4 days was not observed. However, the error in subtracting tissue background at this later time was large and computed values of liver content were not reliable. There was considerable spread in results of blood and urine samples.

To obtain a more reliable uptake measurement, the dogs were sacrificed as described in the revised protocol. Results of the in-vitro measured P-32 content in the liver are shown in Table VIII for a total of thirteen dogs. This additional data was not very conclusive since no difference in the total liver content was evident between normal and damaged liver and depended primarily upon the liver weight in each case. However, the specific uptake (%/gm) was found to be considerably higher for the resected liver and a suggested increase was observed for the ischemic dog. A wide spread in urinary excretion was found.

Conclusions:

The results of this short term study did not verify the hypothesis that an increase in liver uptake of inorganic phosphate in ischemic damaged or resected livers was responsible for the drop in blood serum level. However, the restricted method of approach in measuring the bremsstrahlung photons limited any precise analysis by scanning method. In the revised protocol, in sacrificing the dog, observation was necessarily restricted to a given period after damage to the liver, i.e., it was only feasible to sacrifice a small number of dogs. To make an extensive follow-up of this study would involve determining the liver uptake by an in-vitro method from 12-96 hours after injection of P-32. However, evidence to date suggests that only a small change in labeled phosphate uptake in the liver would be found and further explanation of the drop in organic phosphorus level in the blood is required.

TABLE VII

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Percentage Retention of Injected Dose in Liver, Blood, and Excreted Urine

			Times after injection of ^{32}P				
			<u>1 Hr.</u>	<u>1 Day</u>	<u>2 Day</u>	<u>3 Day</u>	<u>4 Day</u>
<u>Ischemic</u>	#P-195	Liver	21%	16%	12%	13%	13%
<u>Dogs</u>		Liver*	11	5	2.3	4.0	3
		Blood	--	--	--	--	--
		Urine	--	3.2	7.0	2.5	3.9
	#L-643	Liver	25.8	19.6	19.1	--	--
		Liver*	12	5.6	5.2	--	--
		Blood	6.6	3.4	3.0	--	--
		Urine	--	5.6	3.2	0.6	--
	#L-658	Liver	27	12.9	12	12	10
		Liver*	14	7	7	7	6
		Blood	8	5	4.6	2.0	--
		Urine	--	4.8	1.7	2.0	1.8
<u>Normal</u>	#L-651	Liver	24	22.9	18	18	17.8
<u>Dogs</u>		Liver*	12.8	11.8	7.5	7.6	6.5
		Blood	8.2	6.0	3.6	3.6	3.5
		Urine	--	7.2	2.8	0.4	--
	#L-653	Liver	20	17.3	16.1	15.7	14.6
		Liver*	9	6	5.2	4.8	3.3
		Blood	9.5	3.9	5	2.8	--
		Urine	--	3.8	0	3.1	0
	#L-668	Liver	16.4	13			
		Liver*	10.0	8.0			
		Blood	10.2	2.8			
		Urine	--	25			

*Corrected for Tissue and Bone Background

TABLE VIII

IN VITRO MEASURED LIVER UPTAKE OF P-32 AS A PERCENTAGE OF INJECTED DOSE

		<u>% in whole liver</u>		<u>Liver wt.</u>	<u>Specific uptake</u>	<u>% excreted in</u>
		<u>1 D.A.I.</u>	<u>1 Hr.**</u>	<u>gm.</u>	<u>%/gm.</u>	<u>urine</u>
Normal	#668	9.55	12.0	598	0.0159	25
	#703	10.08	12.4	663	0.0152	15
	#711	13.09	--	721	0.0184	3
	#713	8.6	--	493	0.0174	12
	#714	9.3	--	498	0.0188	0
	#735	10.4	--	510	0.0171	10.4
Ischemic	#679	12.8	15.6	694	0.0184	4.2
	#700	9.8	13.2	525	0.0186	10
	#702	11.6	--	604	0.0192	11
60% Resection	#707	8.07	--	418*	0.0193	8.0
	#709	7.49	--	370*	0.0202	7.5
	#728	6.173	--	225*	0.0274	8.7
	#741	12.41	--	324*	0.0382	5.3

*Weight of Remaining Liver in Dog

**Computed from the ratio of integrated counts over the liver at 1 hr. and 1 D.A.I. and the in-vitro result at 1 D.A.I.

5. Evaluation of ^{18}F Scanning Results

Objectives:

To evaluate the effectiveness of F-18 sodium fluoride in the management of patients with malignant disease, especially to show the contribution of quantitative scanning and computer analysis of the data in comparison with photo-scanning. The usefulness in the various forms of malignancy and the detection of lesions not found on radiographs will be estimated.

Materials and Methods:

The Sloan-Kettering Institute Cyclotron produces F-18 sodium fluoride twice weekly. Periodic checks for sterility and freedom from pyrogens are made under a procedure approved by the FDA (IND #5373). Patients with malignant disease give informed consent, and receive 1.0 mCi intravenously (children under 35 kg 0.5 mCi). Scans are done only because of medical indications. No untoward reactions have occurred. The scan is performed 2 to 3 hours later after having the patient void, using one of 2 dual 5 x 3 inch crystal rectilinear scanners.

Digital data are displayed 1/2 of the real size by the IBM 1800 computer utilizing a line printer and an alphabetic code. Linear interpolation is used but no data averaging occurs in the standard displays, which are 10 or 20 equal levels or on the basis of the statistical reliability of the differences between counts - usually 2 and 3 standard deviations. Correction for physical decay during the scan is routinely made. The display of the computer analysis is usually by an alphabetic array, in which any desired characters can be assigned or suppressed.

Results:

From May 1, 1970, through April 30, 1971, we have utilized F-18 sodium fluoride for 422 bone scans. Cases examined include a full spectrum of malignant disease. Most of the scans have been of the total body search type, with miniaturized photoscans and an extensive computer analysis of the digital data. We are averaging 45 scans a month at present. This is not a sufficient productivity to satisfy the clinical demand for such studies, however, and patients frequently must be treated before a scan can be scheduled.

With miniaturization of the photoscan, computer analysis is essential for proper interpretation. Changes of 2 standard deviations above the contralateral bone are usually not interpretable as abnormal, although they have heralded lesions later seen in subsequent scans of radiographs.

Figure 39 shows a computer display of anterior knee areas and a repeat of this scan 3 months later. Note the increased uptake in the left knee at both times. This was not apparent in radiographs taken at the early date. Changes of 3 standard deviations above the contralateral part are suspicious and 4 standard deviations are interpreted as definitely abnormal. The causes of increased uptake are non-specific, however, and the diagnosis must take into account the clinical and radiographic findings. That is, the uptake of F-18 is not specific to malignant tumors in bone.

Many lesions have been detected which are not seen on radiographs. In a series of 71 bone scans in 60 patients with lymphoma, 21 scans or 30 percent of those performed reveal lesions not detected on x-rays. The scans greatly assisted in the management of the lymphoma patients, advancing the patient to stage IV (bone or other non-lymphoid organ involvement) in 7 instances, revealing 8 additional new lesions not previously identified in the radiograph, and confirming by a negative scan the benign nature of 4 bone islands in patients with Hodgkin's disease.

Fluorine-18 is also being supplied to collaborating investigators in other institutions. Their preliminary experience is briefly summarized:

Dr. Philip M. Johnson of Columbia Presbyterian Hospital New York studied 32 patients with known cancer in whom skeletal metastases were suspected or were to be excluded. "The examinations generally were excellent in quality and provided useful clinical information affecting the management of our patients."

Dr. Walther H.O. Bolme of the Hospital for Special Surgery, New York, has performed 47 scans having diverse diagnoses such as osteoarthritis, osteonecrosis, osteomyelitis, compression fracture, rheumatoid arthritis, femoral neck fracture, avascular-necrosis, normals and malignant metastatic bone disease. A comparison study between F-18 and Sr-85 is being continued in selected cases.

Dr. A.D. Crosett Jr. of Overlook Hospital, Summit, New Jersey, has studied 59 patients with F-18 over the past 7 months. "It is my opinion that the use of fluorine-18 is far superior to any agent which I have used for bone scanning including strontium-85 and strontium-87m. It is of enormous help in initial diagnosis and, of course, in followups in treated areas for activity. We have noticed disappearance of osteoblastic activity in previously treated areas on 3 occasions and in one instance have been able to make a sharp differentiation between a zone of osteoblastic activity around the periphery of a very large osteolytic lesion which is something we have not been able to do with the rather poor statistical information afforded us by strontium-85.

2 cm

L.S. 6-4-70 ANT. KNEES ¹⁸F

2 cm

L.S. 9-17-70 ANT. KNEES ¹⁸F

Fig. 39. Computer display of a F-18 anterior knee area scan showing elevated uptake on the left side which is enhanced three months later. Letters signify count ranges whose midpoints are separated by two standard deviations.

Dr. Roger A. Bauman of Massachusetts General Hospital has supplied the following comments from his experience with 14 oral administrations of F-18 sodium fluoride. Some patients had unusual findings. In one, the scan showed radiofluorine distributed throughout both lungs as well as the skeleton. Either the known presence of pulmonary edema or possible metastatic ossification was proposed as an explanation. Another patient with Hodgkin's disease showed unusual retention of radioactivity within the gastrointestinal tract. The absorption of fluorine may have been affected by involvement of the bowel wall by lymphoma.

Conclusions:

Important decisions about patient management, such as the selection of chemotherapy versus radiation, or the size of a radiation portal depend on such information about the extent of disease. The F-18 bone scan, because of the rapid clearance of radionuclide from non-osseous structures permits visualization of the skeleton on the day of the scan, and interpretations are often typed on the following day when the computer analysis is complete.

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

1. Effect of Phosphate Administration on Ca-47 Kinetics

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 five patients to date; four patients with hypercalcemia due to primary hyperparathyroidism and one patient with mild hypocalcemia (serum calcium 8.7%) associated with carcinoma of the breast with metastases to bone. Techniques employed have included metabolic balance, radiocalcium kinetics, and urinary hydroxyproline excretion. Patients were hospitalized on the metabolic research ward of the Clinical Research Facility. Complete metabolic balances of calcium, phosphorus and nitrogen lasted six weeks in each case. Control phase of two weeks was followed by a treatment phase of four weeks, when 2 to 3 gm of phosphate supplements per day were added as Neutra-phos, a solution of monoblastic and dibasic sodium and potassium phosphate. A fourteen day Ca-47 kinetic study was performed twice on each patient, once during the control phase and again during the last two weeks of therapy. For the kinetic study 50 μ Ci of Ca-47 were administered intravenously as a single dose. The kinetic analysis was made according to the method of Bauer et al.(1). The total body retention of the isotope was measured using the High Energy Gamma-Ray Scanner. In addition, the scanner was used in serial external point measurements of radioactivity over several parts of the skeleton at set time intervals following administration of this isotope.

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 patient with breast cancer although the urinary calcium decreased in this patient during treatment. Metabolic balance studies in the hyperparathyroid patients showed a shift to a more positive calcium balance, the change from pretreatment balance being in the range of +60 to +234 mg calcium per day. However, in the patient with breast cancer there was a shift towards a less positive calcium balance. Phosphate therapy did not change nitrogen balance which remained positive in all patients. The phosphorus balances which were positive in two patients and nega-

tive in three before phosphate administration became markedly positive in all patients during phosphate therapy.

Calcium-47 kinetic studies during the pretreatment and treatment phases demonstrated a fall in bone resorption rate during treatment in the hypercalcemic patients and an increase in the bone resorption rate in the hypocalcemic patient with cancer. The accretion rate and total exchangeable calcium pool did not change significantly in any patient. Urinary hydroxyproline excretion which was measured in three hypercalcemic patients, decreased in all three patients following phosphate therapy. External radioactivity measurements obtained over several bony sites revealed that relative uptake of Ca-47 (expressed as percentage of the retained dose of Ca-47) was the same before and during phosphate therapy. This indicates that the proportion of Ca-47 moving into bone compared to the amount retained in the body at any time is not altered by phosphate as already shown by accretion rate measurements.

Conclusions:

Oral phosphate given to patients with hypercalcemia 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 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 hypercalcemic, normocalcemic, and hypocalcemic patients. We plan to confirm our recent findings on the effect of oral phosphate therapy and to investigate further the effect of phosphate on calcium kinetics in hypercalcemic patients with cancer (with and without bone metastases) and in patients with bone metastases with normal or low levels of serum calcium to determine whether the effect of phosphate is different depending on serum calcium levels.

b) Animal studies

Objectives:

To study the effect of phosphate administration on bone and soft tissue uptake of Ca-47 in the rat.

Materials and Methods:

Groups of rats have been treated at three different dosage levels of phosphate added to their drinking water: (1) 10 mg/day,

TABLE IX
Percent Dose Per Gram of Tissue
Percent Dose Per Gram of Plasma

TISSUE	MEAN $\pm$ S.E. MEAN		LEVEL OF CONFIDENCE	
	No. Experimental	No. Control	T-Test	Rank-Sum Test
Brain	22 .850 $\pm$.058	21 .762 $\pm$.023		
Heart	22 .339 $\pm$.017	22 .304 $\pm$.012		
Large Intestine	22 1.263 $\pm$.134	23 1.062 $\pm$.114		
Small Intestine	21 1.031 $\pm$.078	23 1.057 $\pm$.098		
Kidney	22 .700 $\pm$.038	23 .604 $\pm$.009	99%	99.88%
Liver	22 .402 $\pm$.028	23 .362 $\pm$.015		
Lung	21 .823 $\pm$.067	22 .778 $\pm$.022		
Muscle	22 .708 $\pm$.060	23 .640 $\pm$.012		
Pancreas	22 1.088 $\pm$.076	23 .956 $\pm$.049		
Spleen	22 .402 $\pm$.016	23 .374 $\pm$.013		
Stomach	22 .815 $\pm$.056	23 .691 $\pm$.015	98%	97%
Cortical Bone	22 189 $\pm$ 20	23 200 $\pm$ 20		
Skull	22 141 $\pm$ 18	22 112 $\pm$ 6		
Tibia	22 222 $\pm$ 25	23 196 $\pm$ 13		

(2) 150-190 mg/day, (3) 230-270 mg/day. Rats were raised in the laboratory with careful measurement of food and water intake and body weight. Experiments ran for a period of up to six weeks. Following treatment, phosphate treated and control rats were given tracer amounts of Ca-47 and sacrificed twenty-four hours later. Blood, soft tissues, and bone radioactivity were measured in all animals. Results were expressed as the ratio of percent of administered dose per gram of tissue (wet weight) divided by percent of dose per gram of plasma. The level of significance of difference of tissue uptake between the phosphate-treated and control groups was estimated by use of the "T" test and the non-parametric rank-sum test. In addition, kidneys were examined in some animals for metastatic calcification using von Kossa stain.

Results:

Rats were able to tolerate the first two dosage regiments but a majority of rats failed to survive the higher dose. In animals treated with the lowest dose, no significant difference in the distribution of tracer uptake was observed between the treated and control groups. Results obtained in rats treated with 150-190 mg/day are summarized in Table IX.

Increased uptake of Ca-47 in the kidney and stomach was noted at a high level of confidence. In the rats treated with 230-270 mg of phosphate per day, of those that survived, significantly increased uptake of Ca-47 was demonstrated also in kidney and stomach. In addition, there was histological evidence of calcium deposition in the kidneys of those animals.

Conclusions:

The data obtained from animal studies so far indicate that the action of phosphate to lower extracellular calcium concentrations is probably partly mediated by increased soft tissue uptake of calcium. An enhanced osseous uptake of calcium does not appear to be involved in phosphate action.

References:

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2. Bone Mineralization Studies

Objectives:

To better define the magnitude of the error in the "single-energy" photon absorptiometer mineral content measure of the forearm bones of individuals having a considerable amount of subcutaneous fat.

To accumulate data on calcium contents of known lengths of excised bone to permit a determination of the proportionality factor which relates the photon absorptimetry measurement of the integral values to grams of bone mineral per cm of bone length (1). The integral value is equal to

$$\Delta \sum_{i=1}^n \ln (I_o^*/I)_i$$

where Δ is the distance traveled in a counting interval, I_o^* is the intensity transmitted through tissue equivalent material plus "soft-tissue", I is the intensity transmitted through tissue equivalent material, soft tissue and bone and n equals the number of integral counting intervals in the bone width.

To carry out bone mineral content measurements on the radius and ulna of the arms of osteoporotic patients before and after calcium infusion treatment to see if the treatment results in a measurable change in mineral content of these bones (2).

To continue to accrue data on bone mineral content of the forearm bones of normal individuals and patients with demineralizing bone conditions.

Materials and Methods:

A photon absorptiometric instrument designed and built in our laboratory (1) was used to study the effect of fat on the bone mineral measurement obtained with this technique. The long term reproducibility for measuring the integral value of the midshaft of the radius was determined by taking six forearm measurements, at one week intervals on the same individual. This was done for several individuals. The integral value measurement, which is proportional to bone mineral content, is used in our laboratory for serial studies of normals and patients and has been given the designation of relative bone mineral index (RBMI). Measurements of the integral values for a plastic block phantom which simulates forearm bone structures (3) were carried out with and without various configurations of subcutaneous fat. This was done to obtain a better understanding of the magnitude of the error to expect in using the "single-energy" photon technique for bone mineral content measurements on individuals with considerable forearm adipose tissue.

Differences, caused by the presence of forearm fat, in bone mineral content measurements for different "single-energy" photon absorptiometric instruments presently in use were estimated on the basis of a forearm scan of an obese individual.

Integral values were determined with the SKI absorptiometric instrument on excised human extremity bones. The bones were from patients with osteogenic sarcoma. However, the portion of the bones used in this calibration study showed no evidence of disease. These defatted bones were cut into segments with parallel faces. The lengths of the segments were measured and the calcium and phosphorus contents of the ashed segments were determined. The calcium was determined by an EDTA-titrametric technique (4) with an estimated error of $\pm 2\%$ and the Fiske-Sulbarow (5) technique was used to determine the inorganic phosphate with an estimated error of $\pm 3\%$. The bone ash was done in Vycor crucibles in a muffler oven at 600°C for 48 hours. These measurements, coupled with the assumption that the weight fraction of calcium in bone is 40%, permit a determination of the proportionality constant relating bone mineral content in grams of bone mineral per cm of bone length to the integral value.

Studies of calcium metabolism until recently have been carried out by means of two major methods:

- (1) Metabolic balance which gives the net gain or loss of calcium from the whole body and
- (2) Kinetics of radioactive calcium which is supposed to give the rate of deposition of calcium in the skeleton as well as the size of the miscible calcium pool.

In combination, both methods yield also a rate of removal of calcium from the body, presumably from the skeleton. Bone-seeking radionuclides have also yielded information about their local deposition by external measurement, as well as rates of removal from parts of the skeleton, reflecting the kinetics of bone mineral.

A considerable amount of variation exists, however, among normal individuals based essentially on sex, age, size of the skeleton, and to some extent on normal differences in calcium metabolism based on diet, activity, and hormonal differences. Since the weight of the skeleton seems to be proportional to the lean body weight, expressing the calcium kinetic data as a function of estimated lean body weight lessens the variability of results among normal individuals of the same anatomical grouping.

However, when one is concerned with patients affected by

diseases causing a generalized increase or decrease in skeletal mineralization and density, such as osteoporosis, hyperparathyroidism, generalized Paget's disease, or wide-spread metastases to bones, the relationship between the skeletal weight and lean body weight is disrupted. The interpretation of results in comparison with normal values then becomes invalid.

For example, we studied an osteoporotic patient with extreme demineralization of the skeleton. His weight was stable over a period of several years. The accretion rate of calcium based on ^{47}Ca kinetics was 0.26 gm/24 hrs. His skeleton on radiographs looked at best 25% mineralized. It is then estimated that the accretion rate per unit weight of bone mineral would have been 4 times the calculated value. We have had until now, of course, no way of expressing calcium kinetics as a function of weight of bone or bone mineral. The latter would be the most valuable.

Results:

The long term precision in measuring the RBMI of the mid-shaft of the radius of several individuals had a percent standard deviation of 2%. Experimental work with scans of obese individuals, as well as with different fat configurations placed over a bone phantom standard, shows that considerable error in the bone mineral content measurement of human arms of obese individuals is possible with a "single-energy" photon absorptiometric bone mineral analyzer and that different analyzers can give considerably different results on the same individual. This variation is dependent primarily on the manner in which the transmission data are used to compute the I_0^* value required in determining the

$$\Delta \sum_{i=1}^n \ln (I_0^*/I)_i$$
, where Δ is the distance travelled in a counting interval, I_0^* is the intensity transmitted through tissue equivalent material and soft-tissue, I is the intensity transmitted through tissue equivalent material, soft-tissue and bone, and n equals the number of integral counting intervals in the bone width. To a lesser extent it is also dependent on the manner in which the arm is maintained in the tissue equivalent material. The measurement of the integral value approaches proportionality to an absolute bone mineral content determination as the fat component of the arm approaches zero. This is ignoring the second order effect of variation in collagen content.

Based on the profile of transmitted intensity for the forearm bones obtained from an obese individual, it can be shown that the RBMI, and hence the bone mineral content determination, for this individual could differ as much as 15% for different photon absorptiometry instruments now being employed in different laboratories.

A linear least squares fit for all of our data on excised bone gives the equation $Y = 0.0332X + 0.265$ where X is the integral value and Y is the mass of bone per cm of bone length determined from the measured mass of calcium in the bone segment and the measured segment length. The data was for eighteen separate bone segments from four different males ranging in age from 14 to 21 years. The equation found by Witt, Mazess and Cameron (3) by determination of the dry ash bone mass of 85 radius and ulna bones was $Y = .0377X + .0747$. In comparing the bone mineral content determinations obtained using the two different linear regression equations, our results give a determination of grams of bone mineral per cm of bone length which ranges from 19% higher for radius bones with small integral values (ca. 15 mm) to 5% for large values (ca 30 mm). For the present time, the data on patients is being analyzed by comparing the integral value to the normal ones available in the larger series of Cameron (6). Various methods of reporting the data are under evaluation. In three cases a combination of metabolic balance of calcium, Ca-47 kinetics and RBMI were carried out simultaneously.

Patient L.U. had osteomalacia secondary to previous subtotal gastrectomy. Patient M.B. had osteoporosis due to a combination of pelvic exenteration, wet colostomy with reimplantation of the ureters into the large intestine and causing chronic hyperchloremic acidosis. Her primary disease had been carcinoma of the cervix. Patient M.A. had breast cancer with extensive osteoblastic metastases, had undergone bilateral oophorectomy and developed severe prolonged hypocalcemia.

The preliminary data indicate the following:

Patient L.U.:

(1) Accretion rate of calcium	0.92 gm/24 hrs. (average normal 0.40 gm)
(2) RBMI	7.8
(3) Normal RBMI premenopausal (Cameron)	23.0
(4) Mineralization ratio: $\frac{\text{RBMI patient}}{\text{RBMI normal}}$	$\frac{7.8}{23.0} = 0.34$
(5) Accretion rate relative to state of mineralization	$\frac{0.92}{0.34} = 2.7 \text{ gm/24 hrs/unit mineralization ratio}$

Formulation: This patient with a severely hypomineralized skeleton has an accretion rate (1) which is about twice the normal average value. When corrected for the fact that her RBMI is one-third of normal the accretion rate per unit mineralization ratio is seven times normal.

Patient M.B.:

(1) Accretion rate	0.26 gm/24 hrs. (average normal 0.40 gm/day)
(2) RBMI	9.5
(3) Normal (premenopausal) RBMI (Cameron)	23.0
(4) Mineralization ratio	$\frac{9.5}{23.0} = 0.41$
(5) Accretion relative to mineralization state	$\frac{0.26}{0.41} = 0.63$ gm/24 hrs/unit mineralization ratio

Formulation: This patient with hypomineralized bone has an accretion rate of calcium which is about two-thirds of the average normal. When corrected for state of mineralization the accretion rate is found to be within normal range.

Patient M.A.:

(1) Accretion rate	2.7 gm/24 hrs (average normal 0.40 gm/day)
(2) RBMI	16.7
(3) Normal premenopausal RBMI (Cameron)	23.0
(4) Mineralization ratio	$\frac{16.7}{23.0} = 0.73$

Formulation: Patient with osteoblastic metastases causing very rapid deposition of calcium in those diseased portions of the skeleton to the point of causing space hypocalcemia, has an accretion rate approximately seven times the average normal value. The uninvolved parts of her bones are hypomineralized while the diseased parts are overmineralized.

The data cannot be interpreted in the same manner as the two previous cases because different phenomena are operative simultaneously. It may be that calcium is mobilized from normal bone and deposited in the osteoblastic lesions. Serial RBMI measurements during the course of disease would help in evaluating this possibility.

An osteoporotic patient was given calcium gluconate in 12 approximately equally spaced intravenous infusions over a period of three weeks from 11/17/70 to 12/4/71. The total infusion resulted in a dose of 15 mg calcium/kg body weight. Scans of the forearm bones were carried out on 10/27/70, 12/10/70 and 12/18/70. There was no significant difference found in the integral values of the radius or ulna bones for the three scans. Studies of ^{47}Ca

uptake for this same individual showed no appreciable increase in calcium accretion rate as a result of the treatment. Metabolic studies showed that the patient remained in calcium balance.

To date RBMI determinations were obtained on eighty-six normal individuals and fifty-two patients. The latter include the following diagnosis: postmenopausal and senile osteoporosis, hyperparathyroidism, pseudohyperparathyroidism associated with malignancy, osteomalacia, metastatic breast cancer with normal serum calcium, metastatic breast cancer with hypocalcemia, and osteolytic bone lesions of undetermined etiology.

Determinations of normal integral values and the distribution of those values among the various age groups and according to sex is being undertaken but is too small at present to permit the establishment of significant values for each group. The recruiting of volunteers among the hospital staff and in the medical school is underway.

Conclusions:

Considerable variation in the bone mineral content measurement of human arms is possible with a "single-energy" photon absorptiometric bone mineral analyzer. This variation is dependent primarily on the manner in which the transmission data are used to compute the integral value and to a lesser extent on the manner in which the arm is maintained in a tissue equivalent material. Since this is the case, it would seem incorrect to consider the calculated measure reported by a user of this technique to be an absolute determination, or even directly proportional to an absolute determination, of bone mineral content in terms of grams of bone mineral per cm of bone length or grams of bone mineral per cm² for the bones of the forearm. The measurement of the integral value approaches proportionality to an absolute bone mineral content determination as the fat component of the arm approaches zero. (This is ignoring the second order effect of variation in collagen content.) This being true, it would seem advisable that the measurements on forearm scans not be reported in absolute terms of grams of bone mineral per cm bone length or grams of bone mineral per cm². It would be more meaningful for inter-laboratory comparisons of data if the results were reported as some relative measurement, such as the RBMI, with the method employed to obtain this integral value explicitly and carefully defined.

The technique does give a precise relative bone mineral content measurement for forearm bones for all individuals regardless of degree of obesity. We have found the long term precision of the RBMI on repeated scans of the same individual's forearm bones to be about 2% in terms of percent standard deviation. Therefore, the method of photon absorptiometry is a very useful tool for the serial studies of bone mineral content of the forearm bones provided there is no drastic change in the subcutaneous fat content in the course of the study.

Our linear regression equation is based upon a relatively small sampling of bones, 18 bone segments from 4 males ranging in age from 14 to 21, and therefore the comparison with the equation reported by Cameron's laboratory will probably change as we obtain more data. The possibility that the difference in the regression equations lies in the methods by which the bone mineral content per cm of bone length was obtained in Cameron's laboratory and in ours should be studied.

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3. Preliminary Neutron Activation Measurements

Objectives:

The original objective of this project, as stated in the Proposal for 1971, was to determine the total body calcium in the living human subject by means of neutron activation of the naturally occurring isotope ^{48}Ca to the short-lived radioactive isotope ^{49}Ca . As explained more fully in the Proposal for 1972, it was decided for various reasons to shift the objective to a study of the ^{49}Ca , ^{24}Na and ^{38}Cl produced by neutron activation in limited volumes of the lower limb bones in-vivo. The technical developments necessary for this study are in progress.

2

Materials and Methods:

The 30-inch cyclotron at the Sloan-Kettering Institute has been used as the neutron generator. Neutrons can be produced by various reactions using beryllium as target material bombarded by He-3 ions, deuterons and protons. The quantitative distributions of neutron flux over an area of 2 x 2 m at 3 m from the source was measured. The result showed that the distribution is uneven with the present neutron target: the flux density at the edge of this area is only about 50% of that at the center. However, the central portion of the neutron beam with cross section of 25 cm x 25 cm was found quite uniform, thus is sufficient for the study of localized irradiation.

Preliminary study of the characteristics of detecting the 3.1 MeV peak of ^{49}Ca by existing scintillation counter systems has also carried out. One system had a 2" x 2" NaI crystal, the other a 4" x 3" crystal. The first was found fair in resolution but very inefficient as expected from its small active volume. The latter was fair in efficiency but very poor in resolution. In order to study the relative yield of ^{49}Ca when irradiated with various geometrical arrangements and with different neutron sources, a Ge(Li) detector has been used.

The dependence of yield of the activated ^{49}Ca on the spectral distribution of the neutron source has also been studied. Neutron beams were produced by He-3 ions, deuterons and protons bombarding a beryllium target. It was found that neutron beams generated by Be-9 (p,n) reaction provided the highest yield of Ca-49. The yield using the Be-9(d,n) reaction was about 80% of that with Be-9 (p,n) and was only one-tenth as great as the yield obtained if Be-9(He-3,n) reaction was used.

Results and Conclusions:

Preliminary study has shown that neutron beams generated by Be-9(p,n) and Be-9(d,n) reactions are appropriate for thermal neutron activation analysis. Detailed information on the dependence of the yield of neutron capture on various geometries and moderation arrangements will be obtained.

In order to control the neutron dose delivered to the subject, accurate and reliable measurements of neutron flux must be secured. At present the relative neutron doses are monitored by the total charge deposited onto the neutron producing target. This is by no means adequate. It is necessary to add several neutron dose monitoring devices, such as a thorium-fission counter, neutron induced ionization chamber, proton recoil scintillation detector, activation foils, etc.

4. Radioisotope Studies of Parathyroid Localization

Objectives:

To develop and evaluate radioisotope localization techniques for hyperfunctioning parathyroid tissue in man.

Materials and Methods:

The currently employed procedure for parathyroid scanning is as follows. Patients are given triiodothyronine 75 μ g/day (25 μ g t i d.) for a minimum of five days prior to scanning to suppress the thyroid uptake. The patient is placed in the supine position with the neck hyperextended and the head is held in place with a sandbag. Cobalt-57 markers are placed in the midline at the angle of Louis, sternal notch, and thyroid cartilage, and using these markers the patients are centered appropriately in the gamma camera field. Three hundred μ Ci of Se-75-selenomethionine are injected intravenously. Beginning five minutes after injection, four-thirty minute scans of the neck and superior mediastinum are obtained sequentially. Each scan is recorded as a photoscan on x-ray film and polaroid film. In addition, digital information is stored on magnetic tape. At the beginning of the final Se-75 scan, 2 μ Ci of Tc-99m pertechnetate are injected intravenously. Following the final parathyroid scan, the technetium photo peak is scanned for thyroid imaging. Photoscans are examined individually and by superimposition of x-ray films for focal persistent areas of Se-75 uptake. Digital information, corrected for nonuniformity of the gamma camera, is analyzed by both decade analysis and two standard deviation levels. Areas of persistent focal activity are noted.

Results:

A total of fifty-seven patients have been scanned to date, eleven patients in the past year. In thirty-six of these we have complete surgical information. Of these thirty-six patients localization with a single dominant focal area was achieved in twenty-two or sixty-one percent. An additional six patients (sixteen percent) had two focal areas; one of which localized the tumor. Eight scans were negative (twenty-two percent); three of these eight had negative explorations and four were found to have adenomas not seen on the scan (false negatives). False positives numbering seven were found including the six mentioned above. One interesting false positive finding was in a patient with metastatic breast carcinoma in whom a persistent focus of Se-75-methionine was localized in a metastatically involved lymph node. In only five of twenty-two studies was the tumor identified by photoscan. This represents one-fourth of those identified by digital analysis. One patient in the series had four gland hyperplasia correctly identified and

localized preoperatively. This patient had a history of chronic renal disease. Another patient had recurrent parathyroid carcinoma which was localized preoperatively in the superior mediastinum. Two patients that had previous negative explorations were correctly localized by this procedure. One patient had a recurrent parathyroid adenoma located deep in the scar tissue of previous surgery ten years earlier. Severity of hyperparathyroidism, as judged by the degree of elevation of serum calcium, failed to correlate with preoperative localization. In addition, at surgery, the tumor was weighed and/or measured accurately in most patients. The weight or volume of the tumor failed to correlate with preoperative localization. Localized adenomas range in weight from 160 mg to 8.1 grams. Seven of twelve tumors accurately weighed and preoperatively localized weighed less than 1 gram.

A total of twelve patients were studied by obtaining multiple tissue samples at times of surgery or subsequent post mortem and at times up to one year following injection. In addition, six patients were followed to a maximum of two years by total body retention measurements. Studies indicated that total body retention measurements correlated well with measurements obtained by excretion analysis. A wide variety of tissues were sampled in these patients. Collaborative work with others using this basic data has provided the basis for calculating various bioradiological parameters. Calculation of biological half-life indicates that the isotope follows at least a three exponential fall off. Approximately thirteen percent has a biological half-life of 0.55 days, forty-four percent - 46.0 days, and forty-two percent - 220.0 days. Fifty percent of the injected Se-75 is excreted by seventy days. Taking physical decay into consideration, the administered activity retained in the body is reduced to fifty percent at forty-seven days. These total body and tissue measurements have permitted estimated dose calculations. The organ receiving the largest dose is the liver; 300 μ Ci giving approximately 8.4 rads plus or minus fifty percent. Whole body radiation is calculated to be 2.4 rads plus or minus fifty percent.

Conclusions:

Continued development of Se-75-selenomethionine parathyroid scanning has resulted in a clinically useful procedure in the preoperative management of patients with hyperparathyroidism. These studies have been concluded and the procedure reported above is now available as a routine scanning procedure at this institution. Tissue and total body studies have permitted calculations of radiation doses delivered by this procedure.

5. 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.

To study the metabolism of sulfur in these tumors.

Materials and Methods:

Patients were chosen who had histologically proven diagnoses of chondrosarcoma or chordoma and in whom the tumors could not be completely removed surgically because of local extent or distant metastases. 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 weight of S-35 sodium sulfate in neutral physiological saline solution 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 mCi/kg body weight. The treatment was repeated at intervals of weeks or months as indicated by the clinical and hematological status. All excreta were collected and health physics precautions were continued until the likelihood of contamination had fallen to negligible levels.

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:

The clinical results are summarized in Table X. The first dose in each case was a test dose; other doses, if any, were therapeutic ones. A marked objective remission was obtained in patient (Pt.) #1. The superficial tumor decreased in size and biopsies at 2 and 6 months after the first dose showed varying degrees of tumor necrosis. In Pt. #2 the tumor appears to be under control but is so deep-seated as to be difficult to evaluate. In one child with chondrosarcoma (Pt. #5) there was definite although temporary control, but in another (Pt. #7) no benefit at all was seen. Patients #3 and #4, to whom S-35 was given prophylactically after what was thought to be incomplete surgical removal of chordoma, have not shown evidence of recurrence, but a longer time is needed for evaluation of effect on this slow-growing tumor. Patient #8 illustrates the importance of attention to diagnosis. On re-biopsy

after a test dose of S-35 the tumor, which was originally reported to be a chondrosarcoma, was found to be a mixed type of osteogenic sarcoma which showed little S-35 uptake and so was not suitable for therapy. The remainder of the patients have been treated too recently for evaluation. All of the patients who received therapy doses showed some degree of bone marrow depression. This was not sufficiently severe to cause complications or require specific treatment, but did limit the frequency of S-35 administration.

The demonstration of a high selective uptake of S-35 sulfate in chordoma tissue is a new finding.

The number of specimens of tumor tissue and bone marrow which have been obtained is now sufficient to permit a tentative estimate of the biological half-times (H.T.) of S-35 in these tissues. At one day post injection the concentration in both tumor and bone marrow is 5 to 6 times the mean concentration of retained dose in the body as a whole. From this initial high, the concentration in the marrow decreased with several H.T.'s of which the first is about 0.5 day and comprises 95% of the total, and the second is about 6 days. A single H.T. of about 30 days was seen in the tumor.

After therapy doses it was possible to localize superficial tumors by external counting of bremsstrahlung. Serial external point counts showed that the S-35 was retained better in the tumors than in symmetrical normal areas.

A finding of minor interest was that radioautography of plucked hairs showed that the hair bulb was heavily labeled 6 days after S-35 injection. The rate of growth of the hair could be determined by measurement of the locations of as many as 3 successive hot spots.

Conclusions:

Sulfur-35 sodium sulfate will cause at least temporary control or remission in some cases of inoperable chondrosarcoma without causing significant morbidity. The method deserves further study to determine what percentage of patients will respond favorably and how long control can be maintained.

Studies of the patients during therapy can be expected to lead to an improved understanding of the metabolism of cartilage tumors and of inorganic sulfate.

TABLE X

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Summary - Patients Receiving S-35 Sulfate

Patients	Sex Age	Diagnosis	Cumulative S-35		# doses	Clinical
			mCi	mCi/Kg		
C.K. #1	F 54	Chondrosarcoma sacrum	1093	23.42	5 doses 48 wks	Regression visible tumor, microscopic evidence cell necrosis
W.M. #2	M 49	Chondrosarcoma R ilium	2546	29.50	6 doses 37 wks	No radio graphic evidence of progression
F.D. #3	M 50	Chordoma sacrum	1196	10.19	3 doses 37 wks	Prophylaxis after surgery
H.S. #4	M 70	Chordoma sacrum	778	10.23	3 doses 35 wks	Prophylaxis after surgery
J.A. #5	M 13	Chondrosarcoma L ilium	768	22.25	5 doses 27 wks	Temporary control tumor growth after each treatment
R.T. #6	M 22	Chondrosarcoma L 1-4 ribs	559	10.18	3 doses 17 wks	No definite effect to date
D.O. #7	M 13	Chondrosarcoma R ilium	388	10.40	3 doses 7 wks	Died without remission 14 weeks after first therapy
L.B. #8	F 39	Osteogenic sarcoma L ilium	13	0.20	Test only	Not treated because not pure cartilage tumor
C.F. #9	F 72	Chondrosarcoma L ischium	718	10.24	3 doses 9 wks	Time Q.N.S. for evaluation
S.H. #10	M 55	Chondrosarcoma sternum	11	0.15	Test only	Test dose only
M.D. #11	F 72	Chordoma sacrum	10	0.14	Test only	Test dose only

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

Objectives:

To compare the sensitivity for the detection of the titanium K_{α} line, by means of an X-ray crystal spectrometer, produced by a beam of cyclotron-accelerated alpha particles (15 MeV) to that obtained with a beam of accelerated electrons (25 keV). An estimate of the relative sensitivities to be expected with electron and alpha particle excitation for the detection of the elements of interest in our studies K, P, S and Mg, will be made from this comparison.

To carry out the sensitivity comparison, it was necessary to confine the alpha-particle beam to within a 1/4" diameter circle centered on the target disk. As previously reported (Progress Report 1970), the collimated beam with the originally constructed specimen chamber did not allow for adequate definition of the α -particle beam. Therefore, modification of the chamber was undertaken to permit adequate beam definition.

Materials and Methods:

A vacuum curved crystal spectrometer (MAC Model 400), previously reported (see Progress Report #3, 1970) to have a resolution capability of 0.1 percent full width at half maximum, which is sufficient to detect line shape changes in the K_{β} band spectra of sulfur, was coupled to a vacuum specimen chamber at the exit port of the Sloan-Kettering Institute cyclotron. A bellows was introduced between the flange at the beam transport exit port and the specimen chamber. This permitted angular adjustment of the chamber to align the axis of the chamber collimators parallel to the α -particle beam.

A target consisting of a 1/4" diameter pellet of "pure" titanium embedded in the center of a disc of copper was used as the sample. The X-ray spectrometer was initially aligned and focused by using the MnK_{α} line emitted by a 1/4" diameter 10 mCi Fe-55 source placed in the identical position as the 1/4" titanium sample. Scans of the TiK_{α} lines were taken with an α -particle beam current of about 3×10^{-9} amps. The target current was measured by means of an electrometer placed between the target and ground. Radioautography of the irradiated target disc was used to determine the position of the impinging α -particle beam.

Results:

The TiK_{α} line, produced in a pure titanium sample by a 3×10^{-9} amp beam of accelerated α -particle (15 MeV), yielded

3.7×10^5 counts/sec/ μ A with a line to background ratio of 32/1 based on the background taken with a copper target. A radioautographic study of the target disc following α -particle bombardment showed the beam to be well within a $\frac{1}{4}$ " diameter circle centered on the disk. This compares with an estimated line intensity of 90,000 counts/sec/ μ A with a line to background ratio of 820/1 for excitation with 25 keV electrons.

Conclusions:

The sensitivity as measured in (line)²/background, for the detection of TiK_{α} radiation produced by 15 MeV α -particles in an infinitely thick titanium target was found to be considerably less than that obtained for excitation with 25 keV electrons. However, the line intensity corrected for self-absorption, obtained with 15 MeV α -particle excitation indicates that a considerable improvement of sensitivity is potentially available over electron excitation if a large fraction of the spectrometer background originating outside the target can be eliminated.

Methods to diminish extraneous background include (a) focusing the α -particle beam to a small spot on the target, which would eliminate the background radiation produced in stopping the α -particles in the collimator material, and (b) the use of coincidence shielding surrounding the detector.

To optimize the line to background ratio for the α -production of characteristic K-radiation of the lighter elements requires going to relatively thin samples, i.e., about 5 μ for a titanium target with 15 MeV α -particles.

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