JOURNAL OF NUCLEAR MEDICINE 6:506-518, 1965

The Distribution, Metabolic Fate and Radiation Dosimetry of ^{131}I Labeled Macroaggregated Albumin

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Lung scanning employing macroaggregated albumin labeled with radioiodine (MAA ^{131}I) is currently being evaluated as a procedure to aid in diagnosing embolism and other pulmonary disease (1-6). The historical development, rationale of use, and clinical evaluation of this material have recently been reviewed by several authors (5,6). Detailed data on body distribution and metabolic fate of MAA ^{131}I are limited to some preliminary studies in dog and man (1,5,6). These studies suggest that large aggregates trapped in the lungs disappear from that organ exponentially with a half-time of 4 to 10 hours in man (5,6). Following degradation of the smaller particles by the liver and other reticuloendothelial (RE) organs, 50 to 75 percent of the radioactivity appears in the urine in 24 to 48 hours, indicating that the whole body disappearance of radioactivity is rapid (5).

To determine the amount of radiation delivered to the lungs and whole body during lung scanning, it is necessary to delineate further the kinetics of body disposal of the ^{131}I labeled macroaggregated albumin.

MATERIAL AND METHODS

Subjects of study were 12 mongrel dogs and 10 patients. The latter were of both sexes, over 50 years of age, and were hospitalized during the study period for a variety of illnesses. Lugol's solution was administered to the patients in doses of 10 drops twice a day for the duration of the study to block accumulation of radioiodide by the thyroid gland. Iodide was not administered to the dogs.

MAA ^{131}I employed in these studies was supplied by E. R. Squibb & Sons.[2] The material was refrigerated and used undiluted except in selected dog studies. Prior to each experiment the material was shaken by hand to assure dispersion of the aggregates. The MAA ^{131}I, suspended in human and dog sera, was evaluated by zone paper electrophoresis in barbital buffer (pH 8.6) followed by radioautography of the paper strip. To determine the amount of ^{131}I not bound

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[2]MAA ^{131}I was supplied by E. R. Squibb as Albumintope L.S. for investigational purposes on a biweekly basis. The material had a specific activity of 800 to 1200 $\mu C/cc$ and contained 1 mg of protein per cc.

to protein, each lot was tested before use by adding a sample to pooled human serum and precipitating with trichloroacetic acid (TCA). Particle size of the MAA ^{131}I was ascertained by chamber counting, and the amount of protein that was denatured defined by settling and precipitation; the latter two determinations performed by the manufacturer.

Whole body and lung scans were started within five minutes after intravenous injection of MAA ^{131}I. Serial scans were performed in some of the animal and human studies as noted below. The scanner was equipped with a 5-inch sodium iodide crystal and 61 hole collimator. Total activity in some dogs was measured serially at a distance of 18 inches from the 5-inch crystal, with suitable collimation and standards.

Blood and urine samples were counted in a scintillation well counter against appropriate standards to a statistical accuracy of 95 percent or better. Multiple serial determinations of total serum and TCA precipitable radioactivity were performed in some of the dog and in all of the human studies.

Serial static measurements of radioactivity at contact over marked points on the upper thorax bilaterally and over the liver, spleen, and heart areas were carried out in all human studies using a 2 x 2-inch sodium iodide crystal with a flat-field collimator. In some of the dogs, whole body counting was performed antemortem and each organ was counted after the animal was sacrificed.

In one animal, a catheter was placed in the pulmonary artery. Multiple determinations of total serum and protein-bound radioactivity were obtained simultaneously from the femoral and pulmonary arteries to determine the initial clearance of MAA ^{131}I through the lungs following femoral vein injection. Lung scans and pulmonary arteriogram were subsequently performed.

A dose range of 150 to 300 μC of MAA ^{131}I was employed in all but four dogs, who received doses of 25 to 30 μC to provide a lower range of radioactivity suitable for whole body counting. These studies at low doses were performed in paired animals, one of which received 150 to 300 μC to assure that the lot of MAA ^{131}I would provide good lung scans. All patients received 215 to 310 μC.

The data on the biological disappearance of MAA ^{131}I from the blood and lungs were analyzed by plotting the daily radioactivity on semi-log paper, curve peeling, and graphic derivation of the earlier components. Data on urinary excretion of radioactivity were analyzed by drawing tangents to the cumulative curve and plotting the resultant slopes as an exponential curve.

RESULTS

Characteristics of MAA ^{131}I. Ninety to 95 percent of the radioactivity of each lot of MAA ^{131}I was TCA precipitable when added to sera during the period of study. On zone electrophoresis with radioautography, most of the radioactive material remained at the origin as denatured protein but a small amount could be detected with other serum proteins and albumin. Seventy-five to 82 percent of the protein was coagulated. When the material used for human studies was diluted 10 times, the particles ranged in size from 10 to 75 microns, 70 to 85 percent being 25 to 30 microns. Satisfactory lung scans were obtained with all

lots of MAA ^{131}I for as long as 10 days after receipt. Material was not used after 10 days storage.

Dog studies. Lung scans five minutes after injection of 150 to 300 μC of MAA ^{131}I showed pulmonary localization of most of the radioactivity. Scans of the lungs and whole body starting as late as one hour after injection indicated that radioactivity was greatly decreased in the lungs, and so imperceptable in liver and spleen that satisfactory scans could not be produced. Twenty-four hours

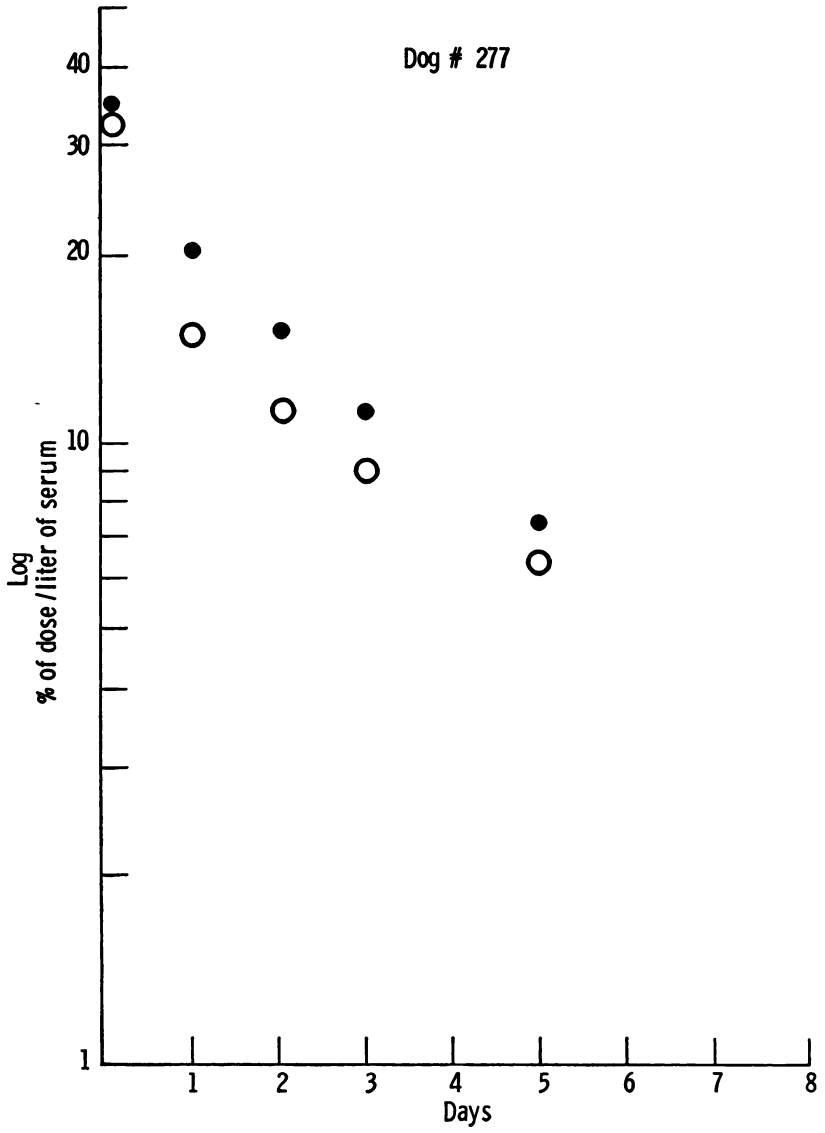

Fig. 1. The biological disappearance of radioactivity from the serum of a dog following injection of 25 μC of MAA ^{131}I. The black dots are the total serum radioactivity and the open circles the protein-bound radioactivity.

after injection, scans of lungs, liver and spleen were unsatisfactory both *in vivo* and when the organs were isolated and scanned directly.

Disappearance of both serum and protein-bound radioactivity from the blood was multi-exponential in all of the dogs followed 7-10 days. In the dogs given 25 μC, whole body radioactivity was measured and also disappeared in a multi-exponential fashion. For the second or slower component, the average biological half-time of whole body disappearance was 2.5 days, and of total

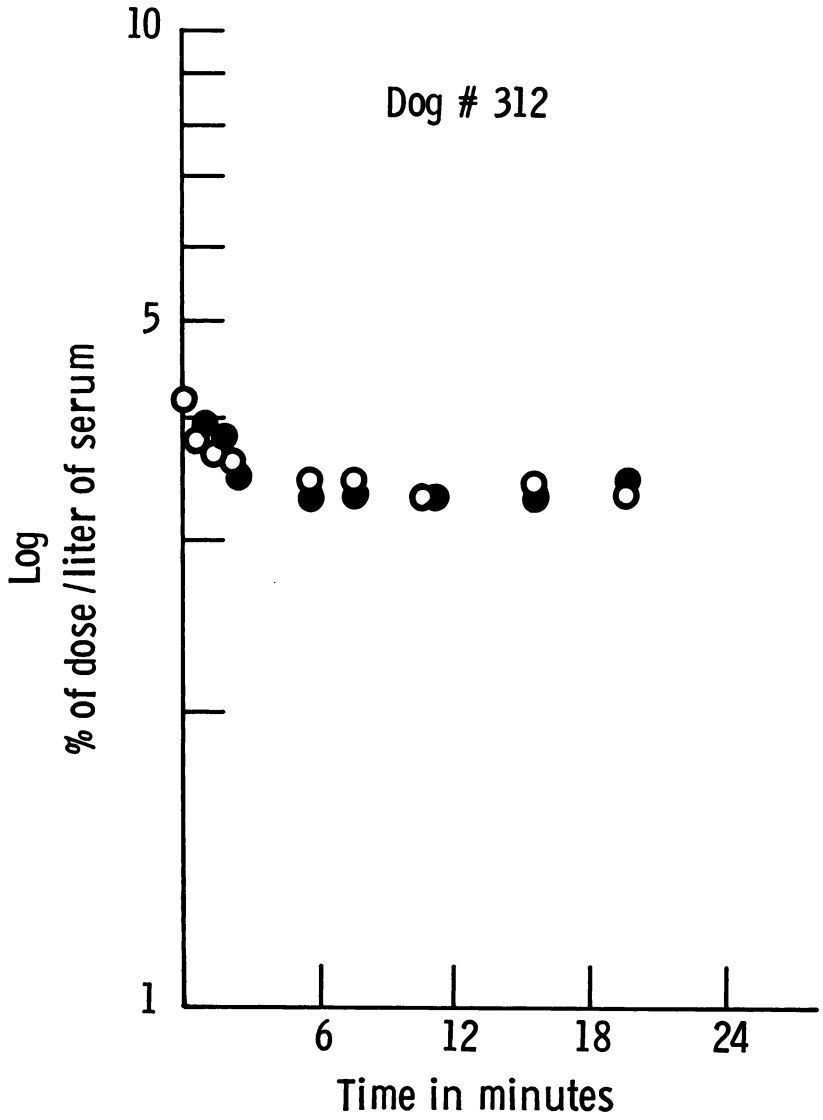

Fig. 2. Radioactivity in the serum of the pulmonary artery (black dots) and femoral artery (open circles) of the dog immediately after the injection of 125 μC of MAA ^{131}I (see text).

serum activity, 2.6 days. The protein-bound activity disappeared more slowly, with a half-time of 3.0 days. Figure 1 illustrates the blood data from one animal. The difference in disappearance rates of total serum and of protein-bound activity has been previously noted.[1]

Total serum and protein-bound activity was determined five minutes after injection of MAA ^{131}I in eight dogs. At this time blood radioactivity resided almost entirely in the protein-bound fraction, as established by counting red cells, serum, plasma, and the TCA precipitable fractions.

In the single study where radioactivity in the pulmonary and femoral arteries was determined, there was no significant difference (Fig. 2).

Distribution of the radioactivity in the dogs was determined by tissue and whole organ counting. Samples of lungs, liver, spleen, and blood were counted two hours after injection. There was a wide range in the ratio of counts per wet weight of multiple aliquots obtained from the same organ.[2] This was especially true of the lung. Furthermore, when calculated whole organ counts based upon counts of aliquots were totaled, the sum of lungs, liver, spleen and blood accounted for only about 42 percent of the whole animal radioactivity. To account for the total retained radioactivity, it was necessary to count not only whole organs, but also the eviscerated carcass. Studies at 24, 72, and 120 hours after injection of MAA ^{131}I suggested that the radioactivity was distributed more or less uniformly throughout viscera and carcass (whole body). For example, at 24 hours, lungs, liver, spleen, heart, thyroid, bowel, bladder, blood, and kidneys contained less than half of the radioactivity found in the whole animal. The majority of the radioactivity was in the eviscerated carcass. The ratio of counts per minute to wet weight was constant in all organs as well as the carcass. (See discussion following).

Human Studies. Satisfactory lung scans were obtained in all subjects immediately after injection of MAA ^{131}I in doses of 215 to 310 μC. Definition of liver and spleen by serial scanning at two hours and at 24 hours was poor.

Disappearance of radioactivity from the lung was multi-exponential (Fig. 3). In nine patients studied for at least seven days, the mean biological half-time of the rapid initial component was 0.25 days, and of the second component, 3.2 days. Table I shows the individual data for lung disappearance of radioactivity in man.

Total serum and protein-bound activity also disappeared in a multi-exponential fashion (Fig. 4). Values for both serum and protein-bound activity were virtually identical in man. The mean biological half-time of the rapid initial blood component was 0.44 days, and of the second component, 4.0 days. The individual data are shown in Table II. In three of the human subjects a third component appeared at about the 6th to 8th day. Although this component was

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[1]Studies in dogs in this Laboratory have indicated that following injection of some ^{131}I labeled compounds, there is a discrepancy between total serum and protein-bound radioactivity. Iodide is not excreted as rapidly as in man, and there is a difference in both character and rate of disappearance of serum and protein-bound activity. (Data to be published)

[2]For example, six different aliquots of lung from the same animal had a range of 12,379 to 68,382 counts per minute per gram of wet weight (mean 48,434 $\pm$ 28,610).

not as accurately characterized, the half-time may well be over 15 days. This observation is being further investigated (see discussion following).

Urinary excretion of radioactivity was measured in all patients. TCA precipitation and chromatography of the urine indicated that about 95 percent of

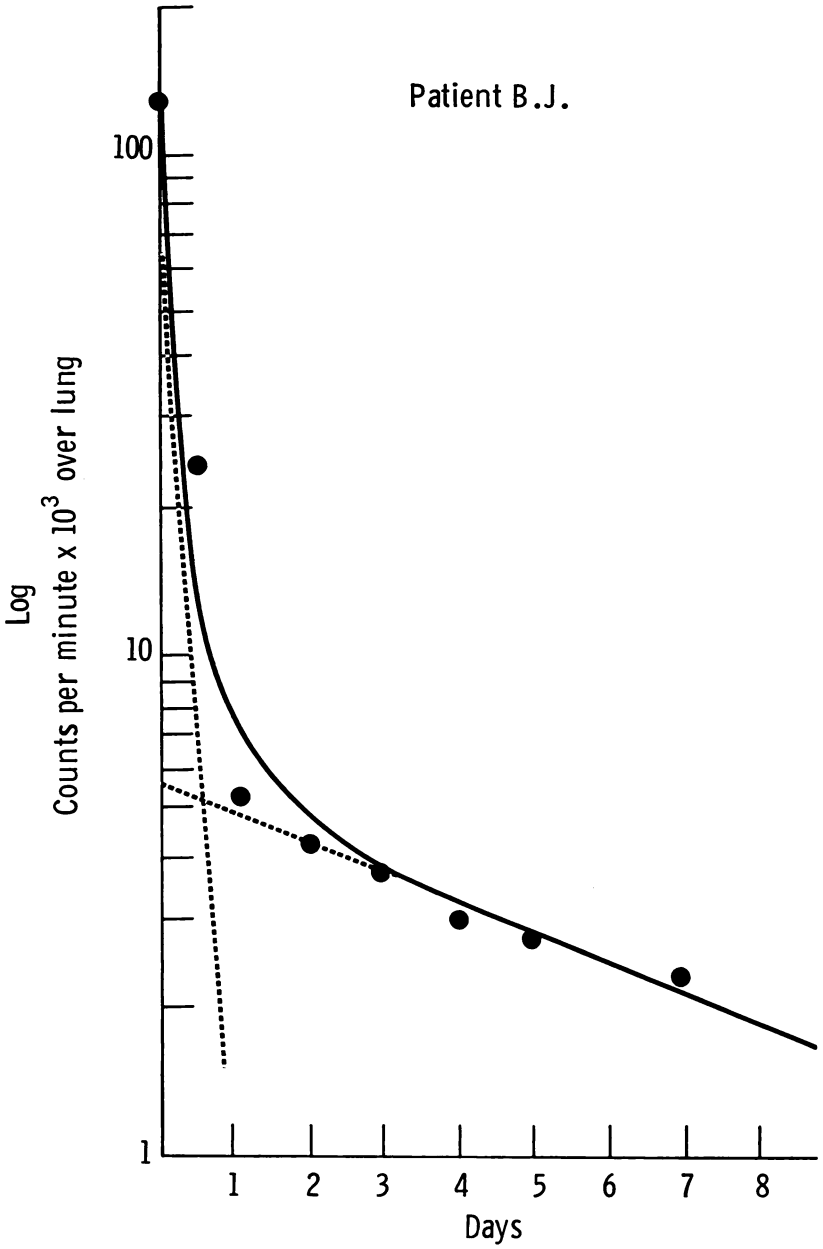

Fig. 3. Disappearance of radioactivity from the lung in a patient as determined by contact counting. The black dots are the actual counts per minute corrected for physical decay. The lines are the fitted curves (see text).

the radioactivity was iodide. The cumulative excretion of the iodide was multi-exponential, with a rapid initial component having a slope similar to the initial rates of lung and blood disappearance. An average of 61 percent ± 11.5 percent of the dose was excreted in the first 48 hours. By seven days a total of 72 percent ± 9.2 percent had been accounted for in the urine. There was no significant fecal excretion of radioactivity in two patients studied for 72 hours.

The concentration of the protein-bound radioactivity in the plasma at five minutes is tabulated in Table III (column 3). These data were used to determine the quantitative distribution of the radioactivity for dosimetry calculations. From the quantitative data so obtained and the data on disappearance of radioactivity

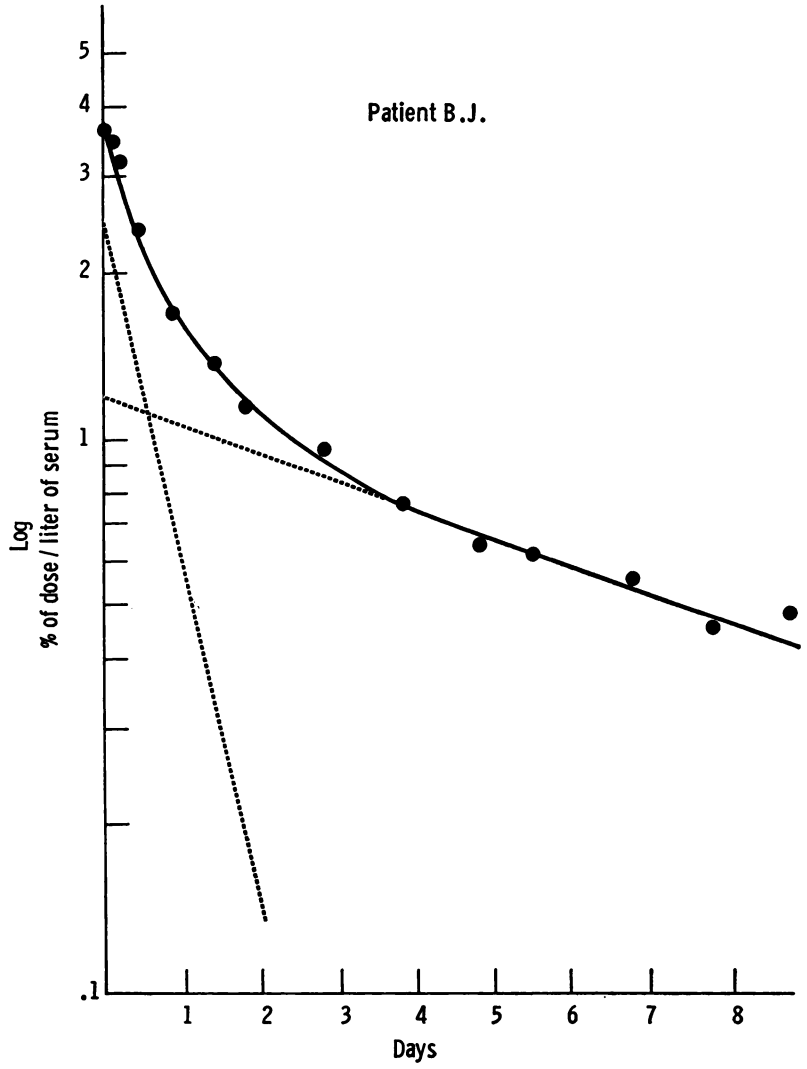

Fig. 4. The biological disappearance of radioactivity from the serum of a patient. The black dots are the values obtained for the protein-bound radioactivity. The lines are the fitted curves (see text).

TABLE I

DISAPPEARANCE OF RADIOACTIVITY FROM THE LUNG IN MAN FOLLOWING INJECTION OF MAA ^{131}I

	First Component		*Second Component*	
Patient	*T½+ (days)*	*"y" intercept* (cpm × 10³)*	*T½+ (days)*	*"y" intercept* (cpm × 10³)*
1	0.30	89.0	1.8	11.0
2	0.21	84.0	2.5	16.0
3	0.21	91.5	2.6	8.5
4	0.12	85.0	3.0	15.0
5	0.21	82.0	2.5	18.0
6	0.21	90.0	2.0	10.0
7	0.21	91.0	4.6	9.0
8	0.21	95.0	5.0	5.0
9	0.58	82.0	5.2	18.0
mean	0.25 ± 0.04	88.0	3.2 ± 1.3	12.0

*See text for explanation of "y" intercept
+Biological half-life

TABLE II

DISAPPEARANCE OF PROTEIN-BOUND RADIOACTIVITY FROM THE PLASMA IN MAN FOLLOWING INJECTION OF MAA ^{131}I

	First Component		*Second Component*	
Patient	*T½+ (days)*	*"y" intercept* (% dose/liter)*	*T½+ (days)*	*"y" intercept* (% dose/liter)*
1	0.460	2.85	3.8	1.85
2	0.460	2.60	4.4	2.90
3	0.210	1.20	3.0	1.20
4	0.330	2.40	4.0	1.70
5	0.500	3.10	3.8	2.50
6	0.420	2.20	3.0	4.00
7	0.630	3.10	5.0	3.20
8	0.570	2.00	5.0	1.15
9	0.375	1.50	5.5	1.20
mean	0.44 ± 0.04	2.35	4.0 ± 1.43	2.17

*See text for explanation of "y" intercept
+Biological half-life

in man, radiation to the lung, blood, and whole body was estimated and is detailed in the Appendix.

DISCUSSION

Macroaggregated albumin is a heat-denatured aggregate of human serum albumin, prepared by acidification, heat and agitation as previously described (1-6). It differs from microaggregated albumin in that particle size is in the order of microns rather than millimicrons. Experiments on the disposition of millimicron aggregates by Biozzi *et al* (7) indicated that this material is removed by the liver and other components of the RE system in virtually one passage of blood. In those studies, 50 percent of the radioactivity appeared in the urine in 24 hours. Iio *et al* (8) determined clearance rates of aggregated albumin and designed indices to quantitatively assess the ability of the RE system to phagocytize such particles.

Because of their large particle size, macroaggregates of albumin are trapped in the pulmonary capillaries. It can be assumed that these larger aggregates are then broken down into smaller particles which, in turn, filter past the capillary bed of the lungs and are phagocytized by the RE system (6). Since the concentration of protein in MAA ^{131}I employed in these studies was less than the saturation level of the RE system, permitting exceedingly rapid clearance (8), and since disappearance of macroaggregates from the lung is rapid, as noted, disappearance of the macroaggregates from the blood and body should also be very rapid.

Dworkin *et al* (1) indicated that in the dog, disappearance of radioactivity

TABLE III

ESTIMATED TOTAL RADIOACTIVITY IN PLASMA AT FIVE MINUTES

Patient Weight (Kg)	*Estimated Plasma Volume* (Liters)*	*$PB^{131}I$ (% dose/liter)+*	*Estimated Total Radioactivity in Plasma+*
50.1	2.25	4.7	10.6
50.2	2.26	5.6	12.7
98.5	4.43	2.4	10.6
57.5	2.59	4.1	10.6
67.0	3.02	5.6	16.9
55.0	2.48	6.3	15.6
60.0	2.70	6.3	17.0
58.8	2.63	5.1	13.4
50.0	2.25	6.2	13.9
68.7	3.09	3.6	11.1
		mean	13.2 ± 2.6

*Based on 45 cc/kg

+Five minutes after injection

following MAA ^{131}I injection was exponential with a half-time of 1.75 to 2.0 days, similar to the 2.5 day half-time in the present study. Taplin (5) and Wagner (6) reported the half-time for the disappearance of MAA ^{131}I from the lungs in man to range from four to ten hours. These authors also indicated that a majority of the radioactivity appears in the urine in 24 to 48 hours. The present studies support these observations, but in addition, define a second slower component from lung and blood of 3.2 and 4.0 days, respectively.

To determine the radiation delivered to the lungs and blood, it was necessary to ascertain how a given dose was partitioned between these organs, and what fraction of the dose in these organs disappeared with the initial rapid rate and with the slower second rate.

The blood data obtained immediately following injection of MAA ^{131}I indicated the blood concentration. Animal data and *in vivo* counting suggested that the radioactive material was initially confined either to the plasma space or to the lungs. If one multiplies the average plasma volume of man (45 cc/kg) (9) by the blood concentration, one can derive an estimate of the total amount of the originally injected dose which is in the plasma (Table III).

The difference between the total amount injected and the quantity of isotope in the plasma affords an estimate of the radioactivity initially trapped in the lung. In man these data suggest that if an average of 13 percent of the injected dose will pass the pulmonary capillaries and circulate in the plasma then a maximum of about 87 percent will be trapped in the lung. Since about 85 percent of the original MAA ^{131}I in these studies was coagulated and of a particle size large enough to be trapped in the capillaries of the lung, the data calculated above appear to be valid.

Because radioactivity disappears from both the lungs and blood at two different rates it is necessary to determine the amount of radioactivity which disappears at each rate. To ascertain this fraction of radioactivity disappearing from the lungs or the blood by the fast and slow components, the respective components were extrapolated back to the origin. The "y" intercept so obtained represents the fraction of initial activity attributed to its respective component. In Table I and II the individual data are presented as well as the mean value for the "y" intercept for each component.

The sum of the two mean "y" intercepts for each organ represents all of the radioactivity in that organ. The percent of the total organ radioactivity that disappears at each rate is then ascertained by dividing the individual "y" intercepts by the sum. In the blood, the original 13 percent of the injected dose is partitioned about equally between the two components. In the lungs, of the total initial activity of 87 percent of the injected dose, 88 percent is removed at the rapid rate and 12 percent at the slower rate.

Calculation of radiation to the lungs (Appendix) indicates that this organ receives 1.9 rads for a 300 μC dose of MAA ^{131}I. Radiation to the blood and body is considerably less (0.049 rads and 0.008 rads, respectively).

The slower components herein defined represent either a compartment of the body in which MAA ^{131}I is being turned over slowly prior to phagocytosis and deiodination, or the disappearance of a distinctly different material. The data

obtained from the studies of the physical characteristics of MAA ^{131}I indicate that it is heterogeneous with regard to both particle size and extent of denaturation. Zone electrophoresis suggested that there was some undenatured material, of which a fraction migrated with albumin. If some of the material injected was unaggregated iodinated albumin, then its disappearance at rates similar to those of normal albumin might be anticipated. Data in the present study indicated the presence of a third slower component which may represent the final rate of degradation of undenatured albumin after equilibration (10, 11). Furthermore, the studies in the dog suggested that after 24 hours, distribution of the activity remaining was fairly homogeneous and in a space larger than the plasma compartment. Such a distribution is seen with iodinated albumin in both man and dog. (11, 12).

CONCLUSION

MAA labeled with ^{131}I is heterogeneous with regard to particle size, denaturation, distribution, and rates of disappearance from various organs and the body. In man, about 87 percent is trapped in the lung, and 13 percent is initially distributed in the plasma space.

MAA ^{131}I disappears from the lung and blood in a multi-exponential fashion. The mean biological half-time of disappearance from lung is 0.25 days for the rapid component and 3.2 days for the second component. The rapid blood component has a mean biological half-time of 0.44 days and a second component of 4.0 days. There may be a third and even slower component.

Based on these data, the radiation to the lungs for a 300 μC dose is 1.9 rads. Whole body radiation is 0.008 rads.

APPENDIX

Radiation Dosimetry

In calculating the dose of radiation delivered to lungs, blood, and whole body, it is estimated that 13 percent of the initial dose is in the plasma at five minutes (Table III) and disappears from the plasma with two rates as defined (Table II). As ascertained from the "y" intercept 52 percent of the blood activity leaves with a biological half-time of 0.44 days, and 48 percent with a biological half-time of 4.0 days. Similarly, of the 87 percent of the initial dose in the lung, 88 percent leaves with a biological half-time of 0.25 days, and 12 percent with a biological half-time of 3.2 days (Table I).

In estimating lung dose from beta radiation, the radioiodine was assumed to be uniformly distributed throughout the mass of the lungs. The beta dose for total decay of the lung radioactivity was derived from the equation:

$$(eq.\ 1) \quad D\beta = 73.8 \times \bar{E}\beta \times T_{eff} \times C \tag{13}$$

For purposes of determining concentration C, the lungs were assumed to weigh a total of 1,000 gm.

For instance, for an adminsitered dose of 100 μC, 87 μC would initially be in the lungs. Eighty-eight percent of this, or 76.6 μC would have a biological half-

time of 0.25 days, or an effective half-life of 0.24 days. The dose due to the beta radiation would then be:

$$D\beta = 73.8 \times 0.19 \times 0.24 \times \frac{76.6}{1000} = 0.26 \text{ rads.}$$

The second component would be calculated in a similar fashion.

In estimating lung radiation from the gamma emission of ^{131}I, the lungs plus mediastinum were considered to be a cylinder of 12 cm radius and 12 cm height. The geometrical factor g was calculated for a point at the center of the cylinder, thus providing a maximum dose estimate (14). The g so derived was calculated to be 160, using an absorption coefficient (μ) of 0.02 as an approximation for lung plus mediastinum. The dose to the lung was then calculated from the equation:

$$(eq.\ 2) \quad D\gamma = 0.0346 \times \tau \times T_{eff} \times C \times \rho \times g \tag{13}$$

For these data, if C is taken as the number of μC per unit mass of the lung tissue itself, then ρ which is usually taken as unity can be calculated here as if the lung mass of 1000 gm were distributed throughout the 11,000 cc of the cylinder. For the same first component the contribution to the gamma dose was then:

$$D\gamma = 0.0346 \times 2.2 \times 0.24 \times \frac{76.6}{1000} \times \frac{1000}{11{,}000} \times 160 = 0.02 \text{ rads.}$$

The second component was calculated similarly for the gamma radiation.

For estimation of whole body dose the plasma activity was assumed to be uniformly distributed throughout the tissues of a 60 kg patient. Then, for the same 100 μC dose, the first component of 6.8 μC in the plasma would have an effective half-life of 0.42 days, and the beta and gamma contributions were so derived. For the second component similar calculations were performed. For the gamma radiation an average $\bar{g}$ of 125 was used and ρ was taken as unity.

This model ignores any beta contribution of plasma radioactivity to the lungs, since the amount of radiation contributed would be quite small.

The total dose to the lungs, the sum of the beta and gamma of the two components for the lungs is 0.64 rads for a 100 μC administered. Similarly, the total radiation dose to the body from the plasma activity is 0.005 rads due to the beta radiation and 0.003 rads due to the gamma radiation or a total of 0.008 whole body rads.

For the estimation of maximum dose to the blood itself, the blood radioactivity was assumed to be distributed in an average volume of 5,500 cc giving a dose to blood itself of 0.049 rads due to beta radiation.

With an average clinical dose of 300 μC of ^{131}I labeled MAA for lung scanning, the lung radiation would be approximately 1.9 rads.

ACKNOWLEDGEMENTS

The authors are indebted to Mr. Martin Gershowitz for his assistance in some of the calculations, to Dr. Karen Corey for her technical advice and assistance, and to Mrs. M. Connell for her clerical assistance.

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