PHYSICS AND RADIATION BIOLOGY

Radiation Absorbed Doses from Co-57- and Co-55 Bleomycin

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Organ radiation doses to the adult patient after intravenous injection of Co-57- and Co-55 bleomycin were calculated using the MIRD methods. From these data somatically effective total-body doses for these radiopharmaceuticals were derived. Source organs are the bladder, kidney, and liver, and the remainder of the body. Residence times, i.e., cumulated activities per unit of injected radioactivity, were derived for each source organ, with their standard deviations, from measurements of Co-57 bleomycin clearance in a small number of patients. Target organs are the gonads and all organs that contribute to the somatically effective total-body dose. For Co-57- and Co-55 bleomycin the somatically effective doses are 0.26 ± 0.03 rad/mCi (70 ± 9 μGy/MBq) and 0.63 ± 0.09 rad/mCi (171 ± 23 μGy/MBq), respectively. The influences of the Co-56 impurity in Co-55, and of the Fe-55 daughter of Co-55 are discussed.

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The high sensitivity of cobalt-57 bleomycin (Co-57 BLM) for tumor scintigraphy is well established (*1–3*), but widespread use of this agent is prevented by the 270-day physical half-life of Co-57. A large percentage of intravenously injected Co-57 BLM is quickly excreted by the kidneys. The urine excreted in the first 24 hr after administration should be collected and regarded as long-lived radioactive waste (*2,4,5*). Other radionuclides have been studied as potential labels for BLM, but the relative tumor uptake was inferior to uptake of Co-57 BLM (*6–8*). The use of Co-55 as label for BLM has therefore been suggested (*7,9–11*). The advantage of Co-55 is its short physical half-life (17.5 hr). Disadvantages are the high gamma energies and the high percentage of positron emission. Scintigraphy should be carried out with a positron camera.

In this study the biological behavior of Co-57 BLM was studied extensively in adult patients in order to estimate the radiation absorbed doses from both Co-57 BLM and Co-55 BLM. Using standard MIRD methods, the radiation dose to various organs, and the somatically effective total-body dose, were obtained.

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MATERIALS AND METHODS

Patients. Fifty-eight patients (51 M, 7 F) were studied. Informed consent was obtained when more than routine scintigraphic study was to be performed. All patients were investigated for the detection and staging of lung cancer. All had normal renal function. The mean age was 63 yr, range 31–78. The 1.0 mCi (37 MBq) of Co-57 BLM was injected intravenously. Preparation of the radiopharmaceutical has been described previously (*12*). The free Co-57 activity varied from 0.1% to 1.4%.

Dose calculation methods. The absorbed radiation dose to a target organ can be calculated using the MIRD scheme (*13*) with the formula:

$$D(t \leftarrow s) = \tilde{A}_s \cdot S(t \leftarrow s), \qquad (1)$$

where $D(t \leftarrow s)$ is the mean absorbed dose in the target organ t from any source organ s; $\tilde{A}_s$ the cumulated activity in the source organ (namely the time integral of the source organ's activity curve); and $S(t \leftarrow s)$ is the so-called S value (*14*), the absorbed dose in target organ t

per unit of activity cumulated in source organ s. $\tilde{A}_s$ depends on the biological behavior of the radiopharmaceutical in the body, $S(t \leftarrow s)$ depends on the radiation characteristics of the radionuclide, the sizes and shapes of the source and target organs, and their spatial relationship in the body.

Sometimes the cumulated activity in the source organ is expressed in terms of the administered dose and the so-called residence time τ_s:

$$\tilde{A}_s = A_0 \cdot \tau_s, \quad (2)$$

where A_0 is the administered amount of radioactivity. Combining Eqs. (1) and (2) we find:

$$D(t \leftarrow s) = A_0 \cdot \tau_s \cdot S(t \leftarrow s) \quad (3)$$

The total target-organ dose is equal to the sum of the contributions from the various source organs:

$$D_t = A_0 \cdot \sum_s [\tau_s \cdot S(t \leftarrow s)] \quad (4)$$

The target-organ dose D_t is expressed in rad, A_0 in μCi, τ_s in hr, and $S(t \leftarrow s)$ in rad per μCi-hr. Pre-SI units are used because the values of S are tabulated that way.

The doses to the target organs can be combined into one figure, the total-body effective dose. This represents the total-body radiation risk, taking into account the individual radiosensitivities of the various target organs. To accomplish this, the target-organ doses are summed with different weighting factors:

$$D_e = \sum_t w_t \cdot D_t \quad (5)$$

where D_e is the total-body effective dose and w_t is a weighting factor for each target organ. This procedure is analogous to the summation of organ dose-equivalents for stochastic effects as mentioned in the ICRP Publication No. 26 (*15*). Since the quality factors for the radiation of the radionuclides considered in this paper are unity, the dose is numerically equal to dose-equivalent. Note that this procedure has not been officially recommended by the ICRP or other agencies such as MIRD. In this sense D_e is not a dose limit in ICRP terms, but may be used as a measure of total-body radiation risk for a radionuclide investigation of the patient.

In ICRP Publication No. 26 (*15*) weighting factors are chosen proportional to the risk factors for tumor induction or genetic effects. Roedler (*16*) considers only somatic effects, and calculates the somatically effective dose D_{se} using Eq. (5) with slightly modified weighting factors, as listed in Table 1. In the summation according to Eq. (5), the target organs listed in this table are used.

Generally, residence times are not precisely known; they have certain standard deviations. These errors propagate in the final results of the calculation, so that all radiation doses are obtained with a standard deviation. Errors in A_0 and in $S(t \leftarrow s)$ can be neglected relative to those in τ_s.

TABLE 1. WEIGHTING FACTORS FOR TARGET ORGANS ACCORDING TO ROEDLER (*16*)

Organ	w_t
Breast=muscle	0.20
Lungs	0.16
Marrow	0.16
Bone	0.04
Thyroid	0.04
Remaining organs	0.08 (5X)
Ovaries	0.00
Testes	0.00
	— +
Total	1.00

The calculation of the organ doses and their errors, and the selection of the target organs needed for the calculation of the somatically effective total-body dose, were carried out with a FORTRAN program in the computer system that is linked to our gamma cameras. The input consists of the names of the source organs, their residence times with their errors, and the name of the radionuclide. The computer automatically retrieves the S values from disk memory and calculates the radiation dose for all 20 target organs mentioned in MIRD Pamphlet No. 11 (*14*).

For the calculation of the somatically effective dose D_{se} according to Eq. (5) and its error, the 20 target organs are separated into three groups: five organs mentioned explicitly in Table 1, 13 so-called remaining organs, and the two types of gonads. The radiation doses in the five organs contribute to D_{se} for all radiopharmaceuticals that use the weighting factors shown in Table 1. From the radiation dose figures of the 13 remaining organs, only the five with the highest values are selected; these are assigned a weighting factor 0.08. The radiation doses in the gonads do not contribute to D_{se} ($w_t = 0$).

Quantitative organ uptake measurements. Absolute organ activity can be determined with a standard gamma camera using the method of the geometric mean (*17*). An anterior and a posterior view of the organ of interest are stored in the computer. From regions of interest over the organ and in the background area, net organ counts in both views can be obtained. The geometric mean of the anterior and posterior counts provides a usable approximation for the amount of radioactivity present in an organ. Dividing this figure by the injected dose and the counting time in minutes, the organ activity can be expressed in cpm/μCi.

The gamma camera is calibrated from a phantom study in which the count rate from a 100-ml bottle con-

TABLE 2. URINARY EXCRETION OF CO-57 BLM, WITH 1 s.d. IN PARENTHESES

Author	% Injected dose excreted during periods shown (hr)				
	0–5	0–6	0–24	0–48	0–72
Schober (*18*)	68 (*6*)		86 (*4*)	90 (*5*)	
Rasker (*2*)		54 (*21*)	82 (*21*)	89 (*5*)	90 (*1*)
Nouel (*19*)		60	80		
Grove (*20*)			70	80	
Alberts (*21*)			82 (*14*)		
Cummings (*22*)			>90		
Woolfenden (*23*)			80		
Lucot (*24*)			80		
Maeda (*25*)			80		
Present study			85 (*8*)	87 (*7*)	87 (*7*)

taining a known amount of Co-57 is determined in a tank with a variable water content. The calibration curve of this phantom study is a plot of the geometric mean of the anterior and the posterior counts (in cpm/μCi) as a function of the water level. On a semi-logarithmic plot of counts against water level, this curve is a straight line for water levels from 5 to 25 cm (half-thickness 10.5 cm). From this calibration curve the conversion factor between counts and amount of radioactivity can be derived. This conversion factor is independent of the position of the bottle in the tank, and thus—in terms of a patient—is independent of organ depth.

When the anteroposterior diameter of the patient is known, the amount of radioactivity in the organ can be calculated from the geometric mean of the anterior and posterior net organ counts using the conversion factor from the calibration curve for that particular patient diameter.

The calibration curve was made once. The window setting of the gamma camera was checked after every patient study by counting the calibration bottle in air under standardized conditions.

Biodistribution of Co-57 BLM. The distribution of Co-57 BLM in the human body as a function of time has been studied by several investigators. Most of the injected radioactivity is excreted in the urine (Table 2), so there will be considerable radioactivity in the kidneys (*2,19,21*) and bladder (*18,20,21*). The liver is a third organ with appreciable uptake (*2,19*). The high uptake of Co-57 BLM in kidneys and liver is also well documented by tissue measurements in rats and mice (*26–28*). The relatively high liver and kidney uptake in man is also demonstrated in Fig. 1, which shows posterior scintigrams of the liver and kidney area in one of our patients over a period of about 2 mo. We assumed that the activity outside of the liver, kidney, and bladder is distributed homogeneously throughout the remainder of the body. Thus, for calculations of radiation dose, bladder, kidney, liver, and residual body were chosen as source organs. Total body is used for the residual body in the extraction of the S values from the MIRD tables. This results in a minor overestimation of the S values, and thus of the radiation dose (*29,30*). The error is negligible, however, compared with the total uncertainty

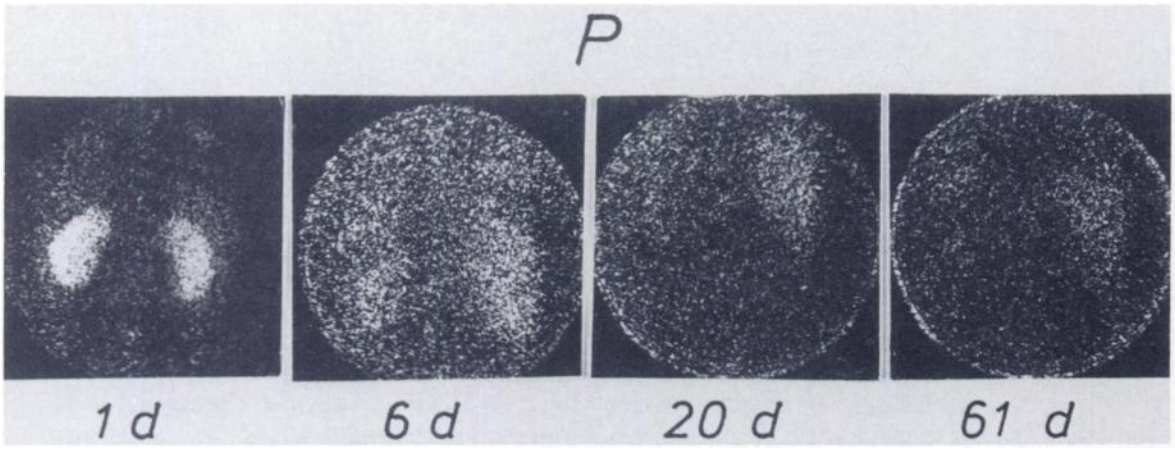

FIG. 1. Posterior scintigrams of upper abdomen after 1, 6, 20, and 61 days in same patient. High kidney uptake is seen only during first few days; liver can be recognized over at least 2 mo.

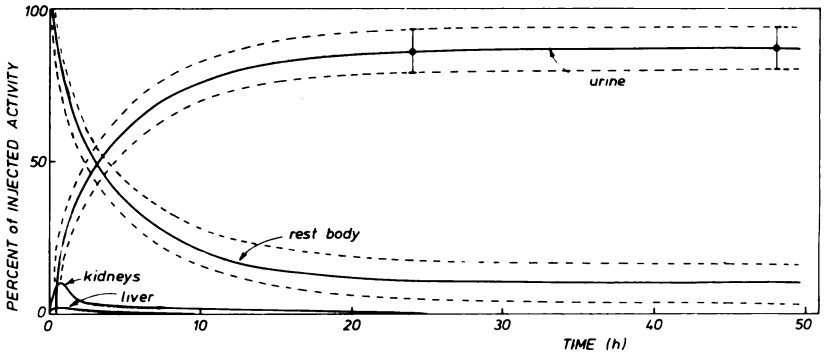

FIG. 2. Curves for urinary excretion of Co-57 BLM, and activity in kidney, liver, and remainder of body. One standard deviation of the mean is indicated on curve of urinary excretion over 24 and 48 hr. Curve of activity in remainder of body is complement of summed curves for urinary excretion, kidney, and liver.

in the calculation of the radiation doses to target organs.

RESULTS

All organ radioactivity measurements are listed ±1 s.d., with both expressed as percentages of the injected dose. Residence times are given in hours, also ±1 s.d.

BIOLOGICAL BEHAVIOR OF Co-57 BLM

Urinary excretion. In 37 patients the radioactivity excreted in the urine was determined by fractionated urine collection. In the first 24 hr after injection, urinary excretion was (85 ± 8)% (n = 35), for 0–48 hr this was (87 ± 7)% (n = 18) and for 0–72 hr (87 ± 7)% (n = 16). The urinary excretion curve for the first 24 hr was also determined in more detail (n = 5). These results are summarized in Fig. 2.

Bladder residence time. This can be calculated from the urinary excretion curve, assuming a certain voiding frequency. With regular voiding, once per hour, assuming linear increase of activity in the bladder over each period, the bladder residence time was 0.42 ± 0.03 hr; for a voiding frequency of once every 2 hr the residence time was 0.90 ± 0.06 hr; and with voiding once every 3 hr this was 1.25 ± 0.10 hr. For the dose calculations a realistic value for the bladder residence time seems to be 1.0 ± 0.2 hr.

Kidney residence time. Kidney uptake was determined in 13 patients using the geometric mean method (Fig. 3). The radioactivity in the left kidney can easily be determined using a region of interest technique. The activity in the right kidney is always mixed with activity from the liver, which raises a problem. In this study only patients with symmetric left and right kidney uptake were included, so that the total kidney uptake could be estimated by doubling the uptake in the left kidney. A

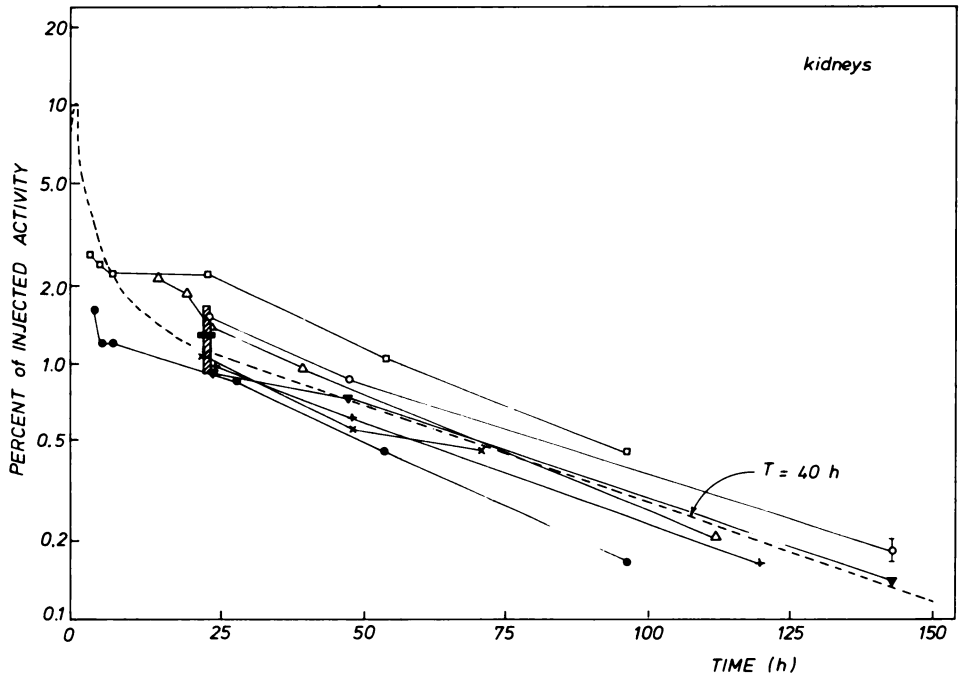

FIG. 3. Washout of Co-57 BLM activity from kidney. Dotted line is mean activity curve derived from three patients; shaded area at 24 hr is mean kidney activity ±1 s.d. as measured in ten patients. To give an impression of error in individual measurements, 1 s.d. is indicated for point measured at 143 hr after injection.

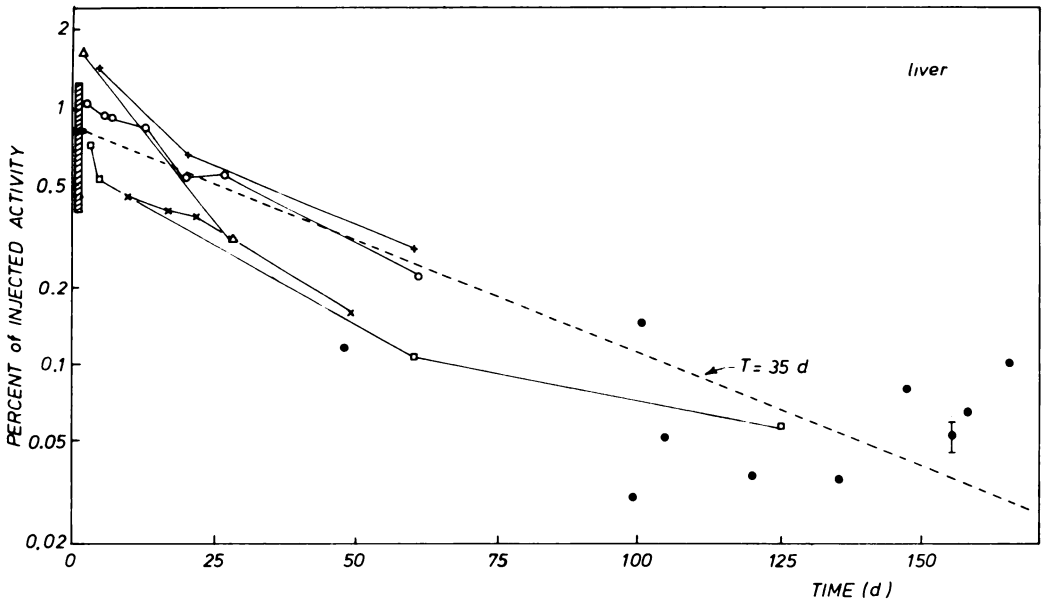

FIG. 4. Washout of Co-57 BLM activity from liver. Shaded area at end of first day is mean liver activity, ±1 s.d., as measured in ten patients. Fully black dots are single measurements in ten different patients at different times; ±1 s.d. is indicated for one of them.

total kidney uptake of (1.1 ± 0.3)% was found at 24 hr.

In a few patients we measured the kidney activity as a function of time (Fig. 3) in some detail over the first few hours (n = 5) and with less detail through 6 days (n = 7). The kidney uptake curve can be described roughly by a biexponential function with half-lives of 1.8 ± 0.5 hr and 40 ± 10 hr, and with extrapolated zero-time uptakes of (8 ± 3)% and (1.7 ± 0.4)%, respectively, of the injected dose. These observations result in a kidney residence time of 1.2 ± 0.4 hr.

Liver residence time. On the 24-hr scintigrams, the liver is always clearly delineated. After 1 mo—and sometimes even after 2 mo—the liver contours can be seen (Fig. 1).

In ten patients we determined the liver uptake a few days after the injection, using the geometric means (Fig. 4). On the 24-hr scintigram the liver and right-kidney activities overlap, but on scintigrams obtained more than 4 days after administration, the kidney activity can be neglected. The absolute 24-hr liver uptake is estimated to be (0.8 ± 0.4)%. The liver activity during the first few hours is slightly higher (about 2%) because of the higher blood activity, but for dosimetric purposes this can be disregarded.

The effective half-life of the liver activity was obtained by recording the upper abdomen activity in anterior and posterior views over a period up to 150 days after injection. Some patients were studied once (after 50 to 150 days), others more frequently. On the scintigrams obtained long after administration, the liver contours could not always be recognized. In these cases a square region of interest was used to follow the disappearance of the radioactivity. All the data were collected in one semilog plot (Fig. 4). The washout appeared to be monoexponential with a half-time of 35 ± 5 days. This figure, together with the uptake at zero time of (0.8 ± 0.4)%, results in a residence time of 10 ± 5 hr.

Rest-of-body residence time. It is assumed that over the first 48 hr the radioactivity in the remainder of the body is at all times the injected radioactivity minus the sum of activities in the urine, kidney, and liver (Fig. 2). By integrating the area under this curve, the residence time over the first 48 hr was found to be 10 ± 3 hr. The activity in the remainder of the body at the end of the second day was 100% minus the urinary activity [(87 ± 7)%], minus the kidney activity [(0.7 ± 0.5)%], and minus the liver activity [(0.8 ± 0.4)%], yielding (12 ± 7)%. The disappearance of this activity was derived from the scintigrams of the abdomen by integrating the counts over a region of interest outside the liver and kidneys, corrected by the background counts found in a person in whom no radioactivity was injected (Fig. 5). This curve can be described roughly by a biexponential function with a fast component (9% of injected dose, $t_{1/2} \sim 2$ days) and a slow component (3% of injected dose), $t_{1/2} \sim 50 \pm 10$ days). By integrating the area under this curve, the residence time for the period after 48 hr is 58 ± 27 hr. Combining this with the residence time over the first 48 hr, we find a rest-of-body residence time of 68 ± 27 hr.

RADIATION DOSE CALCULATION FOR Co-57 BLM

On the basis of the Co-57 BLM residence times thus found for the source organs (Table 3), our computer program can calculate the radiation doses in the target organs and the somatically effective total-body dose

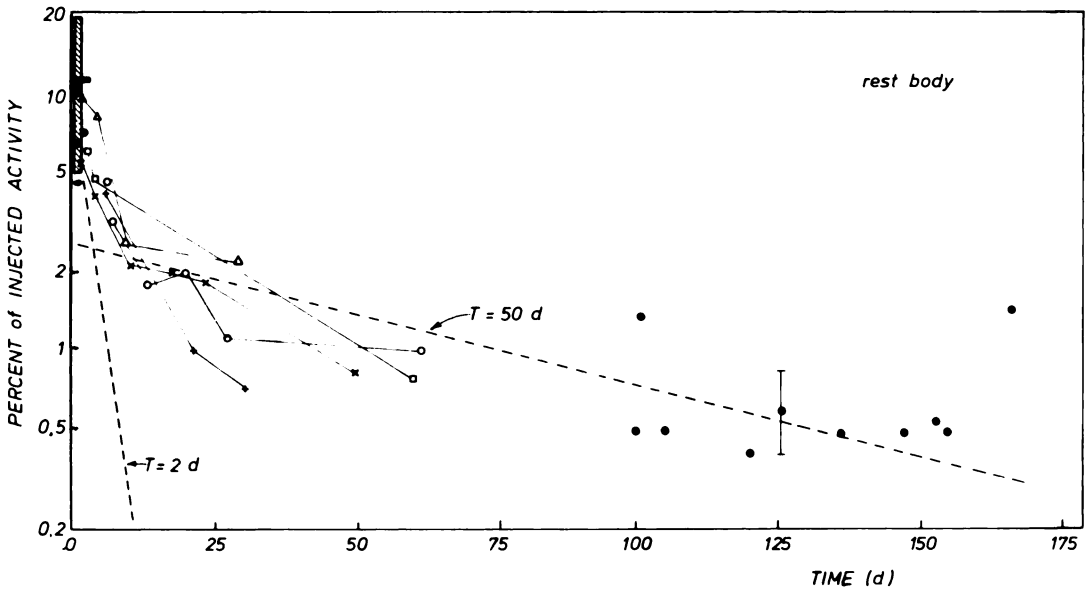

FIG. 5. Washout of Co-57 BLM activity in remainder of body. Shaded area at end of second day is complement of summed urinary excretion, kidney, and liver activities, with 1 s.d. indicated. Fully black dots are single measurements in 13 patients at different times, with 1 s.d. indicated for one of them.

(Table 4). The total-body effective dose is estimated to be 0.26 ± 0.03 rad/mCi (70 ± 9 μGy/MBq).

The error in the total-body effective dose was calculated with the method of error propagation, assuming that the errors in the residence times of the four source organs are independent. There is, however, a relation between the urinary activity and the residual body activity because the latter is low if the former is high, and vice versa. Nevertheless, it has been demonstrated that the error in the bladder residence time is determined mainly by the voiding frequency rather than by the variations in urinary excretion. Therefore, the errors in the bladder residence time and in the rest-of-body residence time can be regarded as being independent.

RADIATION DOSE CALCULATION FOR Co-55 BLM

Residence times. The source-organ residence times for Co-55 BLM can be calculated by correcting the observed biodistribution of Co-57 BLM for the physical half-life of Co-55 (17.5 hr). The resulting residence times for Co-55 are presented in Table 3. For a voiding frequency of once every hour, a bladder residence time of 0.35 ± 0.04 hr is found; with voiding every 2 hr it becomes 0.73 ± 0.05 hr; and with voiding every 3 hr it is 1.0 ± 0.1 hr. For the dose calculations a bladder residence time of 0.9 ± 0.2 hr was assumed.

TABLE 3. RESIDENCE TIMES OF Co-57 BLM AND Co-55 BLM, WITH 1 s.d. IN PARENTHESES

Source organ	Residence time (hr) Co-57	Co-55
Bladder	1.0 (0.2)	0.9 (0.2)
Kidneys	1.2 (0.4)	0.5 (0.2)
Liver	10 (5)	0.2 (0.1)
Remainder of body	68 (27)	5 (2)

Radiation dose. The S values for Co-55 are not tabulated in MIRD Pamphlet No. 11 (14). For our dose calculations we used a complete S value table obtained from Health and Safety Research Div., Oak Ridge National Laboratory, Oak Ridge, U.S.A.

Using the Co-55 BLM source-organ residence times as presented in Table 3, the radiation doses to the target organs and the somatically effective total-body dose were calculated (Table 4). The total-body effective dose is 0.63 ± 0.09 rad/mCi (171 ± 23 μGy/MBq).

Contribution of Fe-55. Cobalt-55 decays to Fe-55 (half-life 2.7 y), which in turn decays by pure electron capture to Mn-55. Because of the long half-life of Fe-55 there is only a small amount of Fe-55 in a Co-55 source (<0.1%). Since 87% of the Co-55 BLM activity is excreted in the first 2 days, the maximum amount of Fe-55 in the body will be approximately 0.1 μCi per mCi Co-55. This results in a total-body dose of about 0.001 rad per mCi Co-55 (*31*), so we may neglect the Fe-55 contribution.

Contribution of Co-56. Contamination with Co-56 is inherent in the way Co-55 is produced (*32*). Assuming that the Co-56 impurity is present as Co-56 BLM, the residence times for Co-56 will roughly equal those of Co-57. This involves an overestimation because the half-life of Co-56 (79 d) is considerably shorter than that of Co-57. A complete set of S values for Co-56 is not available, but according to ICRP-30 the S values for Co-55 and Co-56 differ by not more than 20% (*33*). Using the S values of Co-55 and the residence times for

TABLE 4. RADIATION DOSES FOR Co-57 BLM AND Co-55 BLM, WITH 1 s.d. IN PARENTHESES*

Target organ	Radiation dose (rad/mCi) Co-57 BLM	Co-55 BLM
Breast=Muscle	0.15 (0.05)	0.21 (0.07)
Lungs	0.17 (0.06)	0.18 (0.07)
Marrow	0.24 (0.08)	0.22 (0.07)
Bone	0.20 (0.07)	0.18 (0.07)
Thyroid	0.11 (0.04)	0.17 (0.07)
Liver	0.7 (0.3)	0.39 (0.11)
Kidneys	0.46 (0.11)	2.2 (0.8)
Bladder	0.33 (0.07)	3.2 (0.7)
Adrenals	0.22 (0.07)	0.32 (0.09)
Pancreas	0.22 (0.07)	— —
Uterus	— —	0.39 (0.09)
Ovaries	0.18 (0.07)	0.26 (0.07)
Testes	0.13 (0.05)	0.25 (0.08)
Total body (som. effective)	0.26 (0.03)	0.63 (0.09)

* Only those target organs are mentioned that contribute to the somatically effective total-body dose (see text) as well as the gonads.

Co-57, we find a somatically effective dose of 3.3 ± 0.4 rad per mCi of Co-56. With our production method (*34*) the Co-56 impurity is less than 1% of the Co-55 activity at the end of bombardment. Such an impurity results in a maximum increase of about 5% in the somatically effective dose of Co-55.

DISCUSSION

Biological data. The biodistribution of Co-57 BLM has been studied in man and in various kinds of animals. The present study was restricted to humans.

As shown in Table 2, the urinary excretion data from different papers agree very well. The 1.1% uptake in the kidneys (24 hr after injection) that we currently found is similar to the data reported by Nouel (*3*), but is far less than the 100% uptake in a previous report from our group (*2*). We are not able to recalculate this figure, but absolute organ uptake was not determined at that time. Nearly all activity is excreted by the kidneys, so a kidney uptake of 100% was used. We now realize that this figure is incorrect, for currently we find a maximum uptake of 10%. The disappearance from the kidney is not monoexponential as has been suggested (*2,18*), but is biexponential, as was also reported by Nouel (*35*). Our present liver uptake data are similar to those of Nouel (*3*). We found a half-time of 35 ± 5 days for the biological disappearance from the liver. This is far longer than the 3–6 days reported in the literature (*2,3*). The disappearance of the activity from the remainder of the body has a slow 2% component with a half-life of 50 days. This is also much longer than the figures for the total body reported in the literature (*2,18*).

We conclude from our measurements that the biological disappearance of Co-57 BLM is complicated and appears to have a few very slow components. Gamma-camera detection of the low activities that remain for a long time in the human body is not ideal. This is the reason why our patient organ data show large variations, resulting in residence-time values with appreciable errors. Accurate whole-body measurements should be performed with a whole-body counter.

Radiation doses. Estimates of radiation dose for Co-57 BLM have been published by many authors. Since these calculations were based on different biological excretion data, large variations in radiation doses are reported. All authors agree that a major fraction of the Co-57 BLM is excreted by the kidneys, and that there is considerable uptake in the liver, so that bladder, kidney, and liver doses are relatively high. The kidney dose estimations in the literature vary from 0.3 to 2.0 rad/mCi (*1,2,18,25,35*). The dose to the bladder ranges from 0.2 to 1.4 rad/mCi (*2,4,18,20,23*), and to the liver from 0.4 to 2 rad/mCi (*2,25,35*). These data agree with our results, as presented in Table 4. Figures for the somatically effective total body dose from Co-57 BLM have not yet been published.

The radiation dose of Co-55 BLM has been calculated by Cochavi et al. (*36*). Their figures are based on the above-mentioned biological data of Rasker et al. (*2*) and therefore indicate extremely high doses to bladder (16 rad/mCi) and kidneys (24 rad/mCi). With our present more detailed biological data, the radiation dose values of Co-55 BLM in the various target organs are roughly equal to those of Co-57 BLM, except those for the bladder and kidneys, which are 5–10 times higher. The bladder dose can be reduced by frequent voiding during the first 24 hr after administration. For the same amount of radioactivity, the somatically effective total-body dose for Co-55 BLM is 2–3 times that from Co-57 BLM. When a sensitive positron camera is used, however, the injected amount of Co-55 BLM can possibly be reduced.

According to our estimates, the radiation dose of Co-55 BLM is similar to the absorbed doses from other diagnostic studies in nuclear medicine.

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