Radiation Dosimetry for the Adult Female and Fetus from Iodine-131 Administration in Hyperthyroidism

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Through a study of the iodine kinetics of 127 patients, we have developed radiation dose estimates to major organs and the fetus for patients with varying degrees of hyperthyroidism. We observed a negative correlation between maximum thyroid uptake and biologic half-time of iodine in the thyroid and used this correlation to predict the biologic half-time at fixed values of maximum thyroid uptake. Dose estimates to the bladder, gonads, marrow, thyroid, uterus, and whole body were estimated for maximum thyroid uptakes from 20% to 100%. Bladder dose varied from 0.6 to 1.0 mGy/MBq and dose to the uterus varied from 0.036 to 0.063 mGy/MBq under different model assumptions. Dose estimates to the fetus and fetal thyroid were approximated at all stages of pregnancy. Average fetal dose was a maximum between 0 and 2 mo of pregnancy, with the maximum ranging from 0.048 mGy/MBq to 0.083 mGy/MBq, depending on model assumptions. Some radiation risks for irradiation of the fetus and the fetal thyroid are discussed.

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Radiation dose estimates have been calculated for euthyroid individuals for several isotopes of iodine by a MIRD Committee Task Group (*1*). This document is very useful for predicting the radiation dose to the thyroid and other major organs from radioiodine administrations. However, the differences in iodine metabolism in patients with Graves' disease are not considered in this model. Although several authors (*2–6*) have estimated doses to the thyroid and some other organs for selected groups of patients with Graves' disease, no comprehensive dosimetry has been done as for the euthyroid case. As radiopharmaceuticals are sometimes accidentally or intentionally administered to pregnant patients, dose estimates for the embryo or fetus may be needed occasionally for the pregnant patient with Graves' disease.

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Using uptake and retention data from patients treated at the Harbor UCLA Medical Center, we have derived a simple model that may be used to estimate the radiation dose to the hyperthyroid patient from administration of iodine-131 (^{131}I). We segregated the patients into groups according to maximum thyroid uptake, which were divided further according to sex and, in the case of females, according to age. Biologic kinetics were studied as a function of maximum thyroid uptake. Radiation dose estimates were derived for the major organs of the body. The radiation dose to the fetus was of special concern, as a majority of hyperthyroid patients are female and may be of childbearing age. In radioiodine therapy studies, the amount of radioiodine administered may be so high that the dose to the fetus from the urinary bladder and other organs may be appreciable. The dose to the fetal thyroid, which may begin to concentrate iodide as early as the tenth week of gestation (*7*), may be extremely high, as this tiny organ concentrates iodide that is available from the mother's bloodstream (*8*).

METHODS

Thyroid uptake and biologic half-time measurements were made on 127 patients treated for hyperthyroidism at the Harbor-UCLA Medical Center. No distinction was made between those with Graves' disease and those with hot nodules, but the majority had Graves' disease. Most uptakes and biologic half-times were measured with ^{123}I, although some measurements were made with ^{125}I. Uptakes were measured at either 2 or 4 hr, and then at 24, 48, and 72 hr. No data on urine clearance or total-body retention were obtained.

The thyroid biologic half-times were determined for all patients through linear regression analysis of the log-transformed data. The biologic half-times were plotted versus maximum percent uptake (rather than 24-hr uptake, as the maximum may occur much earlier then 24 hr in patients who are severely hyperthyroid) to see if the biologic half-time varied with higher maximum percent uptake. The patients were then segregated into groups of maximum thyroid uptake of 20%–30%, >30%–40%, >40%–50%, >50%–60%, >60%–70%, >70%–80%, >80%–90%, and >90%. The patients were further segregated by sex, and then the females were segregated into two groups (those of age less than 45 yr and those aged 45 yr or more) to see whether or not a clear

difference could be detected between the biology of pre- and postmenopausal women. (This break point is rather arbitrary, and could result in a misclassification of some patients. The specific diagnosis of women as pre- or postmenopausal was not available from the medical records.) The average biologic half-time for each group was estimated from the peak and later thyroid uptake values; the maximum thyroid uptake was assumed to be the largest value between 0 and 24 hr. Regression curves of biologic half-time versus maximum thyroid uptake were derived for each group.

Radiation doses were estimated using the standard MIRD technique (*9*) for the adult female phantom (*10*). Radiation dose estimates for the adult male or large adult female will be slightly lower, as the organ masses are slightly larger. As in MIRD Dose Estimate Report No. 5 (*1*), the total-body residence times were derived from the uptake and elimination biologic half-times in the thyroid. Residence times in the urinary bladder were estimated from the assumed whole-body retention using the dynamic bladder model of Cloutier et al. (*11*). The dose to the nongravid uterus was used to estimate the dose to the embryo during the first month. The dose to the fetus from the urinary bladder was estimated from the results of the model of Cloutier et al. (*11*) for months 1 through 9. As absorbed fractions from other organs for all nine months are not available, the fetal dose from maternal organs was approximated by assuming that the bladder contributed a constant percentage of the total dose for a given maximum thyroid uptake (i.e., if the bladder contributed 70% of the total dose in the nongravid model for a given maximum thyroid uptake, each of the fetal doses from the bladder in months 1 through 9 were divided by 0.7 to obtain the estimate for total fetal dose). Fetal dose from placental crossover of radioiodide (assumed to be significant after month 2) was estimated by assuming that the fetal concentration of iodide was 75% of that in the mother's whole body (*12*) and using the absorbed fractions for photon dosimetry in MIRD Pamphlets 3 and 8 (*13,14*). Radiation dose estimates for the fetal thyroid for months 3 through 9 were taken from two sources: Watson (*8*), who assumed a constant biologic half-time in the fetal thyroid at all ages, and Elsasser et al. (*15*), who assumed a variable biologic half-time over the gestation period.

RESULTS

Figure 1 shows the regression of biologic half-time versus maximum thyroid uptake for all patients and the results of the regression analyses. In this plot, the intercept has no physical meaning, but is merely part of the expression that may be used to predict biologic half-time at a given value of maximum thyroid uptake. The data were negatively correlated, but the scatter of data about the regression line was considerable ($R^2 = 0.1$). The scatter led us to investigate the significance of the negative slope; for the number of data points available, the slope was significantly less than zero at the 0.001 level. We also plotted the biologic half-time versus maximum thyroid uptake for males, females under 45, and females over 45 using average values within each thyroid uptake interval. All of these plots showed a negative correlation, but only the slopes for males and females *under* 45 were significantly less than zero. Although the slope for females over 45 was not

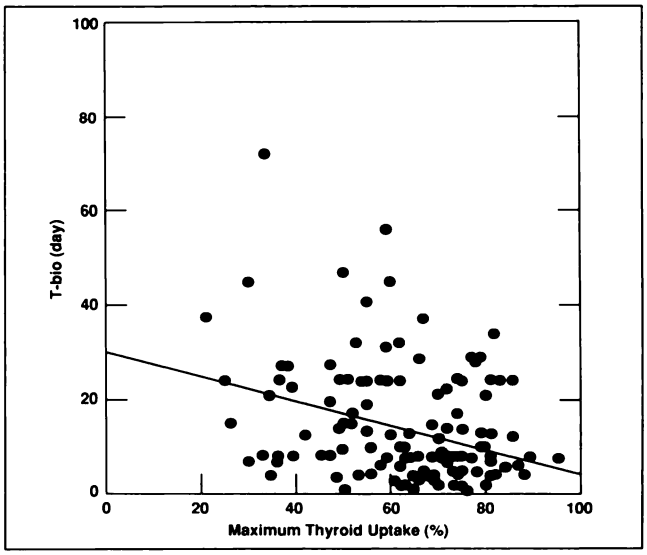

FIGURE 1. Regression of biologic half-time versus maximum thyroid uptake for all patients.

significantly less than zero, it was also not significantly different than slope of the average line for all patients, at the 0.05 level. In fact, none of the slopes were different than the average at the 0.05 level. Therefore, the three slopes were not significantly different from each other.

Table 1 gives the residence times derived from the metabolic models for the different values of maximum thyroid uptake and thyroid uptake half-time. Table 2 shows radiation dose estimates for the adult female for the urinary bladder, thyroid (12.4 g), and total body as well as for uterus, gonads, and red marrow at five discrete values of maximum thyroid uptake. The thyroid biologic half-times were derived from the equation which described this parameter as a function of maximum thyroid uptake for all patients. As shown in Table 2, two values of thyroid uptake biologic half-time were chosen: 6.1 hr, which was taken directly from the value in MIRD Dose Estimate Report No. 5 for a maximum thyroid uptake of 25%, and 2.9 hr, which was chosen to represent the individual whose maximum thyroid uptake occurs earlier than 24 hr. The

TABLE 1
Residence Times Used in the Various Models

	Residence Time (hr)				
	20*	40*	60*	80*	100*
T(u) = 2.9 hr					
Bladder	2.34	1.93	1.59	1.36	1.35
Thyroid	42	79	110	125	117
Remainder	4.1	4.1	4.1	4.1	4.1
T(u) = 6.1 hr					
Bladder	2.11	1.76	1.47	1.29	1.34
Thyroid	41	77	110	120	110
Remainder	8.5	8.5	8.5	8.5	8.5

* Maximum thyroid uptake (%).
T(u) is the thyroid uptake half-time.

TABLE 2
Radiation Dose Estimates for ^{131}I in the Hyperthyroid Patient* as a Function of Maximum Thyroid Uptake

Organ		Estimated radiation dose (mGy/MBq)				
		20†	40†	60†	80†	100†
Bladder	1‡	1.0	0.85	0.70	0.60	0.60
	2‡	0.94	0.79	0.66	0.59	0.61
Ovaries	1	0.032	0.030	0.028	0.027	0.026
	2	0.047	0.045	0.044	0.043	0.043
Red marrow	1	0.062	0.10	0.13	0.15	0.14
	2	0.076	0.12	0.14	0.16	0.15
Testes	1	0.026	0.024	0.022	0.021	0.021
	2	0.039	0.037	0.036	0.035	0.035
Thyroid	1	410	780	1070	1240	1150
	2	400	760	1040	1200	1100
Uterus	1	0.049	0.044	0.040	0.036	0.036
	2	0.063	0.058	0.055	0.052	0.053
Total body	1	0.16	0.29	0.39	0.45	0.42
	2	0.17	0.30	0.39	0.45	0.42

* Adult female (58 kg).
† Maximum thyroid uptake (%).
‡ 1 = thyroid uptake half-time 2.9 hr; and 2 = thyroid uptake half-time 6.1 hr.

total-body biologic half-times were used as input into the dynamic bladder model (*11*).

Table 3 shows the radiation doses to the fetus for maximum thyroid uptakes of 20%, 60%, and 100% and for both thyroid uptake biologic half-times. These values are plotted as a function of stage of gestation in Figures 2 and 3. The figures clearly show the slight increase during the first month, as the growth of the fetus causes a higher fraction of the photon energy emitted from activity in the bladder to be absorbed, and a steady decrease after this, as the increase in fetal mass offsets the increase in absorbed fraction. The figures also show that a higher thyroid uptake

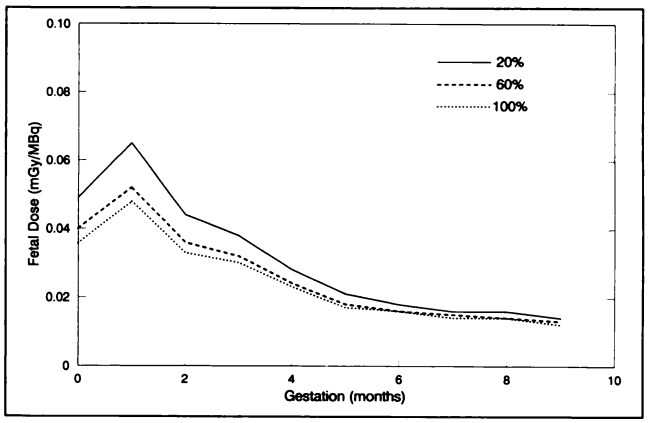

FIGURE 2. Average whole-body dose to the fetus at all stages of pregnancy for patients with maximum thyroid uptakes of 20%, 60%, and 100% and a thyroid uptake half-time of 2.9 hr.

results in a lower radiation dose to the fetus, as more of the iodine is held up in the thyroid and decays before reaching the urinary bladder. Radiation dose estimates for the fetal thyroid have been estimated by Watson (*8*) and Elsasser et al. (*15*). Watson assumed a constant biologic half-time in the infant's thyroid, while Elsasser et al. assumed that the biologic half-time increased with gestational age. Watson's estimates of fetal thyroid dose per unit activity administered to the mother were: month 3, 260 mGy/MBq; month 4, 550 mGy/MBq; month 5, 640 mGy/MBq; month 6, 1200 mGy/MBq; month 7, 810 mGy/MBq; month 8, 620 mGy/MBq; month 9, 490 mGy/MBq. Elsasser et al. estimated the fetal thyroid dose per unit activity administered to the mother to be: month 3, 43 mGy/MBq; month 4, 220 mGy/MBq; month 5, 370 mGy/MBq; month 6, 840 mGy/MBq; month 7, 620 mGy/MBq; month 8, 520 mGy/MBq; month 9, 430 mGy/MBq. In both sets of estimates, the maximum thyroid dose per unit activity given to the mother is seen in month 6. This is the time at which the fetal thyroid

TABLE 3
Radiation Dose Estimates for the Fetus at All Stages of Pregnancy from Administration of ^{131}I to the Mother

Age (mo)	Estimated radiation dose (mGy/MBq)*					
	20%†		60%†		100%†	
	T(u) = 2.9 hr	T(u) = 6.1 hr	T(u) = 2.9 hr	T(u) = 6.1 hr	T(u) = 2.9 hr	T(u) = 6.1 hr
1	0.065	0.083	0.052	0.072	0.048	0.071
2	0.044	0.055	0.036	0.043	0.033	0.048
3	0.038	0.055	0.032	0.046	0.030	0.048
4	0.028	0.042	0.024	0.035	0.023	0.037
5	0.021	0.032	0.018	0.028	0.017	0.030
6	0.018	0.029	0.016	0.026	0.016	0.027
7	0.016	0.027	0.015	0.024	0.014	0.025
8	0.016	0.026	0.014	0.024	0.014	0.025
9	0.014	0.024	0.013	0.022	0.012	0.023

* Absorbed dose to the fetus per unit activity administered to the mother.
† Maximum thyroid uptake (%).
T(u) is the assumed thyroid biologic half-time for uptake.

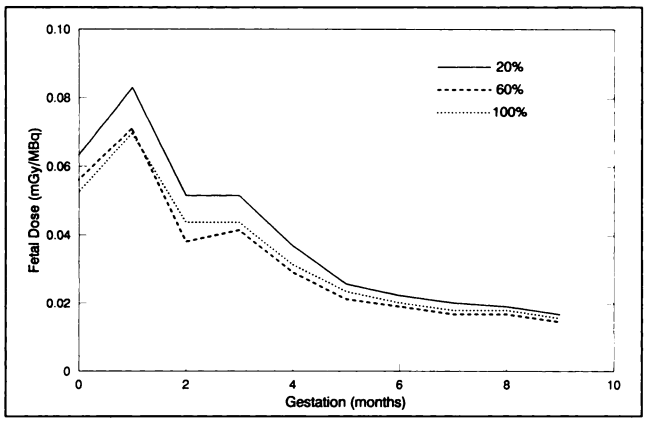

FIGURE 3. Average whole-body dose to the fetus at all stages of pregnancy for patients with maximum thyroid uptakes of 20%, 60%, and 100% and a thyroid uptake half-time of 6.1 hr.

concentration (% of injected activity per gram) is the highest, according to Evans et al. (*16*).

DISCUSSION

The purpose of this paper is not to give radiation dose estimates for the thyroid of the hyperthyroid patient. There are many variables not treated in this paper that may influence the thyroid dose estimate; this can best be calculated on a patient-specific basis by the attending nuclear medicine physician. For instance, if the thyroid is greatly enlarged, the radiation dose estimates given in Table 2 will overestimate the true value, as the radiation dose is approximately an inverse function of mass. The dose estimates given in the tables are meant to be representative averages for patients of certain characteristics that may be used by the attending physician to estimate some of the radiation hazards associated with administration of therapeutic amounts of ^{131}I. Thus, the values of radiation dose to the bladder, gonads, uterus, and total body are useful in determining a representative value for a patient once the thyroid metabolism is known. The values of radiation dose to the fetus and fetal thyroid similarly may be considered to be typical values for persons with characteristics similar to those described in the model.

The considerable scatter about the regression line in the curve for all patients (Fig. 1) indicates that the simple expression given for biologic half-time as a function of maximum thyroid uptake does not completely describe the relationship between the variables. A third variable, probably associated with the patients' normal iodine diet, would most likely clarify the true dependence of these variables on the state of the individual patient. Such data were not available from this patient data base. Furthermore, in the clinical setting, the physician does not have the time to extract this kind of information from the patient before proceeding with therapy. Therefore, the values in this paper are useful in determining an approximate average radiation dose to major organs or a fetus once the patient's maximum thyroid uptake is known. The negative correlation between biologic half-time and maximum thyroid uptake is certainly reasonable, and the expression derived from the regression analysis has been used to give some idea of the change in radiation dose to the major organs as a function of the extent of hyperthyroidism. As noted in Table 2, some of the estimated doses do not change greatly with thyroid uptake. This is partly because the residence times for the remainder of the body (which contributes significantly to the dose for some of the body organs) remain constant (Table 1).

Differences in this patient population as a function of sex or age, according to the groupings employed, were not clearly discernable. Although some differences could be seen in the regressions between males and females, the individual variations masked any real differences between the groups.

Table 2 shows that the radiation dose to the bladder, ovaries, testes, and uterus decreases with increasing maximum thyroid uptake. The thyroid uptake half-time has a more pronounced effect on the radiation dose to these organs than to other organs. The increase at the longer uptake half-time is due to the increased contribution from activity in the remainder of the body. The radiation doses to the total body and red marrow, on the other hand, increase with increasing maximum thyroid uptake and are not highly dependent on thyroid uptake half-time.

The average absorbed dose to the whole fetus is highest at 1 mo, and then decreases steadily over the period of gestation. This work predicts that the highest absorbed dose to the fetus from administration of ^{131}I to a pregnant female would occur at 1 mo into the pregnancy with a 6.1-hr biologic half-time for uptake into the mother's thyroid and 20% maximum thyroid uptake. The estimated absorbed dose to the fetus under these assumptions would be 0.031 Gy from 370 MBq of ^{131}I administered to the mother. NCRP Report 54 (*17*) states: "[The risk of congenital effects] is considered to be negligible at 5 rad [0.05 Gy] or less when compared to the other risks of pregnancy, and the risk of malformation is significantly increased over control levels only at doses above 15 rad [0.15 Gy]." Otake and Schull (*18*), from an analysis of mental retardation data from the atomic bombing survivors, predicted a probability of occurrence of mental retardation of 0.40 Gy^{-1}. In more recent re-analyses of those data (*19*), they found essentially the same relationship for doses received in the 8th to 15th week of gestation (the most radiosensitive time), with a linear, nonthreshold model fitting the data well. For doses received during 16–25 wk, however, a quadratic or linear-quadratic model appeared to fit the data better, suggesting a threshold of 0.2–0.7 Gy. The recent BEIR V report (*20*), in its conclusions about these effects, support these observations, suggesting a frequency of severe mental retardation of 43% at 1 Gy, with a possible threshold at 0.2–0.4 Gy. It should be noted that fetal dose

estimates given in this paper between the 8th and 15th week of pregnancy would predict doses around these thresholds for therapeutic administrations of ^{131}I (3700–7400 MBq).

The dose to the fetal thyroid is predicted to be highest when administration occurs during the sixth month of gestation, although the magnitude of the dose is somewhat in doubt. The absorbed dose is very high, and various incidents involving pregnant women treated with therapeutic amounts of ^{131}I have resulted in infants having depressed or absent thyroid function at birth (*21–24*). Pfannenstiel et al. (*24*) concluded that depressed thyroid function in a newborn was due to administration of radioiodine to the mother at a fetal age of 72 days. Therefore, extreme care should be taken to ensure that pregnant women are not inadvertently given therapeutic quantities of ^{131}I. Mossman (*25*) concluded that it is not cost-effective to use pregnancy testing to screen all potentially pregnant patients before exposure to ionizing radiation in radiodiagnostic procedures. In the case of therapeutic use of internally administered radiopharmaceuticals, however, the risks are greater, and pregnancy testing may be a valuable tool in preventing unwanted exposure to the fetus.

CONCLUSIONS

1. A reasonable picture of the radiation dosimetry for hyperthyroid patients from ^{131}I-sodium iodide may be obtained by assuming a negative correlation between maximum thyroid uptake and biologic half-time.

2. In this patient population, no differences were seen in the biologic half-times as a function of sex or age.

3. Radiation dose estimates for the urinary bladder decrease with increasing maximum thyroid uptake. The thyroid uptake half-time has little effect on the radiation dose received by the urinary bladder wall, red marrow, or total body. The uptake half-time has a more pronounced effect on the dose received by testes, ovaries, and uterus.

4. The radiation dose to the nongravid uterus decreases as the maximum thyroid uptake increases.

5. Radiation doses to the fetus from activity in the mother's body are highest at one month's gestation and then decrease over the period of gestation. The highest radiation dose estimate generated from these data is for 20% maximum thyroid uptake and a thyroid uptake biologic half-time of 6.1 hr: 0.083 mGy/MBq. Because of the potential risks of physical malformation and mental retardation, great caution must be exercised to prevent therapeutic administrations of ^{131}I to the pregnant patient.

6. Radiation dose estimates for the fetal thyroid are highest at 6 mo. Therapeutic administrations of ^{131}I to pregnant women have been shown to produce depressed or nonexistent thyroid function in the infant whenever the administration occurs while the fetus' thyroid is functioning.

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Selected manuscripts from the issues of *The Journal of Nuclear Medicine* published 15 and 30 years ago.
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MAY 1976

Iodinated Bleomycin: An Unsatisfactory Radiopharmaceutical for Tumor Localization

William C. Eckelman, Haruyo Kubota, Barry A. Siegel, Toru Komai, Waclaw J. Rzeszotarski, and Richard C. Reba

Bleomycin is widely used for cancer chemotherapy. Cobalt-57-labeled bleomycin localizes in tumor tissue and is a useful radiopharmaceutical for clinical tumor imaging. However, the long physical half-life of ^{57}Co has discouraged its widespread acceptance. Bleomycin compounds labeled with radionuclides of indium, copper, gallium, and technetium are less stable chemically and give less satisfactory results than ^{57}Co-bleomycin. As an alternative to metal binding, we studied the properties of iodinated bleomycin. Our results suggest that it will not be satisfactory for tumor imaging.

Iodination

Bleomycin was iodinated both directly in the imidazole ring and indirectly by reaction with N-succinmidyl 3-(4-hydrozyphenyl) propionate. All the direct iodinations were performed with ^{125}I in 0.1 *N* NaOH and chloramine-T. In a typical reaction, 70 μl of 1 *M* phosphate buffer was added to the vial containing the ^{125}I. The bleomycin and chloramine-T then were added. The solution was mixed for 60 sec and then $Na_2S_2O_5$ was added to reduce any remaining iodine. The yield was calculated as the percent of total iodide incorporated into bleomycin, and from this and the initial molar ratios of iodide to bleomycin the percentage of labeled bleomycin molecules was calculated.

The N-succinmidyl 3-(4-hydrozyphenyl) propionate was iodinated by the method of Bolton and Hunter. Iodination also was attempted using lactoperoxidase.

Cobalt-57-bleomycin was prepared by adding carrier-free $^{57}CoCl_2$ to bleomycin. To test the effect of chelated cobalt on the distribution of iodinated bleomycin, equimolar amounts of $^{57}CoCl_2$ and directly iodinated bleomycin were mixed.

Tissue Distribution Studies

The distributions of the radiolabeled bleomycin compounds were determined in female Fischer-344 rats implanted with 13762 mammary adenocarcinoma.

Discussion

Our results indicate that the iodinated bleomycins are unsatisfactory for tumor imaging. Although both directly and indirectly iodinated bleomycin were stable in vitro, neither compound was stable in vivo, and by 24 hr after injection in rabbits, nearly half of the remaining plasma activity was in the form of iodide. The tumor-to-blood ratios achieved with iodinated bleomycins were substantially lower than those with ^{57}Co-bleomycin. The iodinated bleomycin concentrations in both tumor and blood decreased with time from 2 to 24 hr, in contrast, the tumor concentration of ^{57}Co-bleomycin was essentially the same at 2 and 24 hr, while the blood concentration decreased. Thus, the tumor-to-blood ratio for ^{57}Co-bleomycin increased with time, while this ratio for the iodinated compounds changed very little. Addition of carrier cobalt to iodinated bleomycin did not materially enhance its relative tumor concentration.

The unsatisfactory tumor localization of iodinated bleomycin and bleomycin labeled with other metal radionuclides suggests that cobalt-labeled bleomycin has unique properties, most likely relating to the chelated cobalt, which are important in determining the high tumor-to-nontarget ratios achieved with this radiopharmaceutical. ■

MAY 1961

President's Annual Report

Titus C. Evans, President, The Society of Nuclear Medicine

We have beome a large and influential Society. We must realize our responsibility and conduct the affairs and policies for the common good. In addition to our original aim of exchanging information about techniques and uses of radioisotopes, we are now confronted with requests for advice and cooperation from other societies. Also, the need for training and standards in the field has become evident. Therefore, we should be pleased that we can now be of help to others, but we must remember that our chief reason for being a society is to promote scientific and investigational progress. Individual professional gains must be secondary, and local problems should be settled in light of national policy.

During the past year, the *Journal* finished its "shakedown cruise" and is now "At Sea Under Full Steam." Our finances are in good shape, but we must be prepared to expect additional expenses as pages in the *Journal* increase in the coming years.

The meetings of the Executive Committee have been extremely well attended and all chapters have been represented. The spirit and efficiency with which the committees worked on the affairs of the Society is worthy of deep appreciation.

I wish to express my confidence in the new President, Dr. Lindon Seed, and to congratulate him and the Society as he takes over and to assure him of my and your continued support during the coming year. ■