

INVESTIGATIVE NUCLEAR MEDICINE

Compartmental Analysis of the Steady-State Distribution of $^{15}\text{O}_2$ and H_2^{15}O in Total Body

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It has been suggested that regional oxygen metabolism may be measured quantitatively by analysis of the steady-state distribution of O-15 ($T_{1/2} = 122$ sec). For this analysis we have developed a compartmental model that incorporates corrections due to clearance and recirculation of water of metabolism. The oxygen utilization rate is simply proportional to the local O-15 activity if water of metabolism is not recirculated from other tissues and is not lost to the circulation for a time long compared with the half-life of O-15. We evaluated the magnitude of biological metabolic water loss and uptake in the steady state. Our analysis indicates that the magnitude of these effects for rapidly exchanging tissues (such as cerebral gray and white matter), may preclude a simple, noninvasive, and quantitative determination of regional oxygen metabolism. Slowly exchanging compartments, however (such as skeletal muscle and perhaps some tumors), appear amenable to correction for clearance and recirculation effects with sufficient accuracy to make determinations of regional oxygen metabolism feasible.

J Nucl Med 22: 959-965, 1981

In 1973 Russ et al. (1,2) developed a steady-state technique for imaging the distribution of gases labeled with oxygen-15 ($T_{1/2} = 122$ sec). Jones et al. (3), and later in more detail Subramanyam et al. (4), suggested a theoretical treatment, applicable to the brain, for obtaining regional oxygen extraction from data obtained by this technique. Their treatment did not include oxygen utilization capability. Another study used the steady-state technique to monitor changes in tumor and surrounding tissues caused by radiation therapy (5,6). This study gave empirical evidence for an oxygen-utilization interpretation of the observed changes based upon the suggestion that tissues exchanging water slowly may not require correction for either water clearance or recirculation.

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Received July 15, 1980; revision accepted June 29, 1981.

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A difficulty for analyses aimed at deriving oxygen-utilization information from the steady-state approach is the need to account for the circulation of labeled water of metabolism (H_2^{15}O) from and to the tissue under investigation following its production in, and clearance from, all body tissue. The purpose of this work is to provide an analysis of oxygen utilization, including recirculation of labeled water of metabolism, based on a multicompartiment model (7). The modeling was carried out with the SAAM (simulation, analysis, and modeling) program of Berman et al. (8,9).

Model for total-body water. We begin with an analysis of water distribution in the whole body. We first establish a three-compartment model consisting of central pool (including the water contained in the arterial blood system), lumped slowly exchanging tissues, and lumped rapidly exchanging tissues. This model is subsequently extended to include cerebral white and gray matter. To establish the parameters for the three-compartment model, we use the data of Edelman (10). His experimental study used D_2O as a tracer for water, and pro-

TABLE 1. FIVE MALE HUMAN SUBJECTS IN DEUTERIUM OXIDE STUDY OF EDELMAN*

Characteristic	Mean \pm standard deviation
Weight	70.8 \pm 5.8 kg
Age	23.0 \pm 4.1 yr
Total-body water	42.0 \pm 2.6 l
% body weight	59.4 \pm 2.7
Zero-time volume of dilution	10.3 \pm 1.2 l
% body weight	14.6 \pm 1.7

* Reference 10.

vided arterial blood clearance data as well as total-body volume of distribution from equilibrium measurements. The characteristics of Edelman's subject population are given in Table 1.

The three-compartment model is illustrated in Fig. 1. The tracer input to Compartment 1 may be either by a bolus injection into the patient's arterial system or by constant administration, e.g., inhalation. The physical radioactive decay constant for the tracer is indicated by λ . The intercompartmental tracer rate constants k_{ij} (these can be derived from clearance half-times: $k_{ij} = (\ln 2)/t_{ij}$) are determined using Berman's SAAM program (8) and the arterial disappearance parameters given in Ref. 10. (For the deuterium experiments $\lambda = 0$, since deuterium is stable.) The results of the rate-constant calculations are given in Table 2. The rapidly exchanging tissues (Compartment 2) have a clearance half-time of 3.9 ± 0.4 min; the slowly exchanging tissues (Compartment 3) 25.6 ± 1.7 min. According to Edelman (10) the viscera form the bulk of the rapidly exchanging tissues, while skeletal muscle and supporting structures (probably skin and connective tissue as well as bone) constitute the slowly exchanging tissues.

Once the parameters k_{ij} have thus been fixed by the bolus experiments, we use the model to determine the $H_2^{15}O$ distributions during steady-state administration of $H_2^{15}O$ into Compartment 1. In this case it is essential to take into account the radioactive decay constant λ , which for O-15 is 0.341 min^{-1} .

These model calculations provide a determination of

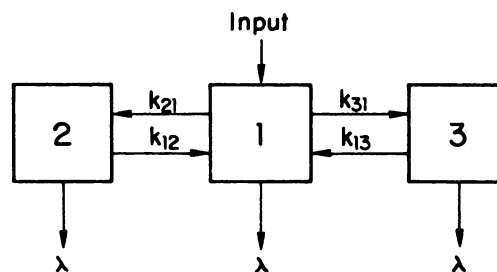


FIG. 1. Three-compartment model for analysis of body-water distribution: (1) central pool, (2) rapidly exchanging tissues, (3) slowly exchanging tissues. Input is by bolus injection or by constant infusion for steady-state studies; λ is the physical radioactive decay constant, and tracer rate constants k , interconnecting the three compartments, are shown.

the activity concentrations (as well as the mean deviations for our patient sample) in the three compartments for any rate of administration of $H_2^{15}O$ activity into Compartment 1. The arterial blood concentration achieved in Compartment 1 during steady-state administration is an essential parameter for analysis of regional cerebral blood flow (11,12). Figure 2 shows the activity concentrations (in $\mu\text{Ci}/\text{cc}$ water) at steady state in the three compartments when the administration rate of $H_2^{15}O$ into Compartment 1 is 1 mCi/min.

We note that the dramatic difference in the two tissue compartments (2 and 3) excludes any simple model where the tissue types are lumped as one. At steady state, the rapidly exchanging compartment shows 34% of the activity concentration of Compartment 1, and the slowly exchanging compartment shows 7%.

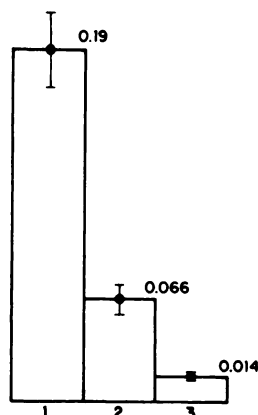
For all compartments the standard deviation as a percent of the mean (across Edelman's patient sample) is approximately 12%. In Fig. 2 and all other figures, this deviation is indicated by the error bars.

Cerebral tissue: steady-state $H_2^{15}O$ distribution. To study exchange effects in cerebral white and gray matter, which turn water over very rapidly, we use the clearance data for O-15-labeled oxyhemoglobin given by Ter-Pogossian et al. (13,14), shown in Table 3, together with water volumes for white and gray matter of 0.58 and 0.51 l, respectively (15-17). The clearance parameters were obtained by averaging data from the frontal, parietal, and occipital brain regions of each patient, then calcu-

TABLE 2. THREE-COMPARTMENT WATER-MODEL PARAMETERS

Male subjects	Tracer rate constants (min^{-1})				Compartment volumes (liters)		
	k_{12}	k_{21}	k_{13}	k_{31}	1	2	3
MC	0.159	0.162	0.0273	0.0486	11.8	12.0	21.0
CB	0.191	0.146	0.0240	0.0605	9.9	7.6	25.0
RHC	0.180	0.250	0.0289	0.0433	10.0	13.9	15.0
NR	0.160	0.174	0.0275	0.0718	8.7	9.5	22.7
PT	0.190	0.177	0.0276	0.0571	11.2	10.3	23.2
Mean	0.176	0.182	0.0271	0.0563	10.3	10.7	21.4

FIG. 2. Steady-state activity concentrations, in μCi per cc of body H_2O , for constant H_2^{15}O administration. $N = 5$ (10).



lating a mean and deviation over the group of patients.

Water clearance can be investigated either by administration of O-15-labeled oxyhemoglobin whose released oxygen is subsequently converted to water of metabolism, or by administration of H_2^{15}O . The subsequent egress rate of water is identical for the two methods within experimental error (13,14). We used the oxyhemoglobin data since they are more directly related to the metabolic process.

Our five-compartment model is shown in Fig. 3 for analysis of the steady-state administration of H_2^{15}O at the rate R_1 to the water compartment (1), with Compartments 4 and 5 representing, respectively, cerebral white and gray matter. Compartment 2 was reduced by an amount equal to the water volumes of white and gray matter, and k_{12} adjusted so that the product of k_{21} with the volume of Compartment 1 (see Table 2) remained equal to the product of the new volume of Compartment 2 with k_{12} (conservation of mass). Compartment 3 is as in Fig. 1. The steady-state activity concentration levels (in $\mu\text{Ci}/\text{cc}$ water) are shown in Fig. 4.

The deviations across the patient sample are again indicated by the error bars. Note that these do not include variations in the water volume or in the clearance parameters of white and gray matter, which were fixed in these calculations.

Clearly H_2^{15}O does not distribute in direct proportion to the water volume in each tissue (the activity concentration is not equal in all compartments). The model would not allow an estimate of the water content of the

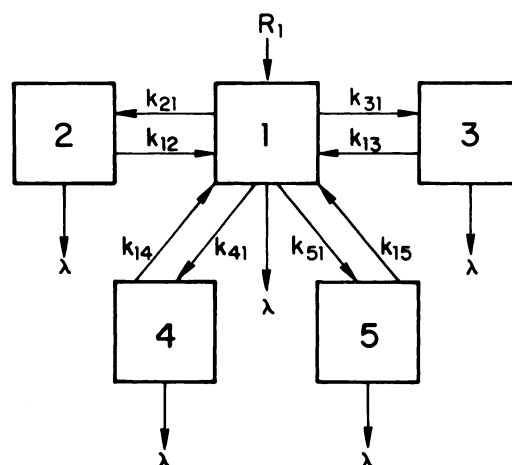


FIG. 3. Five-compartment model, with cerebral white (4) and gray (5) compartments, for analysis of body-water distribution.

various tissues more accurate than that indicated by the error bars in Fig. 4, even in a group of individuals who closely approximate the Edelman sample. Although the model may be further elaborated, it is also evident that compartmental activity is not directly proportional to perfusion (18). This confirms similar conclusions in other studies (11,12).

Steady-state $^{15}\text{O}_2$ distribution (water of metabolism). Once our model for body-water distribution has been developed, it can be used to investigate the concentration of H_2^{15}O of metabolism derived from $^{15}\text{O}_2$ utilization. In this case, the H_2^{15}O is produced in Compartments 2 and 3 by metabolism of $^{15}\text{O}_2$, rather than being introduced initially into Compartment 1 as H_2^{15}O . Figure 5 shows the compartment model used to evaluate the dynamics of water of metabolism.

On the plausible assumption that the oxygen metabolism of brain, heart, kidney, liver, and lung can be described as components of Compartment 2 (rapidly exchanging water) with 79% of the total-body oxygen metabolism, the rest of the body's oxygen metabolism (21%) is assigned to the slowly exchanging Compartment 3 (19). This is equivalent to setting $R_2 = 0.79R_1$ and $R_3 = 0.21R_1$, where the R_i are the constant rates at which oxygen is supplied to the various tissues, i , by the arterial blood. Total oxygen utilization used for these calculations is 22.13 l oxygen/hr in the resting state (20). The specific activity of the delivered oxygen is taken to

TABLE 3. OXYGEN CEREBRAL BLOOD-FLOW PARAMETERS*

Matter	Clearance half-times (sec)			rCBF \pm s.d. (ml/min/100 g)
	Low	High	Mean \pm s.d.	
Gray	30.9	38.0	34.4 \pm 3.6	126 \pm 13
White	127.4	142.0	134.7 \pm 7.4	27.2 \pm 1.5

* Reference 13. Two males aged 41 and 42 and two females aged 68 yr with brain disease.

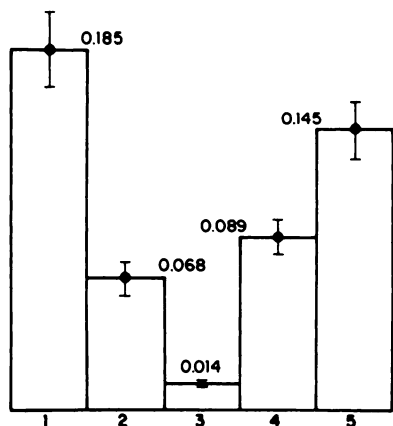


FIG. 4. Steady-state H₂¹⁵O activity, in μCi per cc of body H₂O, for five-compartment model. N = 5 (10) plus 4 (13) human subjects.

be 1 mCi/l of oxygen gas.

The resultant distribution of activity (in mCi) for the model of Fig. 5 is shown in Fig. 6. The shaded distribution is that due to metabolism, assuming it is not redistributed within the body after its formation (the central compartment, 1, would have no activity without recirculation). Error bars indicate the variation over the patient sample, which is approximately ± 3%.

Figure 7 shows a breakdown of fast and slow compartments giving percentage gain and loss relative to 100% produced—e.g., 8.4% gain and 34.1% loss for the fast compartment. Much smaller changes are seen for the slowly exchanging tissues, with the difference between produced and observed activities being only + 6.6 ± 3%.

Oxygen metabolism with cerebral tissue. Our five-compartment model for oxygen of metabolism, including brain white and gray matter (Compartments 4 and 5, respectively), is shown in Fig. 8. Combined white and gray cerebral tissue accounts for 21% of the body's oxygen metabolism (19,21). Both in-vivo and in-vitro studies indicate that the rate of metabolism in gray matter is about twice that in white matter (22,23). This ratio is confirmed in recent studies of cerebral glucose metabolism (24,25). Hence $R_4 = 0.07R_1$ and $R_5 = 0.14R_1$. The rapid body compartment is then reduced to 58% ($R_2 = 0.58R_1$).

Assuming that the activity is delivered at 1 mCi/l oxygen, the resultant millicurie contents for Compartments 1-5 are 0.260 ± 0.015 , 0.487 ± 0.021 , 0.252 ± 0.008 , 0.0460 ± 0.0006 , and 0.0449 ± 0.0011 , respectively.

Figure 9 shows the predicted contents for white and gray matter, normalized to 100%, together with recirculation gains and losses. White matter shows a 47.7% loss and 8.1% gain; gray matter shows a 77.8% loss and 7.2% gain.

When the parameters of Table 3 for brain water clearance are varied ± 1 s.d. around the mean values

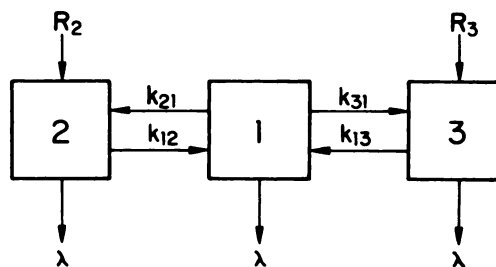


FIG. 5. Three-compartment model for water of metabolism.

(with the other model parameters held at their average values) the observed values of Fig. 9 vary by ± 4% and ± 10% for white and gray matter, respectively. Obviously the loss component of the correction is most sensitive to variations in the clearance parameters.

DISCUSSION

The ability to perform low-hazard, noninvasive, and reasonably accurate regional oxygen utilization measurements in vivo promises great value for the assessment of changes in oxygen metabolism caused by disease—e.g., infarcts, necrosis, inflammation, tumor growth, and tumor destruction produced by treatment. It is generally believed that functional disturbances occur earlier than structural changes caused by disease and disease treatment, and that in most cases earlier appreciation of functional abnormalities would improve the success of treatment. The initial suggestion that steady-state administration of ¹⁵O₂ might provide such a method (1) was followed by preliminary reports that local functional changes could apparently be monitored in the brain (26)—and in locations possibly involving tumors—where water is exchanged slowly (5).

The results of the multicompartmental analysis provided by this study allow a quantitative determination of the accuracy with which the oxygen-15 steady-state method (1,2) can be applied to measure regional oxygen utilization in tissues that exchange oxygen-15-labeled water of metabolism at a variety of rates, and in which

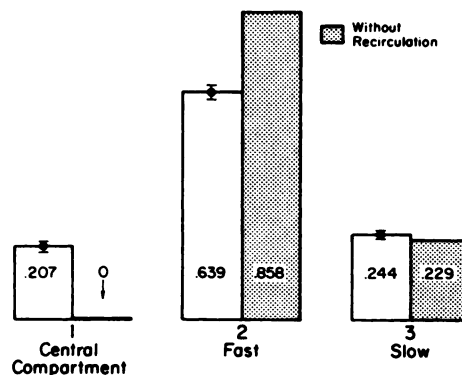


FIG. 6. Steady-state activity contents (in mCi) for three-compartment water of metabolism model of Fig. 5, with recirculation (clear) and without (shaded). N = 5 (10).

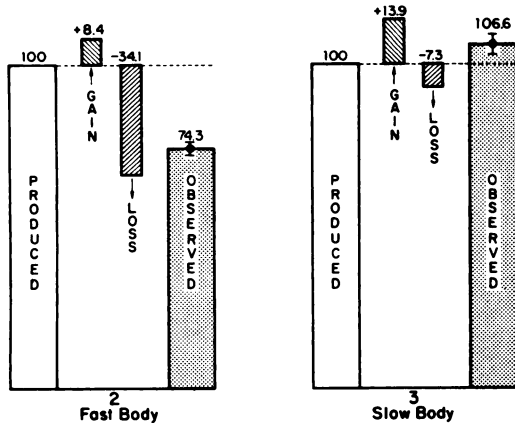


FIG. 7. Steady-state distribution of water of metabolism, with percentages of activity produced, gained, and lost from recirculation, for fast and slow body compartments. $N = 5$ (10).

recirculation of oxygen-15-labeled water of metabolism is evaluated.

Qualitatively we can expect that tissues with low blood flow would exhibit slow loss to the bloodstream of locally produced water of metabolism. In contrast, tissues such as brain, with high blood flow, will show rapid removal of water of metabolism from the site. Although one can anticipate large recirculation corrections from tissues with high blood flow, it is important to recognize that neither metabolism nor water exchange is simply proportional to blood flow (11,13,14). Cerebral circulation is demand-limited, regulated by the metabolism itself (27), whereas other tissues may be limited by cellular exchange rates rather than by circulation (10).

The oxygen-utilization results for slowly exchanging tissues can be appreciated from the right half of Fig. 7. As expected (5), a relatively small fraction (7.3%) of the water of metabolism produced in these tissues is cleared from them. Recirculation provides a 13.9% increase. These results show that a model without clearance or recirculation (one compartment) would require a correction of $+7 \pm 3\%$. In either case, for Edelman's (10) patient sample (Table 1) the variation across the group

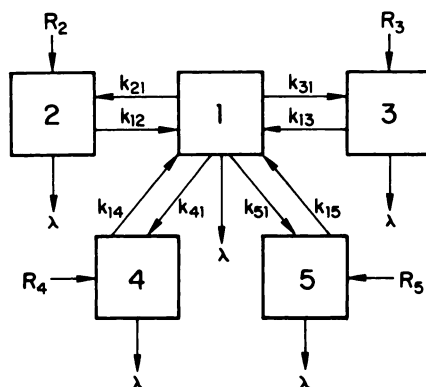


FIG. 8. Five-compartment model, including cerebral white and gray tissue, for analysis of distribution of water of metabolism. $N = 5$ (10) plus 4 (13).

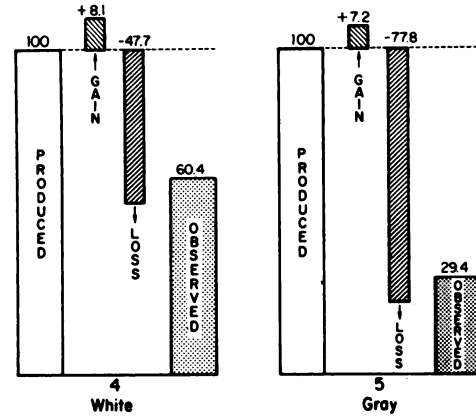


FIG. 9. Steady-state distribution for white and gray cerebral tissue, obtained from five-compartment model of water of metabolism, with percentages of locally produced water of metabolism gained and lost from recirculation.

is approximately $\pm 3\%$. If a $H_2^{15}O$ or deuterium oxide bolus infusion study, with arterial disappearance measurement, were carried out on each patient, this variation could be further reduced.

The water-exchange situation for gray and white matter can be evaluated from Fig. 9. Without the model, the error in predicting the amount of water of metabolism produced from that observed in white matter would be -40% , and in gray matter it would be -71% .

The magnitudes of these recirculation corrections were seen to be sensitive to the cerebral water-clearance parameters. Evaluation of the cerebral water kinetics experimentally in each patient would require a carotid-artery administration of the tracer ($H_2^{15}O$) and measurement of regional brain-activity disappearance (13). It is possible that the cerebral clearance parameters could be determined less invasively by using a single inhalation of $C^{15}O_2$ with subsequent arterial sampling. Note that if oxygen utilization is to be measured in a region of the brain (such as a tumor site), the rate for clearance of water from the region must be determined from the brain disappearance data. This is not likely to be possible with the probe system in current use (13), at least for small tumors.

If white and gray matter cannot be resolved quantitatively so as to determine the fraction of each tissue type in a region of interest, our model-derived correction would be between that of all white and all gray matter (-40% to -71%). Currently available imaging procedures cannot resolve gray and white matter quantitatively unless the object size is known (28). A high-resolution transaxial transmission computed tomographic image of the region could provide the data on object size, thus reducing this error substantially.

The effects of clearance and recirculation of water of metabolism can be reduced by using a tracer for oxygen with a shorter half-life. Oxygen-14 ($T_{1/2} = 71$ sec) is suitable for this purpose, and it has been prepared in

amounts adequate for medical imaging (29). Its steady-state imaging characteristics have been compared with those of oxygen-15 ($T_{1/2} = 122$ sec) (30). The primary concern with the use of oxygen-14 is the fact that in 100% of the decays it emits a 2.3-MeV gamma photon in coincidence with the positron emission.

CONCLUSIONS

From the results of our model calculations, we conclude that corrections and errors will render absolute measurement of oxygen metabolism in the brain by the steady-state method more difficult than has been generally appreciated. This is especially true for cases of brain disease, since the kinetics are likely to be modified in an unpredictable manner. Furthermore, if the resolution of any quantitative imaging device were insufficient to resolve white and gray matter, additional uncertainties would be introduced.

The absolute regional measurement of oxygen metabolism in tissues that exchange water slowly may be measured in vivo in humans, noninvasively and with reasonable accuracy, without corrections for either clearance or recirculation of water of metabolism within the body.

We are currently using the oxygen-15 steady-state technique in conjunction with positron tomography (31) to extend to humans the earlier evaluation study of tumor therapy in animals (5). We expect to gain new insight into the responses of neoplastic and normal tissues to radiation and chemotherapy, and this information should result in improved therapeutic procedures.

ACKNOWLEDGMENTS

We express our gratitude to Dr. John S. Laughlin for his support and encouragement of this work.

This research was supported in part by the U.S. Department of Energy Contract #EE-77-S-02-4258; by the NIH-National Heart, Lung and Blood Institute #HL-22371; and by NIH-National Cancer Institute Core Grant CA-08748.

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The Education and Research Foundation of the Society of Nuclear Medicine welcomes applications for Student Fellowships and Pilot Research grants. These awards are made possible through donations from SNM members as well as from various commercial firms whose products are used in the practice of Nuclear Medicine. Applications received prior to December 15 of any year will be evaluated by the ERF Board on a competitive basis. Awards will be announced on or about February 15 of the following year.

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SPECIAL ANNOUNCEMENT: SECOND TETELMAN MEMORIAL AWARD

A fund has been established in the ERF by friends of Marc Tetelman, M.D., who was a tragic homicide victim while attending the SNM meeting in Atlanta in June, 1979. This fund will permit an award of \$3,000 to be made in June, 1982 to a young investigator (35 years of age or younger) who is pursuing a career in Nuclear Medicine. This award is to be repeated annually. It is possible that additional contributions to our fund will permit the stipend to be increased in future years. Applicants should submit prior to March 1, 1982 a curriculum vitae together with data supporting current research efforts.

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The Society of Nuclear Medicine invites manuscripts for consideration for the Fifth Annual Berson—Yalow Award. Work will be judged on originality and contribution to the fields of basic or clinical radioassay. The manuscript will be presented at the 29th Annual Meeting of the Society of Nuclear Medicine in Miami Beach, FL, June 15-18, 1982, and a suitably engraved plaque will be awarded to the authors by the Education and Research Foundation of the Society of Nuclear Medicine.

The manuscript should be approximately ten pages in length (typed, double-spaced). A letter requesting consideration for the award, including the author's full mailing address and telephone number, should accompany the manuscript. Original manuscript and eight copies must be received by January 18, 1982 at the Society of Nuclear Medicine office, 475 Park Ave. So., New York, NY 10016, Attn: Mr. Dennis L. Park.

DEADLINE FOR RECEIPT OF MANUSCRIPTS: January 18, 1982