LETTERS TO THE EDITOR

Deadtime Correction for Radionuclide Angiocardiography

We have read the article by Adams et al. (*1*) with great interest. They demonstrate the need to calculate, under actual scattering conditions, the percentage of data loss during a quantitative first-pass radiotracer cardiac examination. Nevertheless, we must disagree with their study on a few points.

1. They consider a scintillation camera as a unique paralyzable system. Such a simplified model is not correct. We have shown (*2*) that a camera is composed of at least three stages. The first two are paralyzable but the third is nonparalyzable.

2. The equation used by Adams is valid only for a Poisson distribution of events. This will not be true at the inputs of both the second stage (analyzer) and the third.

3. The double-source technique is not useful in the evaluation of multistage systems, because it is based on a single overall deadtime. In the case of a scintillation camera, this technique provides a faulty data-loss percentage, especially in the presence of scatter.

4. A deadtime varying with experimental conditions is unrealistic because the resolution time of each stage is fixed, depending on electronic components, and is not changed by external factors. The only external factor that affects data losses is the photofraction, as shown by Wicks and Blau (*3*). The photofraction is the ratio of window-accepted events to all events at the input of the pulse-height analyzer. It includes the effects of window width, photopeak centering, scatter, and pile-up proportion. The photon energy was found to modify only slightly the first paralyzable stage and could be neglected for data-loss determination.

There are two methods for the correct calculation of data-loss percentage. One is to determine the photofraction under the conditions of the examination and then to use a decaying source (*2,4*). The other, which is simpler, is to observe the variations in the count rate from a small source placed at the border of the camera field (*5*). These two methods are applicable to cameras of recent or older design and can be proposed for the survey of deadtime performance of cameras.

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Reply

We are grateful to Dr. Devaux for his thoughtful comments on our article and are pleased to answer the questions he has raised.

Our purpose in developing this method for the measurement of paralyzing deadtime was to evaluate camera performance for quantitative nuclear cardiography at counting rates of clinical usefulness, in which data losses do not exceed about 25%. Greater rates, we believe, incur additional radiation exposure of the patient without commensurate improvement in counting statistics. When data losses reach 27%, for example, an increase of 2% in activity yields only a 1% increase in the observed counting rate. Another purpose was to develop a protocol that any good technologist can perform in 15 min without the use of a computer.

We have shown (Fig. 4 of Ref. 1) that four models of scintillation cameras perform in the presence of scatter almost as simple paralyzable systems throughout the clinically useful range of counting rates as defined above. The Picker 4–15 and the Ohio Nuclear 120 cameras continued to follow the paralyzable model precisely up to their maximum counting rates. The Searle LEM deviated from the paralyzable model only above 65,000 cps, and the General Electric Maxicamera showed such deviation only above 50,000 cps. These deviations are of no clinical significance; the Searle camera lost 25% of the data at 36,000 cps, and the Maxicamera lost 25% at 30,000 cps. Therefore the paralyzing deadtime, obtained from the two-source method and the associated equation, predicts data losses with adequate accuracy for quantitative nuclear cardiography.

Whether or not the term "deadtime" can be applied to a quantity that varies with experimental conditions depends entirely on the definition of "deadtime." We define "paralyzing deadtime under scatter conditions simulating quantitative nuclear cardiography" as a term of mathematical convenience, which may differ from pulse-pair resolution of a camera, or the nonparalyzing and paralyzing components obtained when it is analyzed as a multicompartment system. The single value of paralyzing deadtime is far simpler to measure and to apply than the more comprehensive analysis published by Dr. Devaux.

We have found the method based on a decaying Tc-99m source much too slow for a survey procedure. Ideally, the source in its scatter phantom, the camera, and the computer should remain undisturbed for a week-end.

Deadtime correction using a small radioactive source in the corner of the camera field (as distinct from prediction of deadtime losses) is a satisfactory method. We have found the pulse-generator method of Levy (2) even more effective. Pulses are injected into the camera circuitry at a constant frequency, such as 1000 Hz, so as to appear in the corner of the computer matrix just outside the camera field. The small spot is flagged as a region-of-interest and generates a data-loss reference curve in the computer with good statistical reliability and without contributing as much to deadtime losses as the radioactive reference source.

Since both of the methods proposed by Dr. Devaux require the use of a computer, we question their usefulness as survey procedures.

We believe the evaluation of deadtime performance to be useful primarily for the estimation of data losses and for the adjustment of the activity administered to the patient to maintain reasonable counting rates. Correction for data losses is needed

only in a few rarely performed procedures, such as cardiac output and certain shunt determinations; it is not required for the ejection fraction.

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Recirculation of Lymphocytes and the Use of Indium-111

A recent editorial in the *Journal* (*1*) stated that Lavender et al. (*2*) had demonstrated "in two normal and two patients with Hodgkin's disease . . . normal recirculation of lymphocytes through lymph nodes back into blood . . . . " We point out that recirculation *per se* was not demonstrated in those experiments; to do so would require thoracic-duct cannulation. The i.v. injection of indium-111-labeled lymphocytes may indeed result in a recirculation of these cells, but this thesis was not proven in the experiments performed by Lavender et al. All that can be claimed from such experiments is that In-111-labeled lymphocytes migrate to lymphoid organs of humans. Proof that they then leave these organs and enter the blood stream through efferent lymphatics and the thoracic duct requires thoracic-duct cannulation (*3*).

One other point regarding the use of In-111-labeled lymphocytes: unlike polymorphonuclear leukocytes and platelets, which are short-lived in the circulation, PBL are long-lived cells (*4*). As Dr. Goodwin rightfully points out, labeling lymphocytes at the dosage used by Lavender results in approximately 10 million atoms of indium per cell and 8.8×10^5 rads per million lymphocytes in self-irradiation. The effects of these intrinsic doses of radiation on long-lived cells is unknown but one must be concerned about their mutagenic and oncogenic potential. We advise caution, therefore, in the use of In-111-labeled lymphocytes and the restriction of their use to patients with shortened life expectancy, until clear evidence that this presents little if any risk is obtained.

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Reply

The published data on In-111-labeled lymphocytes is limited at present to two papers on rats and mice (*1,2*), and one on humans (*3*); so our knowledge of the method is necessarily small. Some preliminary conclusions may nevertheless be reached.

Rannie et al. (*1*) showed normal recirculation and normal lymph-node images in rats labeled with up to 300 μCi per 10^6 – 10^8 lymphocytes. Similar results have also been reported by Frost et al. (*2*). Frost also showed diminished recirculation with doses in excess of 100 μCi/10^8 lymphocytes, and Rannie showed damage at levels of 200 μCi/ml (10^8 lymphocytes). Both these authors suggested the potential use of the method for the study of lymphocyte distribution and recirculation in man. The points of concern are: (a) damage to the lymphocytes from toxic contaminants such as metal ions in the $InCl_3$ or oxine, or other impurities in the oxine, as well as the self-radiation; and (b) oncogenic transformation induced by the self-irradiation.

Lavender et al. (*3*), using 200-500 μCi in humans, showed cervical, inguinal and mediastinal lymph-node accumulation of activity at from 2 to 36 hr, similar to the distribution shown by Rannie et al. in rats (*1*). Lavender also showed blood disappearance curves in two patients; blood activity decreased immediately to 50% of the injected dose, followed by a slower clearance to 25% at 12 hr. There was then a rise in blood activity of about 10%, followed by a much slower clearance. Although it is true, as Frost states, that thoracic-duct cannulation is necessary to prove that the cells are entering the blood through efferent lymphatics, the organ distribution and the blood disappearance curves found in these patients provides strong, if indirect, evidence for normal recirculation of the In-111-labeled lymphocytes in humans.

Concerning the possible neoplastic transformation of In-111-labeled circulating lymphocytes, the following evidence suggests this is extremely unlikely. In his paper (*1*), Rannie quotes human studies delivering equal or greater radiation to lymph tissue (Ref. *4*: Au-198 and Y-90 therapy of rheumatoid arthritis of the knees), and so far (*5*) no neoplastic events have been noted. Rannie also points out that 10^7 – 10^8 cells represent only 0.1% of the total recirculating lymphocyte pool. The great majority of these cells are nondividing and hence of low oncogenic potential.

More direct evidence bearing on this problem comes from studies on the biologic effects of intimate self-irradiation on mammalian cells labeled with tritiated thymidine (H-3 thymidine) that has been incorporated in DNA of cell nuclei (*6*). This delivers a radiation dose of the same type (low-energy β) and order of magnitude [0.38 rad per decay for H-3 vs. 0.138 rad/decay for In-111 (personal communication, D.J. Silvester)]. Note however that the tritium dose is almost all delivered to the cell nucleus, whereas the In-111 dose is divided between nucleus and cytoplasm with the nucleus receiving less. Biologic end-points determined in the H-3 thymidine experiments include cell death, growth delays, chromosome aberrations, DNA strand breaks, and the induction of mutations. Neoplastic transformation has not been noted.

In view of the existing evidence, which suggests that neoplastic transformation will not be a safety risk, I cannot agree with the recommendation Drs. P. and H. Frost to restrict the use of In-111-lymphocytes to patients with shortened life expectancy. Of more concern is the viability of the labeled cells as a function of the labeling procedure and radiation dose. The determination of these labeling parameters will require carefully planned human studies.

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