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Reply

We thank Dr. Gjedde for supporting our point that variability in rate constants for deoxyglucose is not a serious problem. Further, as mentioned in our letter (*1*), we agree that the more important problem is possible variations in the lumped constant. In our brain-tumor article (*2*), we emphasized that the results (showing high uptake in high-grade gliomas) were obtained strictly with F-18 deoxyglucose (FDG) and do not necessarily reflect actual glucose utilization. Nevertheless we are perhaps more sanguine that such a correlation exists (i.e., that the lumped constant is relatively unchanged). In tissue-culture lines obtained from six of the patients, we indeed found a strong correlation between the in vitro glucose uptake and the tumor FDG activity observed in situ by positron emission tomography (*3*).

We emphasize, however, that the usefulness of the brain-tumor study rests primarily on the empirical correlation with tumor grade and not on the theoretical indication of glucose utilization. In fact, if it should unexpectedly turn out that glucose utilization, unlike FDG, is not increased in high-grade tumors, then the use of FDG would be *de rigueur* for this application.

Finally, we wonder whether "oversimplification," like beauty, lies mainly in the eye of the beholder.

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Re: Time-of-Flight Positron-Emission Tomography Status Relative to Conventional PET

In the editorial by Thomas F. Budinger, some of the analyses of the factors affecting the usefulness of time-of-flight positron-emission tomography may lead, if not properly interpreted, to erroneous conclusions (*1*). Table 1 includes a comparison of the sensitivities of BGO (0.62) and BaF_2 (0.30) crystals for the coincidence detection of annihilation photons. From these values the statement is made that "the poor efficiency of the scintillation detector detracts from the relative sensitivity gain of TOFPET over conventional PET." The values tabulated are for crystals 30 mm in depth, and that thickness was apparently selected as "representative of contemporary approaches." There is no good reason for selecting this particular crystal thickness for TOFPET detectors. Indeed, the three TOFPET devices that have been constructed so far use crystals from 40 mm (LETI) to 45 mm (Washington University and University of Texas) thick. If Table 1 were to include a sensitivity figure for a BaF_2 (or a CsF) crystal 45 mm deep, the crystal's efficiency coincidence would be about 0.74 (*2*). While it is true that the linear absorption coefficients for 511-keV photons in CsF or BaF_2 are lower than for BGO, it does not follow that sufficiently thick CsF or BaF_2 crystals cannot yield an efficiency comparable to thinner BGO crystals. Mullani et al. (Ref. 14 in the above editorial) have demonstrated experimentally that the difference in efficiency yielded between properly designed CsF and BGO crystals is small.

In the above editorial (p. 76), an expression for the spatial error resulting from a difference in interaction depths in opposing detectors is incorrect and incomplete. The maximum timing error for crystals of length z and refractive index n is:

$$\Delta t = \frac{z}{c}(n - 1) \tag{1}$$

and from Eq. 1 of the editorial

$$\Delta x = \frac{z}{2}(n - 1) \tag{2}$$

not

$$z - \frac{z}{n} \tag{3}$$

as shown in the editorial.

Equation (2) provides the value of Δx for one coincidence event. For a number of events the maximum value for Δx is bounded by:

$$z(n - 1) \tag{4}$$

In addition, this expression is inadequate because it does not take into account the exponential absorption of the annihilation photons, whereby this maximum error becomes a very low-probability event. In a thorough analysis of this effect, Gregory has calculated a 53-psec FWHM contribution to time-of-flight uncertainty for 5.13-cm CsF detectors (*3*).

In the editorial, the heart is used as an example of an organ for which the utilization of TOF would yield marginal gains because of the small size of the distribution of the activity. While it is established that the TOF gains decrease with the size of the area imaged, the human heart is an unfortunate selection of an example of that situation because this choice overlooks an important practical aspect of cardiac imaging. In the overwhelming majority of human subjects, a portion of the heart is coplanar in transverse tomographic planes with the liver (see Fig. 1), and the liver often highly concentrates the radiopharmaceuticals (such as labeled

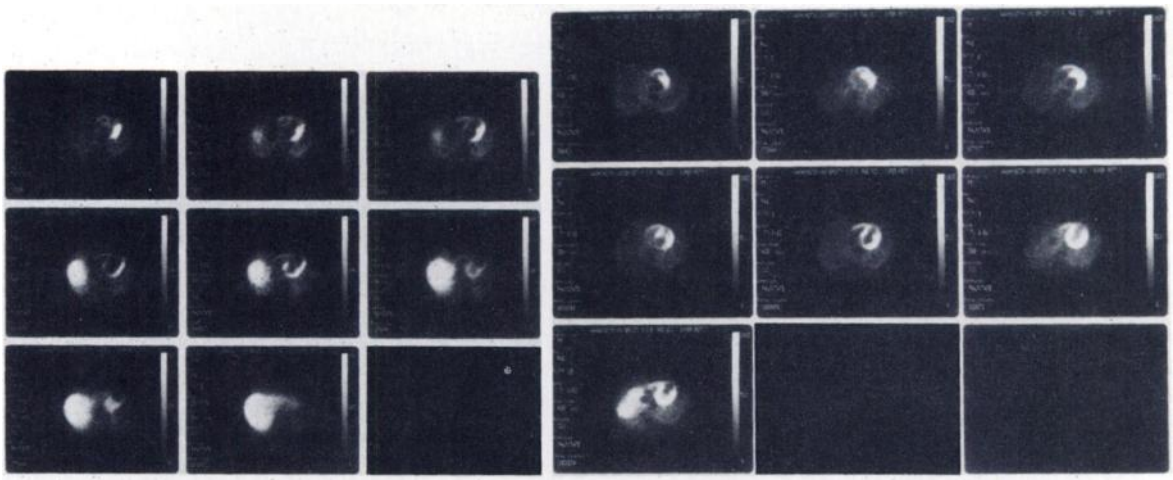

FIG. 1. Transverse tomographic PET images obtained in chest of two human subjects following intravenous injection of C-11-labeled palmitate for assessment of myocardial metabolism. Note high concentration of C-11 activity in liver slices co-planar with some images of the heart. These images were obtained by means of time-of-flight positron-emission tomograph Super PETT I.

palmitate and ammonia) used for the imaging of the myocardium. Other radiopharmaceuticals that have been used with success in the imaging of the heart (such as Rb-82) also exhibit an often high concentration of activity in organs other than the heart (including the liver, lungs, and spleen), which may be transversally co-planar to this organ. This situation is worsened if the tomographic section is selected in the attempt to image the heart in tomographic planes approximately perpendicular to the heart's long axis. It is our experience, from clinical studies carried out for the past 10 mo, that the utilization of time-of-flight has been *particularly favorable* for the imaging of the human heart with C-11 palmitate and Rb-82.

In the editorial the statement is made that "another problem of TOFPET systems at present is the lack of small phototubes required for achieving a spatial resolution competitive with conventional PET." This statement is puzzling. Indeed, one of the smallest photomultiplier tubes currently available for *either* TOFPET or PET applications (Hamamatsu R1635) has a diameter of ⅜th of an inch. However, if one wishes to incorporate smaller crystals into the design of a PET device (with or without TOF) it is possible to couple optically more than one crystal to the photocathode of a photomultiplier tube and use a coding scheme to identify individual crystals. Schemes of that sort are currently being incorporated by several groups (including our own) into the design of conventional and TOFPET systems. To our knowledge, spatial resolution in TOFPET is not limited by the size of photomultiplier tubes and it is competitive with conventional PET.

The above comments are meant only to improve an otherwise perceptive and potentially useful analysis of time-of-flight in PET by clarifying some factors that could lead to misconceptions about this modality.

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Reply

I agree with the clarification of the error in the index of refraction problem. A few years ago I expressed my concerns with respect to the tradeoff between achieving the optimum in time of flight with limited depth crystals and at the same time maintaining high efficiency.

With regard to the efficiency issue, I would like to make the following observations, which might lead to some clarification.

1. The detection efficiency of 0.74 from Vacher et al. is a theoretical efficiency with no description or justification (*1*). I suspect that this is a gross detection efficiency and includes multiple-crystal interactions that are normally rejected electronically. I think we have discussed a similar difference for the single-photon compared with positron issue.

2. I believe that N. Mullani's measurements (Ref. 14) support the conclusions of Table I in the tutorial article. First, he made measurements on 2 × 2 × 3 cm BGO compared with 2 × 2 × 7 cm cesium fluoride. Even with this important difference in the depth of crystals, the coincident efficiency ratio was still $(0.4/0.52)^2 = 0.59$. The conclusion from Table 1 in my article is 0.48 for 1.5 × 3 × 3 cm crystals. Based on these arguments, I believe that CsF and BGO do not compete well. Clearly, as one uses deeper crystals, the efficiency will improve, but then that is at some cost; this was the main point I endeavored to make in the discussion of index of refraction.

Whereas the liver does protrude into the field when examining the apex of the heart, particularly in a nontilt mode, the overwhelming majority of human subjects have this contamination in only one section. The major sections we have usually examined in our rubidium studies do not have liver contamination. Of course, to examine the posterior wall and inferior wall of the heart well, one should tilt the system, and this will lead to a larger effective number of resolution elements. Whereas light piping is always a solution, it comes at some cost.