becomes negligible and the expression reduces to

$$C_B(t) = \lambda S(t - \lambda/f),$$

which describes a straight line of slope λS, intersecting the time axis at the point $t = \lambda f$. Since, by definition, the slope of the arterial concentration $C_A(t)$ compared with time (t) is S, the partition coefficient, λ, can be determined by comparing the slope of $C_A(t)$ with the slope $C_B(t)$ as obtained in an experiment with a constant value of f. Once λ is known, the value of f can be obtained from the intersection λ/f. The ramp injection of tracer permits the establishment of slope and intercept parameters by linear regression analysis. If the model is valid, then λ can be evaluated for each region of interest, eliminating the assumption of an average λ value.

The PET/autoradiography approach to measurement of cerebral blood flow requires a tracer that maintains its chemical integrity throughout the course of the study, and that data collection must not begin until the arterial concentration is defined as a constantly increasing function. Ginsberg et al. (*8,9*) used a modified ramp technique, but were limited to short-duration PET studies due to the in vivo instability of [C-11] 4-iodoantipyrene. We have used the ramp injection technique and the above model for CBF measurements with 10 ml (40-50 mCi) of $H_2{}^{15}O$ injected into baboons positioned in the PET VI. Three 30-sec scans are collected every 60 sec beginning 3 min after the onset of the ramp injection. The ramp approach is particularly suited to research with animals, since it permits physiological parameters to be altered during a series of experiments in which the animal serves as its own control.

We would prefer the bolus injection technique and a PET/autoradiographic model in which the assumptions are minimized. In this regard we have described (*10*) an algorithm to reconstruct PET count-rate curves from total counts. A source of error may be due to the radioactive decay. With the ramp injection, this error (*8*) is less than 0.02%, but with the bolus injection the error may be larger; Raichle et al. (*3*) claim less than 4% error for bolus injection as determined by simulation. We wrote about this error (*10*) and have described a more precise estimate of the correction needed when the counting time is larger than one minute. The algorithm (*10*) is being adapted for utilization in the simultaneous determination of CBF and λ following bolus injection of tracers. Without the aid of appropriate algorithms, we agree that it is preferable to minimize the duration of a PET determination of CBF to less than 1 min following the bolus injection of the tracer.

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Reply

We appreciate the detailed comments of Lambrecht and Rescigno, which relate not only to our adaptation of the Kety autoradiographic technique to positron emission tomography (PET) (*1,2*), but also to their own work in this field (*3,4*). They raise several issues worthy of comment.

Our approach and that of Lambrecht and colleagues are both based on the Kety tissue autoradiographic technique for measuring local cerebral blood flow. However, we use a bolus intravenous administration of radiotracer, rather than the ramp arterial input used by Lambrecht et al. (*3*). To our knowledge, Kety and his colleagues did not specify a ramp injection technique, they used a continuous intravenous infusion of radiotracer over one minute (*5-7*). This results in a sigmoid shaped arterial time-activity curve (*8*). Ginsberg (*9*) noted, in fact, that the exact form of the arterial concentration function is not critical, although a monotonically increasing function—not necessarily a ramp—is required to ensure a unique solution of the operational equation for flow. However, as we and others have shown (*1,10,11*), because the PET autoradiographic approach involves an integration of Kety's operational equation, one does *not* require that the arterial concentration be a monotonically increasing function with time. Furthermore, although Ginsberg et al. did use a modified ramp technique (*12*) to measure CBF in the rat with an external detection system, their one-minute radiotracer infusion time was not limited by the "in-vivo instability of C-11 4-iodoantipyrine" since they used oxygen-15 water as the flow tracer. In the study using C-11 iodoantipyrine (*13*), regional CBF was measured by indicator fractionation, not the Kety autoradiographic method, and a bolus radiotracer injection, not a modified ramp. Because the indicator fractionation method demands a very brief infusion period, a short study length (7 sec) was used (14).

We wish to clarify the statement of Lambrecht and Rescigno that a bolus input requires "guesswork associated with starting the PET data collection at precisely the time when the peak radioactivity reaches the brain." We stated that the PET data collection is started at the time of arrival of radioactivity in the brain. This is easily accomplished by observing the bank pair coincidence counting rate of the PETT VI system. Furthermore, this start time

is *not* critical, although it must be recorded accurately for subsequent data processing.

We agree that the effect of data collection length appears to be a feature specific to the Kety autoradiographic model, and we indicated that infusion length is a factor in the tissue sampling or autoradiographic approach as well as in its PET adaptation. Although Ecklöf et al. (*15*) attributed this effect to a permeability limitation of the flow tracer, we have also observed this phenomenon with C-11 butanol, a freely diffusible tracer. Thus the basic one-compartment approach of Kety may inadequately characterize radiotracer behavior in the brain, and we are currently studying extensions of this model.

Lambrecht and Rescigno have contrasted their mathematically innovative approach, which requires a ramp arterial concentration of radiotracer, to our technique using a bolus injection of tracer. Their operational equation requires a knowledge of the instantaneous tissue concentration of radiotracer as a function of time. This function cannot be measured directly, due to the limited temporal resolution of PET, but rather it is calculated from accumulated tissue counts (*3,4*). Lambrecht and colleagues have successfully designed a complex servo injector system to provide a ramp arterial radiotracer concentration (*3*). They have recently described PET measurements of CBF in cats (*3*), and also indicate that their approach has been used in baboons. However, its extension to human subjects may be limited. The servo injection device requires the placement of an arteriovenous shunt, which is considerably more complex than the use of the arterial catheter required by other techniques for measuring CBF with PET (*2,16,17*). Furthermore, a ramp infusion of radiotracer that lasts several minutes and yields sufficient tissue counts to permit accurate reconstruction of the required instantaneous count rate function may result in high radiation exposures and/or may require initially a large amount of radiotracer activity in the infusion syringe. This appears probable if the 40–50 mCi activity used in baboons is extrapolated to humans.

Lambrecht and Rescigno indicate that the ramp method has the useful feature of permitting repeat experiments to be performed in experimental animals serving as their own control, and they have demonstrated this approach (*3*). Other techniques, including our own, which use the short-lived flow tracer $H_2{}^{15}O$ (*2,16,18*), have this capability for human as well as animal studies. We have used the PET autoradiographic method with an intravenous bolus injection to obtain eight separate flow measurements under different physiologic states in the same subject over a 2-hr period. We agree that the approach of Lambrecht and colleagues, as well as methods proposed by others (*16,19*), which allow the simultaneous determination of cerebral blood flow and partition coefficient of the flow tracer, are of value, although they are not essential should the proposed method, such as ours, be relatively insensitive to error in the assumed value of partition coefficient (*1*). In this regard we note with concern that repeat experiments with the ramp approach of Duncan, Lambrecht, Rescigno et al. gave substantially different values for partition coefficient for 4-[F-18]fluoroantipyrine at different flow values in the same animal (*3*), namely 0.61 at a flow of 0.46 ml/(min-g), and 1.0 at 0.2 ml/(min-g). This result is puzzling because the partition coefficient has been defined and used by Kety and numerous other investigators (*5–7*) as the equilibrium brain-to-blood radiotracer concentration ratio, and barring pathological changes in tissue, has been treated as a constant that is independent of both flow and time.

Lambrecht and Rescigno have noted, as we have, that a method for correcting the tomographic scan data for radioactive decay is required, since this is not done by the PETT VI tomograph. This is more complex for a bolus input than for a ramp. While it is true that preliminary simulation of a broad range of theoretical activity profiles shows the expected errors of our decay-correction method to be less than 4%, even extreme *biological* examples can be shown to have much less error. For example, consider the case of an instantaneous bolus, i.e., delta function, of $H_2{}^{15}O$ arriving at the brain at the start of a 40-sec scan, and a rapid washout with CBF = 100 ml/(min-100g). Assuming an initial tissue counting rate of 100 cps, a tracer partition coefficient of 0.95 ml/g, and a decay half-life of 123 sec, the actual counts collected during the scan would be 2614, and the true decay-corrected counts 2886. Using our decay-correction equation, the correction factor would be 1.118, yielding an estimated true count equal to 1.118×2614, or 2922. Comparison of the true actual decay-corrected value (2886) with the estimated value (2922) shows that the error is +1.2%. We believe that this error represents the true "worst case" that would be encountered using this decay-correction method and $H_2{}^{15}O$ injection. An alternative method is to incorporate the radioactive decay constant into the formulation of the operational equation (*20*).

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Re: Quantitative Hepatic Arterial Perfusion Scintgraphy and Starch Microspheres in Cancer Therapy

In their recent paper (*1*), Ziessman et al. described an innovative addition to intraarterial chemotherapy of hepatic tumors. They proposed infusing degradable starch microspheres (DSM) into the hepatic artery, together with the chemotherapeutic agent, so as to slow hepatic arterial flow and increase contact time between drug and tumor. They pointed out that this effect would be achieved only if there was no offsetting increase in shunting away from the liver, and they desribed infusion of Tc-99m macroaggregated albumin (Tc-99m MAA) with DSM, to detect any changes in shunting.

Chemotherapeutic tumor dose is determined by the fraction of injected drug that reaches the tumor and by the duration of tumor exposure to the drug. Vascular occlusion by DSM attempts to increase tumor dose by prolonging exposure, while increase in extrahepatic shunting would decrease tumor dose by decreasing the fraction of drug reaching the target. It is necessary to measure extrahepatic shunting, and one must also measure intrahepatic flow distribution, as this is equally important in determining tumor dose. Intraarterial infusion of Tc-99m MAA shows that there is preferential perfusion of tumor in many patients (Fig. 1). Kaplan et al. (*2*) have shown that this pattern of preferential perfusion is associated with a positive response to hepatic-artery chemotherapy, whereas poor or absent perfusion is associated with no response. It is important that intraarterial injection of DSM not redistribute flow away from tumor towards normal liver, as this would

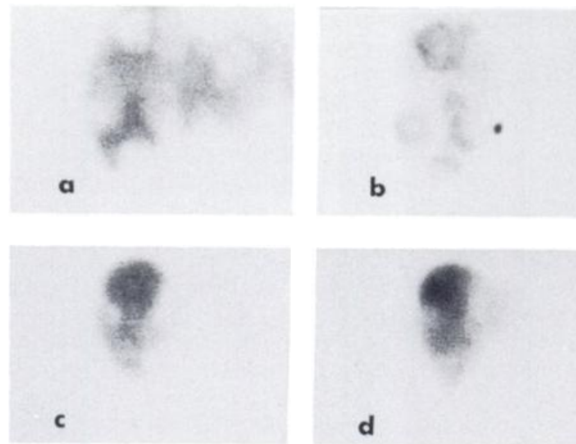

FIG. 1. Scintiphotos of liver, taken after i.v. injection of Tc-99m sulphur colloid (A & C) and after hepatic-artery infusion of Tc-99m macroaggregated albumin (B & D). A & B show preferential perfusion of tumor in right lobe, and C & D show poor perfusion of tumor throughout.

reduce the fraction of drug reaching the tumor. Such redistribution would not be detected by measurements of extrahepatic flow; studies of intrahepatic flow would be necessary.

Intrahepatic distribution could be measured at the same time as extrahepatic shunting, using serial infusions of Tc-99m MAA and DSM as described by Zeissman et al. Any major changes in the pattern of hepatic perfusion should be apparent on subtraction images of the liver. Zeissman et al. obtained images of the liver in the course of measuring extrahepatic shunting, but did not describe their findings in this regard.

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Reply

The purpose of our recent article (*1*) was to describe a quantitative method of calculating extrahepatic perfusion and A-V shunting to the lung using Tc-99m MAA hepatic-arterial perfusion scintigraphy (HAPS). In this study we demonstrated how this extrahepatic component changes with increasing doses of degradable starch microspheres (DSM), a new adjunctive agent for intraarterial chemotherapy. Extrahepatic flow can potentially result in less drug delivery to the tumor, with increased systemic exposure and potential toxicity. Drs. Valk, Guille, and Crea correctly point out that intrahepatic changes in blood flow away from the tumor towards uninvolved liver during starch administration