LETTERS TO THE EDITOR

Re: In Vivo Methods for Measuring Regional Glucose Metabolic Rate (GlMR)

I am writing to comment on in vivo methods for measuring regional glucose metabolic rate (GlMR) using deoxy-D-glucose. The three compartment model developed by Sokoloff (*1*) for autoradiographic studies has been extended by Phelps (*2*) and Huang (*3*) and recently been recast by Brooks (*4*) for in vivo clinical studies with tomographic imaging. In addition to the tissue activity at time T and the time activity blood curve to that time, the method utilizes values of the model's rate constants. The method presumes that the real values of the rate constants do not vary from the normal values sufficiently to affect the accuracy of the method. My concern is that readers may conclude that the values for rate constants are only indirectly related to glucose metabolic rate, and that when evaluating abnormal metabolic rates the problems associated with abnormal rate constants may be overlooked.

Given that the three-compartment model is valid, the GlMR is related to rate constants and stable glucose in the blood, Cp, in the following manner:

$$GlMR = \frac{1}{LC}\frac{k_1 k_3}{k_2 + k_3} Cp \qquad (1)$$

Therefore, regional GlMR can not change without regional changes in k_1, k_2, or k_3. Conversely, the expected values for the rate constants can in theory vary significantly while GlMR remains absolutely constant. Intuitively, if the rate constants are the model's parameters describing transport of tracer, then every aspect of transport (including metabolic rate) must be a direct function of the rate constants. Equation 1 is given in the literature, but its implication is not stressed.

The Sokoloff method is dependent upon the tissue activity containing sufficient information about GlMR to make exact knowledge of the rate constants unnecessary. Patlak (*5*) has shown this to be true if dephosphorylation is minimal ($k_4 = 0$) and the entire area under the time-activity curve can be evaluated. Unfortunately, the dephosphorylation is significant. In addition, measurement of the total area under a blood curve can be difficult. Small components with long residency periods may be indistinguishable from background and still represent a significant portion of the total area.

Phelps evaluates the tissue activity at a finite time and incorporates all the rate constants including k_4 into the working formula. If the variations in the rate constants stay within a certain range, a reasonable estimate of GlMR is achievable. It is inappropriate to refer to these variations as errors in the rate constants, since it is precisely these changes that lead to the regional variation in GlMR. As a result, an exact measurement of GlMR, which must be conducted in a finite time period and in the presence of dephosphorylation, is impossible without exact values for the rate constants.

Huang (*6*) discusses the expected error as rate constants deviate from their normal values. Using his example, it can be shown that an abnormal GlMR (33% of normal) can lead to error in the predicted values as much as 50% depending on how the values of rate constants that lead to the reduction in GlMR are altered [$k_1 = 0.025$, $k_2 = 0.225$, $k_3 = 0.176$ (min^{-1})]. It is also conceivable that changes in the rate constants could double or triple the predicted value of GlMR while the real GlMR remains unaltered ($k_1 = 0.125$, $k_2 = 0.025$, $k_3 = 0.009$). The possibilities expand if the value of k_4 varies.

This is not to say that any of these variations actually occurs. In the second example, the value of $k_1 = 0.125$ is normal, but the values of k_2 and k_3 combine to give a blood/tissue partition coefficient that would be very unusual. Nonetheless, it is important that the rate constants be re-evaluated for each new situation to which the method is being applied. As was mentioned at the Miami meeting, the UCLA group (*7*) is rigorously monitoring the rate constants and the effect of any changes on the accuracy of the glucose method. However, values recently reported for GlMR in cerebral gliomas (*8*) or in case of acute ischemia (*9*) were presented without any re-evaluation of the rate constants. In general, clinical application of this method should be postponed until those groups most familiar with the method have had the opportunity to map out the variations in the rate constants and evaluate their effect on the accuracy of the method. It would also be constructive to have a comparison between GlMR determined with and without measuring the rate constants in a manner similar to Huang's analysis of his computer simulations.

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Reply

Dr. Selikson's comments are appropriate in stressing the well-known fact that the FDG rate constants may change unpredictably, not only from patient to patient, but also from one brain region to another within the same patient, particularly in pathologic conditions. The effects of such changes on the calculated GlMR have been the subject of theoretical (*1-2*) as well as patient (*3*) studies. The results of these studies demonstrated that large changes in rate constants could result in relatively marked errors on calculated GlMR. In our paper (*4*), we pointed out that the GlMR values found in stroke patients using the in vivo autoradiographic approach of Phelps et al. (*5*) (which includes k_4, the FDG-6P dephosphorylation rate constant) should be interpreted with caution, a fact stressed earlier by Kuhl et al. (*6*). We also indicated that more accurate GlMR measurement could be obtained if kinetic analysis of the F-18 cerebral accumulation curve is performed, a procedure by which the FDG rate constants can be estimated regionally. We are currently analyzing the data in this way and comparing in the same patients the GlMR values measured by both methods in order to establish further the validity of the autoradiographic approach using adapted (e.g., "ischemic") rate constants. We therefore agree with Dr. Selikson's suggestion that more work is needed if reliable measurement of regional GlMR in pathologic conditions is desired.

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Reply

No one can argue with the fact that deviations in the dynamic rate constants for the transport of deoxyglucose will affect values of glucose metabolic rate (GMR) as determined by the Sokoloff method. However, the situation is not as black as Dr. Selikson indicates. For one thing, he failed to point out that the simplified formula presented in his Ref. 4 reduces the error caused by these deviations, and this reduction ranges from 10% to 50% for the two examples cited. Another fact not mentioned is that, by doing patient scanning during the dynamic uptake period, one can completely eliminate the effect of the deviations (*1*).

It is not correct that the cerebral glioma project at our institute did not include a rigorous monitoring of the rate constants. As mentioned in the article (*2*), and as reported in more detail at the American Neurological Association meeting (*1*), we have measured these constants in gliomas by dynamic scanning and found them to be relatively unchanged.

Finally, one should be very cautious about recommending the abandonment of noninvasive clinical measurements because their accuracy is in question. It is often difficult in medicine to measure basic quantities with absolute accuracy. The point is that the quantity measured, even if it includes "contaminating" effects, may be of great clinical value. This has proven to be the case in our glioma study, where any shifts in rate constants and lumped constant (which may be of even more concern) have not prevented this method from becoming the most successful technique for diagnostic grading of these lesions.

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Re: Indium-111 Tropolone Versus Oxine

We should very much like to support the comments of Dr. Goedeman (*1*) on the following subjects.

1. The solubility of oxine in aqueous acidic solutions is good, and crystalline oxine may be dissolved directly in concentrated acid at concentrations of 100 mg/ml, thus avoiding the need for ethyl alcohol as a solvent. This is apparently the case for both commercially available European oxinates (*2,3*).

2. The comments regarding the labeling efficiency with tropolonate (*4*), subsequently supported by the work of Danpure et al. (*5*), show that in plasma, cells can be labeled only if concentrated five- to tenfold, and the labeling efficiency is then only 50-70%. In contrast, the indium-binding ligands, oxine, acetylacetone, and tropolone, will all, in the absence of plasma and in physiological cell concentrations, give almost quantitative labeling efficiency in very short labeling times of less than 2 min (*6*). This is the case for both platelets and leucocytes of common laboratory animals and man.

3. It is dangerous to extrapolate platelet labeling data obtained from canine experiments, since canine plasma is less effective than human plasma at inhibiting indium-oxine uptake. This is probably due to a decreased concentration of lipoproteins in the dog (*7*).

We stress further that in the search for the ideal cell-labeling method, cell function in vivo must be retained at all costs. This can