results confirm this trend on a larger scale (*4*). In 59 apparently healthy male nonsmokers aged 19–73 yr (mean = 49.8 ± 13.5 yr), the regional uptake of thallium in the thighs and calves was found to be negatively correlated with age ($r = -0.40$; $p < 0.001$ and $r = -0.23$; $p < 0.05$). Indexes of asymmetry in the calves only were also weakly but significantly correlated with age ($r = 0.23$; $p < 0.05$). This suggests subclinical peripheral vascular disease in some patients although none of them had coronary artery disease or smoking habits. This study shows how difficult it is to define normal values for indexes of asymmetry, particularly in older male patients who have a relatively high prevalence of subclinical atherosclerosis. Nevertheless, asymmetry seems to be a more specific sign of peripheral arterial disease, although it remains to be quantified at each level of the legs with the buttocks being more asymmetric than the thighs and calves. In another study (*5*), 114 male patients with proven coronary artery disease exercised at levels near their maximum capacity. Whole-body thallium scintigraphy showed an asymptomatic interextremity asymmetry in 54% of the cases. The prevalence of this sign increased with age, from less than 14% for those younger than 45 yr to 65% in patients older than 65 yr. These results were obtained by both the lecture of analogic images and quantitative analysis which confirmed (1) the relatively low prevalence of decreased unilateral or bilateral fractional uptake in the whole population and (2) the lack of correlation between the prevalence of this sign and age.

I believe that whole-body thallium exercise scintigraphy has to play an important and growing role in the noninvasive detection of silent or subocclusive peripheral vascular disease and the evaluation of multifocal atherosclerosis. Normal distribution of thallium during exercise in the legs should be more precisely defined and quantified in larger populations. The performance of such a method clearly depends on this fundamental step, at least in its diagnostic applications.

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REPLY: Dr. Tellier states that asymmetry is a more specific sign of peripheral arterial disease than fractional thallium uptake on whole body imaging. This is true, but experience has taught us that the sensitivity and overall accuracy of the study is improved by adding other quantifiable measures such as fractional uptake. Bilateral disease causing a balanced reduction of flow is not rare and would be overlooked if one relied solely on the presence of asymmetry. I was disturbed by Dr. Tellier's finding that 54% of male patients with coronary artery disease who do not have claudication show interextremity thallium asymmetry. It would be important to know the degree of asymmetry. We have found that an interextremity symmetry ratio of ≤90% is a specific disease marker in asymptomatic older men. I agree with Dr. Tellier that the normal distribution of thallium in the legs following exercise should be studied in larger populations. However, anyone can easily and quickly generate a practice-specific normal data base that can be immediately applied to clinical practice.

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Fluorodeoxyglucose, Myocardial Perfusion and Myocardial Cell Death

TO THE EDITOR: The success of positron emission tomography (PET) in the clinical setting depends upon the credibility factor, i.e., the demonstration that the science behind cardiac PET is sound. Otherwise, PET will be slowed down by uncertainties.

Opie and Camici (*1*) wrote a provocative editorial in the August issue of *JNM* on myocardial blood flow, deoxyglucose uptake (FDG) and myocyte viability in ischemia. Bianco and Wilson also wrote an editorial (*2*) which is pertinent to several sections of the Opie and Camici editorial and is consistent with our experimental findings and with the work of others. I would like to discuss some of the controversial scientific points.

Myocardial Hibernation

This clinical entity, the most important indication for a cardiac PET scan, can be assessed with: PET and FDG, PET and ^{11}C-acetate, the stress/reinjection ^{201}Tl technique or with dobutamine wall motion echocardiography. As Opie and Camici state, and contrary to opinions by others, FDG does not measure the metabolic rate of glucose. In fact, as shown by Lear and Ackermann (*3*), FDG studies underestimate energy production when substrates other than glucose are being metabolized. FDG studies also underestimate energy production when glycolysis occurs. One must note that glucose and FDG may both have differences in affinity for the transmembrane sugar transporter and for hexokinase (*1*). Opie and Camici accurately state that crucial data linking glucose extraction and myocardial blood flow have been missing. Stanley et al. (*4*) showed that after 50 min of myocardial ischemia (blood flow = 40% of control) the rate of glucose uptake in swine did not change, although its extraction was significantly increased, regional blood flow was decreased and delivery of glucose was curtailed. Under these conditions, increased glycolysis is not related to glucose uptake but rather to accelerated glycogen breakdown.

Finally, the data from Bergmann's laboratory (*5*) indicate that FDG activity in reversible as well as in persistently dysfunctional myocardium is markedly variable. Therefore they recommend that ^{11}C-acetate rather than FDG should be used to detect dysfunctional but still viable myocardium in patients likely to benefit from coronary revascularization. The science behind the use of FDG for detecting viability and for predicting improvement after revascularization is in its infancy.

Acute Myocardial Ischemia

Opie and Camici discuss the research of Kalff et al. (*6*), in which FDG uptake during acute myocardial ischemia without reperfusion was higher than myocardial blood flow until regional cardiac blood flows were less than 20% of normal. However, Opie and Camici say that Kalff et al. did not measure glycolytic flux or cell necrosis. Thus, the issue of myocardial cell protection cannot be proven.

In our studies (*7*) of myocardial ischemia with reperfusion using high-resolution cardiac autoradiography and quantitative histology (not referenced in the editorial), FDG uptake occurred in some areas that showed acute myocardial infarction. We have postulated that under these conditions, FDG uptake may be occurring in inflammatory cells such as macrophages (*8*). There are data that indicate that FDG and PET are less reliable as a metabolic descriptor in patients with recent myocardial infarction (*9,10*). According to Opie (*11*), PET imaging may not completely resolve cell admixture (viable versus nonviable cells during ischemia). After all, border zones in the ischemic myocardium are less than 1 mm in width. Thus the role of FDG in the evaluation of acute myocardial infarction is unclear.

Conclusion

FDG and PET may have major limitations in assessing the hypothesis that glucose metabolism and glycolysis may sustain myocardial viability in myocardial ischemia. Certainly, ^{11}C-glucose, ^{15}O-water, or ^{11}C-acetate or NMR spectroscopy (e.g., ^{13}C turnover studies of the Krebs cycle) may provide the means to test the hypothesis that glycolysis delays or prevents ischemic cell death.

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REPLY: Dr. Bianco refers to the question of myocardial ischemia followed by reperfusion, a subject we had not emphasized in our editorial (thus explaining why his recent article (*1*) had not been referenced). In his article, it is evident that the longer the duration of ischemia in his rabbit heart model, the less uptake of deoxyglucose administered during the reperfusion period. As stressed by Dr. Bianco in his letter, the measurement of the uptake of tissue deoxyglucose does not allow the computation of glucose oxidation nor of glycogen synthesis. However, the uptake of deoxyglucose reflects the utilization of exogenous glucose since both share the same transmembrane transporter, although with different affinities, and are good substrates for hexokinase. If the value of the lumped constant (a factor which corrects for the differences in affinity between glucose and deoxyglucose is known, then exogenous glucose utilization (μmol/min·g) can be computed with deoxyglucose. Certain suggestions can be made in relation to the data in the article by Sebre et al. (*1*), bearing in mind the above observations. The severity and consequences of acute myocardial ischemia are dictated by a number of factors, including the degree of coronary blood flow reduction and its duration, which in addition seems to be a species-specific phenomenon. However, it is reasonable to assume that ischemia times of up to 15–20 min should not induce significant tissue necrosis. Under these circumstances, myocardial glycogen breakdown is invariably activated while the uptake of exogenous glucose is dependent on residual flow. This explains why increased postischemic deoxyglucose uptake, which probably reflects tissue glycogen repletion, can be easily detected following an episode of transient ischemia. By contrast, deoxyglucose uptake during transient ischemic episodes may be variable (*2*). The shorter the duration of ischemia, the more likely the myocardium will be viable, which would explain the greater relative uptake of deoxyglucose after 15 min of ischemia compared with 30 min in the paper by Sebre (*1*). This is not given by the ^{201}Tl data in their Table 2.

In postischemic, but predominantly nonviable myocardium, there is a mixture of dead and viable cells, so that deoxyglucose data would reflect low overall rates of uptake although a high rate may be present in viable postischemic cells. This may explain the apparently poor performance of deoxyglucose as a marker of necrosis, as shown in Sebre et al.'s Fig. 1.

In clinical studies, however, the myocardial signal derived from deoxyglucose would be compared with that derived from $^{13}NH_3$ or another flow marker. The concept would be that a reduction of deoxyglucose uptake may occur both in viable and nonviable myocardium. Only in viable myocardium is the reduction of deoxyglucose less relative to that of the degree of reduction of flow in that segment. As far as we can see, this concept is not negated by the data of Sebre et al., in which coronary flow was apparently not measured. Our editorial did not touch on the subject of hibernation, however, this subject is covered in a recent review by one of us (Uren and Camici, *Cardiovasc Drugs and Therap*, 1992;6:273–279). That article emphasizes that the mismatch of blood flow to metabolism has a high predictive accuracy for the recovery of contractile function after revascularization.

We agree with Bianco that factors governing the uptake of deoxyglucose are complex and cannot be simplified. As we stated in our editorial: "crucial data must still be collected" to show a relationship between decreased glycolytic flux and cell necrosis. We agree that multiple approaches, experimental and