PET Scan Controversy Aired

Critics say that some of the biochemical assumptions that underlie positron-emission tomography are invalid

Positron-emission tomography (PET) has achieved considerable prominence, and with good reason. The technique, which has been developed through the past 7 years, produces colored, contour images of the brain that are supposed to reveal areas of high and low neural activity. The potential applications of PET to research on brain function and to clinical diagnosis of a range of pathologies are obvious and explain why the National Institutes of Health has been willing to sink well over $20 million into almost a dozen centers since 1979. Many of these programs are up for review, with "glowing" reports being turned in. "PET is an investment that has paid off," says one NIH official.

Behind the enthusiasm over apparently being able to image the activity of a living human brain, however, there has rumbled a dispute that challenges some of the key biological assumptions that underpin the technique. If these assumptions do turn out to be invalid then PET, as currently operated, would at best give poor quantitative resolution and at worst be virtually useless qualitatively.

The key arguments revolve around what appear to be prosaic points of brain biochemistry where matters of fact ought to be readily resolved. This, however, has been far from the case.

Differences of opinion over the basic biochemistry upon which PET depends have been voiced both privately and publicly in the strongest terms, with little apparent movement towards building bridges between the two sides. "Lots of groups are publishing numbers that are hogwash," contends William Pardridge, of the Center for the Health Sciences at the University of California, Los Angeles. "The criticisms are not based on scientific grounds," retorts Louis Sokoloff, of the National Institute of Mental Health, Rockville, Maryland, who, with Martin Reivich, of the University of Pennsylvania School of Medicine, developed a metabolic model that helped open the way to PET. Sokoloff shared the 1982 Lasker Award for his part in developing the technique.

With considerable scientific and institutional momentum now behind PET, there is an understandable disinclination to change course with the project, still less halt it. Yet critics suggest that unless the underlying brain biochemistry is more clearly understood, any effort to interpret brain function using PET is certain to devolve into what they derisively call "psychobabble." Proponents of the technique do not deny the existence of certain problems, but say the critics' quibbling will slow the evolution of the system.

The basic concepts behind PET are appealingly simple and its technical implementation masterfully impressive. The biochemistry depends on the brain's requirement for glucose, which is taken up from the blood, as its sole energy source. And the more active a particular brain center is, the more glucose it needs to drive the activity. In principle, PET builds up a profile of energy demand throughout the brain by measuring glucose uptake in a series of "slices" or planes.

> The criticisms of PET are not based on scientific grounds, its proponents say.

The source of radioactive signal upon which PET depends—positrons—is not in contention in this context. Positrons are short-lived, and when they annihilate they emit two equal gamma rays simultaneously in diametrically opposite directions. Computerized detectors pinpoint where a positron decayed. With some kind of positron-labeled glucose circulating in a patient's blood, energy demands of different areas of the brain are reflected in differential densities of positron annihilations, which can be translated into colored contour maps.

The dispute over PET's validity centers on the nature of the positron-labeled glucose—actually, a glucose analogue—and the way it is handled metabolically in brain cells. This uncertainty reflects a broader unease that glucose metabolism in the brain might be more complex than is presently understood. Perhaps subtleties in the way nerve cells handle glucose undermine the mathematical transformations that underlie PET.

From the beginning Sokoloff and Reivich have argued that, because glucose use is both very complex and very rapid, it would make sense to substitute an analogue that would go some way along the metabolic chain and then stop, thus making measurement less uncertain. Based on somewhat parallel work on autoradiography in animal brains, they decided to use a deoxy derivative of glucose. This glucose analogue can go only one step along the energy-releasing pathway, being converted to deoxyglucose-6-phosphate by the enzyme hexokinase. (In fact, the molecule used in PET is a flourine derivative of deoxyglucose, because the halogen is readily positron-labeled in a cyclotron. Access to a cyclotron is therefore a prerequisite for any PET program.)

A key part of the Solokoff-Reivich model is that not only does deoxyglucose-6-phosphate come to a halt in the metabolic pathway, but also it does not go back, by losing its phosphate residue, at any significant rate. This supposed stability of deoxyglucose-6-phosphate has been an issue of contention for more than 5 years.

The most vociferous, and possibly most extreme, of the PET critics is William Sacks, of the New York State Rockland Research Institute in Orangeburg. "There is no way to untangle the deoxyglucose data to interpret the results," he says. "You can't infer anything about glucose metabolism from these data." According to Sacks, Solokoff incorrectly concludes that glucose itself is too rapidly metabolized to be monitored accurately. Radioactively labeled glucose will, says Sacks, give reliable measurements that do not have to be subjected to the full mathematical battery made necessary when using the deoxy derivative.

"The quantitative errors incurred in using glucose are so enormous that it would not be worth the trouble," counters Solokoff. The rapid metabolism of glucose would force one to rely on very early measurements, which in turn would depend on very accurate determinations of rate constants, he contends. Any tardiness in making measurements would invalidate the rate constants, resulting in errors of as much as 400 percent. "That's why we go to the deoxyglucose, which is trapped for a relatively long time."

At the core of Sokoloff and Reivich's mathematical treatment of data on deoxyglucose is a correction factor called the lumped constant. It consists of components to reflect the rate at which the

glucose analogue crosses the blood-brain barrier, is phosphorylated in nerve cells, and loses the phosphate again. It also contains manipulations to account for metabolite pool sizes, thereby allowing the rates to be compared with those for glucose itself.

"Sokoloff led people to believe that the lumped constant, once determined for a particular species, need not be worried about," says Pardridge. "But probably only one component is constant. The lumped 'constant' is lumped, not constant." Richard Hawkins of the Hershey Medical Center agrees, saying that figures for the constant vary according to when data are obtained.

Sokoloff concedes that there is a problem with the lumped constant and that this is exacerbated in various pathological conditions. "It would be nice if it were like pi, but it's not," he says.

The skirmishes over the validity of the lumped constant appear mild, however, when compared with the differences of opinion over the supposed stability of glucose-6-phosphate. Hawkins and his former colleague Alexander Miller, who is now at the University of Texas Medical Center, San Antonio, have for 5 years been concerned that the degree of instability of the phosphate derivative that they see in their experiments means that an accurate measure of glucose flux is impossible with PET. When deoxyglucose-6-phosphate is dephosphorylated, the deoxyglucose produced is free to either diffuse out of the cell or become rephosphorylated. Either way the glucose flux measured by PET is likely to have at least some margin of error.

Hawkins and Miller recorded a half-life for deoxyglucose-6-phosphate of about 70 minutes in rat brains, whereas Sokoloff claims there is virtually no breakdown by this time. There have been numerous exchanges in the literature on this point, each side suggesting that the other is in error in some way. Hawkins wrote a strongly worded letter to Sokoloff in April 1982, pointing out where he thought Sokoloff had erred in calculating the stability of the phosphate molecule and complaining about what he interpreted as misrepresentation of his and Miller's work. Hawkins invited a reply but received none.

Meanwhile, Richard Veech and Mingta Huang, of the National Institute on Alcohol Abuse and Alcoholism, Rockville, Maryland, had been working on the enzyme that carries out the dephosphorylation reaction in the brain, glucose-6-phosphatase. The debate between Hawkins, Miller, and Sokoloff over the rate of dephosphorylation was taking place against a background in which the enzyme activity was generally believed to be rather low. So, when in 1982 Veech and Huang demonstrated that dephosphorlyation goes on at more than 25 percent of the rate of phosphorlyation in the rat brain, there was quite a stir among brain biochemists. "Veech's findings open up possibilities for reinterpretations that are profound," comments Britton Chance of the University of Pennsylvania.

Chance is referring not only to the implications for PET but also to biochemists' established view of energy metabolism in the brain. If glucose-6-phosphatase really is very active in normal brain cells, this would seem to imply that the brain is being rather inefficient, that it indulges in what biochemists call a futile cycle. Why would brain cells phosphorylate glucose on the way to metabolic release of energy and yet have an enzyme that at least partially subverts the pathway?

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This apparent puzzle, suggests Chance, gives an indication of how little is really known about glucose metabolism in the brain. A more complete picture, however, might accommodate this seemingly wasteful phosphorylation reaction. Veech agrees. "I think Sokoloff could be asking the wrong questions by being trapped in the wrong paradigm."

Sokoloff acknowledges the existence of the enzyme but still argues that its activity is so low as to be of little consequence. Veech's experiments are "complicated," he says, and there are "many alternative explanations" for his observations. "The people who believe in the enzyme's high activity won't give up that belief," says Sokoloff.

Sokoloff finds many supporters, including Michael Phelps and David Kuhl, of the University of California, Los Angeles, and Alfred Wolf of the Brookhaven National Laboratory. "If the phosphatase activity was as high as Veech says, it would be a major perturbation, but it would not negate the model," says Wolf. However, he and the UCLA researchers see only a 5 percent reduction in glucose-6-phosphate after 90 minutes. Nevertheless, concedes Kuhl, although the metabolic rate can be measured pretty well across relatively large areas of the brain, the resolution is not so high as one would like. "But that's not the fault of the model," he says. Geometry and physical limitations of the positron detectors impose considerable constraints on resolution.

The disparity in different people's data that are derived from ostensibly the same systems, and the sharpness of the exchanges over them, clearly betrays a degree of uncertainty that many PET researchers have been unwilling to admit. The uncertainties are unlikely to be cleared up until a great deal more of what Chance calls good old fashioned biochemistry has been done. But there is more at stake here than simply clarifying metabolic pathways of the brain. PET has become a virtual "industry" with its own momentum and a powerful constituency to promote it, say the critics. They argue that these forces make it increasingly unlikely that the problems will get the thoughtful analysis they need.

Nevertheless, there are some clear, repeatable PET patterns that can be of use in clinical diagnosis, with Alzheimer's disease, multiple infarct dementia, epilepsy, and stroke, for instance. "You can distinguish them better with PET than with any other method," says Kuhl. For the less definable psychiatric disorders, the picture is much less clear.

No one, not even the critics, denies that PET images are captivating and that some general, useful patterns can be derived. "The dispute is really on calling it a quantitative measure," observed one protagonist, whose opinion is shared by many of the PET critics, although a few consider this still too mild. There is a growing interest in circumventing the alleged problems of using glucose analogues in PET by instead using positron-labeled oxygen, which would also track energy changes in brain activity. Meanwhile, some people are beginning to examine alternative techniques, such as single photon emission computed tomography and nuclear magnetic resonance spectography. Both techniques, while in their infancy as applied to scanning brain metabolic activity, might develop as competitors to PET, particularly if wrangles over its reliability remain unresolved.—**JEFFREY L. FOX**

Additional Readings

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