EDITORIAL

Targeting Glucose Transporters for Tumor Imaging: "Sweet" Idea, "Sour" Result

Many would agree that PET imaging with the glucose analog FDG is emerging as the preferred diagnostic imaging modality in a variety of human cancers (*1–5*). Unfortunately, the considerable cost of PET scanners, the limited availability of FDG (in part due to governmental "assistance") and a somewhat anti-technology posture (i.e., "not another MRI!") by health care payers—at least in the U.S.—have limited the availability of PET in many locales. If a lower cost single-photon emitting analog of FDG could be made with comparable biodistribution characteristics to FDG, this would be of great clinical utility. Nelson and colleagues explore this possibility in this issue of *JNM* (*6*).

Increased rates of glucose metabolism in cancers have been recognized for many years as well as the potential for targeting this increased metabolism with FDG (*1,7–9*). Several enzymatic alterations have been described in human cancers, including increased glucose transport rates, increased rates of glucose phosphorylation and generally very low rates of glucose-6-phosphate dephosphorylation (*10–15*). A variety of papers have assigned differing levels of significance to each of these three alterations in glucose metabolism, although all probably contribute to the intense tumor signal seen when imaging many cancers with FDG (*13–15*). It must be realized that, while FDG is used as an indicator of glucose metabolism, it is not handled in precisely the same fashion as glucose by cells, and the affinity of membrane transporters, hexokinase and phosphatase enzymes can vary between FDG and glucose (*15,16*). Additionally, FDG is a poor substrate for phosphoglucoisomerase and other glycolytic enzymes (*1*).

Perhaps the greatest biological attention has recently been given to overexpression of facilitative glucose transporters in cancers, a group of proteins cloned in the last several years (*12,14,16–19*). Several researchers have noticed this overexpression as a common alteration in oncogene-transformed cells in vitro and in human cancers in vivo. A log or more increase in transporter density have been reported following transformation of cells with oncogenes (*17–24*). Such observations of excessive expression of glucose transporters have been made both by messenger RNA analysis, by direct immunohistochemical staining for glucose transporters and by direct measurement of glucose transport rates in transformed cells versus the non-transformed parental cells (*17–24,28–31*).

We have previously reported a rather typical overexpression of the Glut-1 glucose transporter in portions of human primary breast cancers versus normal breast tissues (*25*). Overexpression in cancers of the high affinity transporters, Glut-1 and 3, have been most typical in cancers of varying types, though the literature is emerging rapidly (*25–29*). It is thus not surprising that efforts to develop radiopharmaceuticals which would target overexpressed glucose transporters would be initiated (*30*). Implicit in such efforts is the expectation that glucose transporters are overexpressed in the disease process to be targeted.

Progress in the area of glucose transporters has been rapid and will be briefly reviewed here. Two major mechanisms have been described for glucose entry into tumor cells, the sodium/glucose cotransporters (SGLT1 and SGLT2), which transport glucose against a concentration gradient, and the facilitative glucose transporters, Glut-1–5 and Glut-7, which allow for transmembrane transit of glucose down a concentration gradient (passive transfer). The SGLT1 is normally expressed in the brush border of the intestine as well as in the proximal tubule of the kidney, while SGLT2 is normally expressed more distally in the renal tubules. Both of the cotransporters are expressed at low molar concentrations and their molecular biology is evolving. While SGLT1 has been reported to be expressed on some low glucose-utilizing colon cancer cells, it has not, to date, been believed to play a major role in tumor uptake of glucose (*31*).

Rather, members of the facilitative glucose transporter family have been the transporters of interest in cancer (Table 1).

While the amino acid sequence of these transporters is now well known, there is still some controversy over the physical arrangement of the transporters in the cell membrane (*32*). Many researchers believe 12 transmembrane spanning domains produce a central pore for glucose passage (*21,22*). Others argue for a beta pleat pattern with more promiscuous passage of substrates, including water and low molecular weight materials (*32*). Clearly, a pore structure is present, and much more remains to be learned structurally and functionally regarding these transporters.

Governance of the rate of glucose utilization in mammals is complex, as many enzymes are involved, but in several human tissues at physiological blood glucose levels, transport of glucose across the cell membrane is rate limiting (*21–24*). This is particularly the case at fasting blood glucose concentrations (e.g., <100 mg/dl) when insulin levels are low in tissues with substantial populations of high affinity (low Km) transporters. This is the case, for example, in the insulin-responsive heart and skeletal muscle. When insulin is given or released by the pancreas as a result of eating, Glut-4 levels at the cell surface can rise 5–40-fold over levels during prolonged fasting due to translocation to the membrane from vesicles and markedly increase glucose utilization (*21*). When glucose utilization is followed with FDG, markedly increased myocardial and skeletal muscle uptake of FDG are seen. This is why myocardial PET studies with FDG are done after feeding and/or with insulin. In this tissue, in the acute state, glucose transport appears to be rate limiting for glucose metabolism, at least in the fasting state.

By contrast, in the liver, the much higher Km Glut-2 lets large quantities of glucose (and FDG) enter, even when serum glucose levels are increased. Moreover, glucose utilization is more probably determined by levels of glucokinase in hepatocytes, which has a much lower affinity and greater capacity for glucose utilization than hexokinase (*17,19,20*).

By contrast, for most non-CNS tissues which depend on Glut-1 for glucose entry, the rate-limiting step at nondiabetic glucose concentrations in the blood is the rate of transport of glucose into tissues, although there is some controversy about this point (*20,23*). Intracellular levels of glucose are generally quite low, or else

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TABLE 1
Facilitative Glucose Transporters

Numerical	Function	Tissue	Kinetics
Glut-1	Basal glucose uptake	Red cells, fetal tissue vessels, many human tissues	Km 5–30 m*M* asymmetrical Km in ≪Km out
Glut-2	Low affinity glucose uptake	Liver, pancreatic B cell kidney, intestine	Km liver 60 m*M* symmetrical
Glut-3	Basal glucose transport	Brain, fibroblasts	Km 10 m*M*
Glut-4	Insulin-stim. glucose trans.	Fat, skeletal muscle heart	Km 2–5 m*M*
Glut-5	Fructose Tx.	Small bowel	High affinity for fructose
Glut-6	Pseudogene	Not known to be transcribed	NA
Glut-7	Glucose release w/ G6Pase	Liver	ND

Table adapted from James (*21*) and Mueckler (*22*).
NA = not applicable; ND = not determined.

the glucose could not passively enter the cells down the concentration gradient (*19*). Thus, an isolated increase in membrane Glut-1 levels—as has been done in transgenic mice for Glut-1 (i.e., Glut-1 constitutively overexpressed in skeletal muscle)—can markedly increase total body glucose consumption and reduce blood glucose levels (*33*). By contrast, the low Km of Glut-1 and Glut-3 transporters mean that relative brain uptake of FDG declines as serum glucose levels rise (*34*). This is also true for breast and other cancers, in which Glut-1 and possibly Glut-3 transporters predominate and in which little or no insulin sensitivity to tracer uptake is seen (*35,36*). It must be noted, however, that it is generally believed that hexokinase levels, not glucose transport, are limiting in brain glucose metabolism (except under severe conditions of stress) (*37*). Indeed, it has been suggested that the levels of Glut-1 expression in the brain are quite sensitive to glucose levels and that Glut-1 in blood vessels will increase with prolonged hypoglycemia or with chronic seizures as an adaptive mechanism (*35*). We have shown that in tumor cells, Glut-1 levels rise in acute hypoxia in vivo and are highest in peri-necrotic zones of tumors, which are likely hypoxic (*38,39*). While there may also be a component of uptake of FDG to nonmalignant inflammatory cells in the tumors, these contributions are modest in many tumor systems but cannot be ignored (*40,41*). Thus, there is some evidence to suggest that Glut-1 expression in humans is greatest in cells with the most marginal glucose supplies. This is often the case for cells within cancers, a phenomenon suggesting, but not proving, transport may be defining the glucose utilization rate.

Thus, several reports show high Glut in transformed cells and some data suggest that in normal tissues expressing Glut-1, that the level of transporter expression may be rate limiting for the level of glucose utilization, though this is not yet proven in cancers. Nelson et al. (*6*) hoped to target increased tumor glucose transporters in their article. Their idea is "sweet," but the poor results appeared to "sour" them on the possibility. Why this initial failure at targeting Glut?

First, Nelson et al. asked the logical question of whether glucose transporters are overexpressed in the tumors they were growing in vivo. If overexpressed, as they expected from the available literature, targeting with molecules reactive with the glucose transporters would seem reasonable. Using cytochalasin B, a substance which binds to several isoforms of Glut (Glut 1–5), (with lower affinity for Glut-2), they found "high" expression of Glut only in the lung cancer xenograft by their analysis by cytochalasin B binding. This was at least partially confirmed for the Glut-1 transporter in immunohistochemical staining using a more specific agent, an anti-Glut-1 antibody. Two of the other human tumors have Glut levels by cytochalasin B binding comparable to brain (a high Glut tissue in most estimates), while two were lower. Somewhat strangely at first inspection, Glut levels were as high in virtually all tissues as they were in brain (their Table 1). Impressive, however, is the known high levels of nonspecific binding with cytochalasin B, a known lipophilic and sticky substance (*6*). In some instances, nearly 90% of the counts bound in vitro were nonspecific. This makes the cytochalasin B assays somewhat challenging due to the need to subtract a large amount of background. This high nonspecific binding, of course, would suggest poor targeting might be expected for radiolabeled cytochalasin B, even if high levels of Glut, especially Glut-1, are seen in tumors.

Immunohistochemistry has been performed on human tumors (this could not be done in rodent tumors due to the available antibodies), and these studies show clear tumor membrane-bound Glut-1 staining in the tumors tested, especially in areas of poor vascularity, which are consistent with the results of other studies, such as Brown's in breast cancer, with limited or no staining with other anti-glucose transporter antibodies. Unfortunately, comparative studies with other normal tissues are not reported for immunohistochemistry or Western blotting.

Thus, while the cytochalasin B studies suggest that Glut overexpression is not seen in all tumors, they also do not clearly indicate high Glut levels in the heart or brain, raising some questions of the background binding in the system. The immunohistochemical methods, which are less subject to background, were not performed in all tumors and were not described in normal tissues. In the studies performed, only the Glut-1 was significantly overexpressed in tumors, especially in poorly vascularized regions. This is partly consistent with our results in human breast cancer and early results in lung cancer (*25,38* and RS Brown, *personal communication*). Thus, while the authors may be correct in that Glut are not increased in some of their tumors, their statement that "only one of five tumors had concentrations of Glut significantly higher than normal tissues, a trend which appeared to contradict published reports of Glut density in human primary tumors," is one that is highly speculative. This concern is raised since the authors did not examine any human primary tumors in their study, and since their immunohistochemistry results show Glut-1 expression in all three human tumor types tested. Their observation that Glut-1 was overexpressed in areas that appeared to have marginal perfusion was of interest and suggests that malignant cells still seem to have regulatory capability for Glut-1 expression (i.e., levels of expression do not purely appear to be determined by malignant transforma-

tion). The results suggest additional immunohistochemical study of *human* tumors removed from patients by immunohistochemistry in a broad range of cancers is in order to address the questions raised by Nelson et al. (*6*). This emphasis on human tissues is important, as the authors point out, because several of the tumors they chose have been passaged for a very long time and thus their resemblance to human tumors is called into question (*6*).

In any case, let us assume the authors are correct and that Glut levels are not elevated in tumors of at least some types. A logical question would be: Is there is FDG accumulation in these low Glut tumors and is it related to Glut levels—i.e., are the Glut levels driving the FDG uptake in vivo? This study apparently was not done, and we are left with uncertainty as to whether or not there is FDG avidity of the low Glut tumors. If, for example, low Glut, but high hexokinase activity were present, perhaps high FDG uptake would be seen, or if there is a very low rate of dephosphorylation in the tumor, and a higher rate in normal tissues, there could still be high FDG uptake, but not due to increased Glut expression (*14,15*). There are some human cancers in which FDG does not accumulate as avidly as others. We have observed this activity in systematic studies of human tumor xenografts and we and others have seen this in clinical studies, where low FDG uptake can be seen in untreated prostate cancers and some hepatomas (*9,41,42*).

The authors, however, reasonably elected to study their Glut binding agents, [^{3}H]cytochalasin B (CB) and [^{125}I]HPP-forskolin (FSK), as well as FDG, in their LX-1 model, the model with highest Glut expression. One would expect that if the Glut targeting were to work, it would do so in the model with the highest Glut-1, the LX-1. It did not work well with the agents chosen. Both radioactive compounds, [^{3}H]cytochalasin B and FSK, had tumor uptake greater than blood at all times and very little targeting of tracer to the Glut-rich brain or heart. By contrast, FDG had the highest uptake in the heart greater than brain and greater than tumor. Both the CB and FSK had high gallbladder activities as well. It is doubtful that the targeting of these tracers to the gallbladder is due to Glut expression. Rather, it is likely due to lipophilicity of the compounds chosen and hepatobiliary excretion. Thus, in vivo targeting is governed by multiple factors, not just Glut binding.

Why didn't this Glut-1 targeting strategy work out when FDG did target LX-1 tumors? While blood flow to tumor is a key determinant of targeting, it should be comparable across groups of animals, as should tumor size and histology. The authors only briefly mention the fact that very high levels of Glut-1 are expressed on normal red cells. Indeed, about 5% of the red cell membrane protein is Glut-1 (*22*). Thus, Glut-1-rich red cells represent the first target the Glut binding agents see, a probable interaction which would divert them from their intended target tumor. Furthermore, the affinities of both experimental potential SPECT agents for Glut are much lower than glucose or FDG for Glut-1 (100 n*M*) versus 5 n*M* (*6*). Additionally, many other potential crossreactive binding sites are present, at least for cytochalasin B, where up to 90% of binding could be nonspecific. As Nelson et al. indicate the ability to phosphorylate and trap FDG as FDG-6P is also, no doubt, important to the signal seen on FDG-PET (*1,6*). Another consideration lies with the location of the cyotchalasin B and forskolin binding sites on the glucose transporter molecules. While there is some controversy in the literature, it seems that the binding sites for cytochalasin B are on the cytoplasmic side of the transporter (i.e., in the cells) and this is probably the case for forskolin (*43*). If so, the sites may not have been as freely accessible as exofacial (outside) sites on the transporter.

Another technical concern is that the studies were done, apparently, without strict dietary control (i.e., the animals appeared to be eating ad libitum and not fasted). In the fed state, insulin levels are relatively high and Glut-4 is translocated in very large quantity to the outside surface of skeletal muscle and myocardium (*17,21*). Thus, increased targeting of FDG was seen to the heart relative to all other tissues, although it is of note that neither experimental agent tested for localization showed profound myocardial uptake. This low cardiac targeting was seen despite the fact that the agents are supposed to bind well to Glut-4.

CONCLUSION

Nelson et al. (*6*) have raised the interesting question as to whether Glut targeting is possible, and, more fundamentally, whether Glut are consistently overexpressed in human tumors. The answer to the latter question is best answered on direct examination of tumors removed from humans by immunohistochemistry, Western blotting or Northern blots. In such studies to date, the overexpression of Glut-1 and/or 3 is common, but more studies are needed. In addition, there are clearly tumors where there is not a high level of overexpression of Glut molecules (*25*). Indeed, some human breast cancers may be substantially (i.e., 90% of cells or more) Glut-negative, with Glut-1 levels highest in areas of marginal blood supply (*25*).

Furthermore, Nelson et al. suggest that Glut targeting is not feasible in vivo. With the agents chosen, this seems to be the case, although perhaps if agents to the exofacial (external) sites of Glut or other overexpressed Glut can be developed of high affinity, such targeting might be feasible. Nonetheless, delivery of the tracers must occur (i.e., flow must be present) and a method to overcome binding to the large Glut-1-expressing population on red cells, the first cells the Glut targeting agents would encounter, would need to be devised. These represent major hurdles.

For now, FDG remains the best agent to image "glucose metabolism." Emerging data suggest that it is imaging, in part, the distribution of glucose transporter molecules in humans, as they are linked to the glucose metabolic rate. The role of hexokinase and ATP levels, however, which have been closely tied to FDG uptake in human tumor imaging studies and of glucose-6-phosphatase activity also warrant additional study for their role in determining the FDG signal in a variety of tumor types. Major challenges remain to better understand the signal seen during FDG-PET and perhaps develop single-photon emitting analogs that bind Glut to image glucose metabolism. The article by Nelson et al. (*6*) indicates that the road to this goal will not be an easy one. Thus a "sweet" idea, but a "sour" result has been seen.

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REFERENCES

1. Som P, Atkins HL, Bandoypadhyay D, et al. A flurioinated glucose analog, 2-fluoro-2-deoxy-D-glucose (^{18}F): nontoxic tracer for rapid tumor detection. *J Nucl Med* 1980;21:670–675.
2. Di Chiro G, DeLaPaz RL, Brooks RRA, et al. Glucose utilization of cerebral gliomas measured by 18F-fluorodeoxyglucose and positron emission tomography. *Neurology* 1982;32:1323–1329.

3. Wahl RL, Cody R, Hutchins GD, Mudgett E. Primary and metastatic breast carcinoma: initial clinical evaluation with the radiolabeled glucose analog FDG. *Radiology* 1991;67:1544–1550.
4. Wahl RL, Quint LE, Greenough MD, Meyer CR, Whyte RI, Orringer MB. Staging of mediastinal non-small-cell lung cancer with FDG-PET, CT and fusion images: initial prospective evaluation. *Radiology* 1994; 191:371–377.
5. Gritters LS, Francis IR, Wahl RL. Initial assessment of positron emission tomography using 2[^{18}F]-fluoro-2-deoxy-D-glucose (FDG) in the imaging of malignant melanoma. *J Nucl Med* 1993;34:1420–1427.
6. Nelson CA, Wang QJ, Bourque JP, Crane PD. Targeting of glucose transport proteins for tumor imaging: is it feasible? *J Nucl Med* 1996;37:1001–1007.
7. Warburg, O. *The metabolism of tumors*. New York: Richard R. Smith, Inc. 1931;129–169.
8. Larson SM, Weiden PL, Grunbaum Z, et al. Positron imaging feasibility studies. II: characteristic of deoxyglucose uptake in rodent and canine neoplasms: concise communication. *J Nucl Med* 1981;22:875–879.
9. Wahl RL, Hutchins GD, Buchsbaum DJ, Liebert M, Grossman HB, Fisher S. Fluorine-18 2-deoxy-2-fluoro-d-glucose (FDG) uptake into human tumor xenografts: feasibility studies for cancer imaging with PET. *Cancer* 1991;67:1544–1550.
10. Weber G, Banerjee G, Morris HP. Comparative chemistry of hepatomas. I. Carbohydrate enzymes in Morris hepatomas 5123. *Cancer Res* 1961;21:933–937.
11. Monakhov NK, Neistadt EL, Shavlovskii MM, et al. Physicochemical properties and isoenzyme composition of hexokinase from normal and malignant human tissues. *J Natl Cancer Inst* 1978;61:27–34.
12. Hatanaka M, Augl C, Gilden RV. Evidence for a functional chain in the plama membrane of murine sarcoma virus-infected mouse embryo cells. Transport and transport-associated phosphorylation of ^{14}C-2-deoxy-D-glucose. *J Biol Chem* 1970;245:714–717.
13. Flier JS, Mueckler MM, Usher P, Lodish HE. Elevated levels of glucose transport and transporter messenger RNA are induced by ras or src oncogenes. *Science* 1987;235:1492–1497.
14. Fukunaga T, Enomoto K, Okazumi S, Isono K. Analysis of glucose metabolism in patients with esophageal cancer by FDG-PET: estimation of hexokinase activity in the tumor and prediction of prognosis: clinical PET in oncology. *Proceedings of 2nd Intl Symposium on PET in Oncology*. Singapore: World Scientific; 1993:87–90.
15. Graham MM, Spence AM, Muzi M, Abbott GL. Deoxyglucose kinetics in a rat brain tumor. *J Cereb Blood Flow Metab* 1989;9:315–322.
16. Bell GI, Burant CF, Takeda J, Gould GW. Structure and function of mammalian facilitative sugar transporters. *J Biol Chem* 1993;268:19161–19164.
17. Lodish HF. Anion-exchange and glucose transport proteins: structure, function and distribution. *Harvey Lect* (1986–87);82:19–46.
18. McGowan KM, Long SD, Pekala PH. Glucose transporter gene expression: regulation of transcription and mRNA stability. *Pharmacol Ther* 1995;66:465–505.
19. Elsas LJ, Longo N. Glucose transporters. *Ann Rev Med* 1992;43:377–393.
20. Devaskar SU, Mueckler MM. The mammalian glucose transporters. *Pediatr Res* 1992;1–13.
21. James DE. Targeting of the insulin-regulatable glucose transporter (Glut-4). *Biochem Soc Trans* 1994;22:668–670.
22. Mueckler M. Facilitative glucose transporters. *Eur J Biochem* 1994;219:713–725.
23. Ismail-Beigi F. Metabolic regulation of glucose transport. *J Membr Biol* 1993;135:1–10.
24. Baldwin SA, Kan O, Whetton AD, et al. Regulation of the glucose transporter Glut-1 in mammalian cells. *Biochem Soc Trans* 1994;22:814–817.
25. Brown RS, Wahl RL. Overexpression of Glut-1 glucose transporter in human breast cancer: an immunohistochemical study. *Cancer* 1993;72:2979–2985.
26. Nishioka T, Oda Y, Seino Y, et al. Distribution of the glucose transporters in human brain tumors. *Cancer Res* 1992;52:3972–3979.
27. Yamamoto T, Seino Y, Fukumoto H, et al. Overexpression of facilitative glucose transporter genes in human cancer. *Biochem Biophy Res Commun* 1990;170:223–230.
28. Su T, Tsai T, Chi C, Han S, Chow C. Elevation of facilitated glucose transporter messenger RNA in human hepatocellar carcinoa. *Hepatology* 1990;11:118–122.
29. Mellanen P, Minn H, Grenman R, Harkonen P. Expression of glucose transporters in head-and-neck tumors. *Int J Cancer* 1994;56:622–629.
30. Mertens J, Terriere D. 3-Radioiodo-phloreitn—a new potential radioligand for in vivo measurement of Glut proteins: a SPECT alternative for [^{18}F]FDG. *J Nucl Biol Med* 1993;37:158–159.
31. Hediger MA, Rhoads DB. Molecular physiology of sodium-glucose cotransporters. *Physiol Rev* 1994;74: 993–1026.
32. Fischbarg J, Vera JC. Multifunctional transporter models: lessons from the transport of water, sugars and ring compounds by Gluts. *Am J Physiol* 1995;268:C1077–C1089.
33. Koretsky AP. Insights into cellular energy metabolism from transgenic mice. *Physiol Rev* 1995;75:667–688.
34. Pelligrino DA, LaManna JC, Duckrow RB, Bryan RM Jr, Harik SI. Hyperglycemia and blood-brain barrier glucose transport. *J Cereb Blood Flow Metab* 1992; 12:887–899.
35. Wahl RL, Henry CA, Ethier SP. Serum glucose effects on tumor and normal tissue accumulation of [^{18}F]fluoro-2-deoxy-D-glucose (FDG) in rodents with mammary carcinoma. *Radiology* 1992;183:643–647.
36. Pardridge WM. Glucose trasport and phosphorylation: which is rate limiting for brain glucose utilization? *Ann Neurol* 1994;35:5:511–512.
37. Clavo AC, Brown RS, Wahl RL. Fluorodeoxyglucose uptake in human cancer cell lines is increased by hypoxia. *J Nucl Med* 1995;36:1625–1632.
38. Brown RS, Leung JY, Fisher S, Frey KA, Ethier SP, Wahl RL. Autoradiographic assessment of the intratumoral distribution of [^{3}H]FDG in breast carcinoma. II. Role of glucose transporter-1 (Glut-1) in FDG uptake. *J Nucl Med* 1995;36:1854–1886.
39. Kubota R, Yamada S, Kubota K, Ishiwata K, Tamahashi N, Ido T. Intratumoral distribution of fluorine-18-fluorodeoxyglucose in vivo: high accumulation in macrophages and granulation tissues studied. *J Nucl Med* 1992;33:1972–1980.
40. Brown RS, Leung JY, Fisher SJ, Frey KA, Ethier SP, Wahl RL. Intratumoral distribution of tritiated fluorodeoxyglucose in breast carcinoma: I. Are inflammatory cells important? *J Nucl Med* 1995;36:1854–1861.
41. Torizuka T, Tamaki N, Inokuma T, et al. In vivo assessment of glucose metabolism in hepatocellular carcinoma with FDG-PET. *J Nucl Med* 1995;36:1811–1817.
42. Shreve PD, Grossman HB, Gross MD, Wahl RL. Imaging of metastatic prostate cancer with FDG-PET: initial findings. *Radiology* 1996: in press.
43. Gould GW, Holman G. The glucose transporter family: structure, function and tissue-specific expression. *Biochem J* 1993;295:329–341.