The Value of "The Putrescine Experience"

In a recent editorial in the *Journal of Nuclear Medicine* (*1*) commenting on the investigation of [^{11}C]putrescine as a brain tumor-specific tracer for PET (*2,3*), the editorialist presents a view of "what went wrong," and asks, "what lessons can be learned from the putrescine experience?"

In the article in question, the tumor specificity of [^{11}C]putrescine in 33 patients was examined by comparing its behavior in gliomas and in nontumor brain lesions. For nearly all of the studies, an ^{18}FDG scan was performed for comparison. All subjects had radiological examination and many had pre- and/or post-PET pathological examination of excised lesion tissue. The time course of total ^{11}C in the arterial plasma was measured and reported for each subject. The study directly demonstrated in a clinical population that [^{11}C]putrescine is not useful for differentially diagnosing tumor from other nontumor lesions in the brain, a finding that was contrary to initial expectations (*4*).

Tumor specificity was a major criteria in the design of [^{11}C]putrescine, and one which was predicted to set it apart from nonspecific tracers like ^{18}FDG, which participate in biochemical processes common to both tumor and nontumor tissue (*4*). Nonspecific tracers like ^{18}FDG are proving to be useful in assessing the degree of malignancy at the time of diagnosis and in characterizing brain tumors and their response to treatment (*5*). Currently available imaging methods, like CT and MRI, however, cannot always reliably differentiate various non-neoplastic entities from malignant brain tumors (*6,7*). It was the view of the authors of this article that the availability of a tracer with specificity for brain tumors over nontumor brain lesions would have an important role in differential diagnosis.

Rather than commenting on this data, the editorialist suggested that "what went wrong" in the investigations of [^{11}C] putrescine arose from study designs which, it was said, suffered from a lack of: (1) tracer kinetic modeling, (2) a radiochemically characterized arterial input function and (3) knowledge of the constraints imposed by in vivo tumor biology and heterogeneity. This analysis and conclusion are misleading.

The study in question is one of the few published PET studies addressing the tumor *specificity* of a PET radiotracer. Uptake of ^{11}C in nontumor lesions was observed after the injection of [^{11}C]putrescine. To put it simply—*there was a signal where one was not expected.* Would tracer kinetic modeling and a radiochemically characterized arterial input function have identified or predicted nonspecific uptake? Of course not. It is not even necessary to apply a kinetic model for this conclusion to be made. The importance of tracer kinetic modeling when performing quantitative PET studies is well known. Researchers at the Brookhaven National Laboratory were the first to make measurements of unchanged radiotracer in plasma, pointing out the importance of this measurement for the quantitation of the kinetics of radioligand-neurotransmitter receptor interaction (*8*). In the absence of experiments designed to probe biological specificity, however, a tracer kinetic model and a plasma input function do not add physiological or functional information to an image. The constraints of in vivo tumor biology and heterogeneity also do not relate to the issue of specificity. What was not realized initially was that polyamine biosynthesis in the brain would be elevated not only in tumors but also in other lesions with platelet aggregation and/or blood-brain barrier breakdown (*9,10*) and that the magnitude of the increase in uptake would be similar for these lesions as for tumors, thereby preventing their differential diagnosis with labeled putrescine.

As with any other scientifically generated hypothesis, validation required testing of the *relevant* parameters. For the case of putrescine, these were not only its rate of uptake by malignant tumors, but also its specificity. The question in the title of the article the editorial addresses, "Is Carbon-11-Putrescine Useful as a Brain Tumor Marker?", is answered in the study. However, the editorial, in our opinion, obscures the central point of these studies by raising issues that are not relevant to the issue of tumor specificity. The editorialist's cautionary advice to others that "these lessons need not be relearned" is inappropriate.

The dynamic and often chaotic nature of the process of building, testing and then reformulating scientific hypotheses leaves many a theory and theoretician bobbing helplessly in its wake. Yet no one seriously argues that we should avoid this process of experimentation and explore only those theories that withstand the blackboard scrutiny of statisticians and or experienced researchers.

There is however, the school of "I Told You So" scientists who, while upholding the necessity of the experimental approach to research, suggest in the same breath that if a certain group had only read this particular article, or applied a specific methodology, then they could have prediced a specific outcome.

The "I Told You So" school of thought denies the subtle differences that separate the poorly conceived experiment from the elegant approach. But indeed, it is the wrinkle in time, the subtle twist of fate that account for the major

advances in science and medicine. These variations are not arrived at by dogmatic adherence to rigid protocols. Rather it is by painstaking and often unsuccessful experimentation that truth is approached asymptotically.

Scientists should not be criticized for a failure to produce a desired result, or overly praised for achieving that result, but should be consistently encouraged for providing additional real data. The unsuccessful experiment that provides a wealth of data is vastly superior to the successful experiment that provides data of limited use.

No one can deny that hindsight, when constructively applied, is a critical part of the research process. However, hindsight where experimental data of direct relevance to the central hypothesis is ignored has neither scientific nor educational value.

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REFERENCES

1. Rottenberg DA. Carbon-11-putrescine: back to the drawing board. *J Nucl Med* 1992;33:200–201.
2. Hiesiger EM, Fowler JS, Wolf AP, et al. Serial PET studies of human cerebral malignancy with [1-^{11}C]putrescine and [1-^{11}C]2-deoxy-D-glucose. *J Nucl Med* 1987;28:1251–1261.
3. Hiesiger EM, Fowler JS, Logan J, et al. Is [1-^{11}C]putrescine useful as a brain tumor marker? *J Nucl Med* 1992;33:192–199.
4. Volkow N, Goldman SS, Flamm ES, et al. Labeled putrescine as a probe in brain tumors. *Science* 1983;221:673–675.
5. Coleman RE, Hoffmann JM, Hanson MW, et al. Clinical application of PET for the evaluation of brain tumors. *J Nucl Med* 1991;32:616–622.
6. Kurtman KE, Bradley WG. Supertentorial neoplasms. In: Stark DD, Bradley WG, eds. *Magnetic resonance imaging.* St. Louis: CV Mosby; 1988:422–424.
7. Kazner E, Wande S, Grumme TH, et al. *Computed tomography in intracranial tumors. Differential diagnosis and clinical aspects.* New York: Springer-Verlag, 1982:33–41, 347–377, 405–462.
8. Arnett CD, Shlue CY, Wolf AP, et al. Comparison of three ^{18}F-labeled butyrophenone neuroleptic drugs in the baboon using positron emission tomography. *J Neurochem* 1985;44:835–844.
9. Koenig H, Goldstone AD, Chung YL. Blood-brain barrier breakdown in brain edema following cold injury is mediated by microvascular polyamines. *Biochem Biophys Res Comm* 1983;116:1039–1048.
10. Nadler SG, Takahashi MT. Putrescine transport in human platelets. *Biochem Biophys Acta* 1985;812:345–352.