study the nature of cancer cells in vivo. Investigation of the invasiveness of cancer cells requires additional study.

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EDITORIAL

The Current and Future Use of Tumor-Localizing Agents

In this issue, a research article by Fujiwara and co-workers suggests that a newly synthesized radiopharmaceutical, N-[18F]fluoroacetyl-D-glucosamine (18F-FAG), be used in conjunction with PET scanning as a potential agent for cancer diagnosis. The work presented is clear, concise, and of high scientific caliber, but one could take exception to some of the conclusions drawn from the data. Although the autoradiographs from the mice bearing spontaneous hepatomas are impressive, and notwithstanding the fact that the tumor had the highest uptake as a percent of the injected dose per gram, the target-to-nontarget ratio for tumor to liver of <1.5 casts significant doubt as to whether the hepatomas would have been differentiated from the normal liver during in vivo PET imaging. With respect to the imaging of the VX-2 carcinoma in rabbits, it is well documented in the nuclear medicine and tumor biology literature that transplanted tumors in the extremities of animals are a very poor model for extrapo-
lation to tumors growing in the abdomen and pelvis of man.

The aim of this editorial, however, is not to critique this manuscript as an isolated research investigation, but rather to review the history of the development of tumor-localizing agents and to put this in context with advances in tumor imaging such as computed tomography (CT) and magnetic resonance imaging. This viewpoint will allow a better understanding of the current role of nuclear medicine with respect to tumor imaging and perhaps even to predict some future trends.

A review of The Journal of Nuclear Medicine since its inception revealed that there were over 500 articles related to the evaluation of radiopharmaceuticals for the external detection of cancer. Perusal of these articles indicates that nearly 100 different radiopharmaceuticals have been suggested as potential tumor-imaging agents. This retrospective search was confined to JNM, since it was not meant to be exhaustive, but to be an example of the lack of success, i.e., clinical utility, of the vast majority of agents proposed as having potential for this purpose. Considering that there are at least a dozen other radiologic or cancer journals which carry articles on tumor imaging agents, it is easy to see that the number of radiopharmaceuticals proposed for this purpose is in the hundreds.

The earliest reports in JNM of agents having tumor-localization capability were abstracts presented at the 7th annual meeting of the Society of Nuclear Medicine (1–4). The first full paper on a tumor-seeking radiopharmaceutical appeared in the July 1960 issue of the Journal (5), in which tumor localization was proven by open biopsy. The first paper to suggest tumor imaging by obtaining high uptake of an agent in the normal organ and no uptake in the tumor (negative imaging agent), appeared in Volume 2 of the Journal (6), again with biodistribution data but no scans. It was not until Volume 3 of the Journal that the first reports showing an in vivo scan (external detection of tumors) appeared (7,8). It is interesting to note that in that same year (1962), an article appeared in the Journal summarizing eight years' experience in positron scanning of brain tumors (9). I am sure that many of the younger physicians and radiopharmaceutical scientists did not realize that positron scanning goes back nearly 30 years. The first reports of technetium-99m-pectechnetate as a brain scanning agent did not appear until late 1964 and early 1965 (10–12).

My own personal involvement in tumor-localizing agents began in 1967 (13) and my first work with a radiopharmaceutical as a "potential tumor-localizing agent" in 1974 (14).

In the early 1970s, the "party-line" was that the savior of tumor imaging would be radiolabeled antibodies (polyclonal). There was a general feeling amongst those working in the area that although the target-to-nontarget ratio was insufficient to allow the use of these materials with alpha- or beta-emitters for internal therapy, there was enough specificity for use with gamma-emitting radionuclides as external detectors of cancer. Our group at the Harvard Medical School and Brigham and Women's Hospital was involved in this now somewhat aborted quest (15).

With the lack of real advancement in the use of polyclonal antibodies for detection, the 1980s heralded the era of the monoclonal antibody labeled with radionuclides, now proposed for both diagnosis and therapy, based on the anticipated increase in specificity of the monoclonal antibody versus the polyclonal material. We have just completed a decade of monoclonal antibody research heavily funded by Federal agencies, and as yet, cannot point to any real success or widespread clinical utility. Certainly, advances have been made and perhaps we are poised on the brink of an era where monoclonal antibodies will attain their previously promised clinical utility for both diagnosis and therapy of malignant disease. But where do we stand at this moment in 1990, as we assess nuclear medicine's role vis-a-vis other imaging modalities in the external detection and quantification of malignant neoplasms? Gallium-67-citrate has been, and remains, the most widely used tumor-avid agent. Its advantages and disadvantages with respect to tumor detection and differential diagnosis versus inflammatory processes are legendary in the medical literature. Thallium-201-thallous chloride is gaining acceptance as a tumor-avid agent in certain specific tumors, and has been the subject of many recent publications. It should be noted that with all of the theoretical discussions of why agents that are metabolically taken up or produced by tumor cells would be advantageous and why moieties such as antibodies should be the final solution, the two most commonly used agents today are simple cations where little is known regarding the mechanism of uptake and the affinity for tumor tissue versus normal surrounding organs.

So what is nuclear medicine's role with respect to other imaging modalities for the diagnosis and evaluation of therapeutic intervention of malignant disease? Certainly, CT has played the major role in the past 15 years for the detection of both primary and metastatic neoplasms. The past few years have seen the emergence of MRI as at least an equally powerful tool when compared to CT, and in certain specific instances, it is clinically superior in the efficacy for detection of neoplasia. While the technology for enhancing CT scans has slowed considerably, we appear to remain on the ascending portion of the curve with respect to MRI technology and its application to medical diagnosis.
The question is: can or should nuclear medicine try to compete with MRI and, to a lesser extent, CT in this area? It is often said that although MRI is very sensitive in finding central nervous system and certain other tumors, it does not do a superb job of defining the extent of physical borders of the tumor. While it is sometimes the case, that signal intensity from edema may cause the tumor to appear larger than it actually is, it is truly not a major drawback for MRI. Additionally, for a nominal increase in cost, a CT scan combined with MRI can give a significantly better definition of the extent of the malignant process.

There is very little evidence to date that suggests that radionuclide scanning, using either planar imaging, SPECT, or PET would give significantly improved two-dimensional or three-dimensional definition of the tumor border, when compared to CT or MRI. Previously, cost has always been brought into the equation as a real advantage for nuclear medicine, initially over CT, and now certainly over MRI. If one considers the article appearing in this issue, namely suggesting the use of PET scanning for tumor detection, then clearly the cost of PET scanning would be equal to and, in my estimation, significantly greater than the cost of MRI. The need for a cyclotron, a positron imaging device, and a team of skillful physicists and radiopharmaceutical chemists will drive the cost of any such positron screening technique higher than that of a competing radiologic modality.

A recent article by Froelich (16) shows that during the past 15 years, the total number of nuclear medicine procedures has been static and that the decrease in brain, liver/spleen, and to some extent, thyroid, has been offset by the increase in lung, bone, and cardiac examinations. The greatest loss occurred in the brain and liver/spleen areas, where the primary nuclear medicine study had been anatomic rather than physiologic, searching for metastatic disease. The anatomic superiority of CT and MRI have clearly taken their toll in this area. Recently, nuclear medicine has been buoyed by expectations of increasing studies in the area of brain and cardiac based on physiologic determinants rather than anatomic findings. As we approach the 21st century, it is the hope of nuclear medicine that physiologic studies of brain and cardiac function based on single-photon emitters combined with SPECT imaging and positron radiopharmaceuticals combined with PET imaging will lead to a significant increase in the value of nuclear medicine procedures to neurologists, cardiologists, and other referring specialists.

The power of PET scanning is to study processes at the organ, tissue, and perhaps even cellular level. This ability is not shared by CT, MRI, or ultrasound, and distinguishes nuclear medicine in general, and PET scanning specifically, from the more anatomic imaging techniques used by our radiology colleagues.

In summary, the past 30 years have seen the evaluation of hundreds of compounds billed as "potential tumor-imaging agents."

Many of these compounds were based on specific biochemical rationale, such as those that sought out melanomas, those that were based on compounds that intercalated with DNA, those that were based on known precursors of agents synthesized within the tumor cells, and those based on known highly successful anti-tumor chemotherapeutic agents. Of all of these, only two simple cationic materials, $^{67}$Ga and $^{201}$Tl, have achieved significant and widespread clinical utility. Given the limitation of manpower in the area of skilled radiopharmaceutical researchers and the financial constraints of both Federal and non-governmental funding agencies, where can we most effectively put our efforts and resources to achieve the goal of improved tumor detection and response to therapy?

A recent article by McAfee et al. (17) showed that of the $20 million spent by the DOE in 1988 on nuclear medicine research, 65% was allocated to PET or PET-related activities, whereas 35% was spent on SPECT, single-photon emitting radiopharmaceuticals, and radioimmunotherapy. In the same year, of the $37.5 million allocated by NIH for nuclear medicine support, approximately 54% was designated for PET instrumentation and imaging agents, whereas the remainder was allocated between SPECT devices, single-photon radiopharmaceuticals, and monoclonal antibody research (both diagnosis and therapy). The vast majority of funds allocated for PET research was in the area of neurology, with cardiac research second, and oncologic activities a distant third. Thus, based on the successes and failures of nuclear medicine as stated above, as well as the competition from competing diagnostic imaging modalities, it would appear prudent to invest our time and money in the areas of monoclonal antibodies for tumor diagnosis and therapy using single-photon emitters and in the study of basic underlying mechanisms of physiology and pathophysiology using positron-emitting radiopharmaceuticals combined with PET scanning.

This is not to say that small molecules and polypeptides labeled with technetium or other attractive single-photon emitting radionuclides should not be developed for improved organ or disease-specific imaging, particularly in the areas of brain and cardiac; but when it comes to tumor imaging, the major area of utility would appear to be in the development of tumor-specific antibodies in conjunction with planar or SPECT imaging, and not to use the very limited and very expensive resource of PET scanning for general clinical tumor screening. Positron emitting radionuclides...
such as gallium-68 and [18F]fluorodeoxyglucose have been available for some time and have been shown to have a certain tumor-localizing capability. These agents have not made any impact on clinical oncologic practice, and it is unlikely that the newly prepared agent by Fujitwara et al. would achieve clinical success as a PET tumor imaging agent.

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