S. James Adelstein, M.D., Ph.D.

Science Applied To A Clinical Need

An increasing interest in translational research has sparked a debate on how best to bring the extraordinary advances in molecular and cellular biology to the benefit of patients. How does one think about applying science to developments in medical technology? Our experience in fashioning a radiolabeled agent now commonly used in the diagnosis of coronary artery disease illustrates some of these issues.

I use the term technology to refer to devices and drugs employed in the diagnosis and treatment of disease. Such medical technologies uniformly derive from scientific advances in biology, chemistry, physics, and engineering. (The obverse is also true. The more sophisticated the experimental science, the more it depends upon technology – in the larger sense – to provide the tools of discovery.)

In general, the questions of science are designed to reveal the secrets of nature: What are genes? How do they work? What are their products? How are they turned on and off, etc.?

The questions of medical technology are designed to meet a clinical need: How can we obtain better anatomical images of an internal organ? Can we distinguish between normal and diseased tissue? Can we stage a cancer (determine whether it has spread) noninvasively?

Differences between science and technology can be minimal and, of course, many scientists are motivated to see practical benefit from their discoveries and may even participate in translating them into clinical tools. For example, studies in stem-cell biology, interesting in

themselves for the understanding of development and differentiation, have obvious relevance to the treatment of failing organs such as the brain, pancreas, heart, liver, and bone marrow.

The tools of technological development are often the results of scientific discovery. Indeed, progress in the development of technologies requires a deep understanding of their underlying science. The invention of MRI required a firm knowledge of atomic properties and how to align and perturb the magnetic moment of atoms, of the interaction of microwaves with matter, the mathematics of image reconstruction, and the engineering of high-resolution magnets. Like many technological developments, it relied upon multidisciplinary activity and a good deal of technology transfer from fields other than medicine. (1)

During 1968, I took on the responsibility for nuclear medical services at the Peter Bent Brigham Hospital, and, subsequently, The Children's Hospital, the Beth Israel Hospital, and the Dana–Farber Cancer Institute. In the job, I needed to establish not only a clinical service but educational and research programs as well. I hoped to launch a program for the development of radiolabeled agents that would be useful in both diagnosis and therapy. I immediately realized that rational progress in diagnostic agents would require knowing much more about the chemistry of the element technetium.

Why, one may ask, be concerned about technetium, that unnatural element, number 43, in the periodic table, below manganese and sandwiched between molybdenum and ruthenium? The answer lay in the peculiarities of the instruments used for imaging radioactivity in the body, in the favorable decay characteristics of technetium-99m, and in the hospital-ready supply of the radionuclide. The instrumentation developed in the late 1960s was optimized for a photon

energy of 140 KeV, exactly the energy of the gamma-ray emission of technetium-99m. (2) Moreover, unlike other radionuclides favored at the time, e.g. iodine-131, technetium-99m emitted no energetic particles to increase the absorbed dose to patients (3), and its half-life of six hours confined radiation exposure to the time required for imaging. In addition, technetium-99m could be easily obtained from a hospital-based generator that could be refreshed every week instead of by daily delivery from outside reactor or cyclotron sources.

At the time, a number of technetium-99m-labeled reagents were available for patient use, but these were based on no chemistry at all or on primitive compounding methods, akin to alchemy. For the development of more specific diagnostic agents, it was clear that more had to be known about the chemistry of technetium. Moreover, as technetium is not an element naturally occurring in the cosmos, its most stable form, technetium-99 (the decay product of technetium-99m), could only be obtained in micromolar quantities.

To help with this, I went to consult with Charles Coryell at MIT. Professor Coryell was an eminent radiochemist who, a victim of cancer, was happy to have his talents applied to medical problems. He recommended that a two-person team be recruited to work on the problem: Alan Davison, an assistant professor of inorganic chemistry at MIT, and Alun Jones, a postdoctoral fellow radiochemist working in Professor Coryell's laboratory. Davison would continue to work at MIT, and I would offer Jones an appointment in the Department of Radiology at Harvard Medical School. Fortunately, both seemed intrigued by the challenge of working on the chemistry of technetium and of working together as colleagues, perhaps because both had been born in Wales.

Within a year and with support first from the NIH and, subsequently, from the Department of Energy, the joint research was begun. The MIT Department of Chemistry brought instrumentation and graduate students to the collaborative effort, and the HMS Department of Radiology provided a source of technetium and post-doctoral fellows. Shortly thereafter, Davison and Jones produced the first crystalline product, a Tc(V)-oxo compound – one that could serve as a core to build on. Subsequently, they found Tc(V)-oxo-N_2S_2 compounds also to have stability, and this finding was exploited by others to produce a popular renal scanning agent.

During the 1970s, the importance of radiolabeled monovalent cations as cardiac scanning agents for coronary artery disease became evident. (In pursuit of this interest, I had spent a sabbatical semester abroad in 1976 working with an experimental cardiologist expert in the field.) The agent in common use was radiothallium ($^{201}Tl^{+}$), which is handled like potassium by heart cells and whose local uptake is proportional to blood flow. Thallium-201 has certain disadvantages: it is produced by a cyclotron, has to be delivered to clinics daily, and the energy of its emitted photon is not ideal for imaging.

Could one construct a technetium-containing compound that would have the same properties? Jones and Davison thought they might be able to do so. By this time they were working on isonitrile (-C≡N-) complexes of technetium as Tc(I). One of these, Tc(I)TBI, a rather oily substance, was found to be taken up avidly in vivo by rat and dog hearts. When it was shown to be taken up by a human heart (mine) (4), New England Nuclear (NEN – shortly to be acquired by DuPont–Merck) showed some interest and provided a small fund to aid further chemical development. Then, sensing this research might have some commercial value, Harvard and MIT jointly filed for a patent with NEN having the right of first refusal

on any useful product. In a preliminary study, 13 of 14 patients with coronary artery disease (CAD) were found to have diminished regional perfusion and decreased wall motion. However, comparison with $^{201}Tl^{+}$ was not favorable due to the slow clearance of Tc(I)TBI from the lungs and liver, immediately adjacent organs.

The problem of eliminating the slow lung and liver clearance was given to a graduate student, James Kraunage, to solve. Although it might be considered to be a true example of "chemical biology," it was not the kind of challenge usually given to a graduate student in chemistry. Nevertheless, the MIT Department of Chemistry allowed Kraunage to pursue it for his PhD thesis. After several chemical manipulations, mostly aimed at varying the lipophilicity and other properties of the ligand, Kraunage found that esterification of the aryl groups of Tc(I)TBI produced a compound with increased clearance from the lungs and liver of animals. This agent, Tc(I)CPI, was found to produce excellent cardiac images in humans, favorable in comparison with $^{201}Tl^{+}$. The results were sufficiently impressive that NEN (now DuPont) paid for toxicity studies and a preliminary clinical trial in Argentina.

From this preliminary study, DuPont decided to adopt the lead compound for robust clinical use. In doing so, they substituted ethers for the esters in Tc(I)CPI producing Tc(I)MIBI (see figure), an agent that has somewhat better pharmacokinetics and can be more easily compounded in the clinic using a kit to which ^{99m}Tc is added. They gave the commercial name of Cardiolite™ to the new agent and proceeded to sponsor phase I and II clinical trials at Harvard (Brigham and Women's Hospital and Massachusetts General Hospital), Yale, and Cedars–Sinai (Los Angeles). These multicenter clinical trials showed that Tc(I)MIBI was safe, cleared rapidly from the blood (essential in an agent that is to image the cardiac wall), and compared well with $^{201}Tl^{+}$ in stress-test imaging for CAD. Further studies from the same

institutions demonstrated that Tc(I)MIBI could be used with SPECT equipment to obtain cross-sectional images of the heart and was reliable in detecting under-perfusion at rest (indicating that patients had previous cardiac damage) and following exercise (indicating reduced cardiac blood-flow reserve). In addition, it could be used to locate abnormalities in heart-wall motion and to measure ejection fraction.

Because of the time required to obtain FDA approval, Tc-sestamibi (Cardiolite™) was first sold successfully in Europe. Eventually it became the leading radiolabeled cardiac agent in the US, capturing 60% of market share, despite a competitive product developed by Amersham. Over a ten-year period it generated ~$2B in overall sales, producing nearly $100M in royalties for Harvard and MIT, split evenly. DuPont Pharma subsequently sold its rights to Bristol–Meyers-Squibb, which is developed new applications, such as identification of breast cancer and of multi-drug resistance. (Subsequently, BMS sold the rights to Lantheus).

What can one extract about the interplay of science and technology in medicine from the development of this agent?

Whereas, by definition, this is an example of technological development proceeding from a clinical need and resulting in a clinically useful product, it is also an example of science pursued for the same end. The scientific question asked – what is the chemistry of the element technetium – came directly from the technological requirement, unlike the classic linear model of technology development, which stipulates science first, translation afterwards. (5) It raises the dilemma of how best to bring the power of contemporary biomedical science into practical utility. Does one look at scientific discoveries and deduce

which are likely to result in useful products or does one state the clinical problem and adapt science to its solution? If the answer is both, and it surely is, then two types of skills are required, the first to see practical benefit in science pursued for its own sake, and the second to argue back from potential technology to required science.

The history of Tc-sestamibi also addresses the matter of academic university involvement in technology development. Working out the systematics of technetium chemistry is clearly an appropriate academic endeavor. How about its application to the development of a cardiac scanning agent? In some ways, the felicitous joining of a "basic scientist" (in chemistry) with an "applied scientist" (in radiology) obviates the question. Inquiry about the fundamental chemistry of technetium properly belongs in a department of chemistry as does the search for a cardiac-imaging agent in a department of radiology. But, what about a graduate student in chemistry perfecting the medical imaging properties of a compound by chemical manipulation? Should we be more careful in preserving the arena of the natural sciences in the academy? Or, are we being persnickety in drawing too carefully these differences?

In tracing out the chronology in Tc(I)sestamibi development, the basic chemistry and the agent progression through Tc(I)CPI were principally supported by federal funds, whereas industry paid for the formulation of the final compound, its toxicology, and clinical trials. The patents were held by the two universities, which profited from a royalty stream. Is this what Bayh-Dole, the legislation that permits universities to hold the patents on inventions made in their laboratories under federal grants, intended? On casual inspection, it would certainly appear so. Would the work in the universities have been done without the Bayh-Dole incentive? Probably – the interest of the problem and the recognition for having solved it were almost certainly sufficient incentive for the inventors. Whether industry would have

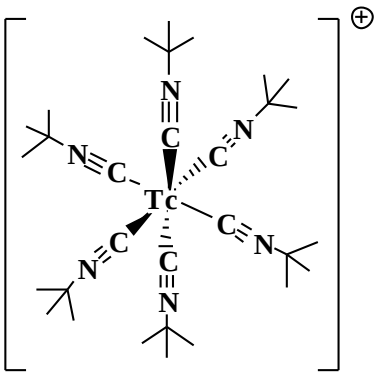
proceeded without patent protection is another matter. And, if the patents were held by industry, the universities might not have profited from the sales of product or, at least, have recovered their shares in the cost of development. (6)

In summary, this account raises a number of the issues central to bringing useful medical technologies out of university laboratories into clinical use. It begins by demonstrating the interplay between clinical need and the motivation to develop the underlying science necessary to meet it. It provides an alternative route of bench-to-bedside and shows that the identification of contemporary science in the service of medicine may not be a simple linear task.

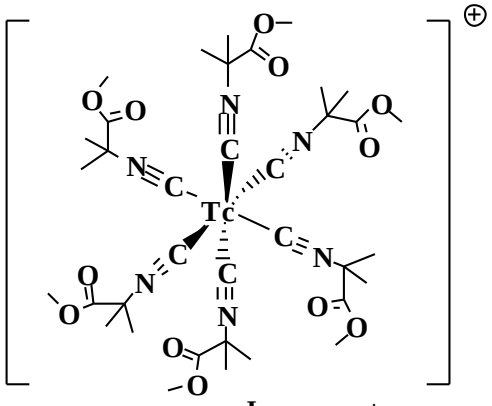
The account also articulates the importance of integrating disciplines not only at a personal level but at an organizational level as well. Institutional barriers to transdisciplinary research are well recognized (7), and this instance of collaboration between a natural science department at MIT and a clinical department at Harvard is a tribute to breaching them. Perhaps, the practical culture of an engineering school facilitated this, although MIT is rightly proud of its accomplishments in pure science as well.

The issue is also raised as to how far in the course of development of useful products the efforts of university faculty members should be directed. In this case, the university laboratories brought the lead product to its penultimate formulation. Can faculty members be diverted from “true” academic pursuits by the promise of commercialization? And who are to judge – and how – when this has taken place? Would this useful product have been realized if a corporation had taken over its formulation earlier or would a company even have been interested?

Finally, and related to the last issue, who should profit from these discoveries and under what circumstances? This debate has raged in universities for several decades and has led to the formulation of guidelines in conflict of interest and commitment to define and contain the limits of faculty participation in commercialization (8). At Harvard, the royalty streams are divided among the central university, the faculty involved (e.g. medical school in the case of Cardiolite™), the home department of the inventor(s), the inventor's laboratory, and the inventor(s) personally. But in this age of biotechnology, profit accrues not only from the sale of product but also from the sale of spin-offs and public offerings. How involved should universities and their faculty members be in these enterprises that capitalize on discoveries made in their laboratories, and when does participation corrupt or appear to corrupt academic values? The example given does not deal with the latter conundrum but its resolution will be a continuing matter of debate.



$[Tc^{I}(TBI)_6]^+$



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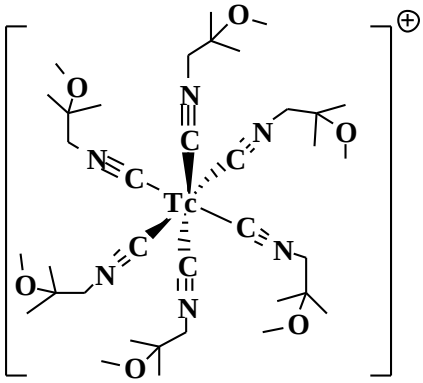

$[Tc^{I}(MIBI)_6]^+$

Footnotes for 03Adelstein.doc

(1) Once the hallmark of technology, multidisciplinary efforts have invaded the sciences of molecular and cellular biology as we try to untangle the myriad of networks that underlie the functioning of cells and of the nervous system.

(2) This discussion is concerned with radionuclides that emit single photons. The development of instrumentation for annihilation photons (PET), although started at about the same time, proceeded more slowly, and the story of the emergence of this other technology is also fascinating.

(3) As a result of the absorbed radiation dose delivered by the other radionuclides employed at the time, The Children's Hospital in Boston would not allow any nuclear medical procedures to be performed with its patients, other than those who had manifested cancer.

(4) Dogs injected with Tc(I)TBI emit a distinctive garlicy odor. Fearful that this would discomfit patients, the inventors looked for a friendly first human subject. Much to their relief, I reported there was nothing to smell or taste.

(5) In his provocative treatise, *Pasteur's Quadrant: Basic Science and Technological Innovation* (Washington: Brookings Institution Press, 1997), Donald Stokes discusses the difference between the linear model of technological development and one that sees science driven by practical need. As examples, he cites Pasteur's remarkable discoveries in microbiology motivated by the needs of the winemaking and the dairy industries.

(6) One could also argue that the NIH should have received a part of the revenue stream and recovered its costs. However, this is a policy question involving the role of government in R&D, tax payer's equity, etc., and not part of the arguments I set out here (see, for example, D. Korn and S. Heinig, "Recoupment Efforts Threaten Federal Research," *Issues in Science and Technology* 20(4) (2004): 26–30).

(7) *Interdisciplinary Research: Promoting Collaboration Between the Life Sciences and Medicine and the Physical Sciences and Engineering* (Washington: National Academy Press, 1990).

(8) See D. C. Bok, *Universities in the Marketplace: The Commercialization of Higher Education* (Princeton: Princeton University Press, 2003).