The Cardiolite Story

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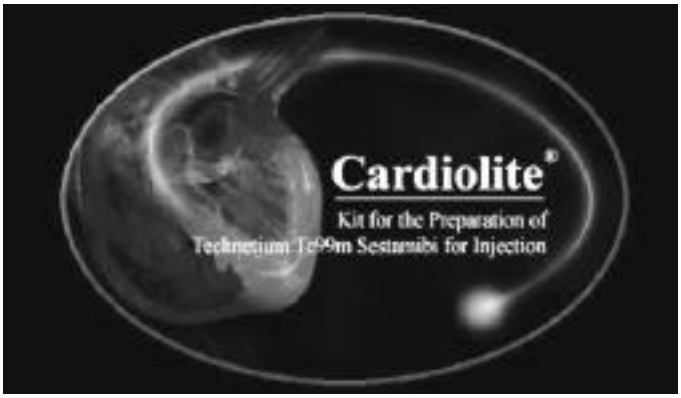
Most heart attack patients and other potential sufferers who have undergone the radioactive imaging test Cardiolite are rarely aware of the origins of its chemical base. But how many of us know what is behind every drug that we use or every test that we undergo? It is important, however, that the MIT community learns about the molecule that was synthesized by chemistry professor Alan Davison and his colleagues and that allows millions of Americans to receive better and potentially life-saving diagnosis and treatment.



Correctly identifying heart attack patients or those with unstable angina is an important medical and financial issue. Symptoms (such as nausea and sweating) are often difficult to distinguish and vague, especially in elderly people. Every year, about seven million people go to emergency rooms in the United States complaining of problems that may be signifying the onset of a heart attack.[1] Only about 25 percent are actually having a heart attack, but the danger of incorrectly diagnosing such a condition is so high that most emergency rooms err on the side of caution, keeping people overnight to measure and monitor cardiac enzymes. About 20 percent of these hospitalizations could be avoided with the use of a recent, non-invasive imaging test called Cardiolite.[2]

On March 14, 2000, during the annual scientific meeting of the American College of Cardiology, it was reported that a Cardiolite test (Kit for the Preparation of Technetium Tc99m Sestamibi for Injection) can accurately predict heart disease risk and cardiac death. The results from this landmark study demonstrate that the procedure can accurately stratify patients into distinct risk groups and potentially identify which older patients can be appropriately redirected from invasive to non-invasive treatments.[3] Non-invasive treatments may include the use of cardiac medication, such as beta-blockers and lipid lowering drugs, and changes in diet and exercise habits.

Cardiolite plays an even more important role in the lives of the 16 million Americans suffering from diabetes. Diabetics are two to four times more likely to have a heart disease. Until now, assessing coronary artery disease in these patients has been difficult because they may have no apparent symptoms; this so-called silent ischemia may result in the under-diagnosis of coronary artery diease in these patients until symptoms associated with late-stage heart disease occur. Diagnostic

intervention for late-stage disease often involves referring patients directly for diagnostic catheterization—a costly, invasive procedure that involves inserting a catheter through a patient's blood vessels and injecting x-ray contrast material. Studies have shown that a Cardiolite test successfully identified patients with diabetes at high or low risk for future heart attacks or cardiac death. While researchers indicate further studies are warranted to confirm these findings, this study suggests that the information the Cardiolite test provides can foster earlier intervention and treatment among this high-risk group and prevent unnecessary catheterization of low-risk patients.

The findings also demonstrated that the test was equally effective in predicting future cardiac events in men and women. Notably, women with diabetes have considerably higher rates of heart attack and are more likely to suffer fatal heart attacks than men with diabetes and women who do not suffer from diabetes. Women aged 55 and older with diabetes are seven times more likely to have heart disease than their counterparts do who do not have diabetes.[4]

Cardiolite is clearly the leading cardiac stress-imaging agent in the United States. It is the only heart imaging agent FDA approved to non-invasively evaluate the heart's pumping ability (function) and gauge the amount of blood flow to the heart muscle itself (perfusion)—and thus can more quickly assess whether a patient has already had a heart attack or is at risk for one in the future. Cardiolite is also the only cardiac imaging agent in the United States approved for acquiring diagnostic information for use in patient management decisions. Thus, it can be performed not only on people who are already complaining of heart-attack symptoms, but also on people who are at risk for a heart attack but have not shown any signs. Furthermore, a comparative study testing the diagnostic accuracy of Tl-201, another popular radioactive tracer, and Tc-99m, the tracer in Cardiolite, showed that both have similar sensitivity for detecting coronary artery disease, but Tc-99m showed better specificity determining the location and extent of artery blockage. Cardiolite is very safe and has been rarely associated with acute severe allergic events of angioedema and urticaria. The most frequently reported adverse events include headache, chest pain/angina, ST segment changes on ECG, nausea, and abnormal taste and smell.[5]

Cardiolite undoubtedly makes a difference in the lives of millions of people, but it is also a big part of the lives of the researchers who synthesized it—MIT chemistry professor Alan Davison

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and professor Alun G. Jones at the Harvard Medical School Department of Radiology. Professor Davison has been at MIT since 1964. He is the recipient of numerous prestigious awards, owns seven patents and is a Fellow of the Royal Society, the United Kingdom's national academy of science. Technecium-99, one member of a class of heart-imaging agents discovered in 1982 and patented in 1984, received FDA approval in 1990 and is being marketed by the DuPont-Merck Pharmaceutical Company under the trade name Cardiolite.

Cardiolite is a coordination compound that is based on a meta-stable form of Technecium-99. Technecium-99m represents 88.75% of the b-decay of Molybdenum-99. This form of Technecium, as implied by its name, is not as stable as regular Technecium-99 and has a half-life of only six hours. Technecium-99m decays into Technecium-99 by emitting a g ray that is used for x-ray imaging. The short half-life allows the test to be performed in one day without any unnecessary, overnight hospitalization. The molecule has to possess certain structural properties that would allow it to perform the function of an imaging agent. After the chemical is injected in the body, it has to retain its properties in this new environment. The positive Technicium ion is surrounded by six cyanide (CN^-) ligands, which make the molecule extremely stable by lowering its overall energy. The chemically inclined readers are probably aware that the cyanide (CN^-) is a p-donor ligand, which means that it forms a bond with Technecium by donating from its s electrons and by accepting electrons in its empty p orbitals. Thus, the bond is stronger than an ordinary s bond. The overall negative charge on the molecule makes it water-soluble but in order for it to be able to cross the lipid of the cell it had to be further modified. Each of the cyanide ligands is modified with an added alkyl group, which makes it more hydrophobic and thus lipid-soluble. The molecule has been modified several times partly in order to improve it and partly in order to allow MIT to keep its patent rights over it.[6]

In addition to the many benefits that Cardiolite offers to patients, it has been one of the most financially successful inventions by an MIT professor. Cardiolite royalties paid to MIT are usually at the top of the institute's licensing revenue list. It was one of the biggest contributors during a record-setting 1997 fiscal year when the Technology Licensing Office reported a record $21 million in licensing payments. The Cardiolite patent is just one of the 1500 MIT patents that have been involved in the licensing process since 1980. MIT usually tops the annual list of American universities for the most patents awarded. There are currently 702 active, exclusive MIT patents under development by companies. These patents are responsible for 2300 jobs and add close to $1 billion to the economy.[7]

To address the issue of patenting as presented in an earlier article ("Gene Patenting—A Threat to Science and More," MURJ, Vol.:3, Fall 2000, pp. 25-28), the patenting of the active chemical molecule in Cardiolite is a good example of the proper use of the patenting law. The inventor of the molecule has exclusive rights over something that was created from scratch, not extracted from nature (as is the case when patenting genes). The inventor has patented the application of knowledge, rather than knowledge itself. The molecule was created from existing, known elements and was not just discovered to exist in nature. Therefore, Prof. Davison and his colleagues are rightfully awarded exclusive rights over their invention.

Cardiolite and other Technicium-based compounds prepared by Prof. Davison and his colleagues will continue to have an ever-increasing role in modern medicine. Cardiolite has shown promise in the detection of breast tumors that cannot be identified by conventional mammography, in a technique called scintimammography. Professor Davison is currently working on a new brain-imaging agent called Technepine that may lead to earlier and more accurate diagnosis of Parkinson's disease and other conditions such as depression in older people and attention deficit disorder. The techencium-based molecule is the first reported compound to cross the blood-brain barrier and accumulate in a selective target —the brain's striatum.[8]

Throughout the years, MIT has produced many important discoveries but those that help save human lives always seem to stand out above the rest, and their inventors, like professor Alan Davison, are definitely people you should know about.

Acknowledgements

Thanks to Prof. Daniel Nocera, whose freshman chemistry lecture on Cardiolite first made me aware of its importance.

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