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Review article

The FDA, HHS, Sestamibi Redistribution and Quantification

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Abstract

The Food and Drug Administration (FDA) and Health and Human Services (HHS) mission statements are very specific. The FDA is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation. The U.S. Department of HHS mission is to enhance the health and well-being of all Americans, by providing for effective health and human services and by fostering sound, sustained advances in the sciences underlying medicine, public health, and social services.

To perform these missions, the pharmaceutical industry and the medical equipment manufacturers are required by law to provide complete and accurate information to the FDA and HHS to obtain approval for the use of their drugs and equipment for use in the diagnosis and treatment of humans and animals. It is also these corporations responsibility to update these Federal Agencies on any new information the companies become aware of regarding these drugs and devices. It is the responsibility of the FDA and HHS to review and investigate these submitted materials and to demand further information to assure the mission statements of these agencies are adhered to.

When these corporations submit material to the FDA, HHS, and/or Federal Courts, which they know, suspect or are given reason to believe could be incorrect, it is the responsibility of these corporations to submit that material to these agencies and when applicable the Courts. The intentional misrepresentation of material to these agencies is intentional fraud. The FDA and HHS are responsible for investigating such fraud and misrepresentation of facts when brought to the attention of these agencies and failure to do so is a violation of these agencies responsibilities as mandated.

The primary author has repeatedly brought to the attention of the FDA, HHS and Federal Courts the misrepresentation, and intentional fraudulent misrepresentations made by several corporations as noted in the body of this paper and as supported by medical findings conducted inter alia at Harvard, UCLA and Cedars Sinai. The FDA, HHS and Federal Courts have failed to address this information despite being made aware of it as noted in the body of this paper, and consequently American citizens have continued to receive higher doses of radiation and radioactive materials during diagnostic testing for heart disease than they should have; increased levels of radiation that represented inter alia marketing by these corporations designed to increase their profits. These agencies have failed the American people and their obligation to investigate this information. They have failed to correct associated Current Procedural Terminology (CPT) codes promulgated by the American Medical Association (AMA) resulting from this intentional misrepresentation of information provided by these corporations to the FDA and HHS and have consequently failed to protect the American people, increasing the profits for these corporations while misdiagnosing heart disease in the process.

Having failed to address these misrepresentation of facts, the authors now submit this peer-reviewed medical publication, calling for a mandatory investigation of the failure of the FDA, HHS and Federal Courts who have failed in their mandated responsibilities to the American people and for the AMA CPT codes to reflect and correct the applicable imaging codes.

Keywords: FMTVDM©℗; B.E.S.T. Imaging ©℗; Breast Cancer; Breast Inflammation; Theranostics; Quantification; AI; Myocardial Perfusion Imaging (MPI); Sestamibi Redistribution; Tetrofosmin Redistribution; FDA; HHS and Nuclear Camera Quantitative Calibration

Introduction

At the 2018 American Society of Nuclear Cardiology (ASNC) Conference this September [1] (Figure 1), after more than two decades of work quantifying myocardial perfusion imaging of both Single Photon Emission Computed Tomography (SPECT)/Planar and Positron Emission Tomography (PET) cameras using nuclear isotopes and measuring the redistribution properties of these isotopes, we presented the first truly Artificial Intelligence (AI)/Machine Learning (ML) method for quantification, not pseudo-quantification [2-12] using Nuclear Cameras; viz. The Fleming Method for Tissue and Vascular Differentiation and Metabolism (FMTVDM) using same state single or sequential quantification comparisons including Breast Enhanced Scintigraphy Test (B.E.S.T.) Imaging.

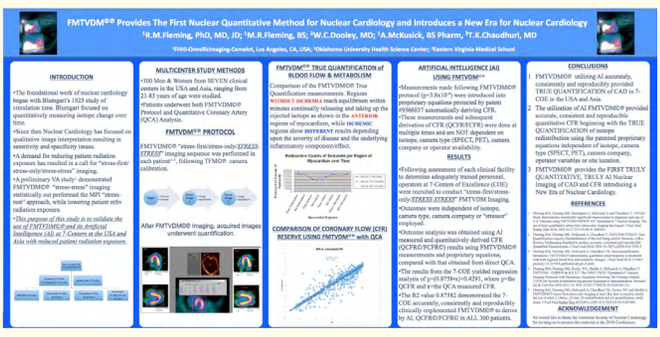


Figure 1: 2018 American Society of Nuclear Cardiology Poster Presentation.
First patented quantitatively diagnostic and theranostic method for CAD and Cancer, including Breast Cancer, measuring metabolic and regional blood flow differences (RBFDs).

The concept of using the redistribution properties of nuclear isotopes is not a new one. The original concept of redistribution was defined using thallium-201 (Tl-201), wherein following a single injection of Tl-201, qualitative comparisons of two sets of images following "stress" were compared, looking for evidence of ischemia and/or infarction. In the late 1980's to early 1990's, two major pharmaceutical companies, DuPont Merck and Bristol Myers Squibb (BMS), competed with each other for control of the cardiac diagnostic imaging market with the introduction of their newest technetium99m (Tc-99m) imaging agents/isotopes.

As a consequence of the shorter half-live of Tc-99m compared with Tl-201, these isotopes could be given in higher radiation doses, which it was believed would result in better image "quality". A considerable amount of money and marketing of these isotopes has attempted to justify requiring physicians to use two-doses of either isotope instead of a single dose as was done with Tl-201, based upon the incorrect premise that these Technetium-99m isotopes do not redistribute; despite significant evidence to the contrary, that these Technetium-99m (Tc-99m) agents like Tl-201 redistribute. The companies would remove the term redistribution in favor of "stress" and "rest" imaging and sell the concept to clinicians who would completely forget about redistribution and accept the companies marketing strategies.

Despite multiple publications [13-47]; (e.g. Figure 2) and presentations to the contrary showing the redistribution of these agents, Sestamibi and Teboroxime and later Tetrofosmin, it wasn't until the 2018 American Society of Nuclear Cardiology (ASNC) Conference [1], where except for Lantheus representatives who now own Sestamibi, everyone else comfortably acknowledged the redistribution of these Tc-99m isotopes and more importantly, everyone is waiting to see how long it will take the FDA, HHS, Lantheus who now owns Sestamibi and GE Healthcare who owns Tetrofosmin, to admit it; reducing patient costs, time and radiation exposure. We no longer need to worry about BMS and Teboroxime, as DuPont who originally owned Sestamibi sufficiently marketed the elimination of the use of Teboroxime in the United States, even though Teboroxime imaging could be done in a fraction of the time (Part II below).

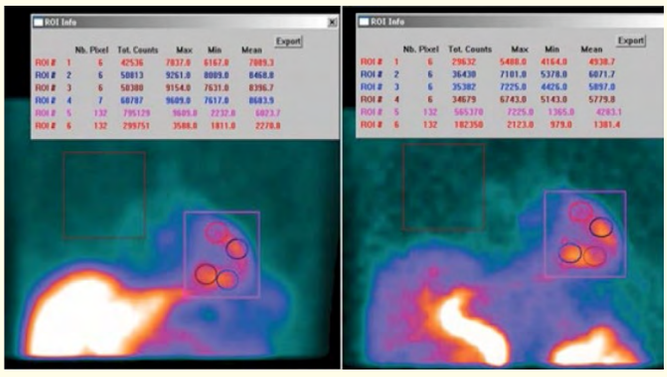
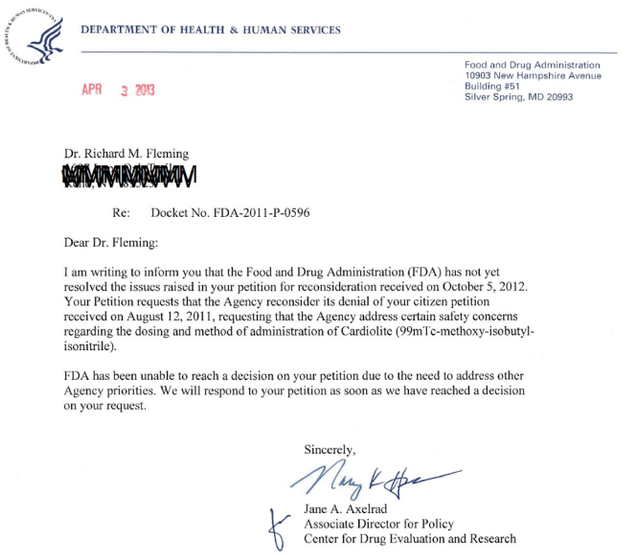


Figure 2: Sestamibi redistribution made apparent when imaging begins soon enough to find it. Here 5-minute and 60-minute "quantified" post stress images demonstrate the redistribution of a single injected dose of Sestamibi.

In Figure2, the 5-minute image is in the left panel and the 60-minute image displayed to the right. Regions of interest (ROIs) demonstrate the measured level of Sestamibi isotope as shown. E.g. the basal anterior wall has an isotope count of 7089.3 at 5-minutes and 4938.7 at 60-minutes. Absent CAD, the Tc-99m isotope decay would be only 10% over this 55-minute period of time for a count

of 6380.4. The measured count of 4938.3 reveals a clinically significant Sestamibi (redistribution) washout revealing coronary artery disease.

Efforts to have the Food and Drug Administration (FDA) as part of the Public Health Service of the Department of Health and Human Services (HHS) have been reintroduced (FDA-2018-P-3102; Figures a-g) to require the FDA and HHS to address this problem. A prior attempt (FDA-2011-P-0596) was ignored by the FDA and HHS, stating they were "unable to reach a decision on (the) petition due to the need to address other Agency priorities." They have not yet addressed the problem.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

APR 3 2013

Dr. Richard M. Fleming
[redacted]

Re: Docket No. FDA-2011-P-0596

Dear Dr. Fleming:

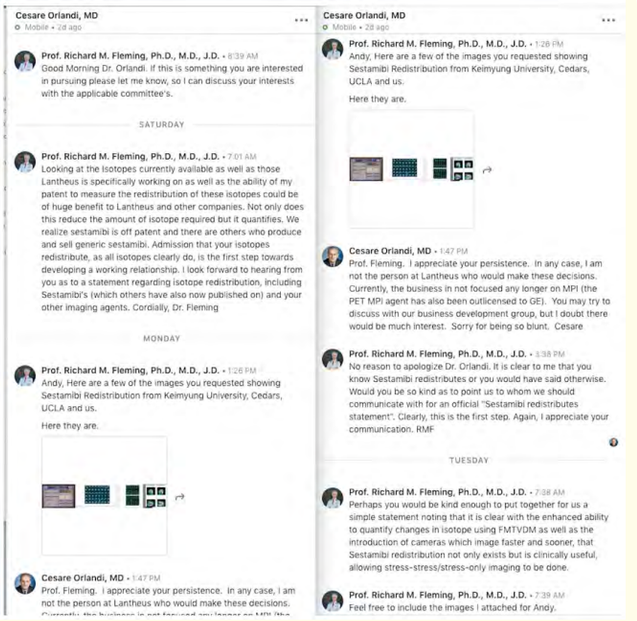
I am writing to inform you that the Food and Drug Administration (FDA) has not yet resolved the issues raised in your petition for reconsideration received on October 5, 2012. Your Petition requests that the Agency reconsider its denial of your citizen petition received on August 12, 2011, requesting that the Agency address certain safety concerns regarding the dosing and method of administration of Cardiolite (99m Tc-methoxy-isobutyl-isonitrile).

FDA has been unable to reach a decision on your petition due to the need to address other Agency priorities. We will respond to your petition as soon as we have reached a decision on your request.

Sincerely,

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

Figure a



Cesare Orlandi, MD

Prof. Richard M. Fleming, Ph.D., M.D., J.D. • 8:39 AM
Good Morning Dr. Orlandi. If this is something you are interested in pursuing please let me know, so I can discuss your interests with the applicable committee's.

SATURDAY

Prof. Richard M. Fleming, Ph.D., M.D., J.D. • 7:01 AM
Looking at the Isotopes currently available as well as those Lantheus is specifically working on as well as the ability of my patent to measure the redistribution of these isotopes could be of huge benefit to Lantheus and other companies. Not only does this reduce the amount of isotope required but it quantifies. We realize sestamibi is off patent and there are others who produce and sell generic sestamibi. Admission that your isotopes redistribute, as all isotopes clearly do, is the first step towards developing a working relationship. I look forward to hearing from you as to a statement regarding isotope redistribution, including Sestamibi's (which others have also now published on) and your other imaging agents. Cordially, Dr. Fleming

MONDAY

Prof. Richard M. Fleming, Ph.D., M.D., J.D. • 1:26 PM
Andy, Here are a few of the images you requested showing Sestamibi Redistribution from Keimyung University, Cedars, UCLA and us.
Here they are.

Cesare Orlandi, MD • 1:47 PM
Prof. Fleming. I appreciate your persistence. In any case, I am not the person at Lantheus who would make these decisions.

Cesare Orlandi, MD

Prof. Richard M. Fleming, Ph.D., M.D., J.D. • 1:26 PM
Andy, Here are a few of the images you requested showing Sestamibi Redistribution from Keimyung University, Cedars, UCLA and us.
Here they are.

Cesare Orlandi, MD • 1:47 PM
Prof. Fleming. I appreciate your persistence. In any case, I am not the person at Lantheus who would make these decisions. Currently, the business in not focused any longer on MPI (the PET MPI agent has also been outlicensed to GE). You may try to discuss with our business development group, but I doubt there would be much interest. Sorry for being so blunt. Cesare

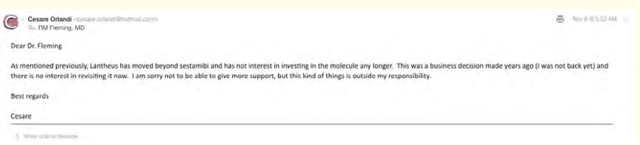
Prof. Richard M. Fleming, Ph.D., M.D., J.D. • 3:38 PM
No reason to apologize Dr. Orlandi. It is clear to me that you know Sestamibi redistributes or you would have said otherwise. Would you be so kind as to point us to whom we should communicate with for an official "Sestamibi redistributes statement". Clearly, this is the first step. Again, I appreciate your communication. RMF

TUESDAY

Prof. Richard M. Fleming, Ph.D., M.D., J.D. • 7:38 AM
Perhaps you would be kind enough to put together for us a simple statement noting that it is clear with the enhanced ability to quantify changes in isotope using FMTVDM as well as the introduction of cameras which image faster and sooner, that Sestamibi redistribution not only exists but is clinically useful, allowing stress-stress/stress-only imaging to be done.

Prof. Richard M. Fleming, Ph.D., M.D., J.D. • 7:39 AM
Feel free to include the images I attached for Andy.

Figure b



Cesare Orlandi

Dear Dr. Fleming

As mentioned previously, Lantheus has moved beyond sestamibi and has not interest in investing in the molecule any longer. This was a business decision made years ago (I was not back yet) and there is no interest in revisiting it now. I am sorry not to be able to give more support, but this kind of things is outside my responsibility.

Best regards

Cesare

Figure c

RM Fleming, MD

Good Morning Joel,

I'm checking in with you to see what thoughts you and Lantheus have on promoting sestamibi's redistribution and the subsequent ability to find vulnerable inflammatory plaques and breast cancer. As you know, October is breast cancer month and I am working with reporters on a story about sestamibi redistribution and it's subsequent ability to find hidden heart disease and breast cancer.

Let me know.

Cordially,

Dr. Fleming

Lazewatsky, Joel L

Good Morning, Dr. Fleming,

You must understand that Lantheus is not going to be spending any resources on Cardiolite at this point. It is off patent and our revenue from it is quite limited. Any additional indications or uses for it benefits our competitors as much as it does us and the upside is very, very limited.

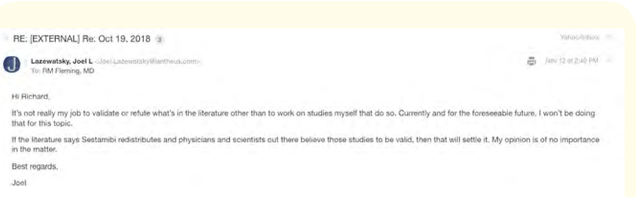
I appreciate your perspective, but there is little I can do to help.

Best,

Joel

Figure d

They also state they have no plans to refute the literature and they have No reason to believe the authors of papers on sestamibi redistribution have misrepresented anything.



RE. [EXTERNAL] Re: Oct 19, 2018

Lazewatsky, Joel L

Hi Richard,

It's not really my job to validate or refute what's in the literature other than to work on studies myself that do so. Currently and for the foreseeable future, I won't be doing that for this topic.

If the literature says Sestamibi redistributes and physicians and scientists out there believe those studies to be valid, then that will settle it. My opinion is of no importance in the matter.

Best regards,

Joel

Figure e

Sestamibi (redistribution) washout revealing coronary artery disease.

Correspondence from both Dr. Cesare Orlandi, Chief Medical Officer for Lantheus, who just so happens to have been at DuPont, at the time Sestamibi was first released by DuPont Merck and whose own published research [16] shows Sestamibi Redistribution and Lantheus Director of Clinical Imaging, Joel Lazewatsky, PhD, who introduced himself to me at the 2012 Society of Nuclear Medicine (SNM; SNMMI) Conference [The same Conference where Keimyong University demonstrated they too saw both Tetrofosmin and Sestamibi redistribution using the methods I had discussed at the 2011 SNM Conference.] during my poster presentation, who told me Lantheus had been following the primary authors publications and presentations on Sestamibi, show that neither Dr. Orlandi, Dr. Lazewatsky nor Lantheus have any intention of correcting the misinformation as there is no profit in it for them to do so.

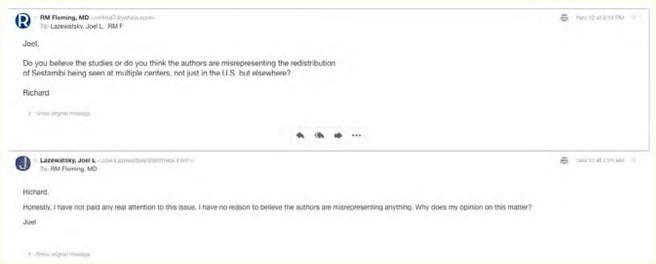


Figure f

As the record shows, the intention is to not address the misrepresentation of facts unless forced to do so by the FDA and HHS and as we can see the FDA and HHS have "other agency priorities", although what could be more important than the consequences of the intentional actions committed by this and the other companies (infra and FDA2018-P-3102), is hard to imagine. These corporations deal with their problems through litigation and for good reason; they make a lot of money through the misrepresentation of information, changing the medical lexicon and the fear of litigation. It is impossible for citizens to engage in the type of litigation necessary to succeed against big corporations and it is the responsibility of the FDA and HHS, who actually work FOR the people, to address these types of problems/crimes.

Today the entire argument continuing to be propagated by Lantheus officially, albeit not so unofficially as the above noted emails demonstrate, is that Sestamibi does not redistribute based upon a single reference listed as "#16" while going on to admit there is redistribution with "chronic heart failure" and other conditions. This type of argument is so inconsistent as to boggle the mind and the idea that anyone would buy into the argument is unconscionable. The argument made by Lantheus [47] is that the "degree" of redistribution could not be clinically imaged and "is certainly beyond what would ever be expected of a radiology resident".

"Myocardial clearance of Tc-sestamibi is slow and the agent does not redistribute to a degree that can be imaged clinically [16]. Note (the following is certainly beyond what would ever be expected of a radiology resident): Heart House Course, Bethesda '93: Sestamibi undergoes minimal (about 20%) redistribution primarily within the first 20 to 60 minutes following injection. This may impact on lesion detection as the differential washout between the normal and ischemic myocardium may result in a reduction in defect size or severity with time. Therefore, their recommendation was to begin imaging 15 minutes following stress injection, and 60 minutes following rest injection. The tracer is retained in normal myocardium for several hours (myocardial clearance T1/2 is about 5hours). Myocardial washout of MIBI is increased in patients with chronic heart failure [104] and in patients with hypertrophic cardiomyopathy- particularly those patients with impaired contractile reserve [159]. An area of reverse-redistribution can be seen following PTCA in patients with acute MI- indicating that the ability of myocytes to retain the tracer may be impaired in stunned myocardium (possibly related to loss of the normal membrane potential or mitochrondrial injury) [84].[https://www.auntminnie.com/index.aspx?sec=ref&sub=ncm&pag=dis&ItemID=54347; "Technetium Labeled Cardiac Imaging."] (emphasis added)".

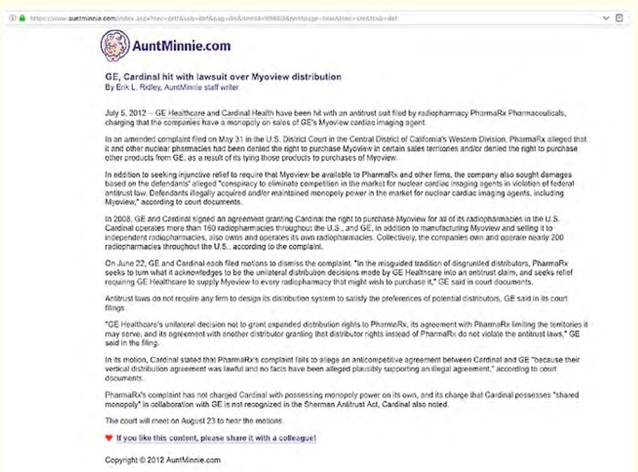


Figure g

It is NOT beyond the radiology residents, radiologists, nuclear medicine physicians or nuclear cardiologists we know. Lantheus now pretends to be completely unaware of the published literature [1-46,48-61] and what we have referenced here is certainly not all of the published material.

Not only that but how does one consider redistribution "minimal" when they state the redistribution is "about 20%" when imaged between 20-60 minutes. The published research also shows that the correct time to "image" for "redistribution" begins at 5minutes; however, that would completely negate all of the marketing (see Part III) efforts put into place by DuPont and now Lantheus, which decimated BMS and gave DuPont control of the myocardial perfusion imaging marketplace.

Based upon with the overwhelming evidence [1-46,48-61] of Sestamibi and the other Tc-99m isotopes, they all redistribute, with the company stating that minimal equals 20%, which is greater when you begin to image correctly, i.e. earlier. We now turn to the real story behind the Corporate LIES, GREED AND CORRUPTION and the need for FDA and HHS actions. "Oh what a wicked web we weave when first we practice to deceive".

Part I: Corporate lies, greed and corruption

Given the significant limitations of "qualitative" myocardial perfusion imaging (MPI) as shown in Figure 3, The Federal Government (CMS), ASNC and the SNMMI finally decided in 2018 that it was time to improve outcome results from our Nuclear Cardiac Imaging studies, by "quantifying" these Heart Tests. A good idea I think; although as you will see, this has resulted in a lot of Nuclear Camera companies declaring they have the ability to "quantify" which means you will want to buy their cameras so you can bill for "quantification", a claim not based upon scientific facts or principles but on methods shown in Figure 14 and discussed below.

Approximately 76.45% of our myocardial perfusion imaging (MPI)/Nuclear Cardiology tests are right in determining if you have heart disease or not. It is important to realize this does NOT mean the tests correctly identify where the problem actually is.

For example, the nuclear study might suggest the problem is in the right coronary artery (inferior wall of the heart) when in fact it's actual in the left circumflex artery (anterolateral wall of the heart).

Above and beyond that it also means that 23.55% of time the tests are completely wrong as to whether you have heart disease or not, missing disease that's there while telling other people they have a problem when they don't. This is that nasty sensitivity and specificity issue we keep talking about in the medical literature. Sensitivity, the ability to identify disease when present and specificity, the ability to exclude disease when absent and remember, we're just talking about having correctly found CAD, not whether the tests correctly identified the actual area/artery, which has the problem.

During the 18-years it took to develop FMTVDM; B.E.S.T. Imaging [1-11], making it possible to quantitatively find Heart Disease and Cancer [1-12], roughly 3 million Americans with Heart Disease and Breast Cancer were misdiagnosed and as a result; they are DEAD (Figure 3). The primary author has felt bad for many years believing it was somehow his fault for not having done a better job of getting the word out, but he also realizes it was not so much his fault as the failure of the FDA and HHS to investigate and take action on the pharmaceutical and nuclear camera companies, that have lead to these deaths. As the FDA documents show, the FDA and HHS had (supra) other priorities to address.

Rather than focusing on improving the actual outcomes/correctness of MPI, the pharmaceutical companies focused their efforts on selling you two doses of radioactive isotopes for each study, thereby increasing their profits, while the Nuclear Camera companies focused their efforts on making "prettier" pictures, requiring you to buy newer cameras and software, thereby increasing their profits. However, more radiation and "prettier" pictures didn't result in greater accuracy. It did, result in more profit for these companies.

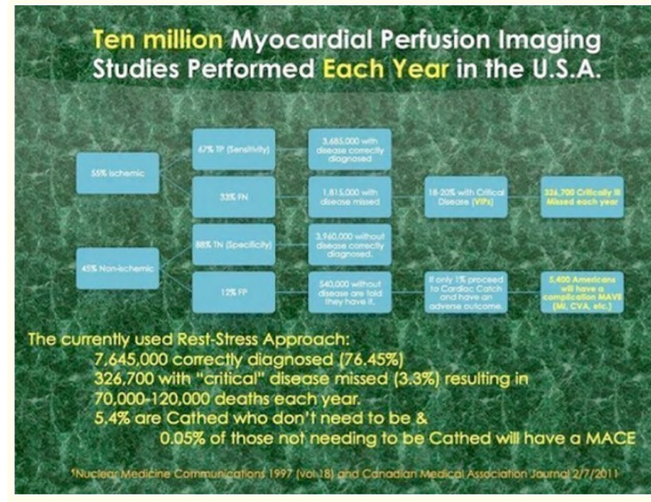


Figure 3: Major adverse cardiac events associated with qualitative errors and utilization of two doses of Sestamibi per study result in more than 325,000 deaths each year in the United States alone.

Nuclear Cameras undergo frequent "quality" control by the nuclear technologists who operate them on a daily basis. The key word here is "quality", aka. Qualitative, not Quantitative (measurement). You would have thought by now somewhere along the way someone would have asked; Do these cameras accurately measure what we think they are measuring? The sad fact is we don't know. Either they thought of it and didn't like the result or they never thought of it, which doesn't increase one's confidence level in the people making and selling these expensive tools (Nuclear Cameras) used for finding heart disease and other medical problems, including cancer.

The first step of FMTVDM; B.E.S.T. Imaging is the calibration step. This first step [2-4,7-11] standardizes the nuclear camera be it SPECT/Planar or PET to the specific isotope being used. When this is done, what becomes apparent is that nuclear cameras are not inherently without problems. In fact, the "prettier" the picture, which adds to Company profits, the greater the inaccuracy of the result (Figure 4), which adds to the clinician and patient problems.

Independent of what clinicians are being told, the "qualitative" results of MPI studies have not truly changed. All that has changed is the cost of the nuclear cameras and the isotopes being sold, in-

dependent of whether you are using SPECT/Planar or PET cameras and independent of whether you use Thallium-201 (Tl-201), the newer Technetium-99m (Tc-99m) agents, or 18-flurodeoxyglucose (FDG) with PET cameras (Figure 5).

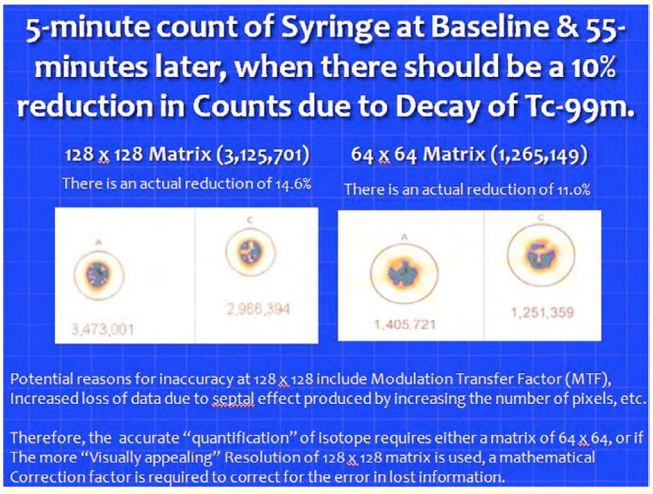


Figure 4: Failure to "quantitatively" calibrate nuclear cameras and the decision by camera companies to encourage choosing images which are more visually "appealing" have lead to additional diagnostic errors beginning with loss of actual data.

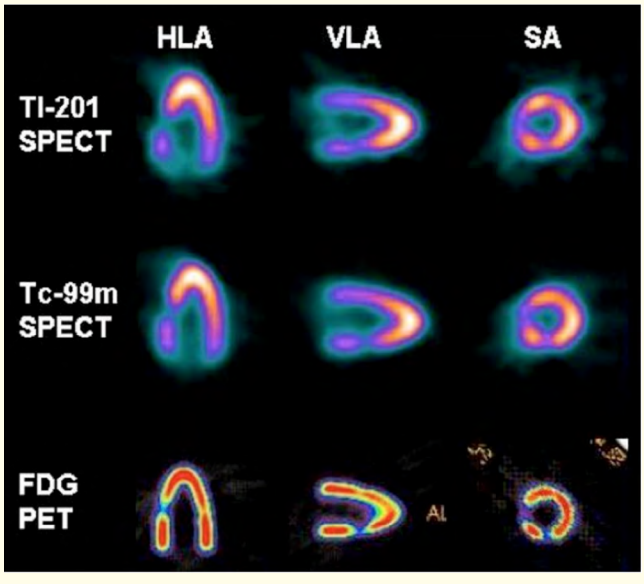


Figure 5: Failure to quantitatively calibrate nuclear cameras have lead to diagnostic errors for both Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) Cameras as efforts to improve the "appearance" of the imaged results has lead to loss of data (Figure 4).

Part II. The importance of true quantification

What does work, what does make a significant difference, is the ability to actually measure what we are doing; to have an objective quantitative outcome. However, this measurement must be of something meaningful, not something randomly chosen out of thin air to support the sale of nuclear isotopes or nuclear cameras [1-12].

It is with this understanding that we turn our attention to what nuclear cameras truly measure when performing nuclear cardiac, oncologic and other nuclear medicine studies; the ability to look at the physiologic response of the tissue once the isotope is injected into it; viz. the measurement of metabolism and RBFDs (Figure 1) determined by the uptake and release (redistribution) of the isotope and the importance of being able to measure (quantify) that phenomena in the region based upon the consequential actions of the tissue.

Merely arbitrarily changing the definitions of what we are looking for [2-4,7,9-11] doesn't validate what we are doing. On the contrary, it invalidates what we are doing. Redistribution, the change in isotope over time under same state conditions, viz. following "stress" allows for the determination of ischemia. Redistribution, the change in isotope over time when that same state condition is "rest" provides information about viability. But the comparison of "stress" to "rest" does not provide ischemia or viability information resulting in erroneous outcomes (Figure 3) almost 25% of the time. The only thing the comparison of "stress" to "rest" images ever did was justify the additional expense and radiation exposure of administering two doses of isotope into a person instead of using the redistribution of a single injected dose to understand the tissue metabolism and RBFDs (Figure 6). As mentioned, "stress-rest" imaging misses 25% of the problems, results in incorrect identification of the target lesion/coronary artery involved and increase the profits of the pharmaceutical companies selling the two-dose methodology.

Further examples of the "quantitative" measurement of Sestamibi and other Isotopes "redistribution" accurately not only identifying the presence or absence of CAD, but also actually finding and measuring the true coronary artery causing the problem are shown in Figures 6-9 and 18. These diagnostic studies were performed at multiple VA, University, and Diagnostic centers around the world, including inter alia Keimyung University, Harvard, UCLA and Cedars Sinai.

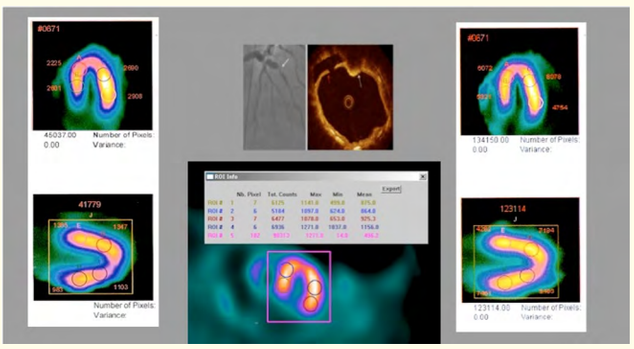


Figure 6: Sestamibi redistribution (wash-in) reveals critically diseased coronary arteries, missed using the two-injection "stress-rest" approach.

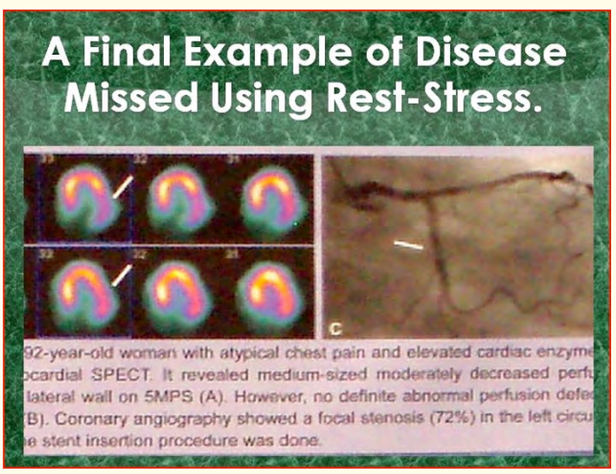


Figure 7: Keimyung University finds hidden coronary artery disease (CAD) present in 40% of patients studied using Sestamibi and Tetrofosmin Redistribution [61].

Figure 8: Vulnerable inflammatory plaque (VIP) discovered using FMTVDM measurement of Sestamibi redistribution.

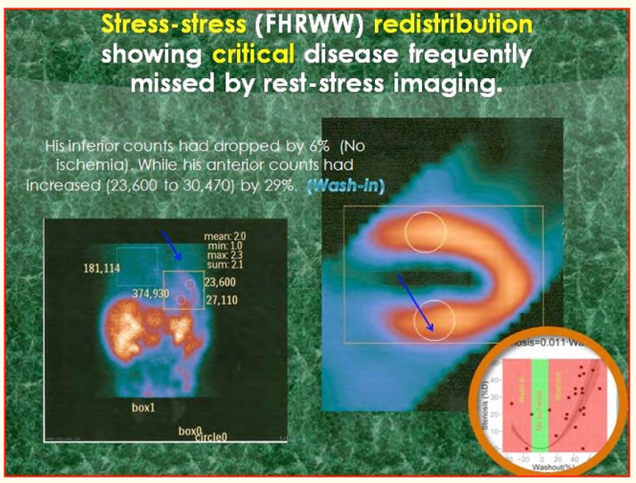


Figure 9: A demonstration of both normal and abnormal redistribution of Sestamibi in the inferior and anteroapical myocardium respectively. There is no evidence of the critically diseased left anterior descending artery (LAD) in the 60-minute image recommended by the pharmaceutical company. The true redistribution of Sestamibi is missed when clinicians wait for the company recommended 60-minute image results.

In each of these examples, the disease was so critical that the only way to find it was to use FMTVDM and to begin imaging at 5-minutes; failure to do so results in people with critically diseased coronary arteries being told they have no heart disease only to go home and die. Some of these studies were presented by Keimyung University at the 2012 Society of Nuclear Medicine Conference where Dr. Lazewatsky (supra) from Lantheus was in attendance and spoke with me following my presentation. It is unconscionable for Lantheus to claim they are unaware of the results of Sestamibi redistribution in humans or that the redistribution is "minimal" or "not clinically imageable".

In fact, of the 72 (38 women, 34 men) people presented by Keimyung University School of Medicine, 40% of the people had CAD only detectable by looking for redistribution beginning at 5-minutes post stress, people whose CAD was missed using the two-injection "stress-rest" approach (Figure 10).

The South Koreans were able to demonstrate in the Cardiology Department at Keimyung University, following the FMTVDM protocol, but not having the proprietary equations to "Measure/Quantify" the actual severity of coronary artery disease, that not only do these Isotopes Truly "Redistribute", the same isotopes the Pharmaceutical Companies are adamant do NOT "redistribute", but that only by understanding and applying this to the tests for Heart Disease could they find the heart disease missed in 40% of the patients, suggesting that our 25% error rate (Figure 3) may underestimate the extent of the problem.

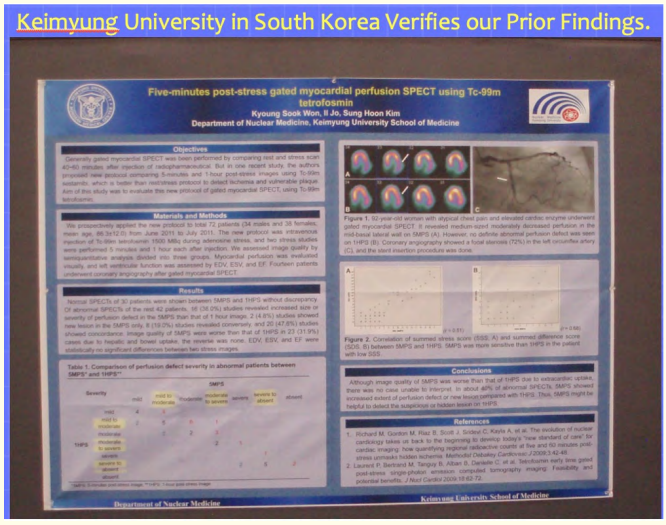


Figure 10: Keimyung University replicates qualitative results of Technetium-99m isotope redistribution, providing an example of Tetrofosmin redistribution, matching what is seen with Sestamibi redistribution. [61].

The approach by the Federal Government (CMS, FDA, HHS) has been to completely ignore this misrepresentation of facts by the radiopharmaceutical companies. The Government has called for "quantification" and while "quantification" is important, if you're not "quantifying" the right thing (viz. redistribution) and you're using equipment which is NOT actually "calibrated" to correctly "quantify" what you are looking for, you haven't improved anything. You've simply shifted the attention without correcting the underlying problems, caused by the misrepresentation of these companies. In fact, as you will see, the Government has only encouraged more lies by encouraging the nuclear camera manufacturers to claim their equipment "quantifies" disease, when the representations of this ability to "measure/quantify" defy the very definitions of what the cameras actually measure.

As for ASNC and the SNMMI, of course they want Nuclear Studies to improve, we all do and quantification is the only real way to do that, but if you're using nuclear cameras which are not accurately quantifying (infra) and if you are accurately quantifying but measuring the wrong thing ("stress-rest" vs. "redistribution"), you CANNOT improve outcomes.

The fundamental problem here, is that there are a lot of people in addition to the nuclear camera and drug companies who are making an awful lot of money from all these imaging studies and when you tell them they can make even more money by billing for "quantification", well you can bet they're willing to do whatever they need to do to make more money.

The important difference between true quantification and pseudoquantification

There are two basic types of nuclear cameras. The SPECT/Planar and PET types of cameras. Each type of camera is used depending upon the energy released from the isotope being used. The only difference between SPECT and planar is that the camera "detectors" are stationary for planar and move around the patient with SPECT. In PET Imaging the camera doesn't move and the "detectors," that part of these cameras, which "detect" the scintillations being emitted from the patient, are positioned 360 degrees around the patient.

Prior to FMTVDM there has been no system for calibrating, quantifying or measuring the outcomes of treatment to determine if the treatment is working or needs to be changed; viz. theranostification. FMTVDM is in fact the only method, which can do so, at least legally until the patent runs out in another 18 plus years. FMTVDM was able to solve these "quantification" problems by beginning with the critical step the nuclear camera companies failed to take into consideration; i.e. do the nuclear cameras accurately, consistently and reproducibly measure the "scintillations" they are designed to "detect".

When you calibrate something you are standardizing it, so that every other similar tool in the world that says it can measure something, accurately, consistently and reproducibly measures exactly what it says it's capable of measuring; no matter where you are or when you measure it.

For example, if I give you a ruler and ask you to measure the length of a piece of paper you can accurately, consistently and reproducibly do so. In fact anyone should be able to take a "ruler" whether it be in inches or centimeters and get the same measurement independent of whether they measure that paper in the U.S., Canada, Australia, France, Vietnam, South Korea or …. Well you get the picture.

Why? Because every ruler in the world is standardized, it is the same. It has been calibrated to a known standard, which has been accepted by everyone and is exactly the same everywhere in the world. Hundreds of years ago people bought yards of fabric in open markets. The length of a yard of fabric in England was the defined as the distance

from the tip of the King's nose to his fingertips. If the King was tall you got a good deal if he was shorter, not such a good deal. Depending upon who the King was or where you were, the "measured" length of a yard of cloth varied. There was no consistent length to a yard of cloth.

With time this approach changed as people wanted consistency. People wanted to know if they paid for something they were getting the same value as someone else was getting and so what we "measured" became standardized. We agreed what we would accept for "measured" length, weight, size, and with time, time itself. In fact, everything we use as a tool to measure something has to be standardized to an accepted "standard" and this process of making everything the same based upon the "standard" is called "calibration" so what someone talks about in Oslo is the same thing someone is talking about in Detroit.

An obvious example of the importance of this being if you buy a car made in Tokyo and it needs repairs in Los Angeles, the tools used to diagnose and correct the problem, will result in you receiving the right parts to repair your car.

Figure 11: Tools are only useful if they provide the same result everywhere and anywhere they are used. To have a tool, which can be used to "quantify", that tool must be standardized against a known control/standard, which is accepted by everyone as representing what it is, we say we are trying to measure.

Every tool measures one thing and one thing only; i.e. it can only measure what it's calibrated to measure. When CMS, ASNC and SNMMI call for "quantification" of MPI studies, they are calling for "quantification" using nuclear cameras, which are designed to measure "scintillations" (Figure 12) and that is what they will need to be calibrated to if they are to accurately, consistently and reproducibly measure/quantify scintillations [2-4,7,9-11].

Figure 12: SPECT/Planar and PET Nuclear Cameras measure "scintillations" not mBq/gram/cc or any other combination of radiation, weight, volume; they only measure scintillations. Reporting mBq/gram/cc is the same as telling someone you measured 8-pounds with a ruler.

If any nuclear camera company tells you they are measuring something other than scintillations, then they are telling you that their cameras are able to measure something other than what they are designed to measure. To understand what we're talking about, lets look at the following example. You would never give someone a ruler and tell them to go weigh something and you wouldn't give them that ruler and ask them for a measurement and expect them to come back and tell you what they measured weighed 8-pounds. Why not? Because rulers don't provide measurements of weight; rulers provide measurements of length. So it defies logic that they would report a measurement of 8-pounds. You would

look at the person with a certain sense of what's wrong with this picture? Yet that's exactly what the nuclear camera companies are attempting to do today. They are attempting to tell you their nuclear cameras measure something other than scintillations.

Nuclear cameras measure the release of energy (scintillations) from isotopes (radioactive drugs) injected into people. Isotopes which are used to look for Heart Disease, Breast Cancer and any of a number of other medical problems.

When the Nuclear Camera is positioned around your body where it is looking to find a specific problem, presuming it is positioned at the right time to find the problem as discussed above, the nuclear camera will detect and quantify the scintillations emitted from the person. We won't do Physics 101 here but the term "scintillation" essentially means "sparkle".

Figure 13: Tools can only measure the one thing they are calibrated/standardized to measure.

SPECT/Planar or PET Nuclear Cameras can only measure what they are designed to measure, scintillations. Just like the ruler, which measures inches or centimeters these nuclear cameras only "measure" scintillations (Figure 14).

This is really all you need to know to fully understand and realize that when companies selling you a SPECT/Planar or PET camera tell you they are "quantifying" or "measuring" heart disease or breast cancer or anything else and that Camera Manufacturing Company reports measurements in what's called Standardized Uptake Value(s) or SUV, they are selling you their ruler measuring 8-pounds [2-4,7,9-11].

Figure 14: The devil is in the details and science doesn't happen by magic. Just because you want something to be considered "quantitative" doesn't mean it is.

SUV values are presented as mBq/gram/cc (mili Becquerels per gram per cubic centimeter), or Bq/cc (Becquerels per cubic centimeter), not scintillations. mBq is a measure of radiation, grams are a measure of weight and cubic centimeters is a measure of volume. Three completely different measurements made by three different tools, none of them SPECT/Planar or PET cameras. It's the person telling you the ruler measured 8-pounds.

It's worse than that actually. It's like the person coming back and telling you the ruler measured 3 red lights per 8-pounds per gallon of gasoline (radiation/weight/volume). Three completely different measurements, none of which the ruler or in this case the nuclear camera actually measures. Nowhere in SUV do you find scintillations reported.

When you dig into the details of how SUVs are derived you will find out they are the result of "mathematical modeling" which means to develop their " SUV model" they inject an isotope into a vein in the arm, usually the right arm and then assume that absolutely none of the isotope moves out of your veins into your body (this appears to be part of the sticky explanation these companies are fond of using), from here the isotope travels from the veins in your arm up into your right atrium, right ventricle, into your lungs with all the

blood vessels there and yet all of the isotope continues back into your left atrium, then left ventricle and immediately after leaving your left ventricle abruptly stops and all of it goes directly into the arteries of your heart (what's called your coronary arteries); even though the vast majority of the blood that comes out of the left ventricle gets pumped to the rest of your body where it is needed (the hearts major job), the isotope apparently just goes into the arteries of your heart.

Nonetheless the assumption is made that essentially the entire isotope is immediately taken into the coronary arteries where the SPECT/Planar or PET (currently only PET cameras claim this) camera can take an image. An image, which is then compared with other areas of the body where it is assumed that there is either no isotope or the original amount of isotope before any of the isotope was taken up by your coronary arteries.

These two images are then compared and voila the Nuclear Camera is suddenly able to measure radiation per gram per volume or radiation per volume and come up with a ratio between the two areas. A ratio that is usually between 1 and 2. In other words between the same and twice the SUV.

An important concept to remember is when someone gives you percentages or ratios (e.g. 1-2), be very leery. If you have 10 of something and someone gives you 10 more, you have a 100% increase and your ratio of what you have to what you had is 2. If you have 1 of something and someone gives you 1 more, you have a 100% increase and your ratio of what you have to what you had before is 2. If you have a million of something and someone gives you a million more, you have a 100% increase and the ratio of what you have to what you had is 2. There's a big difference between having $20, $2, and $2 million. These dollar values are absolute, true numbers; not ratios. Most of us would agree that it is better to have won the $2 million dollar lottery than the $20 dollar lottery or the $2 dollar lottery.

As so clearly stated by Dr. Keys [62], "when viewed objectively, the SUV … is so flawed as a quantitative measure as to be virtually worthless for the purpose for which it is usually used." Noting that the use of SUV should be "discouraged", Dr. Keys sums it up by calling SUV a "silly useless value".

In a textbook of PET [63, p. 279], the editors kindly refer to SUV as a "semiquantitative" value, viewed as qualitative and "insufficiently" standardized. Something we have repeatedly emphasized [2-4,7,9-11].

Another sign that PET manufacturers aren't providing you nuclear cameras, which provide true quantification, is when they report the sensitivity and specificity of their cameras. As you remember from our earlier discussion of qualitative imaging, sensitivity is the ability to correctly find disease when present and specificity is the ability to correctly exclude disease when absent. This is not a measurement it is a light switch approach to disease. If SUV was an actual "measurement" it wouldn't have a sensitivity/specificity issue associated with it and yet (Figure 15) it does.

Table 2 Level-by-level diagnostic performance of three methods (CT, PET/CT with best SUVmax cut-off, and PET/CT with level-based modified SUVmax cut-off)

	TP	FN	TN	FP	Sensitivity 95 % CI	Specificity 95 % CI	PPV 95 % CI	NPV 95 % CI	Accuracy 95 % CI
CT	12	16	215	7	42.9[a,b] 24.6–61.2	96.8 94.5–99.1	63.2 41.5–84.9	93.1 89.8–96.4	90.8[c] 87.2–94.4
FDG-PET/CT using best SUVmax cut-off (3.5)	19	9	210	12	67.9[a] 50.6–85.2	94.6 91.6–97.6	61.3 59.8–62.8	95.9 93.3–98.5	91.6 88.2–95.0
FDG-PET/CT usinglevel-based modified SUVmax cut-off	20	8	213	9	71.4[b] 54.7–88.1	95.9 93.3–98.5	69 67.6–70.5	96.4 93.9–98.9	93.2[c] 90.1–96.3

TP true positive, *FN* false negative, *TN* true negative, *FP* false positive, *PPV* positive predictive value, *NPV* negative predictive value, *CI* confidence interval

[a] The sensitivity of FDG-PET/CT with best SUVmax cut-off (3.5) was significantly higher than that of CT ($p = 0.023$)

[b] The sensitivity of FDG-PET/CT with level-based modified SUVmax cut-off was significantly higher than that of CT ($p = 0.013$)

[c] The accuracy of FDG-PET/CT with level-based modified SUVmax cut-off was significantly higher than that of CT ($p = 0.041$)

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Figure 15: The inclusion of sensitivity and specificity results defines a "qualitative" method of finding disease, not a "quantitative" measurement.

By the very definition of qualitative (it looks like) versus quantitative (it is), SUV is "qualitative" yet you can bet these camera companies are telling people they can "quantify" disease with these cameras, so they can and will get paid by CMS and the Insurance Companies for "quantifying" patients disease when they use one of these nuclear cameras.

When you measure something, the question isn't whether there was something there to measure or not (sensitivity/specificity), the question is how accurate, consistent and reproducible is your measurement and to know that, you have to know that the person using the tool, in this case a Nuclear Camera (SPECT/Planar or PET), knows exactly how to use it. For our ruler example is was just about anyone. For our Nuclear Cameras it needs to be someone specifically trained in how to use and calibrate the cameras.

That person would be a Nuclear Technologist and the only way for them to accurately use it to measure "scintillations" is to be provided with a way to calibrate the camera to a known standard [2-4,7,9-11]. Nuclear technologists perform "qualitative" calibration on a periodic basis but this "quality control" is different from "quantitative" calibration. Qualitative control includes spatial resolution, center-of-rotation (COR), uniformity correction, sinogram and tomographic uniformity control, to name just a few of the jobs the Nuclear Technologist is responsible for overseeing to assure that the appearance of the "image" being seen by the clinician is acceptable.

However, this is not "quantitative" calibration (FMTVDM) of the nuclear camera. The important question behind "quantitative calibration" is how accurately, consistently and reproducibly can the camera measure the scintillations being emitted from the patient. In fact, the results of qualitative calibration produces images, which are for lack of a better term, "prettier." Unfortunately, prettier isn't better. As shown in Figure 16, when this particular nuclear camera was calibrated, comparing the 64 x 64 matrix and the 128 x 128 matrix settings, the prettier pictures produced by the 128 x 128 matrix resulted in a 33.9% quantitative loss of data. Not only did this result in incorrect quantification of the results but the resulting qualitative visual images produced from this 33.9% loss of information, while qualitatively appearing prettier, was the result of lost data (scintillations) and a smoothing effect of the resultant image; adding to further error associated with reader bias and "inattention blindness" further invalidating the study.

True quantification of SPECT/Planar and PET cameras can only occur once these nuclear cameras are calibrated to the standard being used for scintillation measurement. Once "quantitatively" calibrated (FMTVDM), just like our rulers and measuring scales, these nuclear cameras can accurately, consistently and reproducibly "quantify" the scintillations being emitted from the patient from a location within the tissue which is the direct result of uptake and release (redistribution) occurring over time.

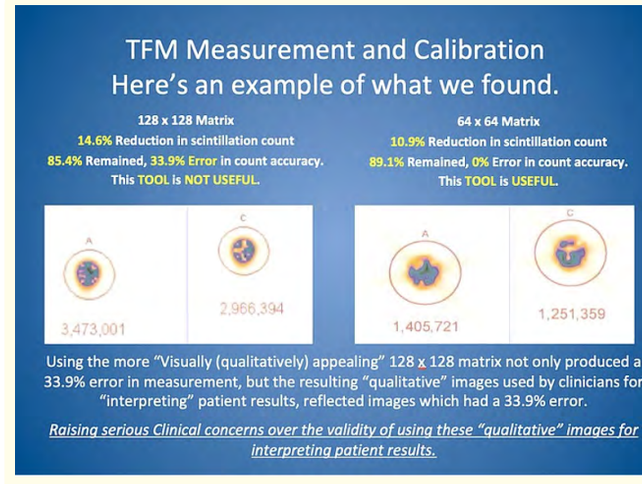

Figure 16: SPECT/Planar and PET Cameras not correctly "quantitatively" calibrated are associated with a 33.9% error in data acquisition, which when coupled with "inattention blindness" and reader bias, produce unacceptable diagnostic errors, leading to misdiagnosis, incorrect treatment, MACEs including death.

Before we move onto the Marketing of Sestamibi and how that cultivated massive profits for the pharmaceutical companies selling it, we want to take a moment to explain the emphasis being placed here regarding the primary author having been issued the patent for FMTVDM; including the components used for calibration, quantification and theranostification?

There are two primary reasons for this emphasis and they both have to do with others acting unethically and illegally

First, I saw a surgeon on a PBS special many years ago; his name was Dr. Judah Folkman. Dr. Folkman had been trying to tell people for years that cancers were blood rich. People didn't believe him because they weren't seeing that much blood under the microscope once the tissue had been processed for examination. The reason for this discrepancy was actually pretty easy to understand. By the time the cancer went from the operating room to the pathology lab, most of the blood had already drained out of the cancers; so by

the time the pathologists looked at the cancer, they were no longer blood rich. So for some time no one believed Dr. Folkman.

Over time other people eventually came to terms with this concept and PBS did a documentary on Dr. Folkman and his "blood rich" cancer concept. I saw the program and called him up and congratulated him; letting him know I had developing a test, which could actually measure changes in tissue including RBFDs to find cancer. We talked for some period of time about the test and what this meant for diagnosing and treating heart disease and cancer. We also talked about a new theory I had proposed about a number of "chronic" diseases, including "Inflammation and Heart Disease." The Theory was published in a Medical Textbook in 1999 (Figure 17).

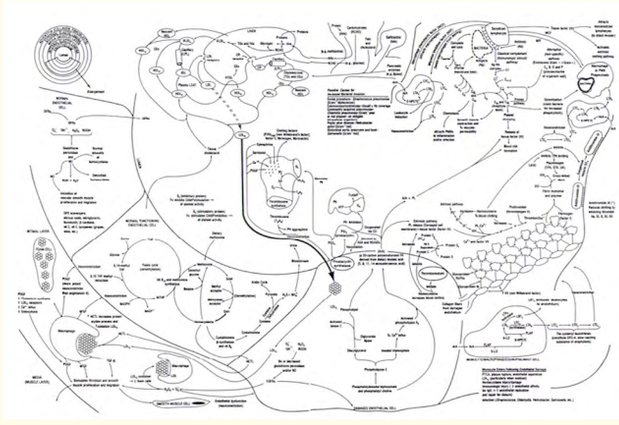

Figure 17: The Fleming Unified Theory of Vascular Disease; aka. The "Inflammation and Heart Disease" Theory.
Fleming RM. Chapter 64. The Pathogenesis of Vascular Disease. Published in the "Textbook of Angiology". John C. Chang Editor, Springer-Verlag New York, NY. 1999, pp. 787-798.

We had what I thought was a nice conversation. Dr. Folkman asked me to tell him how I thought my theory (FUTVD) might be of value to treating cancer. It struck me almost immediately that a major approach to treating cancer would be to starve the cancer of its blood supply. To give it a "cancer attack." Deprive the cancers of their much needed blood supply, and like every other tissue in the body, the cancer would die. Since FMTVDM worked by enhancing and measuring regional blood flow and metabolic differences, applicable to cancer, heart disease and a number of other diseases, we could actually kill the cancers and measure the affect. Our conversation ended.

The next thing I know, Dr. Folkman was telling the world, that he had developed a new test to find cancer and a new treatment idea for cancer; STUPID me. That was a major wake up call. Instead of being able to share information, information, which I thought would help advance the field, I learned that by sharing information and not making a public announcement about it beforehand, the ethical person, physician, scientist would acknowledge whose work it really was. After what Dr. Folkman had been through with his blood rich cancer idea and the documentary, I expected him to appreciate that. He appreciated the information but not for the reasons I suspected. I stopped communicating with Dr. Folkman and soon the information he had to give to the media dried up and he was left with nothing more to say.

The *second* reason comes from when I was on 20/20 in 2004 talking about my "Inflammation and Heart Disease" Theory and a book I had written ("Stop Inflammation Now!), which discusses various contributing factors affecting "Inflammation and Heart Disease" and what you can do to lower your risk of heart disease, cancer and other inflammatory diseases. The local evening news aired an interview they did with a local Doctor, before the 20/20 segment. I had never heard of this Doctor and yet there he was on television telling people I didn't know what I was talking about. The network hadn't bothered to call me. All I could think of was wow! In this doctors news interview he said inflammation clearly had nothing to do with Heart Disease and I had no idea what I was talking about. After the 20/20 program aired, there were Doctors and other people from all over the country claiming they had come up with the theory of "Inflammation and Heart Disease". I went from I didn't know what I was talking about to everyone else claiming they had developed the theory.

Since then, everyone I know who has any idea what this patented method (FMTVDM) can truly do and who actually cares about me, tells me the same thing; be careful! What are they worried about? They're worried that the pharmaceutical and camera companies will try to steal the patent. They

wouldn't actually be stupid enough to outright steal the patent, they would simply try to figure out a way to do emulate it and then with time and money, file law suits like they have with so many other inventors, digging deep into their deep financial corporate pockets to outspend and outmaneuver me. Until I either sell them the patent, or end up homeless.

There have already been proposals to buy the patent. The other approach as mentioned is for the nuclear camera companies to pretend they already have a method for "quantifying" (supra) nuclear images. Hence, the importance of making it crystal clear [2-4,7-11], that what is being called "quantification" by these camera companies, is NOT actual quantification and in no way could seriously be thought of as quantification; unless you buy the 8-pound ruler argument.

The battles over FMTVDM and Sestamibi redistribution continue to this day. However, with time the pharmaceutical companies, the nuclear camera companies and those supporting them simply hope I will die or go away. That now having being said, it's time to look at the motives behind what the pharmaceutical industry has been doing and what it plans to continue to do absent action by the FDA, HHS or the Federal Government.

Part III: How dupont put bristol myers squib out of the nuclear imaging business.

In the late 1980's, roughly 1988-1989, the pharmaceutical industry began to introduce a new generation of isotopes, which as DuPont and BMS would lead us to believe, would greatly improve the "quality" of nuclear images we were seeing by allowing more radiation to be given to patients undergoing cardiac studies than before.

These newer imaging agents combined the radioactive isotope Tc-99m with a half-life of 6 hours with another molecule carrying the isotope to tissues for emission imaging.

The reason the FDA allowed more radiation per injected dose is based upon the shorter Tc-99m half-life, compared with the 72-hour half-life, which Tl-201 has. Tl-201 was the isotope of choice for Heart Disease studies. The longer the half-life, the smaller the dose patients could receive. Tc-99m's shorter half-life meant that up to 30 mCi could be given compared with 2-3 mCi for Tl-201 studies.

However, imaging with Tl-201 used a single injection of 2-3 mCi, which was injected following "stress" with images sequentially obtained following the redistribution of Tl-201 to determine if ischemia was present or infarction was present or not. The same should have been done for the Tc-99m isotopes (supra); however, the marketers, i.e. the pharmaceutical companies DuPont and BMS both encouraged clinicians to use a double-injection technique, dropping the use of redistribution in favor of their "stress-rest" or "rest-stress" approach, where clinicians were encouraged to buy two doses of Tc-99m in place of the single Tl-201 dose.

Given the higher dose of radiation (20 mCi vs. 2-3 mCi), the pictures were more visually appealing ("prettier") even though they were not more diagnostic [64-74]. In fact, the change from "redistribution" to "stress-rest" completely distorted the comparison of images, both qualitatively and quantitatively [2-4,7,9-11, 64-74].

Having effectively eliminated Tl-201 as the isotope of choice, the companies turned their attention towards who would control the cardiac imaging marketplace. The competition between DuPont and Squibb Diagnostics would begin somewhat cordial. It began with simple name changes to attract the Physicians and Hospitals into using each of them. DuPont changed the name of its drug/isotope to Cardiolite and Squibb would change it's to CardioTec. DuPont would then change the name from Cardiolite to Sestamibi and eventually to MIBI. Squibb would then change CardioTec to TEBO. The competition was to see if a catchy name would make the difference; it didn't.

The marketing turned toward the timing of when imaging would or could begin within the nuclear laboratory and while the actual redistribution of both Sestamibi (DuPont Merck) and Teboroxime (BMS) show the agents redistribute beginning at 5minutes post stress injection (passim for Sestamibi; 64-75 for Teboroxime), BMS admitted to it's early washout (redistribution) and marketed Teboroxime as allowing faster and greater throughput of patients, while DuPont denied it's rapid washout and emphasized (passim) that you could image patients anywhere between 1-4 hours after injecting Sestamibi making it easier for nuclear laboratories to schedule images and work around the more "generous" time for imaging; an approach that in the end won out as nuclear labs dealt with increasing demands with limited resources (nuclear cameras and technologists).

The only problem with this approach however is that all three Tc-99m labeled compounds; Sestamibi, Teboroxime and later Tetrofosmin once it was introduced by GE, as we have shown (passim) begin their redistribution around 5-minutes post stress injection. Meaning not only is there no advantage to waiting for 60-minutes as the DuPont and later Cardinal Health, Lantheus and GE marketing teams would have you believe, but you have now double dosed people with radiation they didn't need (without a benefit) and as you now know, this results in critically diseased coronary arteries being missed due to the failure to detect wash-in [redistribution shown in Figures 1, 6-10 and 18] requiring the 5-minute images for comparison with the later 60-minute images.

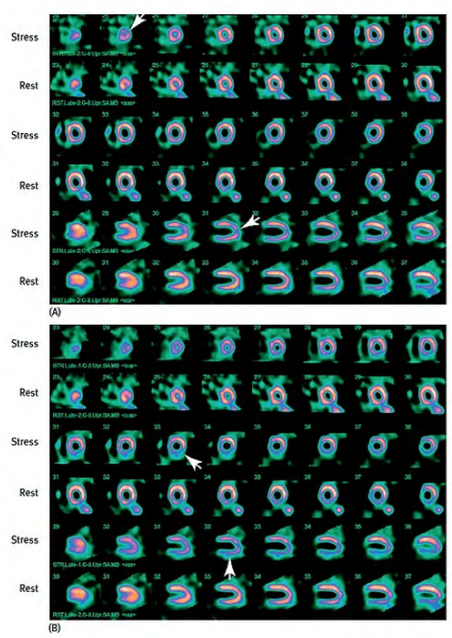

Figure 2. Tc-99m-sestamibi SPECT MPI performed with the D-SPECT camera: (A) 70 minutes post-stress showing perfusion defects (white arrows) in the apical segments of the left ventricle and the apex; (B) 8 minutes post-stress showing exercise-induced perfusion defects (white arrows) in the apical segments of the left ventricle and the apex as well as in the inferolateral and inferior walls of the left ventricle. The latter defects are not present at rest and on images acquired 70 minutes post-stress.

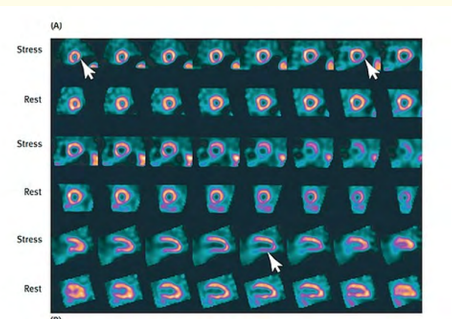

Figure 4. Tc-99m-sestamibi SPECT MPI performed with the D-SPECT camera (A) 60 minutes post-stress showing perfusion defects (white arrows) in the anterior and anterolateral walls of the left ventricle extending mid to apex; (B) 6 minutes post-stress showing perfusion defects (white arrows) in the lateral and inferolateral walls of the left ventricle.

Figure 18: Documented cases of Sestamibi redistribution provided by Cedars Sinai, Harvard and UCLA imaging of the heart, finding earlier redistribution changes than the Pharmaceutical Company states can possibly exist; redistribution changes which are "clinically significant".

Even though Figure 18's legends very clearly explain that these images were obtained at 6-minutes and 60-minutes "post-stress", the pharmaceutical companies have done such a wonderful job of removing redistribution from the medical lexicon, that the nuclear camera imaging software labeling these images, doesn't display them as 6-minute and 60-minute post stress redistribution images, but rather as "stress" and "rest".

The initial argument, which could have been used by DuPont, Cardinal Health, Lantheus and GE to justify their position, was that earlier nuclear cameras might not have been fast enough or sophisticated enough to perform cardiac imaging at 5-minutes when Sestamibi and Myoview were first introduced, so the companies didn't originally know or fully appreciate the extent of their isotopes redistribution; despite their earlier publications (supra) showing redistribution. However, that argument can no longer be made given the wealth of publications, even just included here (1-75), which confirms the clinical importance of the redistribution of all three isotopes. As Lantheus has admitted, they have no plans to refute the literature or to doubt the publications; they simply have no interest in Sestamibi anymore.

It is interesting to note however that even though there are no plans to correct the record, the "package inserts" for Sestamibi have had some interesting changes over the years moving from Sestamibi doesn't redistribute, to Sestambi redistributes in dogs but not in people, to Sestambi redistributes in dogs and we don't know what it does in people. Clearly, we do know what it does in people. It redistributes and this clinically important redistribution is easily detectable if you begin imaging at 5-minutes post-stress; however, once that is admitted, the entire marketing plan that made Sestamibi THE imaging isotope for cardiac patients and removed BMS from this market comes into question. The only question is what are the FDA and HHS going to do about it. If history is any indication, FDA-2011-P-0596, they will do nothing about it; however, we again call upon the FDA (FDA-2018-P-3102) to do the right thing and address this problem.

Now that we have shown that the corporations knew Sestamibi, Teboroxime and Tetrofosmin redistribute and that only a single dose of isotope is required to perform patient cardiac imaging, independent of whether that be done qualitatively or quantitatively; although quantitatively is clearly more accurate, consistent and reproducible and allows for

patient-focused, patient-specific, patient-directed individualized treatment saving time, money and lives; let's address the issue of why these companies profited so much by marketing the two-injection "stress-rest" approach.

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Food and Drug Administration
Silver Spring MD 20993

August 8, 2018

Richard M. Fleming, MD, JD
[redacted]

Dear Petitioner:

Your submission requesting that the Commissioner of Food and Drug (1) address the misinformation regarding redistribution of the Technetium-99m Isotopes Sestamibi and Tetrofosmin, (2) address the misinformation reporting that the current SPECT and PET cameras are "quantifying" disease when in fact they are not, (3) address the misinformation and promotion of "mini-dose" 3D-tomosynthesis equipment as being diagnostic and having less radiation when they yield more radiation per breast image than conventional mammography and do not contribute to survivability (4) that CPT coding be dropped as a method for reimbursement, and (5) petitioner wishes to assist the FDA by making FMTVDM available. was received by this office on 08/08/2018.

It was assigned docket number FDA-2018-P-3102. Please refer to this docket number in future correspondence on this subject with the Agency.

Please note that the acceptance of the petition for filing is a procedural matter in that it in no way reflects an agency decision on the substantive merits of the petition.

Sincerely,

Dynna Bigby
Supervisory Administrative Proceedings Specialist
Division of Dockets Management
FDA/Office of the Executive Secretariat (OES)

Figure 19: FDA Citizen Petition FDA-2018-P-3102.

Part IV How the pharmaceutical industry made hundreds of millions if not billions of dollars by marketing the two-dose stress-rest approach

This explanation detailing the corporate profits made below holds true for both Technetium-99m isotopes, Sestamibi (and generics) and Tetrofosmin. The use of $40 per dose was obtained directly from Cardinal Health representatives. The examples provided are based upon the actual marketing of these isotopes; they are a classic example of how to make more money with the same amount of material; the material in this case being radioactive medical isotopes.

Imagine you have a drug to sell and you call it Sestamibi (or Tetrofosmin) and you sell it for $40 a dose. Each dose that you sell is 30 millicuries (30 mCi) and you break that 30-mCi dose into 30 individual pieces, with each red ball representing 1 mCi. Each red ball now represents 1 mCi of Technetium-99m attached to a carrier molecule, which when combined together equals 1mCi of Sestamibi. You're original dose of 30 mCi is now represented by a big bag of 30 red balls, worth $40. FYI. This $40 price is what hospitals and physicians who order a lot of studies get charged. Smaller hospitals and physician orders cost even more, which mean patients and insurance companies, including Medicare and Medicaid pay even more.

30 mCi = 30 red balls = $40 = ONE Big Bag of Red Balls

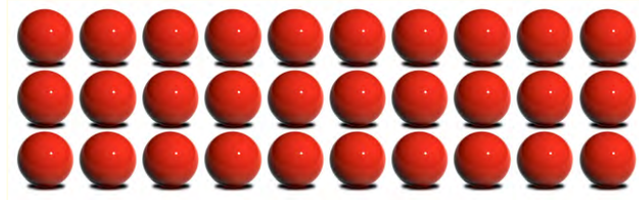

Figure h

Now imagine the Federal Government and the Insurance companies let the pharmaceutical companies break that big bag of 30 red balls (the 30 mCi dose) into 3 equal parts (3 bags of 10 red balls each) and let's the pharmaceutical company sell each of those smaller parts, now only 10 mCi (ten red balls) per dose for the same price as the original 30 mCi (30 red balls) dose. This means that each 10 mCi (ten red balls) is now worth $40 for each, even though each smaller dose is now only 10 mCi (10 red balls). This is like paying for a Lexus and getting a Yaris. You don't have to imagine this because it's true.

Now the original big bag of 30 red balls (30 mCi) has become worth $120, just by breaking it into three little bags of 10 reds balls (10 mCi) each, with each 10 mCi now selling for what the original 30 mCi sold for.

The 30 mCi = 30 red balls (big bag) worth $40, now becomes worth $120.

10 mCi = 10 red balls = $40 = Little Bag of Red Balls

Figure i

Plus 10 mCi = 10 red balls = $40 = Little Bag of Red Balls

Figure j

Plus 10 mCi = 10 red balls = $40 = Little Bag of Red Balls

Figure k

Only the FDA/HHS/Federal Government and the Insurance industry would let the pharmaceutical industry get by with something like this and then have the audacity to tell you they are worried about keeping drug prices down.

Now imagine you, "the pharmaceutical company", convince everyone including the FDA, HHS, the Federal Government, the Insurance Companies and Doctors/Hospitals that everyone needs to buy two different doses, a 30 mCi and 10 mCi dose, for each patient they want to do a heart study on. The two doses are necessary because unlike Tl201 which only requires one dose because it redistributes, you convince people that your Tc-99m Sestamibi (or Tetrofosmin) isotope drug doesn't redistribute, so they need to buy two doses to get two sets of images and instead of calling the images "stress-redistribution" you now call them "stress-rest".

An additional confusing factor to giving the two injections of isotope to get two sets of images, which is never talked about, is whenever you give the second injection, there is no way to separate whether the isotope you are seeing comes from the first injection or the second injection; they're the same isotope.

The only upside to all of this is for the pharmaceutical company, which now gets to sell two doses/bags (one big 30 mCi and one little small 10 mCi) of red balls for the same price, making twice as much money from each patient, without using twice as many of the red balls. However, this is only the tip of the iceberg.

Each patient now makes the Pharmaceutical Company twice as much profit as it would have, if the companies would have admitted that Sestamibi or Tetrofosmin redistributes and the patient only needed one injected dose. Instead of just needing a big bag (30 mCi) for $40, the patient and doctor/hospital are now told they need a big bag (30 mCi) for $40 AND a little bag (10 mCi) for $40, now costing the patient $80 instead of $40.

30 mCi = 30 red balls = $40 = ONE Big Bag of Red Balls

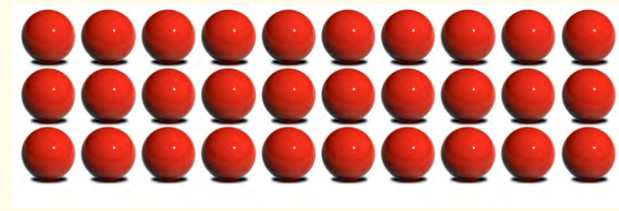

Figure l

10 mCi = 10 red balls = $40 = Little Bag of Red Balls

Figure m

Plus you are left with two other smaller doses (little bags) made by breaking the larger dose (big bag) into three smaller parts to get the smaller dose to sell to this patient.

Plus 10 mCi = 10 red balls = $40 = Little Bag of Red Balls

Figure n

Plus 10 mCi = 10 red balls = $40 = Little Bag of Red Balls

Figure o

Don't be fooled by the cost being only $40 versus $80. First, in and of itself, this is wrong. Secondly, they sell millions of doses every year and finally, as we will now explain, while the pharmaceutical companies are making twice the profit from each patient, the pharmaceutical companies are making a much larger profit.

Remember the two smaller (10 mCi each) doses you were left with after breaking up the bigger (30 mCi) dose for the last patient? Each one of those smaller (10 mCi) doses (little bags) gets sold to another patient. Once you work through the math, for every THREE patients, the pharmaceutical company gets to sell the Doctor/Hospital four big bags of red balls, consisting of 3 big (30 mCi) bags of red balls ($40 each x 3 = $120) AND 3 little (10 mCi) bags of red balls ($40 each x 3 = $120).

The significance of this becomes even more apparent when you take into consideration the massive numbers of these studies performed each year. Nuclear cardiac studies are the most frequently ordered nuclear test and in 2011 there were 10 million in the U.S. alone.

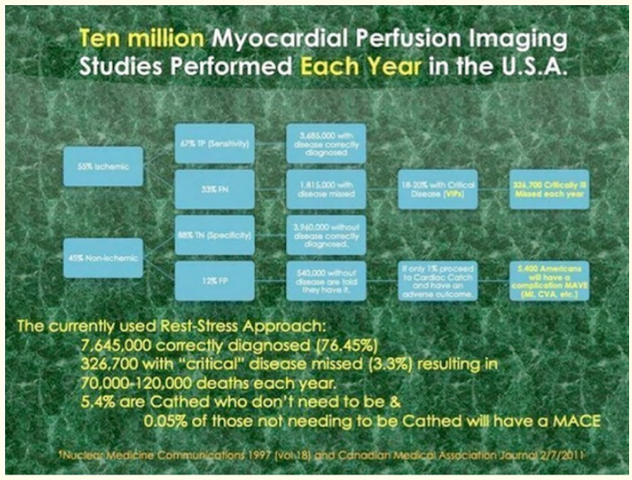

Figure 20: This information is based upon what was available as of 2011.

These costs/profits don't take into account the additional cost in human lives and suffering resulting from the errors made using this qualitative two-injection stress-rest approach promulgated by the pharmaceutical companies. But for now, we will only focus on the pharmaceutical profits resulting from this approach.

Adding insult to injury

Now that you're beginning to understand just how much money we're talking about; it's time for one last piece of disappointing news; for you that is, definitely not for the pharmaceutical companies.

Over the last several years, there has been considerable concern over the potential benefit versus health risks associated with radiation exposure. You can tell just how good a marketing job these corporations have done, because even with all the published literature, no one recognized the excessive radiation being given to people by the two-dose "stress-rest" approach. My guess is it's because the second dose (10 mCi), while not needed, is viewed by many to "not be that much" compared with the larger 30-mCi dose.

With the increased concern over radiation, the emphasis has been on either giving a single dose called "stress-only" encouraged by those who want to cut down on radiation exposure to patients but who haven't read the literature realizing that what it should be is "stress-redistribution" with the emphasis on getting that first image at 5-minutes instead of 60-minutes; or giving smaller doses of the isotope (e.g. 8 mCi). An even better idea would be to lower the dose and do stress-redistribution imaging (FMTVDM).

That being said, you might think the radiopharmaceutical companies like inter alia Lantheus, Cardinal Health and GE might not like this. After all, if they are discouraged from selling the larger doses, won't they lose money? Remember the Lexus Yaris example? Selling you a smaller dose of isotope doesn't cost these companies money, it makes them more money because they don't sell based upon the mCi, they sell based upon the dose and the amount of mCi in a given dose doesn't matter.

This has become another gold mine for the pharmaceutical industry. The earlier example of selling the second dose, the "rest" dose for the same price as the first "stress" dose but only giving 1/3 (10 mCi versus 30 mCi) the dose at "rest" is based upon the limits of how much radiation can be given to someone, when the isotope has a 6-hour half-life; which is the half-life of Tc-99m and the "stress" "rest" injections are performed on the same day.

Staying true to form and that ratio (3:1), with the call for reducing the amount of radiation given to patients, the pharmaceutical companies have adopted a 21 mCi (stress) and 7 mCi (rest) dosing. Using our red ball example, this is what it means for the pharmaceutical industry.

Instead of having to go to another big (30 mCi) bag of red balls (1 mCi each) to find the smaller resting dose to accompany the larger dose, they can actually harvest both doses

(21 mCi and 7 mCi) right out of the first big (30 mCi) bag of red balls and have millicuries to spare.

From the original 30 mCi big bag of red balls which is made up of 30 red (1 mCi each) balls, which originally sold for $40, these pharmaceutical companies can now sell your Doctor/hospital everything you need to fill the larger "stress" (21 mCi) and smaller "rest" (7 mCi) dose, needed for their two-dose "stress-rest" approach.

The original 30 mCi = 30 red balls = $40 = ONE Big Bag of Red Balls.

Is now turned into $80:

21 mCi = 21 red balls = $40 AND 7 mCi = 7 red balls = $40 Plus 2 mCi left over Plus (*left over*)

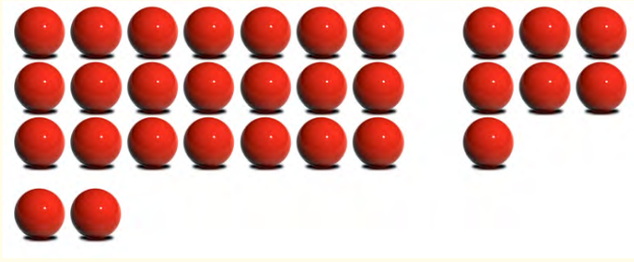

Figure p

Now instead of the pharmaceutical company selling physicians and hospitals four big bags, to image three individuals, for which the pharmaceutical company was paid $240; by agreeing that we should reduce the dosage, but continue with the "stress-rest" approach, the pharmaceutical company now gets paid $320 (4 bags x $80) and has 8 mCi left over, which you can bet they will sell as one of those 7 mCi doses for another $40; bringing their new payment to $360 for what they will sell to the physician and hospitals.

What was once such a profitable drug has now become generic, so everyone can get in on the profit of selling a two-injection, stress-rest imaging approach. This also means Lantheus is no longer interested in investing in "the molecule" (Figure q) and as we have already seen, they are not interested in refuting any information or investing their time and/or money into Sestamibi. They are moving on to new profits.

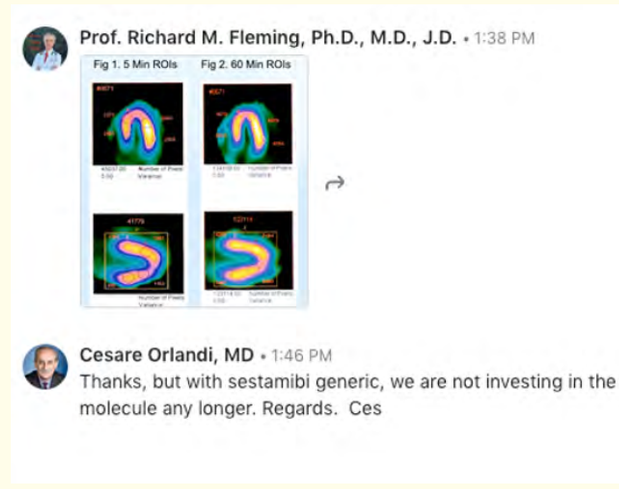

Figure q

Conclusions

Medicine has become for many a business. For physicians it remains a calling or an attempt to do something to help people. To do that requires the ability to be confident in the tests, including our imaging tests, we are using to diagnose and monitor treatment progress. To have confidence in these tests, means we must have confidence in the FDA, HHS, and other agencies that are designated to make certain that what the diagnostic imaging companies and pharmaceutical industry companies are telling us is true and accurate. When we lose confidence in these agencies to do their job, we lose the confidence we need to order the tests necessary to allow us to take the best care of our patients.

The FDA, HHS, CMS and other Federal Agencies have failed here. Nuclear imaging is a massive industry with multiple complex parts, including those who produce the radioactive isotopes and those who produce the nuclear cameras. Our technologists can only provide valid results, if what they are being told to do is correct. Our imaging studies can only produce the best results if the way in which we conduct the studies are correct.

When the marketing and profits of these corporations, rather than the science, dictate how these studies are to be done, American healthcare is in trouble. The companies involved in the marketing and sales of these isotopes, as well as the camera companies needed to do the imaging of these isotopes, have all in their own way, mislead, misinformed

and outright lied about the properties of the isotopes and nuclear cameras and how they work and should be used. The evidence is now very clear. It was not a mistake nor was it misinformation provided to these companies by someone else. The physicians and research scientists who have worked diligently with these nuclear cameras and isotopes have repeatedly published data showing the truth. These companies have simply chosen to ignore it and the FDA, HHS and CMS have done nothing about it.

These companies repeatedly state they do not practice medicine; that this up to physicians. This is true but no physician except the very brave will base their diagnosis and treatment upon science in the face of any industry that is so powerful and demonstrate they are willing to take whatever actions are necessary to maintain the power and prestige they currently enjoy.

In the end this boils down to nothing more than good old-fashioned greed and common theft. The obvious question is why now in the face of so much evidence, do the FDA, HHS and CMS not do something about it? Have our institutions we have come to depend upon become afraid of these corporate powers? Absent a demand by physicians, scientists, patients, nurses, nuclear technologists and everyone who's lives have or are being affected, through either the use of these cameras and/or isotopes or as a result of the harm suffered from misdiagnosis; the FDA, HHS and CMS will do NOTHING about the industry it is in bed with. The choice is yours and mine. Carpe Diem Quam Minimum Credula Postero!

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