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Review Article

Definitive Human Studies Demonstrating Clinically Important Sestamibi Redistribution

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Abstract

The manufacturers and distributors of Sestamibi have long held that two doses of isotope are required for myocardial perfusion imaging (MPI), based upon their representation to physicians, hospitals, clinics, insurance companies including Medicaid and Medicare, the FDA and the Federal Courts, that Sestamibi does NOT redistribute. The requirement of two doses of injected isotope has not only increased the profits made by the companies who have owned Sestamibi, but it has also increased the amount of radiation that patients and clinical staff are exposed to.

If these corporations are correct, then the initial and sequential images displayed here, will by virtue of having "no redistribution," be easily "qualitatively" matched by the reader, as they will have to be completely "identical" to each other, for each individual patient. If; however, the reader is unable to "match" these sequential images, which must be "identical" by virtue of the corporations "no redistribution" representation, then the evidence speaks for itself; i.e. that Sestamibi redistributes and the corporations misrepresentations to physicians, hospitals, clinics, insurance companies including Medicaid and Medicare, the FDA and the Federal Courts are fraudulent. Furthermore, given the prior plethora of published studies showing Sestamibi redistributes, when imaged at the proper times to see the redistribution, which the company has been made aware of, this misrepresentation is accordingly intentional.

Keywords: Redistribution; Sestamibi; FDA

Introduction

For decades the backbone of myocardial perfusion imaging (MPI) has been the "qualitative" comparison of two different images obtained sequentially. Thallium-201 (Tl-201) provided a single injection of isotope following efforts to change a patient's blood flow by "stressing" them; a method well understood to put increased demand on the heart and increase coronary artery blood flow along with isotope, which is then delivered to myocardium for imaging. The pharmacokinetics and pharmacodynamics of Tl-201 required an hour before the initial image (called "stress") could be obtained. The redistribution characteristics of Tl-201 required three additional hours for a comparison image (called "redistribution") to be obtained. The advantage was the use of a single dose of Tl-201, while the drawback was the amount of time required and a 72-hour half-life limiting the amount of Tl-201, which could be given in the single injection.

During the late 1980's newer isotopes, with shorter physical half-lives (6-hours) allowed for higher millicurie (mCi) or European equivalent (mBq) doses, of the isotope to be given, improving "qualitative" appearance. The manufacturers and distributors of one of these agents, Sestamibi, a technetium-99m (Tc-99m) based compound have long held that Sestamibi, unlike Tl-201, does NOT redistribute and for that reason, two doses of the drug are required to look for evidence of MPI defects, comparing what would become commonly, albeit incorrectly [1,2], known as "stress" and "rest" imaging.

To convince physicians, hospitals, clinics, insurance companies including Medicaid and Medicare, the FDA and the Federal Courts, that these two injections are required to obtain serial images for comparison, the companies selling Sestamibi, directed physicians to begin "stress" imaging one-hour after Sestamibi injection, even though the companies have always maintained in the package insert that initial uptake of the isotopic compound begins as early as 5-minutes after injection. The "resting" [1,2] image acquisition can either be performed before or after the "stress" imaging is completed and there are various protocols proposed; all of which require a second dose of Sestamibi pursuant to the "Sestamibi does NOT redistribute" statements of the pharmaceutical companies which have sold Sestamibi.

Multiple papers [1-75] have now been published showing Sestamibi does in fact "redistribute." Despite the abundance of evidence to the contrary [1-75], of which these references are not inclusive of all the published material available the corporations, which sell Sestamibi have refused to correct the record.

These multiple publications not only include our work [1-11,48-60] but work published in numerous peer reviewed medical journals by physicians and physician-scientists from around the world, including but not limited to, Brighman and Women's, Harvard, Cedars Sinai and UCLA [13] showing Sestamibi Redistribution revealed by imaging earlier enough to see Seatmibi redistribution, in addition to Tehran and Shiraz Universities [14,15] showing the importance of acquiring images earlier enough to see Sestamibi redistribution. This research provided additional information supporting for the previously published studies showing Sestamibi redistribution, done by Taillefer [47] at the University of Montreal, who showed that despite the reports that Sestamibi didn't redistribute, Sestamibi does in FACT redistribute and that it is preferable to image earlier noting a time period of 15-30 minutes post isotope injection and Li's [18] worked discussed immediately below.

DuPont itself, the original owner of Sestamibi published research, which included the CMO for Lantheus [16], published research showing how ischemic tissue impairs mitochondrial retention of Sestamibi, work which was further discussed by work from the Faculté de Médecine, Clermont-Ferrand, France [19] showing washout kinetics of Sestamibi by 28-minutes after injection. Further research published out of the University of Naples showed that the very fact that Sestamibi redistributes (washout) is clinically important in the treatment of cancer [20].

Other research work from Harvard [17] discussed the failure to see early Sestamibi redistribution when imaging is delayed for 60-minutes. Researchers from Johns Hopkins University [18] also resulted in the statement that "Tc-Sestamibi clearly undergoes myocardial redistribution" noting that timing and the extent of ischemia were important determinants of redistribution detection.

Several studies looked at the importance of looking for this redistribution and pulmonary uptake in relation to cardiac uptake by looking at results obtained 4-minutes following Sestamibi injection in 1500 sequential patients [21-28], with an explanation of this failure to retain Sestamibi and increased Sestamibi washout (redistribution) resulting from damaged mitochondrial function [29] provided by research from the University of Fukui.

Further work from Yale and the University of Virginia [46] concluded there is in fact redistribution of Sestamibi. It is not the intent of this paper to review yet again each of the papers referenced in this publication. The reader is encouraged to read all the references establishing Setamibi redistribution. The references do NOT include all of the published research establishing Sestamibi redistribution.

To find Sestamibi redistribution, or for that matter the redistribution of any isotope used for medical imaging, it is a requirement that images be obtained at the times of redistribution. Acquiring images at the wrong time are no more useful than asking someone to describe the events of a traffic accident when that person failed to be looking at the site where the accident happened at the time it occurred. Coming upon the traffic accident later and claiming you know what happened does not make what you say true. Rather, it is a misrepresentation of the facts and if you do it intentionally and knowingly, it is something far worse than simply being wrong.

If the corporations are correct, and Sestamibi does not redistribute, then sequential images obtained after only a single injected dose of Sestamibi, completed in less than 4-hours, must be identical. If the images are not identical, i.e. if the "defects" noted on the first and second images obtained following a single injected dose of Sestamibi are different, then Sestamibi MUST be redistributing or the images would be identical and could not "qualitatively" be different; consequently demonstrating the pharmaceutical companies have been and continue to misrepresent the information they have been submitting to physicians, hospitals, clinics, insurance companies including Medicaid and Medicare, the FDA and the Federal Courts.

Ten patient studies following single injection showing sestamibi redistribution

It would be too easy to provide the sequential images for people to compare and then listen to justifications as to why the images really are the same. To establish the truth as to SESTAMIBI REDISTRIBUTION, we are presenting the reader with 10-patients, each with an initial and sequential image for comparison. A letter of the English alphabet represents the initial image. An English number represents the sequential image. Each of the 10-patients signed an Informed Consent (IC) for myocardial perfusion imaging (MPI). The acquisition of the initial 5-minute image did not require IRB approval as it merely included the collection of an additional set of images following "stress" and injection of the isotope, all of which were covered under the standard IC. All patient information was redacted.

If there is no redistribution, then the reader should have no difficulty matching each initial image "A" through "J", with the corresponding sequential image "1 through 10". Such matching types of questions are not uncommonly used in testing scenarios to determine what students have and have not learned. For those who have been trained in how to "interpret" MPI, and given the companies representation that the initial and sequential images must be identical pursuant to there being "no Sestamibi redistribution" then this should be an easy examination. If however Sestamibi redistributes, then the matching will be more problematic; at least for those trained to read MPI. Unlike crossword puzzles, where the reader can find the correct answers by looking for them on another page, the correct answers will not be provided in this particular paper.

Readers are encouraged to submit their answers to the primary author through the email provided with this publication. The primary author will tally the results and report the findings in a future paper. One thing is crystal clear, either Sestamibi Redistributes or it doesn't. If it doesn't redistribute, the reader should have no difficulty matching the images. If there is NO redistribution, the initial image and the sequential image will match; i.e. they will have the same defects/disease. E.g. if the initial image has a basal inferior defect, then there should be a corresponding sequential image with only a basal inferior defect. Each initial and sequential image provides all the necessary information to perform the matching.

The matching of images is of course contingent upon the reader being able to see the exact same imaging defects on the initial and sequential images. If however, the isotope DOES redistribute and there is either Sestamibi "wash-in" or "washout" then there will be no matching images as there will be change; i.e. "redistribution" of the isotope. The inability of a clinician, trained to read myocardial perfusion imaging (MPI), to successfully match these images provides indisputable proof that Sestamibi must be redistributing in humans; just as it does in dogs, as specifically stated in the Sestamibi package insert required by and submitted to the FDA as shown in the Figure below.

CARDIOLITE® Kit for the Preparation of
Technetium Tc99m Sestamibi for Injection
513121-1007

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[Organ concentrations expressed as percentage of injected dose; data based on an average of 5 subjects at rest and 5 subjects during exercise].

Table 7.0

	REST				STRESS			
	Heart		Liver		Heart		Liver	
Time	Biological	Effective	Biological	Effective	Biological	Effective	Biological	Effective
5 min.	1.2	1.2	19.6	19.4	1.5	1.5	5.9	5.8
30 min.	1.1	1.0	12.2	11.5	1.4	1.3	4.5	4.2
1 hour	1.0	0.9	5.6	5.0	1.4	1.2	2.4	2.1
2 hours	1.0	0.8	2.2	1.7	1.2	1.0	0.9	0.7
4 hours	0.8	0.5	0.7	0.4	1.0	0.6	0.3	0.2

A study in a dog myocardial ischemia model reported that Technetium Tc99m Sestamibi undergoes myocardial distribution (redistribution), although more slowly and less completely than thallous chloride Tl-201. A study in a dog myocardial infarction model reported that the drug showed no redistribution of any consequence. Definitive human studies to demonstrate possible redistribution have not been reported. In patients with documented myocardial infarction, imaging revealed the infarct up to four hours post dose.

Figure 1

The pharmaceutical company has supported its position that it need not go back and change what it has submitted to the FDA, because the company has held the position that it does NOT tell physicians how to practice medicine. However, the resulting package insert and stance of the FDA has been taken by the Federal Courts to mean that physicians must practice this two-injection method to compare sequential images for determination of heart disease or they are committing billing fraud. Hence, both the pharmaceutical company and Courts are now practicing medicine and directing how physicians must practice medicine.

Pursuant to the Company, and consequently the FDA and The Courts, comparison images for the purpose of myocardial perfusion imaging (MPI) are only clinically valid IF two injected doses of Sestamibi are administered to the patient given the statement by the Company that Sestamibi does NOT redistribute. Hence, the company is determining the practice of medicine and the pharmaceutical company's fraudulent submission of information to the FDA has resulted in the FDA, Insurers, CMS and the Federal Courts, not to mention Physicians, Hospitals and Clinics where MPI is performed, to concluded that MPI requires two injected doses of Sestamibi; whereas only one injected dose of Sestamibi is actually required to perform sequential imaging and determine MPI if Sestamibi redistributes.

Conclusion

While the literature is embarrassingly replete with evidence [*inter alia* 1-75] that Sestamibi and all isotopes actually redistribute, this particular pharmaceutical company continues to refuse to correct their misrepresentation of facts. This paper is the second part of a three part series. In the first paper [76] a detailed discussion of facutal information, explanations and emails as to why the company would wish to continue to promote this misinformation is provided.

In this second paper, we discuss some of the published papers detailing Sestamibi redistribution and provide 10-specific patient examples for the reader and provide the reader with an opportunity to match 10-patients following a single injection of Sestamibi following "stress." These images include the initially acquired 5-minutes and their sequential images for each patient. The reader is encouraged to try to match these 10-patients based upon the premise that Sestamibi is immediately taken up by myocardium and is retained without redistribution. If this is in fact the truth, then the reader will have no difficulty matching the 10-patients initial and sequential images as they will be identical. If challenged, then the reader is left with the obvious conclusion; that the images are NOT identical and Sestamibi must in fact be redistributing between the initial and sequential images.

In the third and final paper, which has already been accepted for publication elsewhere, the results of the efforts of 19 trained professionals, "experienced" with MPI, to match these 10-patients will be published. Those results show that these "experienced professionals" were in fact unable to successfully match these 10-patients, proving the initial and sequential images are in fact different from each other and that by definition, Sestamibi redistributes.

Initial Image Letter	Sequential Image Number
A	
B	
C	
D	
E	
F	
G	
H	
I	
J	

Table: Matching initial and sequential MPI.

For each initial image, place the corresponding sequential image number in the column to the right of the initial image letter.

Initial Images of 10-patients with different ischemic coronary artery disease labeled Image A through J.

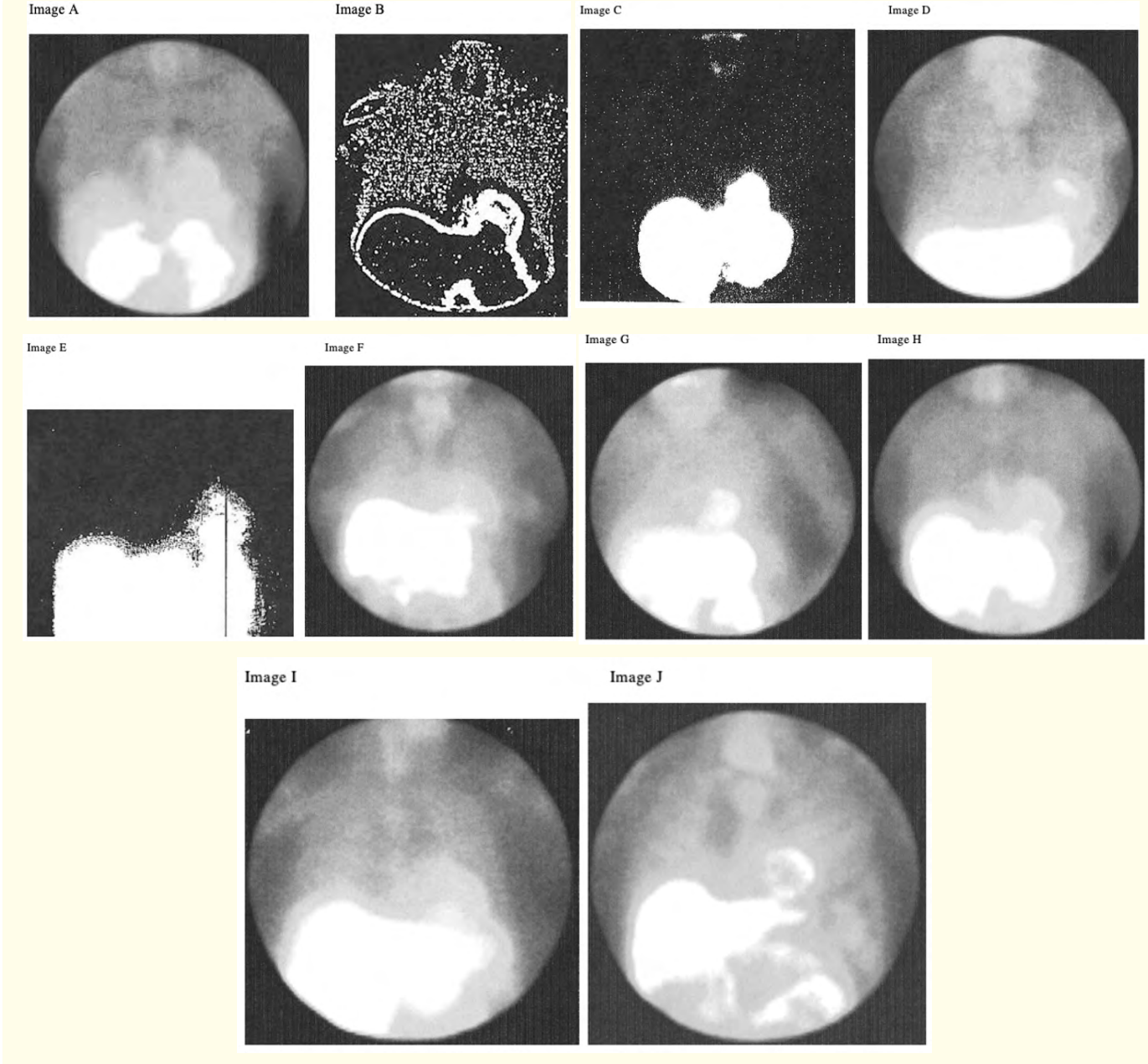

Figure 2

Sequential Images of 10-patients with different ischemic coronary artery disease labeled Image 1 through 10.

Image #1

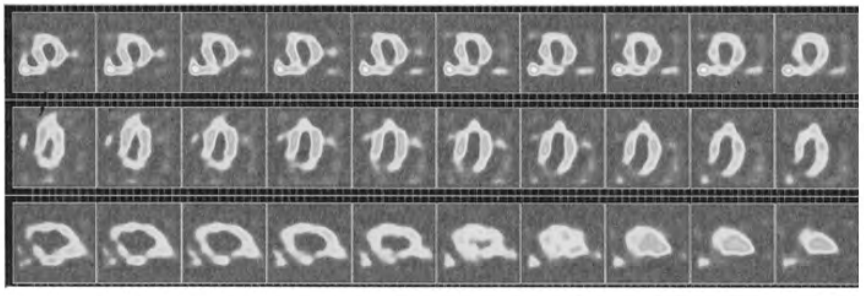

Image #2

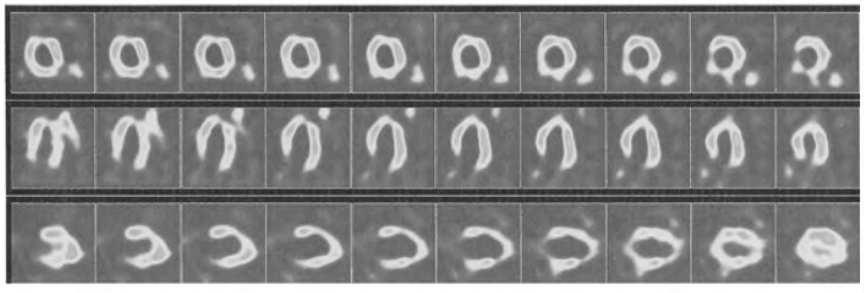

Image #3

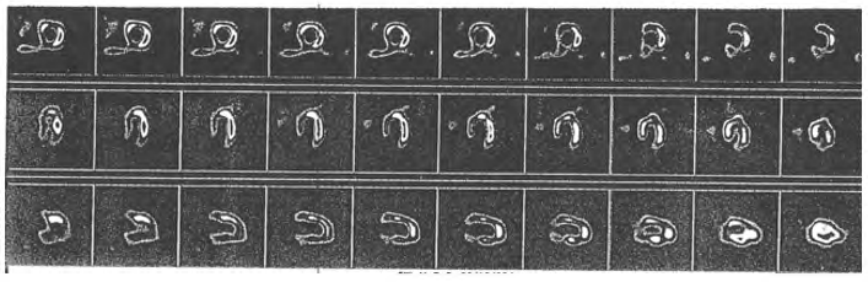

Image #4

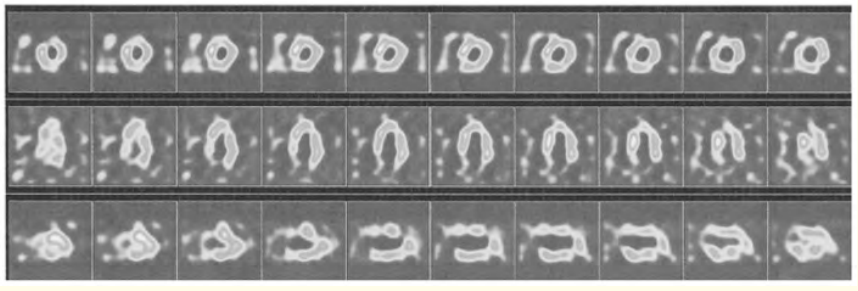

Image #5

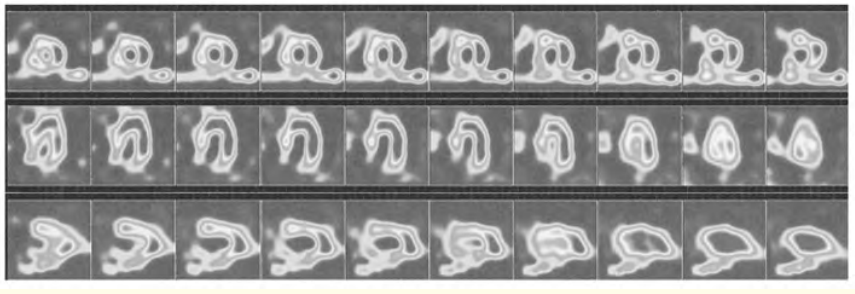

Image #6

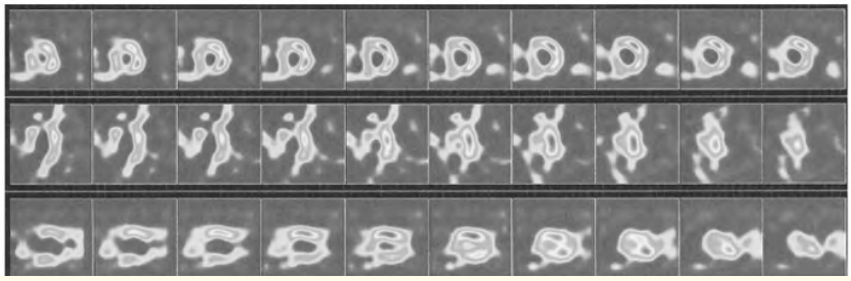

Image #7

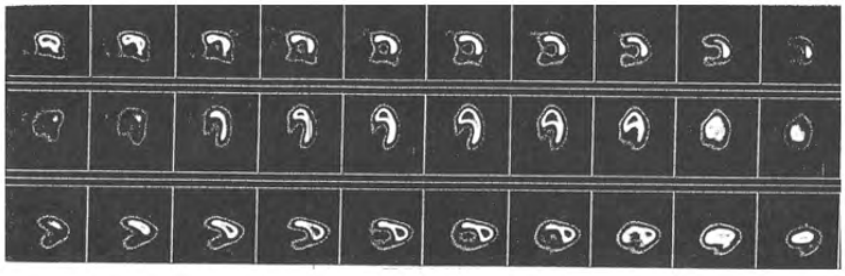

Image #8

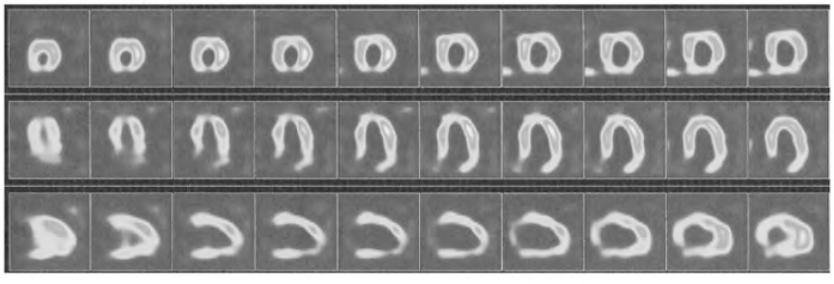

Image #9

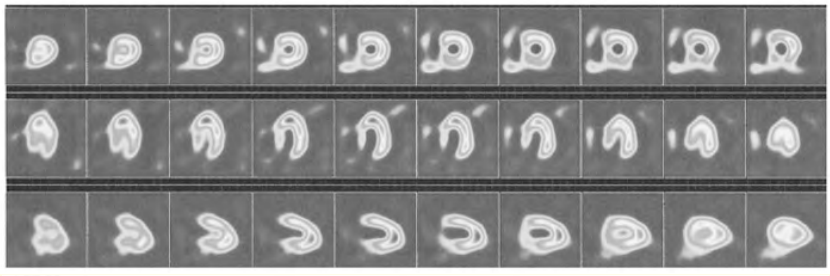

Image #10

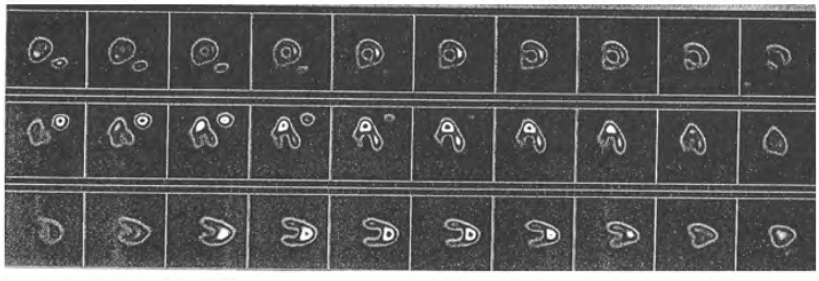

Figure 3

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