Rapid Washout of Technetium-99m-MIBI from a Large Parathyroid Adenoma

TO THE EDITOR: In the February 1995 issue of *JNM*, Bénard et al. (*1*) presented a case of rapid ^{99m}Tc-sestamibi washout in a large parathyroid adenoma. Their finding contrasted the good diagnostic utility of double-phase ^{99m}Tc-sestamibi scintigraphy initially described by Taillefer et al. (*2*). Histological examination of the parathyroid adenoma revealed that it was mainly composed of water-clear cells with rare dark chief cells and lacked oxyphil cells. Most parathyroid adenomas are rich in oxyphil cells that are rich in mitochondria.

The authors hypothesized that the delayed ^{99m}Tc-sestamibi washout usually observed in parathyroid adenomas is caused by tracer retention in mitochondrial-rich cells and explained the rapid washout by the lack of oxyphils. This hypothesis is based on an article written by Sandrock et al. (*3*), who showed that the detectability of abnormal parathyroid glands by ^{201}Tl/^{99m}Tc subtraction scintigraphy partially depends on the presence of mitochondria-rich oxyphil cells. Bénard et al., however, did not provide sufficient evidence on how findings from a ^{201}Tl/^{99m}Tc subtraction protocol can be implemented in ^{99m}Tc-sestamibi scintigraphy.

The pharmacological differences between ^{201}Tl and ^{99m}Tc-sestamibi are well documented. Wackers et al. (*4*) as well as others found different uptake mechanisms for ^{201}Tl and ^{99m}Tc-sestamibi, and Piwnica-Worms et al. (*5*) demonstrated the divergent kinetics of ^{201}Tl and ^{99m}Tc-sestamibi in cultured chick myocytes.

Furthermore, we challenge Bénard's hypothesis for the pathophysiological basis of dual-phase ^{99m}Tc-sestamibi scintigraphy based on our own clinical findings: We studied 37 patients with primary hyperparathyroidism who had surgery as well as pathohistological work-up and found no correlation between oxyphil cell count and the regional sensitivity of ^{99m}Tc-sestamibi scintigraphy (Spearman correlation coefficient: -0.04; $p = 0.9$). The oxyphil cell count in our population ranged between $<10\%$ and 100% (median 25%).

In conclusion, the oxyphil cell count in parathyroid adenoma does not seem to be the crucial factor for determining the sensitivity of dual-phase ^{99m}Tc-sestamibi scintigraphy in parathyroid adenomas.

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REPLY: We thank Staudenherz et al. for their interest in our report. We described an unusual presentation of a parathyroid adenoma characterized by a rapid washout of sestamibi (*1*). Our clinical observation does not stand in contrast to the good results obtained by Taillefer et al. (*2*), but reflects an atypical scintigraphic pattern. We routinely use the double-phase technique in our clinical practice with excellent results. The main point of our study is to be wary of any increased uptake close to the thyroid, even if the washout rate is not slow compared to thyroidal washout. As our article illustrates, one may not rule out a parathyroid adenoma in the face of such a scintigraphic pattern, and an iodine scintigram may be helpful in such instances.

We hypothesized that mitochondrial content influences sestamibi retention based on the observations of Chiu et al. (*3*). These authors clearly have shown that sestamibi retention is proportional to the cellular and mitochondrial transmembrane potential gradient. Subcellular fractionation has identified mitochondria as the site of sestamibi retention in the cells of many tissues (*4*). The reference to the excellent study done by Sandrock et al. (*5*) was intended to make an analogy to the effects of mitochondrial content on thallium uptake, not as proof confirming our hypothesis. It seems obvious to us that only a controlled study, not a single case report, can support or confirm our explanation for the atypical pattern observed in our patient. The lack of oxyphil cells was the only unusual finding in our case.

Staudenherz et al. cite their work in progress as evidence challenging our hypothesis. It is unfortunate that their methods and results have not yet been published. It is not clear if they also correlated the number of oxyphil cells with absolute or relative sestamibi uptake or with the washout rate from parathyroid adenomas. Without several false-negative studies, it would be difficult to correlate the number of oxyphil cells with the sensitivity of sestamibi parathyroid scintigraphy. As we explained in our previous report, adenomas may be identified despite rapid tracer release. One would need to study many adenomas presenting rapid washout to determine whether there is a true relationship to the absence of oxyphil cells or to a low mitochondria per cell ratio.

It might be better to correlate the rate of tracer washout from parathyroid adenomas with mitochondrial content of these tumors to provide better insight on the mechanisms of tumor uptake and retention. The sensitivity of sestamibi scintigraphy is probably also dependent on other factors, such as adenoma size. Because the role of mitochondrial content on the washout rate of sestamibi parathyroid adenomas remains to be clarified, we hope that the work of Staudenherz et al. will address these issues when their their findings are published.

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TO THE EDITOR: In a recent *JNM* Newsline article entitled "Scintimammography: Magic Bullet or False Promise" by Deborah Kotz (*J Nucl Med* 1995;36:15N–20N), Dr. Khalkhali from the UCLA School of Medicine in Los Angeles is quoted as saying that the radiation dose to the patient from this procedure " . . . was equal to the amount of radiation a person gets when he/she flies round-trip from New York to Los Angeles." I believe it important to point out that this statement is inaccurate. The total body absorbed dose from an injection of 740 MBq (20 mCi) of ^{99m}Tc-sestamibi used in scintimammography is approximately 3.3 mGy (330 mrad) (*1*). The effective dose rate from background radiation at an altitude of 10 km (33,000 ft.) is 5 μSv/hr (0.5 mrem/hr) (*2*). Since the body is uniformly irradiated, this dose is equivalent to an absorbed dose rate of 5 μGy/hr (0.5 mrad/hr). For a 5-hr commercial airline flight across the United States, the total absorbed dose is thus 25 μGy, or 50 μGy (5 mrad) round-trip. This is a factor of some 66 times lower than the sestimibi absorbed dose.

The situation, however, is actually worse than this. A proper comparison of radiation risk requires comparisons of effective dose (*3,4*) which take into account the differing tissue sensitivities to radiation, and not absorbed dose, which measures only energy deposition per unit mass of tissue and does not include biological factors. Using the appropriate tissue weighting factors (*3,4*) and the absorbed doses from ^{99m}Tc-sestamibi to individual organs (*1*), the administration of 20 mCi of sestimibi results in an effective dose of 570 mrem to women (410 mrem for men), as determined from data presented in Table 4 of the Cardiolite kit. Thus, the ratio of increased radiation risk for scintimammography versus a round trip airline flight coast to coast is closer to 114:1.

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REPLY: We wish to acknowledge the dosimetry comparison error pointed out by Dr. Behrman; the total body absorbed dose from 740 MBq (20 mCi) ^{99m}Tc-sestamibi is indeed about 3.3 mSv (330 mrem) and a cross-country round trip air flight is about 0.05 mSv (5 mrem). The effective dose cited in ICRP no. 62 (*1*) is 5.5 mSv (555 mrem) for exercising adults and 6.20 mSv (629 mrem) for resting adults, which is even higher than Dr. Behrman has calculated.

However, the fact that we have an absorbed dose factor of about 125 between the two sources does not mean that we have a risk factor difference of 125. It is entirely possible, and at this point probable, that chronic absorbed doses of radiation at these low levels engender no risk at all. Indeed, the radiopharmaceutical dose could more easily be regarded as hormetic than hazardous. There are no valid epidemiologic data documenting harm at these low absorbed doses.

The linear, no-threshold hypothesis may have been appropriately conservative in the early decades of our study of the biological effects of ionizing radiation, when a limited amount was known. When a lot of smart people spend much money and a hundred years looking for harm without finding any, it probably is not there. When they occasionally find examples for which low doses exert beneficial effects, after a few decades, it is certainly time to stop hypothesizing the "healthy worker effect," "biological subgroup differences," "confounding variables," or "insufficient sample size" and state the most sensible scientific conclusion: Low doses of ionizing radiation do not appear to have deleterious effects and appear, on occasion, to be beneficial.

The recent work published in *Science* on the DNA repair enzyme system(*2–7*) provides ample evidence for repair of damage from low levels of a variety of environmentally encountered hazardous agents, of which oxygen is perhaps the most hazardous of all. In addition, stimulation of such repair systems by one agent could protect against other hazardous agents and could quite simply account for hormetic effects.

It is time for us to get away from the tired old guard, the antinuclear terrorists, the environmental lawyers and uneducable regulators, and switch paradigms at long last. Try reading Rosalyn Yalow (*8*), Bernard Cohen (*9*) and Zbigniew Jaworowski (*10*). Delve into T.D. Luckey's 1991 textbook *Radiation Hormesis* with over 1000 references(*11*). We think it most probable that the emperor has no clothes.

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