Re: Does Lemon Candy Decrease Salivary Gland Damage After Radioiodine Therapy for Thyroid Cancer?

TO THE EDITOR: In their paper on salivary gland damage after high-dose radioiodine ablation therapy, Nakada et al. discuss an interesting and practical issue (*1*). The authors propose a radiation protection paradigm based on a concept of the dynamics of salivary gland function. The authors claim to have compared 2 radiation protection regimens in similar patients groups: a group that started sucking lemon candy straight after radioiodine treatment (group A), versus a group that started 24 h later (group B). Based on this comparison, the authors recommended that patients start sucking lemon candy no earlier than 24 h after radioiodine treatment.

Some aspects of this study are puzzling.

First, the authors state that "On encountering unexpectedly higher salivary gland side effects in group A, the patients in group B tended to be treated more intensively with steroids or nonsteroidal antiinflammatory drugs for sialoadenitis and with a drug containing zinc acetate or vitamin B_{12} for taste dysfunction" (*1*). Might these differences in medical treatment (which were not specified quantitatively) have contributed to the observed reduction of radiation damage in group B?

Second, as cited by the authors, the reported incidence of salivary gland injury varies considerably depending on the diagnostic criteria (*2–5*). The incidence of sialoadenitis, dry mouth, and loss of taste was investigated. Which criteria were used to define these primary endpoints?

Third, which criteria were used to consider including sialoscintigraphy in the assessment of salivary function? What was the total number of these procedures in each group, and what was the outcome? We believe that these data are relevant because of the reported disagreement between subjective symptoms and sialoscintigraphy.

Fourth, the authors' concept of salivary gland function has not been studied physically. It is uncertain whether at any time point there is indeed an imbalance of the salivary blood flow and the counteracting saliva flow. Whether delayed stimulation of the salivary glands has a radioprotective effect therefore remains a matter of debate. If delayed stimulation is indeed beneficial, why should the optimal starting point of sucking lemon candy be 24 h?

If this extra information could be supplied, the clinical significance of this study would be greatly enhanced.

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Marnix G.E.H. Lam, MD
Johannes W. van Isselt, MD, PhD
University Medical Center Utrecht
Utrecht, The Netherlands

REPLY: Our concern regarding the sucking of lemon candy early after radioiodine therapy was radioactivity in the blood and saliva (*1*). Radioiodine is constantly transported into the salivary glands until excretion is terminated. Because the thyroid gland has been removed from the patients, the radioactivity of ^{131}I in their blood is higher than that in healthy subjects. Additionally, clearance of ^{131}I from the body is considerably slowed in hypothyroidism. My colleagues and I determined radioactivity in the saliva and blood 24 h after 3.7 GBq of ^{131}I therapy had been administered to 4 patients. The saliva-to-blood ratios of the radioactivity ranged from 33 to 51 (mean, 41). Our finding seems compatible with a previous report that the concentration of ^{131}I in the salivary gland is 30–40 times higher than that in the blood (*2*). Our specific answers to the 4 questions of Drs. Lam and van Isselt are as follows.

First, parasympathetic and sympathetic refluxes mediate blood flow and salivary secretion in salivary glands. Therefore, enhancement of salivary secretion is not always proportionate to the increase in salivary blood flow caused by gustatory stimulation (*3*). A Doppler ultrasound study showed no significant correlations between salivary secretion and the maximum velocity, minimum velocity, and pulsatility index of the facial artery in the submandibular gland after sucking of a lemon slice (*4*).

Second, we used mainly methyl prednisolone sodium succinate (125–250 mg/d) as the steroid and ibuprofen (600 mg/d) as the nonsteroidal antiinflammatory drug (NSAID) in treating acute sialoadenitis. Vitamin B_{12} (mecobalamin, 1,500 μg/d) and zinc (polaprezinc, 225 mg/d) were used to treat taste dysfunction. A combination therapy of steroids, vitamin B_{12}, and zinc was given to a patient in whom both sialoadenitis and taste dysfunction were present. Because none of the drugs was used for prophylactic treatment, they must not have affected the incidence of acute side effects. Of 84 patients with acute sialoadenitis or taste dysfunction in group A, 44 (52%) were treated with steroids or NSAIDs, vitamin B_{12} and zinc, or combination therapy. Similarly, 50 (81%) of 62 patients with sialoadenitis or taste dysfunction in group B underwent either of the symptomatic treatments. We eventually found 14 patients with xerostomia in group A and 7 in group B. Of these patients, 4 in group A and 2 in group B were not receiving any medications because they did not experience acute side effects. Of the remaining patients, 6 (60%) in group A and 5 (100%) in group B were given either of the medications. Therefore, whether there was a relationship between the incidence of late xerostomia and the incidence of symptomatic treatment is uncertain.

Third, acute side effects were monitored by regular visits from nuclear medicine physicians to patients during hospitalization. At discharge, the patients were instructed to contact our staff anytime they suspected themselves of having sialoadenitis or taste dysfunction and to visit our outpatient clinic. The diagnostic criteria for xerostomia consisted of a visual analog scale and salivary scintigraphy (*1*). When a marking in the severe-dry-mouth zone on the visual analog

scale was associated with a nonfunctioning pattern in all 4 major salivary glands on the time–activity curves, xerostomia was confirmed. All patients underwent salivary scintigraphy at least once within 13 mo after radioiodine therapy. In patients who experienced acute side effects or who were suspected of having xerostomia, scintigraphy was repeated at 3- to 6-mo intervals. Forty-three (41%) of 105 patients in group A and 65 (52%) of 125 in group B underwent scintigraphy twice, and 28 (27%) in group A and 40 (32%) in group B were evaluated more than 3 times within 2 y after radioiodine therapy. The salivary function of the patients was monitored for at least 24 mo after ^{131}I therapy. We still monitor the salivary function of the patients enrolled in the study. We have not encountered additional patients who met our criteria for xerostomia after 25 mo. Thus, 24 mo after radioiodine therapy seems an appropriate endpoint for monitoring salivary function.

Fourth, delaying the sucking of lemon candy for 24 h was based on a hypothesis that the majority of ^{131}I administered should be excreted into the urine and that lemon candy–induced enhancement of blood flow may not enhance irradiation in the salivary gland. To determine optimal timing, a study with a variable start time seems essential (e.g., 6, 12, 24, and 48 h).

Recent studies have proposed novel perspectives on the mechanisms of irradiation damage to the salivary gland. It has been suggested that water secretion is selectively hampered during the first day after a single-dose irradiation without loss of the acinar cells, because of selective radiation damage to the plasma membrane of the secretory cells, disturbing muscarinic receptor–stimulated watery secretion (*5*). Also, it has been suggested that the sodium iodide symporter is detected mainly in the basolateral membrane of ductal cells and that radioiodine is transported mainly by ductal cells, not by acinar cells (*6,7*). Continuous stimulation of salivation may increase the radiation exposure of ductal cells, which are more sensitive to irradiated damage than are acinar cells, even if the residual time of ^{131}I in the salivary gland is shortened. We consider that radioprotection may be better achieved by suppressing radioiodine uptake in the salivary glands (*8*) rather than by stimulating salivation alone.

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Kunihiro Nakada, MD, PhD
Hokkido University Graduate School of Medicine
Sapporo, Japan

Tomographic Imaging in the Diagnosis of Pulmonary Embolism: Still, We Do Not Know

TO THE EDITOR: Reinartz et al. have to be commended for reassessing ventilation–perfusion scintigraphy for diagnosis of pulmonary embolism in light of recent advances such as SPECT methodology and ^{99m}Tc-based ultrafine aerosols (*1*). They are correct in stating that comparisons with pulmonary CT angiography should incorporate these technological advances.

There are good reasons to believe that tomographic imaging could supersede the sensitivity of planar techniques, simply by avoiding the overlapping of small perfusion defects by normal tissue. For example, phantom experiments have shown that perfusion defects in the mediobasal segment of the lower lobe would go unnoticed on planar images (*2*). As expected, the data of Reinartz et al. (*1*) support the better sensitivity of SPECT over planar techniques. Moreover, pulmonary angiography, which was used as the reference method in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, may underdiagnose pulmonary embolism (*3*).

So, there is a need to reassess scintigraphy for diagnosis of pulmonary embolism both because technology has progressed and because weaknesses of prior assessments have been recognized. On the other hand, the limitations of the retrospective study by Reinartz et al. (*1*) should be acknowledged as well. In their study, the final diagnosis was subjectively based on all imaging data together with clinical data, including follow-up and D-dimer levels. Therefore, the final diagnosis may have been biased to various degrees by the techniques to be compared, as well as by the clinical decisions that had been made from them.

Therefore, one should exercise caution before definitively adopting the authors' proposal to report all mismatches as embolisms. It may be hard to admit to the referring physician that, after all the trouble we and our patient took to perform a perfusion–ventilation study, *still, we do not know* whether the patient has pulmonary embolism. Yet, this may be the most honest answer and is preferable to guesswork. The intermittent-probability category is just a way of identifying those patterns that do not allow a final conclusion and that may require further diagnostic studies. Besides, management studies have convincingly shown precisely how to resolve these indeterminate cases by further diagnostic examination, if at all necessary (*4*).

This will always involve a further cost. Therefore, if such patterns can be avoided by technical improvements (e.g., because of additional mismatches identified on a tomographic study), all the better. Or if they are at error, because of limitations in the PIOPED studies that have defined them, one should of course eliminate them. But if such patterns are the result of conceptual limitations inherent in perfusion scintigraphy, we would probably do better to continue to label them as indeterminate readings.

There is reason to believe that such limitations are inherent in perfusion scintigraphy, a technique that reveals arterial or arteriolar obstruction, instead of clots. Indeed, any defect seen on a perfusion scan opens up the differential diagnosis of obstruction, which could be due to a lesion either in the lumen, in the vessel wall, or outside the vessel. Distinguishing between matched and mismatched perfusion defects does not completely resolve this differential diagnosis; for example, apart from embolism, mismatches may occur with vasculitis or with extrinsic tumors that spare the airways. Neither would a concurrent chest radiograph, as proposed by

the authors (and also mandatory when using the PIOPED scheme) allow one to settle all diagnostic questions. Reinartz et al. (*1*) point out that "the PIOPED study gives no physiologic explanation of why large mismatch defects should be a sign for pulmonary embolism while small ones are not." But the experimental finding from the PIOPED study that small mismatches do not always mean embolism may just signify that in small mismatches the other differential diagnoses are relatively more frequent or that the matched or mismatched nature is more difficult to certify for small defects. Alternatively, this finding could have been an error introduced by the limited sensitivity of pulmonary angiography. At this point, however, no definitive proof of this assumption exists. So, it seems likely that some scan patterns will never allow one to rule in or to rule out pulmonary embolism and would be most appropriately termed "indeterminate." A further practical consideration is that small defects, even when due to pulmonary embolism, may not always be the harbinger of life-threatening pulmonary embolism and therefore may sometimes be left untreated.

How should we proceed further, then? Because a favorable patient outcome does matter more than a correct diagnosis (only embolism that needs to be treated should be detected), outcome studies withholding anticoagulant treatment from patients with a low diagnostic probability are probably the best way to assess the sensitivity of diagnostic modalities for clinically relevant pulmonary embolism. Such data exist for some diagnostic strategies, including planar ventilation–perfusion scintigraphy, but they are lacking for tomographic scintigraphy. In stark contrast, a recent management study has shown that multidetector-row CT can even be used as the sole imaging study (*5*). If perfusion–ventilation scintigraphy is to survive in clinical practice, we will need that same level of evidence. More, if sensitivity is our strong point, as suggested by the data from Reinartz et al. (*1*), it would be in our interest to compare the 3-mo embolic risk in cohorts diagnosed by either ventilation–perfusion scintigraphy or CT.

Given the lack of a reference method with 100% sensitivity (which would be needed to identify all patients without pulmonary embolism), the specificity of a diagnostic modality for pulmonary embolism is even more difficult to judge, although this is an important issue in view of the hazards of anticoagulant treatment. Assessing the specificity will involve a comprehensive search for alternative diagnoses, but care should be taken to mask readers of scintigraphy for the results of this search.

In conclusion, the work of Reinartz et al. (*1*) provides an impetus for further prospective and more rigorous studies on ventilation–perfusion scintigraphy for diagnosing pulmonary embolism. As indicated by Reinartz et al., these will need to incorporate state-of-the-art techniques and revised interpretation criteria. Until those are proven that way, however, I am afraid that from time to time, it will be wise to admit that *still, we do not know*.

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Frank W. De Geeter, MD
Saint-John's General Hospital
Brugge, Belgium

REPLY: We appreciate Dr. De Geeter's interest in our article (*1*). Indeed, it is true that lung scintigraphy—like all other diagnostic procedures developed so far—is tainted with a certain probability of error. Although the same applies to multislice spiral CT, apparently the radiologic community has sufficient confidence in their method to give definitive diagnoses. Sure enough, scintigraphic mismatch defects can be caused by nonembolic diseases. On the other hand, it cannot be excluded that some of the segmental or subsegmental clots detected by CT are, rather, partial-volume artifacts or other phenomena instead of embolisms. Because no perfect gold standard exists for the diagnosis of pulmonary embolism, there is no possibility of verifying the scan results objectively. To sum it up, we could say of nuclear medicine physicians—still, they do not know, and of radiologists—they do not know either but continue to give definitive diagnoses anyway, and with considerable success.

In our opinion, it is well founded to diagnose embolism on lung scans when mismatch defects are detected. Apart from embolism, such mismatch defects are induced by only a few and, more important, rare nonembolic diseases or therapeutic interventions such as arteritis, vessel stenosis, lung cancer, nodal enlargement, and radiation therapy (*2*). Some of these conditions can be excluded by anamnesis or plain chest radiography so that the probability of a false diagnosis is further reduced. In this context, it appears reasonable and well balanced to use the diagnostic approach proposed by Howarth et al. (*3*), according to which embolism should be diagnosed in cases of mismatch defects of half-segment size or larger. By doing so, they achieved a sensitivity of 0.98 and a specificity of 0.96 in a study group of 924 patients. These data are indeed impressive and underline the diagnostic power of lung scintigraphy.

As far as concerns Dr. De Geeter's notion that "only embolism that needs to be treated should be detected," we strongly disagree. Although it is true that not all embolic clots are "the harbinger of life-threatening pulmonary embolism," it is also true that at autopsy, 50% of the patients dying from pulmonary embolism show residuals of earlier embolic events (*4*). In our opinion, a diagnostic procedure should be as exact as possible in reflecting pathologic changes. It is not within the competence of the diagnostician to decide about therapeutic options. All the diagnostician should do is provide accurate information to the physician responsible for the patient. To withhold or disregard any findings because they may be irrelevant for treatment is, in our opinion, irresponsible, especially because the therapeutic regime for pulmonary embolism is under constant evolution. Who can predict what therapeutic impact subsegmental embolisms may have in the future?

If we answer with "maybe" once too often, there is a good possibility that no one is going to ask us anymore. In conclusion, we can only stress the importance of striving for and expressing definitive diagnoses.

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Patrick Reinartz, MD
Ulrich Buell, MD
University Hospital Aachen
Aachen, Germany

Expression of Tracer Concentration

TO THE EDITOR: In a recently published article, "Metabolism of [^{13}N]ammonia in rat lung," Arthur Cooper and I briefly discussed the issue of units for reporting tracer concentration in tissue. Because I thought this would be of interest to *JNM* readers, I quote that discussion below (*1*).

2.6. Expression of Tracer Concentration

Expression of tracer concentration in tissue as "percent dose per g" (or per kg), which seems a natural choice to many workers, has an inherent disability: *the artifact of dilution by body mass.* If a tracer is similarly distributed in two individuals, one with twice the body mass of the other, all "percent dose per gram" values found in the larger individual will be *half* those found in the smaller one. This difficulty was recognized by the pioneer medical physicist, G. Failla, and, following his advice, Woodard and coworkers introduced a *body mass-normalized* unit (they called it the "differential absorption ratio") for expressing ^{32}P concentrations in excised tissues of cancer patients given a tracer dose before surgery (Kenney et al., 1941). This mode of expression failed to gain a significant following and, 30 years later, other investigators rediscovered the need to express tracer concentrations in mass-normalized units. Thus, Oldendorf et al. (1971) introduced "percent mean body concentration" and Oldendorf (1974) advocated its general use in a letter to the Journal of Nuclear Medicine. Rakusan and Rajhathy (1972) introduced "a new index. . . percentage of ^{86}Rb uptake/relative organ weight (percentage of body weight)". Blau (1975), in a letter to the Journal of Nuclear Medicine, pointed out that the improper use of tracer concentrations measured in dogs (which had been expressed in the artifact-prone "percent dose per g"), had caused investigators to greatly overestimate the tracer's radiation dose to humans. In their letter to the Journal of Nuclear Medicine, Woodard et al. (1975), recalled Failla's 1941 contribution, supported Oldendorf's and Blau's observations and proposed the name "relative concentration" for the mass-normalized unit. (As a coauthor (BRF) of that letter and this report remembers, the term was a compromise and not Woodard's first choice.) Subsequently, the field of quantitative in vivo nuclear medicine experienced a similar "reinvention" of mass-normalized concentration units ("standardized uptake value," "differential uptake ratio," "dose absorption ratio" and the like), with little, if any, acknowledgment of their antecedents.

Our experience has been that the term "relative concentration" masks the unit's universality and makes the concept appear vague, thereby limiting its use. In retrospect, we think that Oldendorf's "percent mean body concentration," modified to "ratio to mean body concentration" (or RMBC, which gives less cumbersome numerical values), has the advantages of clarity and specificity. We propose to use this nomenclature for reporting our ^{13}N concentration data and recommend it for general use. Defined most simply, for any specimen of tissue (including whole organs), RMBC is the decay-corrected fraction of injected tracer recovered in a specimen divided by the fraction of body weight contained in that specimen. (This is the *same* as "tracer found per g of specimen divided by tracer injected per g of body weight," where it is understood that for many radiotracers, quantitation requires correction for physical decay.) It is important to recognize that this unit is *dimensionless*. Also, it must be emphasized that this formulation is not limited to radiotracers. The tissue concentrations of *any* measurable substance introduced into the body (e.g., drugs) may be expressed in this form.

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Barry R. Freed, PhD
Memorial Sloan-Kettering Cancer Center
New York, New York

Nomenclature of ^{99m}Tc-Technetium-Labeled Radiopharmaceuticals

TO THE EDITOR: Dr. Tewson is quite right when he points out in his letter that technetium chemists are somewhat lax in the description of their agents (*1*). In his example, ^{99m}Tc-ciprofloxacin is internally contradictory in that it implies that ciprofloxacin contains the atom technetium, which of course it does not.

The pharmacopoeias do use the correct names: for example, technetium ^{99m}Tc medronate. Apart from sestamibi and one or two others, in general the chemical names of radiopharmaceuticals do not include technetium so "technetium ^{99m}Tc" must be added in each instance, which really is unworkable for routine use. It's too late to close the barn door.

He also makes the point that an exact chemical structure is required for reproducible results to be obtained. The aforementioned technetium ^{99m}Tc medronate is a constantly changing mixture of several complexes, all of which are taken up by bone and have been used, apparently reproducibly, for 30 y in the most popular nuclear medicine procedure in the world.

However, I would like to make this proposal: I will lobby the SPECT community to tighten up its nomenclature if he can persuade his colleagues in the PET world to discard the incorrect term ^{18}F-fluorodeoxyglucose (FDG) when they really mean ^{18}F-2-deoxy-2-fluoro-D-glucose!

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James R. Ballinger, PhD
Guy's and St. Thomas' Hospital
London, United Kingdom