Radiation Health Experts Criticize the Methodology and Presentation of FDA's Diagnostic Iodine-131 Study

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– Center for Devices and Radiological Health

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Radionuclides such as technetium-99m, thallium-201, and gallium-67 have replaced iodine-131 (^{131}I) as the diagnostic workhorses of nuclear medicine. Although diagnostic use of ^{131}I is disappearing, the radioisotope plays a major role in the treatment of thyroid disease. Because of ^{131}I's prominent role in thyroid disease therapy and its past significant role in diagnosis, the nuclear medicine community is concerned with the recent release of a Food and Drug Administration (FDA) study (*1*) implying that diagnostic ^{131}I may cause cancer in children.

Since the FDA's Center for Devices and Radiological Health (CDRH) released the study on the health effects of diagnostic ^{131}I last August, many well known experts on radiation health, one of whom was on the FDA's advisory panel to the study, have viewed it as methodologically flawed and have criticized the way it was presented to the public. The Society of Nuclear Medicine (SNM) Committee on the Radiobiologic Effects of Ionizing Radiation and the American College of Nuclear Physicians (ACNP) Environmental Radiation Committee are drafting a critique of the Center's study and plan to ask the FDA to reassess the results.

The Center's Findings

The Center's researchers performed a cohort study of 3,503 children and adolescents who received diagnostic doses of ^{131}I between 1946 and 1967, following the exposed group for 93,442 person-years. The FDA researchers — Peggy Hamilton, Richard P. Chiacchierini, PhD, and Ronald G. Kaczmarek, MD — also studied 2,594 children and adolescents in two groups who did not receive ^{131}I and followed them for 66,797 person-years. One group of control subjects consisted of patients who had thyroid function tests or a similar diagnosis to the exposed group, and the other consisted of siblings of the exposed population. The radiation doses in the exposed group ranged up to 2000 Rad, with the majority receiving less than 100 Rad. The researchers found six malignancies, five in the exposed group and one in the test control group. No malignancies were found in the diagnostic controls. They also noted an increased risk of benign thyroid conditions in the exposed group, observing eight benign conditions in the exposed group and one in each of the two control groups. In the abstract of the study, however, the researchers acknowledge that "The results. . . failed to fulfill the requirements for statistical significance because of the small number of cases. . ." but they go on to state that the results ". . .are suggestive of a radiation effect."

Some radiation health experts have taken issue with the FDA for releasing results that are not statistically significant. David V. Becker, MD, professor of radiology and medicine, director of the division of nuclear medicine at New York Hospital-Cornell Medical Center in New York City, a member of the SNM Committee, asks, "If it's not significant, then the relationship doesn't exist, so what are they talking about?" Eugene L. Saenger, MD, Professor Emeritus of Radiology, Director Emeritus of the Eugene L. Saenger Radioisotope Laboratory at the University of Cincinnati in Ohio, a member of the FDA's advisory committee to the study, wrote in a letter to John Villforth, director of the Center, "There are serious questions as to whether the conclusions of this report as reflected in the several recent publications are in any way accurate. . . . it is my belief that immediate steps should be taken to clarify these issues."

Charles Land, PhD, health statistician at the National Cancer Institute (NCI) in Bethesda, Maryland says, "I

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don't object to trying to publish [preliminary data]. I think that one should do that. That's how it gets out and gets criticized. But I do disagree with their conclusions." Dr. Land views the Center's study as a negative rather than a positive study. "The number of cancers observed are quite below, significantly below, what you would expect to see with X-rays. They seem to be trying to present it as a positive thing — that the risk from iodine-131 is increased. I don't see it."

Dosimetry and Diagnoses Questioned

Radiation health experts have questioned various aspects of the study's methodology, particulary the dosimetry and pathology data. David R. Brill, MD, chief of the section of nuclear medicine, assistant director of the department of special imaging radiology at Geisinger Medical Center in Danville, Pennsylvania, chairman of the ACNP Committee, told *Newsline*, "We are concerned about the study design and some of the ways they collected data." Dr. Brill notes, "This is a dosimetry study. They were trying to prove an effect of radiation on the thyroid gland, for which they need accurate dosimetry. They made a number of assumptions about the mass of the gland. This may be OK for the general population, but these people were referred for testing because of a health problem." In addition, says Dr. Brill, "They made no attempt at fractionation of multiple doses. We do not feel that their dosimetry was very accurate, and we are somewhat concerned about their diagnoses."

The FDA researchers arrived at their diagnoses through either pathologist review of specimens if they were available and retrospective review of pathology reports if they were not. Stanley J. Goldsmith, MD, director of the department of physics-nuclear medicine at Mount Sinai Medical Center in New York City, a member of the SNM and ACNP Committees, notes that there is no data on how many cases were, in fact, reviewed by pathologists. Dr. Brill says, "This concerns us. It doesn't seem to be very good quality control."

In his letter to Mr. Villforth, Dr. Saenger wrote, "Because the diagnoses made at surgery are somewhat confusing, as for example in the case [of] metastatic papillary thyroid carcinoma, one wonders exactly what these cases included. It is strange to believe that such a document could be published without including, at least in some detail, the specific case histories and interpretations of [these] few cases of carcinoma since they are of particular importance. In addition, there is no specific discussion as to the methods used in the pathological review." Dr. Goldsmith says, "Blinding of reviewers is of particular importance in a study such as this."

Although one of the criteria for inclusion into the follow-up study was the absence of preexisting hyperthyroidism or thyroid cancer problems, Dr. Brill asks, "if there was no thyroid problem, why did these children get radioiodine? It would be important to exclude patients with preexisting thyroid problems to remove any possible bias in the later development of a thyroid condition." Dr. Kaczmarek says that the thyroid test was given to rule out thyroid problems and added that the patients who later developed malignancies had been diagnosed with cold intolerance, obesity, chronic thyroiditis, congenital megacolon disease, suspected central nervous system disease, or anxiety neurosis.

Rosalyn S. Yalow, PhD, senior medical researcher for the Veterans Administration, who was awarded the Nobel Prize in Physiology/Medicine in 1977, noted in an editorial in the April 1990 *Endocrinology* that, unlike a Swedish study by L. E. Holm and his colleagues (*2*), the Center's study "did not address the question as to whether the thyroidal doses in excess of 1 Sv (100 Rem) were given to about 1/6 of the patients because at the time of the study abnormalities of the gland were suspected. The omission of consideration of this very relevant fact was striking since the paper was very lengthy and considered extensively other factors of lesser importance" (*3*).

Another major criticism of FDA researchers is their inclusion of the case of a women with a malignancy that was identified just two years after she received diagnostic ^{131}I. Dr. Becker notes that it is generally agreed that radiation should not be considered the cause of solid tumors occurring less

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than five years after radiation exposure. In his letter to Mr. Villforth, Dr. Saenger wrote, ". . .the case with the two year latent period should have been excluded. Once such an exclusion is made, the questionable statistical significance becomes even less convincing."

Suspected Bias

The SNM and ACNP Committees are critical of the Center's presentation of the data both in an article in CDRH's *Radiological Health Bulletin* and in a poster exhibited during the Radiological Society of North America (RSNA) Meeting in November-December 1989. Dr. Goldsmith says, "The *Bulletin* uncritically reported the views of this seriously flawed study. Given the potential impact of such findings, if valid, investigators, agencies, and editors need to be critical of such reports to assure that unfounded conclusions are not endorsed as fact." The RSNA poster presentation entirely omitted the qualifying statement that the results did not meet requirements for statistical significance.

In a response to Dr. Saenger's letter to the Center, Dr. Chiacchierini indicated that the researchers did not knowingly omit the qualifying statement about significance. He wrote, "There was no inconsistency in the various presentations and publications concerning the statistical significance of the results. Although the poster at the Radiological Society of North America Meeting inadvertently omitted the sentence stating that the results failed to achieve statistical significance, the published record of the abstract. . . did include the statement. . . ."

Nevertheless, the study's methods and the manner in which it was presented have led scientists to question the validity of its conclusions. Dr. Saenger wrote in his letter, "Since publicity of this curious study is being pushed with great alacrity and enthusiasm by the Center for Devices and Radiologic Health, one might wonder whether there is any scientific basis for the strange conclusions purportedly reached by the authors."

Furthermore, Dr. Brill says that the SNM and ACNP Committees "are concerned that there may have been some bias among the authors about what they should find." Referring to a statement within the study monograph about the radiosensitivity of the growing thyroid to potential radiation exposures from nuclear medicine studies and nuclear power plant emissions and to another statement that "increased study size may well provide evidence of an effect associated with diagnostic levels of ^{131}I," Dr. Brill says, "it appeared that they were trying to force a conclusion." Dr. Becker agrees that "bias appears in those kinds of statements" and adds, "The study was poorly reported and poorly presented. It's an important database, an important population, but they have not been able to come up with what appears to be a reasonable scientific analysis of the data. They've come up with a biased conclusion that isn't supported by their data." Adds Dr. Brill, "The bottom line is that there was no statistically significant effect observed in the study population."

Advisory Committee Left Out

In a break from the normal channels of peer review, the Center excluded their own advisory group to the study after the very preliminary stages. Dr. Saenger told *Newsline*, "The advisory committee never had a chance to look at the final data. . .they could have sent us a draft like everybody else does." Dr. Saenger noted that in a letter requesting that he serve on the FDA's advisory group to the study, the FDA indicated the advisory group "acts in an

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advisory capacity for all phases of the study from approval of the study protocol through review and approval of final reports." He noted that he "attended several meetings and engaged in considerable correspondence in this study from that time through about 1982, when, for some reason, activities on this particular project ceased. Since our responsibilities in this project were never requested after 1982, nor did we see a draft of the final report, it seems that the carefully structured plan to ensure a proper conclusion to this study was breached."

The Center plans to submit the report to peer-reviewed journals for publication. Dr. Kaczmarek told *Newsline* that the patient with the two year latency has been removed from the study and that the authors are further reviewing the study. The SNM and ACNP Committees are concerned that if the paper is published with its current conclusions, it will be misleading. Says Dr. Becker, "The paper is dangerous because many people won't read it in its entirety but rather will just look at the abstract, title, and conclusions. Their conclusions may then be quoted without qualification and would eventually be accepted at face value."

According to Dr. Brill, the Committees would like the Center to remove the statement claiming that with more data an effect might be proved and to let stand the statement that the data fail to show a significant effect "until and unless a peer-reviewed study can prove otherwise."

Original Protocol Not Completed

Defending the study in his response to Dr. Saenger, Dr. Chiacchierini wrote, ". . .the study was designed to follow 6,500 exposed and 6,500 unexposed patients for an 80% chance of detecting a threefold increase in the risk of thyroid cancer at the 5% significance level. The CDRH report describes the entirety of the study to date. According to Dr. Kaczmarek, the researchers calculated a relative risk of 2.86 from all the malignancies occuring at least five years after exposure.

Dr. Chiacchierini wrote to Dr. Saenger, "We feel the results are suggestive enough to warrant completion of the original protocol even if it cannot be done here at CDRH. As you and the other committee members stated, the results of the study, when completed, "are critical to the national health." He noted that "the findings are the result of the follow-up of only about one half of the planned study population." But, counters Dr. Becker, "if it's not an adequate follow-up, don't publish the study yet."

NCI Withdrew Support for Study

The diagnostic ^{131}I study, which Dr. Kaczmarek notes began over 30 years ago, was supported over the years through interagency agreements with the Nuclear Regulatory Commission and the NCI. However, according to Dr. Land, after the NCI provided some funding for the project, an outside review committee for the NCI's Radiation Epidemiology Branch "turned it down" because "there seemed to be a lot of difficulty in achieving the original goals. . .locating cases and controls." Dr. Land allowed that the process of following patients over the years in such a prospective study "is difficult to do" because people move and often women get married and change their names.

The major complaint with the study is that its data don't support its conclusions. Dr. Saenger summarizes, "They've suggested that we did a mountain of damage to those children, and I don't think the data that they've assembled has shown that." Says Dr. Brill, "They ran out of money, they ran out of time, they ran out of everything else, and they just threw what they had into a bag. It's a harmful document . . . .Given the impact on legitimate societal activities involving the production or use of ^{131}I, a great deal more care should have been taken on this study."

Sarah M. Tilyou

References

1. Hamilton PM, Chiacchierini RP, Kaczmarek RG. A follow-up study of persons who had iodine-131 and other diagnostic procedures during childhood and adolescence. HHS Publication FDA 89-8276.
2. Holm L-E, Wiklund KE, Lundell GE, et al. Thyroid cancer after diagnostic doses of iodine-131:a retrospective cohort study. *J Natl Cancer Inst* 1988; 80:1132.
3. Yalow R. Editorial: The contributions of ^{131}I to the understanding of radiation carcinogenesis. *Endocrinology* 1990; 126 (4):1787–1789.

PET Booklet Available

The Mallinckrodt Institute of Radiology at Washington University School of Medicine, in St. Louis, Missouri, has produced a color publication on PET, *Positron Emission Tomography: The Imaging of Function Rather than Form.* Commissioned and funded by the Department of Energy (DOE), the 15-page booklet describes PET's history, development, and up-to-date medical applications. The report was prepared by Michael J. Welch, PhD, professor of radiation chemistry and radiology at Washington University, and Michaele R. Gold, director of public relations and marketing at Mallinckrodt. "The DOE had received numerous requests from VA hospitals and other institutions all over the country to produce a booklet that would introduce PET, since many of them were considering establishing a PET system," says Paul Cho, PhD, senior staff member of the DOE's Office of Health and Environmental Research.

The publications can be obtained at no cost by writing to Paul Cho, PhD, U.S. Department of Energy, Office of Health and Environmental Research, ER-73, Washington, DC 20545. ■