Final Report

Advisory Committee on Human Radiation Experiments

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Part II

Nasopharyngeal Irradiation

Nasopharyngeal irradiation,[a] introduced by S. J. Crowe and J. W. Baylor of the Otological Research Laboratory at the Johns Hopkins University, was employed from 1924 on as a means of shrinking lymphoid tissue at the entrance to the eustachian tubes to treat middle ear obstructions, infections, and deafness. For this treatment, intranasal radium applicators (sealed ampules containing radium salt) were inserted (at least three insertions per treatment cycle) into the nasopharyngeal area for twelve-minute periods.[b] The therapeutic effect of the treatments resulted from the penetrating radiation emitted from the radium source (gamma and beta rays), not

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a. Nasopharyngeal irradiation was studied in adults as well as children. In the early 1940s, 732 submariners were subjects of a controlled experiment designed to test whether nasopharyngeal radium treatments could be used to shrink lymphoid tissue surrounding the eustachian tubes, thereby preventing and treating aerotitis media in submariners by equalizing external and middle ear pressure. This treatment was successful in 90 percent of the cases. H. L. Haines and J. D. Harris, "Aerotitis Media in Submariners," *Annals of Otology, Rhinology, and Laryngology* 55 (1946): 347-371. In a 1945 journal article, it was noted that a controlled study was considered by the Army Air Forces, but rejected because of the urgent need to treat fliers immediately and keep them flying. However, the published report describes differences between various dose groups, implying an uncontrolled experimental comparison was made. Captain John E. Hendricks et al., "The Use of Radium in the Aerotitis Control Program of the Army Air Forces: A Combined Report by the Officers Participating," *Annals of Otology, Rhinology, and Laryngology* 54 (1945): 650-724. Tens of thousands of servicemen were subsequently given this nasopharyngeal radium treatment.

Relying on the risk estimate developed in the Sandler study, Stewart Farber, a radiation-monitoring specialist with a background in public health, has projected 51.4 excess brain cancers over a fifty-year period in the 7,613 servicemen irradiated in the Navy and Army Air Forces studies noted above. Stewart Farber, Consulting Scientist of the Public Health Sciences, to Stephen Klaidman, ACHRE Staff, 8 March 1995 ("Nasopharyngeal Radium Irradiation-Initial Radiation Experiments Performed by DOD on 7,613 Navy and Army Air Force Military Personnel during 1944-45"). Alan Ducatman, M.D., of the University of West Virginia School of Medicine, who coauthored a letter with Farber to the *New England Journal of Medicine* regarding the radium exposure of military personnel, wrote that he found "no convincing evidence of excess cancer in the exposed population." He added, however, "there is also no good evidence for the null hypothesis." Alan Ducatman, West Virginia University School of Medicine, to Duncan Thomas, Member of the Advisory Committee on Human Radiation Experiments, 22 February 1995 ("I'm sorry I could not respond . . .") (ACHRE No. WVU-021795-A).

Han K. Kang, with the Environmental Epidemiology Service of the Veterans Health Administration, is currently conducting a study to assess the feasibility of an epidemiologic study of Navy veterans who received radium treatments. Han K. Kang, Environmental Epidemiology Service, Veterans Health Administration, "Feasibility of an Epidemiologic Study of a Cohort of Submariners Who Received Radium Irradiation Treatment," 23 August 1994. It is not clear, however, that sufficient numbers of treatment-documented personnel can be identified, as a group representing submariners has apparently been able to identify only six former Navy personnel from of a pool of twenty-seven whose records indicate they received radium treatment. (It is not clear whether the data being collected by the VFW with the support of Senator Joesph Lieberman of Connecticut will be from a representative sample of respondents. If, in fact, these data are from a highly nonrepresentative sample, the study may not be considered scientifically valid.) However, the Veterans of Foreign Wars organization apparently is now processing hundreds of surveys filled out by veterans who say they underwent nasopharyngeal radium treatment. Once this task is completed, Senator Lieberman plans to present the data to the Department of Veterans Affairs with a recommendation that an epidemiologic study be conducted.

b. Samuel J. Crowe, "Irradiation of the Nasopharynx," *Annals of Otology, Rhinology and Laryngology* 55 (1946): 31.

from the internal deposition of radium itself. Crowe and his colleagues reported that "under this treatment, the lymphoid tissue around the tubal orifices gradually disappeared, marked improvement or complete return of the hearing followed, and in many the bluish discoloration of the tympanic membrane also disappeared."[c] This method was used for more than a quarter century as a prophylaxis against deafness, for relieving children with recurrent adenoid tissue following tonsillectomy and adenoidectomy, and for children with chronic ear infections. Asthmatic children with frequent upper respiratory infections were also often considered for this type of irradiation.

An average of 150 patients a month, mostly children, were given the treatment at the Johns Hopkins clinic over a period of several years.[d] Many children received the treatment more than once as recurrent lymphoid tissue was considered an indication for treatment.

Crowe and his colleagues reported that the results following irradiation of the nasopharynx alone were not only as good as, but often better than, those following removal of tonsils and adenoids.[e] In review articles, they noted that approximately 85 percent of treated patients responded with decreased numbers of infections and/or improved hearing when treated at young ages. They also concluded that "it is effective, safe, painless, inexpensive and has proved particularly valuable for prevention of certain ear, sinus and bronchial condition in children."[f] Although early articles by Crowe and colleagues indicate that nasopharyngeal radium treatments were accepted as standard procedure for the prevention of childhood deafness, these treatments, like most standard interventions in medicine, had not been subjected to formal scientific evaluation. A controlled study was conducted from 1948 to 1953 by Crowe and his colleagues to determine "the feasibility of irradiation of the nasopharynx as a method for controlling hearing impairment in large groups of children associated with lymphoid hyperplasia in the nasopharynx; to draw conclusions concerning the per capita cost of such an undertaking as a public health measure."[g] Crowe et al. wrote in an NIH "Notice of Research" that "the procedure of treatment is not new, as an individual measure; this is the first adequately controlled experiment of sufficient size for accurate statistical analysis."[h]

This work was funded by NIH for the entire period of study. As recorded in an NIH grant application, the study involved approximately 7,000 children screened for hearing impairment.[i] Of those screened, approximately 50 percent were selected for further study based on the chosen criteria for hearing loss. Half of this study group was irradiated with radium, while the other half served as a control group. Crowe and colleagues reportedly concluded from this study (published in 1955) that the radium treatments did shrink swelling of lymphoid tissue and improve hearing.[j] This type of therapy was ultimately discontinued because of newly available antibiotics and the

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c. Ibid., 30.

d. Ibid., 33.; Dale P. Sandler et al., "Neoplasms Following Childhood Radium Irradiation of the Nasopharynx," *Journal of the National Cancer Institute* 68 (1982): 3-8.

e. Ibid., 33.

f. Ibid.

g. S. J. Crowe et al., The Johns Hopkins University School of Medicine and School of Hygiene and Public Health, to Federal Security Agency, Public Health Service, National Institutes of Health, July 1948 ("The Efficiency of Nasopharyngeal Irradiation In the Prevention Of Deafness in Children, Notice of Research Project, Grant No. B-19") (ACHRE No. HHS No. 092694-A).

h. Ibid.

i. Ibid.

j. Ibid.

use of transtympanic drainage tubes, as well as awareness of the potential risks of radiation treatment.

In addition to the targeted lymphoid tissue, the brain and other tissues in the head and neck region, including the paranasal sinuses, salivary glands, thyroid, and parathyroid glands are also exposed to significant doses of radiation during the radium treatments, prompting concern that these treated individuals might have been placed at increased risk for radiation-induced cancers at these sites. Dale P. Sandler et al., in their 1982 study of the effects of nasopharyngeal irradiation on excess cancer risk for children treated at the Johns Hopkins clinic, found "a statistically significant overall excess of malignant neoplasms of the head and neck among exposed subjects," based however on only four cases in comparison with 0.57 expected.[k] This excess was accounted for mainly by three brain tumors that occurred in the irradiation subjects. One other malignant tumor, a cancer of the soft palate, was also reported. The Department of Epidemiology at the Johns Hopkins University has undertaken a further follow-up study of the Crowe et al. cohort of children irradiated there, previously studied by Sandler et al.[l] Verduijn et al., in their 1989 study of cancer mortality risk for those individuals (mostly children) treated by nasopharyngeal irradiation with radium 226 in the Netherlands, reported that "the present study has found no excess of cancer mortality at any site associated with radium exposure by the Crowe and Baylor therapy. Specifically,
the finding of Sandler et al. of an excess of head and neck cancer was not found in this study group."[m]

Among the Japanese atomic bomb survivors, no excess of brain tumors was found. However, several studies have noted an increased risk of both benign and malignant brain tumors following therapeutic doses of radiation to the head and neck region during childhood.[n] From the Committee's own limited risk analysis of these experiments, we concluded that the brain and surrounding head and neck tissues would be put at highest risk and estimated the lifetime risk at approximately 4.35 per 1,000 and an increased relative risk of 62 percent.[o]

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k. For the combination of benign and malignant neoplasms, there were 23 cases, for a relative risk of 2.08 with a 95 percent confidence interval of 1.12 to 3.91. Sandler, "Neoplasms Following Childhood Radium Irradiation," 5.

l. Jessica Yeh and Genevieve Matanowski, fax to Anna Mastroianni (ACHRE), 7 July 1995 ("Nasopharyngeal Power Analysis"), 1-3.

m. Verduijn et al., "Mortality after Nasopharyngeal Irradiation," *Annals of Otology, Rhinology, and Laryngology* 98 (1989): 843.

n. S. Jablon and H. Kato, "Childhood Cancer in Relation to Prenatal Exposure to Atomic-Bomb Radiation," *The Lancet*, ii (1970): 1000-1003.; M. Colman, M. Kirsch, and M. Creditor, "Radiation Induced Tumors," in *Late Biological Effects of Ionizing Radiation, Vol. I* (Vienna: International Atomic Energy Agency, 1978), 167-180; R. E. Shore, R. E. Albert, and B. S. Pasternak, "Follow-up Study of Patients Treated by X ray Epilation for Tinea Capitis: Resurvey of Post-Treatment Illness and Mortality Experience," *Archives of Environmental Health* 31 (1976): 17-24; and C. E. Land,"Carcinogenic Effects of Radiation on the Human Digestive Tract and Other Organs," in *Radiation Carcinogenesis*, eds. A. C. Upton et al. (New York: Elsevier, 1986), 347-378.

o. The radiation dose estimate to the head and neck region was calculated according to the following assumptions: (1) Source description: 50 mg of radium, active length 1.5 cm, filtered by 0.3 mm of Monel metal. (2) Average treatment: 60 mg/hrs; based on three 12-minute treatments (radium applicators inserted through both nostrils)= (12x3x50x2)/60 mins per hour= 60 mg-hrs. (3) Dose rate at points in a central orthogonal plane surrounding the source: for distances up to 5 centimeters dose estimated using published data (Quimby Tables, Otto Glasser et al., *Physical Foundations of Radiology*, 3d ed. [New York: Paul Hoeber, Inc., 1961]) for linear radium sources with dose increased by 50% to allow for the reduced

The Hopkins nasopharyngeal study raises different ethical issues than those posed by the other experiments reviewed in this chapter, all of which offered no prospect of medical benefit to the children who served as subjects. By contrast, the nasopharyngeal irradiation experiment was designed to determine whether children at risk for hearing loss would be better off receiving radiation treatments or not receiving such treatments. A central issue here was whether it was permissible to withhold this intervention from "at risk" children. The application of radium was at this point a common, but scientifically unproven, treatment for children at risk of hearing loss; the risks of the treatment were not well characterized. If it was really unknown which was better for children--receiving radium or no intervention--then the medical interests of the children were best served by being subjects in the research because, as a consequence, they would have a 50 percent chance of receiving the better approach. The nasopharyngeal experiment thus belongs to a class of research the Committee did not investigate--therapeutic research with children.

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filtration provided by the applicator wall and converting roentgen to rad by a multiplication factor of 0.93. For distances greater than 5 centimeters, the dose rate is reduced in accordance with the inverse square law, with a proportionality constant of 690 rad-cm^2. There was no dose correction for attenuation of the gamma rays by tissue absorbtion, which has been calculated to be about 2%/cm (yielding a dose reduction of about 20% at 10 cm).

The local gamma dose to the head and neck region was assumed to be distributed according to an inverse square law $d(r) = 690/r^2$ rad. The Committee approximated the exposed region of the body by a sphere with radius 10 centimeters. This was felt to be a conservative assumption, because although the dose does not go to zero at the base of the neck, a 10-centimeter sphere would also extend outside the skull. Averaging this dose distribution over the exposed sphere, the average dose to the head was found to be 20.7 rad. The exposed volume is about 4189 cm^3, or 29 percent of the total body, so the average whole body dose is about 6.0 rad. Multiplying this by the BEIR V risk coefficient for children exposed at age five, 1.4/1,000 person-rad, produces a lifetime risk of about 8.4/1,000. This calculation assumes that the brain and other head tissues have average radiosensitivity. BEIR V also gives absolute-risk coefficients for brain cancer ranging from 1 to 9 per million person-year-rad, with 3 being a reasonable average. Applying this figure to an average head dose of 20.7 rad, the Committee estimates a lifetime risk of about 4.35/1,000. The corresponding relative risk coefficients average about 3 percent per rad, so this dose would correspond to an excess relative risk of 62 percent.