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Epidemiologic Studies of Thyroid Cancer in the CIS

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Abstract. Despite the great international interest in Chernobyl and the need for quantitative risk information on the carcinogenic effectiveness of the radioiodines, there has been relatively little epidemiologic research on thyroid cancer following the Chernobyl accident. The reasons for this are many, diverse, and difficult to eliminate, although some progress is being made. Among them are the natural priority of public health concerns, a weak infrastructure for conducting studies in chronic disease epidemiology, and the difficulty of assigning thyroid dose estimates to individuals for study. In spite of the difficulties a number of significant studies have been begun or are planned, and several valuable reports have appeared. From the descriptive studies it is now known that the latent period for thyroid cancer in children exposed to radioiodines is not 5 to 10, but probably three years, that the magnitude of the increase in thyroid cancer among children is beyond anything previously experienced or expected, and that there is a strong correlation between thyroid cancer and environmental radiocesium contamination levels in the Gomel region of Belarus, and between thyroid cancer and average regional levels of I-131 dose to the thyroid in Ukraine. However, even today, there is very little hard scientific information on the relation of thyroid cancer in children and their exposure to the radioiodines in the fallout from the Chernobyl accident. This is information that only well-designed scientific epidemiologic studies, based on firm dose estimates, could be expected to provide. With that purpose in mind, the US has planned with Belarus and Ukraine long-term cohort studies of many thousands of subjects with thyroid activity measurements.

1. Introduction

For the Post-Accident Review meeting at the International Atomic Energy Agency (IAEA) in August, 1986, the documentation provided by the USSR State Committee on the Utilization of Atomic Energy [1] revealed considerable concern among Soviet authorities about the effect of the accident on thyroid disease, especially cancer. In the medical annex, where this concern is most clearly evident, plans for the medical surveillance of the exposed population are briefly described. Included there (p 68 in the English translation) are two significant statements:

"A special study will be made of the functioning of the thyroid gland and over extended periods the frequency of development of adenoma and malignant neoplasms," and

"In dose ranges presenting even minimal risk of dysfunction of the thyroid gland (the pediatric) examination will be complemented by special dynamic observation of the endocrinology of the thyroid gland, using hormones--thyroxine, triiodothyroxine, thyroid stimulating hormone and others."

In May, 1987, there were two meetings on epidemiologic studies of the post-Chernobyl experience, one at the World Health Organization (WHO) Regional Office in Copenhagen, the other at the IAEA in Vienna [2], both chaired by Professor Albrecht Kellerer. At both meetings it was assumed that epidemiologic studies of thyroid cancer would be undertaken, and specific methodologic suggestions were made. In neither report, however, is there an expectation that thyroid cancer could become the problem that confronts the CIS today, especially Belarus.

In October, 1987, the Nuclear Energy Agency of the Organization for Economic Cooperation and Development held a workshop in Paris entitled "Epidemiology and Radiation Protection" at which the principles and practice of radiation epidemiology were extensively reviewed. The only reference to Chernobyl was contained in a paper by Kaldor and Parkin detailing plans to study leukemia through cancer registries throughout Europe, including Belarus and parts of the Russian Federation; the first paper on this study was published in 1993 [3], and a second is in process of publication [4].

In the spring of 1990 the WHO began planning its International Program on the Health Effects of the Chernobyl Accident (IPHECA), based on a request from the Minister of Health of the USSR. Thyroid disease was one of five radiation effects initially targeted for pilot studies, the others being leukemia and related hematologic disease, brain damage from pre-natal exposure, epidemiologic registers, and oral health in Belarus. The protocol for the thyroid survey visualized a case-control study built on a population screening effort in heavily contaminated (Cs-137 deposition greater than 550 kBq m^{-2}) areas with controls selected from the same areas and from less contaminated areas in anticipation of obtaining adequate dose information [5].

In the fall of 1990 the IAEA carried out an epidemiologic field survey in 7 villages in strictly controlled zones and 6 villages in lightly contaminated areas in Belarus, the Russian Federation, and Ukraine. Although by late 1990 the increase in thyroid cancer among children had begun in both Belarus and Ukraine, the careful thyroid screening by IAEA teams revealed no difference between heavily and lightly contaminated villages with respect to the prevalence of thyroid nodules [6]. The samples of children were too small for the IAEA survey to demonstrate a difference that had just begun to emerge.

Also in 1990, under an earlier US-USSR agreement to cooperate in the field of civilian nuclear reactor safety, thyroid cancer and leukemia were selected as subjects for collaborative epidemiologic investigation. In 1995 thyroid studies are just beginning in both Belarus and Ukraine.

In short, the catastrophe set in motion an intensive effort to screen children for nodules and cancer, national and international groups have attempted to organize epidemiologic studies with scientific as well as public health objectives. The effects of the radioiodines released during the accident on thyroid disease, especially cancer, has caused considerable concern and interest. Although the radioiodines are known to have caused thyroid cancer among the Marshallese, the cases were few, doses were difficult to establish, and the respective roles of I-131 and short-lived radioisotopes could not be clarified [7]. Exposure to both x and gamma rays has shown the thyroid to be highly sensitive to their carcinogenic potential; indeed, the thyroid is regarded as one of the most sensitive organs, especially in children [8-10].

2. The Need for Scientific Information on the Carcinogenic Effect of Radioiodine

Radiation protection strategies depend in part on scientific risk estimates derived from medical exposures and from the atomic bombing of Hiroshima and Nagasaki. Thus far information obtained from the medical use of I-131 has been inconclusive, partly because it rarely pertains to children or juveniles and little or no risk has been demonstrated among adult patients treated with I-131 [8]. Although the Marshallese experience does demonstrate the carcinogenic potential of radioiodine, it is estimated that the thyroid dose was principally due to short-lived radioiodines, especially I-132 and I-133. Animal experiments have confirmed that I-131 can induce thyroid cancer but without producing a sure basis for adjusting the human risk estimates for x and gamma rays. In sharp contrast to this paucity of information on the risk of radioiodine exposure to children is the fact that the extent of their vulnerability in case of nuclear accidents such as Chernobyl remains unknown and may be great if Chernobyl is any guide. Nuclear power reactors have large inventories of radioiodine and their accident rate, although low, is not zero. Also, if, as many believe, I-131 is much less effective than x or gamma radiation, we need to know why this is so, whether it depends on the protraction of dose within the gland or on some other mechanism. From the available data Shore has estimated that I-131 may be only 20-25 percent as effective as external radiation in inducing thyroid cancer among juveniles [9].

3. The Opportunity for Epidemiologic Study

However tragic the Chernobyl accident, it demonstrated the need for additional information on radiation protection and provided an unparalleled opportunity to create the information on which radiation protection must depend. Comparative figures on accidental releases of I-131, recently summarized by Becker et al. [10] are: Three Mile Island, 15-20 Ci (about 0.6 TBq); Windscale, 20,000 Ci (0.7 PBq); Hanford, from 1944-1947, 690,000 Ci (26 PBq); and Chernobyl, 40-50 million Ci (1-2 EBq). The Chernobyl accident exposed hundreds of thousands of people living within a relatively small area to doses that ranged well above a Gray. Soviet physicists were well aware of the potential hazards of radioiodine fallout and made literally hundreds of thousands of direct thyroid radioassay measurements, especially in Belarus and

Ukraine. These measurements, used in conjunction with personal histories of residence and nutritional sources, offer promise in dose reconstruction. Endocrinologists were not slow to initiate systematic screening programs. Within a comprehensive epidemiologic framework that includes information on individual dose, these programs could be expected to provide scientific information hitherto unavailable. Although only one area (Belarus) had a cancer registry in operation at the time of the accident, the highly organized and standardized medical care system in place at the time, and subsequently, constitute important assets in the conduct of large-scale epidemiologic studies.

4. The Effort To Establish Epidemiologic Studies of Thyroid Cancer

According to the preliminary WHO catalogue issued in the fall of 1994 [11], in each of the three now separate countries with significant fallout an indigenous cohort study of some size, 6,000 in the RF, 50,000 in Ukraine, and 20-30,000 in Belarus, was begun in 1986. In early 1990, following extensive collaboration between the USSR and WHO on matters relating to Chernobyl, the Ministry of Health of the USSR asked WHO to develop an international program, "to mitigate the health consequences of the Chernobyl accident." Although the thyroid component of the program was mainly a disease-detection effort in children living in highly contaminated areas and under 16 at the time of the accident, there was hope that the prevalence of thyroid disease could be related to thyroid dose from the Chernobyl accident. The case-control approach would be used, and dosimetric investigations were prescribed. In addition to the case-control approach a number of descriptive and ecologic methods were to be used [5].

Meanwhile, systematic case-detection continued in response to public health concerns, and additional studies were planned or begun in all three countries. In 1990 the Japanese Sasakawa Health and Medical Foundation began its extensive program of humanitarian aid to affected areas of all three countries, concentrating on case-finding by the most modern means. By the time the WHO issued its first draft Catalogue on Studies on the Human Health Effects of the Chernobyl Accident, depending on the criteria one uses for an "epidemiologic" study, there were 4 or more such studies in the RF, 6 or more in Ukraine, and 8 or more in Belarus. The criterion used here is that a study seeks, by comparison, to relate a health outcome to some measure of radiation exposure [12]. Most of the studies are of the "cohort" type, only a few, "case-control." It remains to be seen what results these studies will produce.

5. US-Sponsored Epidemiologic Studies

Probably the most ambitious plans for epidemiologic studies of thyroid disease following the Chernobyl accident are those being sponsored by the US National Cancer Institute with the support of the US Department of Energy and Nuclear Regulatory Commission in collaboration with the Ministries of Health of Belarus and Ukraine. They are planned with explicit scientific objectives, with concrete plans for dosimetry, with sampling plans based on existing files of subjects with thyroid measurements in 1986 and on power calculations related to the scientific objectives, with precise descriptions of clinical and laboratory methods, and with an emphasis on quality assurance. Procedures for data collection, storage, and retrieval, and for storage of specimens, are specified. Equipment and supply needs are detailed together with the pattern of bi-national collaboration, a plan for the management of the project, and guidelines for the preparation and release of reports on the work. Scientific objectives include the estimation of risk coefficients, as functions of dose, for nodules, for cancer, and for hypothyroidism, a search for ancillary risk factors, and the detection of hyperparathyroidism and lymphocytic thyroiditis. On the basis of estimated dose distributions, calculations were made to determine the power of each study not only to detect a dose-response relationship but also to discriminate among various effectiveness ratios for radioiodine in comparison with risk estimates derived for external radiation.

6. The Difficulties

The difficulties are many, diverse, and hard to eliminate, but some progress is being made.

6.1. Infrastructure.

A serious difficulty stems from the academic and research experience of investigators and allied personnel in the countries of the former USSR. Although many aspects of public health, including infectious disease epidemiology, appear to have been essential parts of the medical school curriculum in the USSR, little or no attention seems to have been paid to chronic disease epidemiology. And opportunities for training overseas were minimal to absent prior to the break-up of the USSR. In contrast, chronic disease epidemiology has flourished in Europe and the US for the past 50 years, is widely taught in the academic environment, and increasingly utilized in the investigation of public health and scientific problems. In the US alone there are professional societies and journals concerned largely with the methods of epidemiology, as well as more specialized societies and journals concerned with areas of application. The broad use of epidemiology as a research tool means that not only universities but also government agencies and private companies are engaged in the collection and analysis of information bearing on the distribution of disease in the population and its links to environmental and genetic causes. There has been very little of this in the CIS, and the absence of suitably trained and experienced personnel has slowed efforts to mount effective epidemiologic studies. It is to the credit of WHO, the European Community, private Japanese organizations, and others in the international community that they have organized training programs under which personnel from the CIS have become familiar with various aspects of chronic disease epidemiology. But if a beginning has been made in this way, the problem is far from solved.

6.2. *Supplies and Equipment*

As the WHO found in planning the thyroid phase of the IPHECA project it was necessary to provide not only large items of equipment such as radioimmunoassay analysers and ultrasound scanners, but also kits for the various assays, pipettes, needles, etc., etc. These needs reflected not merely the scale of the projected studies, but also the paucity of up-to-date equipment and the lack of funds for expendable supplies. Similarly, in planning its collaborative studies with Belarus and Ukraine the US National Cancer Institute developed pages of needed items of supply and equipment.

6.3. *Communication*

Communication networks have been slow and inefficient, partly because necessary equipment such as facsimile machines and computers have been in short supply, and telephone systems inadequate for both domestic and international communication. Communication has also been difficult because of habitual attitudes toward the ownership of information and toward collaborative work among different administrative entities. Epidemiologic work on the scale necessary to realize the potential of the opportunity presented by the Chernobyl accident requires teams from different disciplines, collaboration among independent institutes, and ready sharing of information. Interpersonal communication has been hampered by language differences and an insufficient supply of interpreters skilled in medical and scientific concepts and terminology, but also by differences in training and experience. Library resources have needed supplementation in all three countries, and inter-library loans have had to be encouraged. As part of this effort the US National Library of Medicine has established e-mail connections with national medical libraries in the Russian Federation, Belarus and Ukraine.

Cultural differences in program development have been especially difficult for US, Belarussian, and Ukrainian investigators and have greatly impeded the progress of their efforts to obtain approval for, fund, and initiate, projects of interest. In part this is because US investigators are required to formulate very explicit research plans and to have them favorably peer-reviewed as a condition of funding, and because of stringent official US regulations to protect the privacy and safety of human subjects of study. These requirements have stressed negotiators on both sides, Belarussian and Ukrainian investigators feeling restrained by them, and US negotiators probing for facts in an unfamiliar environment.

6.4. *Dosimetry*

All the scientific questions to be addressed on the basis of the post-Chernobyl experience with thyroid disease require adequate dosimetry if they are to be answered. The development of a basis for adequate individual dose estimates seems likely to be a slow and difficult process, despite the large number of direct thyroid measurements made in 1986 shortly after the accident. These measurements were not made in all cases under highly standardized conditions and with the same, uniformly calibrated, equipment. It may be helpful to remember that the present DS86 dosimetry for the A-bomb survivors was developed in 1986 and replaced the T65 dose estimates generated in 1965, and that in 1995 there is dissatisfaction with the neutron components of the DS86, 50 years after the bombings. The two dose reconstruction tasks are quite different, of course, but environmental dose reconstruction is never an easy task. Environmental measurements of radioiodine were few and the plume carrying radioisotopes was subject to the vagaries of the winds. Environmental measurements of radiocesium are much more numerous, but the relation between radiocesium and radioiodine is variable. Moreover, the Marshallese experience warns that all radioiodines may not be equal, and that estimates of I-131 dose alone may not suffice. Also, the ultimate thyroid dose to an individual derives from both inhalation and ingestion, depending on location, calendar time, shielding, and food contamination. This means that the contribution of the various radioiodines to the total dose of an individual is also a variable, and one on which very little information is likely to be forthcoming. If studies are confined to subjects with good direct measurements, as seems necessary, there remains the problem of estimating the temporal variation in the ingestion of contaminated food. Obtaining good dietary information retrospectively must be much more difficult than obtaining the shielding histories for the A-bomb survivors. On the positive side is the fact that all these difficulties are well known to dosimetrists and that some highly competent people are working to ameliorate or solve them.

6.5. The Worsening Economic Situation

In 1988, when the US-USSR agreement was made, it was possible to plan on an equitable sharing of the economic burden of specific research projects. In-country expenses for indigenous personnel, space, communication, etc. was to be covered by the host country. In 1995 this is no longer true: to put a project in the field local assistance must be provided to the host country and the in-country expenses of visiting collaborators must be borne by the collaborator. Local scientists with language skills are tempted to emigrate, and sending personnel abroad for training enhances the temptation. Official salaries are often so depressed by inflation that physicians and scientists have been forced to work at outside jobs in order to maintain their living standard. All these factors work against the development of secure, ongoing relationships necessary for the maintenance of a research organization. Finally, at least one international funding agency has expressed concern over the share of the national budget dedicated to the amelioration of the effects of the Chernobyl accident. Such pressure would seem inevitably to depress research budgets for Chernobyl research.

6.6. Locating Subjects for Study

Screening endeavors need not be limited to fixed cohorts. In fact, the public health interest driving them favors regional case-finding where all subjects of interest may be examined. It is possible, on this basis, to build case-control studies of considerable rigor, but difficulties are experienced at the level of dose. In this approach one finds the 1986 files of individuals with direct thyroid measurements to be of little help. In the recent case-control study of Astakhova et al. [13] only 12 among its 107 cases were in the thyroid measurement file for Belarus. With the cohort approach, which is the preferred design for tight inferences and for mapping the long-term consequences of an exposure, locating subjects for study may pose difficulties. In Belarus, for example, Voronetsky et al. conducted a pilot study [14] of a representative sample of 600 children drawn from the thyroid measurement file for Belarus. They found that the original measurement file lacked sufficient identifying information to make tracking its members an easy task. It would be much more efficient to select subjects by mapping large external files of dispensaries, etc. into the measurement file. This would be at some sacrifice of numbers and also affect the integrity of the sample as a basis for making inferences about the period from 1986 to the date of selection.

7. Progress to Date of Epidemiologic Studies of Thyroid Cancer in the CIS

Perhaps very little of the progress to date can be attributed to epidemiologic studies. Certainly the most important contribution has been that made by the pathologists [15-17] in validating the overwhelming majority of diagnosed cases in Belarussian children. The best epidemiologic report, although not based on a specific epidemiologic study, is that of Abelin et al. [17] who combined the evidence from pathology and incidence. They showed, as had Kazakov et al. earlier [18], that incidence rates by oblast in Belarus correlated well with estimated fallout deposition, and that they were well in excess of expectation based on the thyroid cancer rates in the better national cancer registries in Europe and the US. By the end of 1992 there could be little doubt that the Chernobyl accident had caused much of the rise in thyroid cancer incidence in Belarus. The first dose-specific demonstration of the relationship of thyroid cancer to thyroid dose appeared in 1995 in a letter to Nature by Likhtarev et al. [19] in which they showed a correlation between incidence and estimated average rates of thyroid cancer in children for 7 zones of Ukraine. In their small case-control study of thyroid cancer in children under age 15 in 1986, Astakhova et al. have shown the dose-specific relationship to be true at the level of the individual thyroid dose [13].

Taken together the various lines of investigation have established that: 1) the cases of thyroid cancer in children meet international clinical and pathology standards of diagnosis, 2) the minimal latent period for radiogenic thyroid cancer in children is on the order of 3-4 years, not 5-10 as previously believed, 3) the excess incidence is unprecedented, 4) the excess incidence is related to the Chernobyl accident, and 5) the dose-response relationship is so strong that individual high-dose cases can be called radiogenic with a very high probability, a fact that lays the groundwork for molecular comparisons between radiogenic and presumably non-radiogenic cancers.

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