

## Thyroid effects

**Report by Prof. E.D. Williams, Cambridge University, UK, who served as the Scientific Secretary, Prof. A. Pinchera, University of Pisa, Italy, who served as Chairman, of Topical Session 2: "Thyroid effects", and Prof. D. Becker, Cornell Medical Center, USA, Prof. E.P. Demidchik, State Medical Institute, Belarus, Prof. S. Nagasaki, Nagasaki University School of Medicine, Japan, and Prof. N.D. Tronko, Institute of Endocrinology and Metabolism, Ukraine, all members of the Session's Expert Committee.**

The population in the area around Chernobyl, particularly southern Belarus and northern Ukraine, was exposed to high levels of fallout from the Chernobyl accident including large amounts of radioactive iodine. As the thyroid gland concentrates iodine, it was exposed to higher levels of radiation than other body tissues. The radioactive isotope of iodine, iodine-131, has been extensively and safely used in the treatment of thyrotoxicosis. Thus, the report of increased numbers of thyroid carcinoma in children in areas exposed to fallout from Chernobyl was surprising to some, both because of the previous lack of thyroid carcinoma in patients treated with radioactive iodine, and because of the very short time (four years) between exposure and the start of the increase.

This report considers the size of the increase in thyroid carcinoma after taking into account the evidence that the increase is related to exposure to fallout from Chernobyl, the isotope or isotopes responsible, and the likely future effects.

The Chernobyl accident was the first time such a large population was exposed to high levels of radioactive fallout. The amounts of radioactive material released were huge, and one of the main constituents was iodine-131. Very short-lived isotopes of iodine were also released. Direct data on the uptake of the very short-lived isotopes of iodine are not available; measurements of iodine-131 uptake were made after the time of peak uptake.

The estimated absorbed doses to the thyroid from iodine-131 in different settlements, which are not necessarily representative of the whole district, ranged from 790-2400 mGy for infants, and 190-370 mGy for adults. Exposure to short-lived isotopes of iodine increases this figure by an unknown amount, and the early estimates of thyroid dose may need recalculation. Some studies suggest that the average dose in Gomel oblast for children aged 0-7 was about 420 mGy, while doses reported in the recent Nuclear Energy Agency appraisal show that the average dose of children aged 0-7 assessed in Gomel oblast was about 1 Gy, with over 9% having doses in the range of 10-40 Gy.

In the first four years after the accident, the numbers of childhood thyroid cancers occurring in Belarus were in single figures, while in 1990, 29 cases were diagnosed, rising to 79 in 1993 and 82 in 1994. At the time of medical operation, about half of the cases showed direct invasion of surrounding tissues, while two-thirds showed lymph node metastases. Only four cases have been seen in children born after 1986, although it must be remembered that they were no more than eight years old in 1994.

At the Endocrine Institute in Kiev, Ukraine, eight to 11 cases of childhood thyroid cancer were diagnosed annually during the first four years after the accident. But the figure rose to 26 in 1990 and to 43 in 1993, with 39 in 1994. Of these cases, 60% showed soft tissue invasion at surgery, and lymph node metastases were present in 60% of cases. Only one of the 114 confirmed cases seen at the Institute was in a child born after 1986. In Russia, only one child with thyroid cancer was recorded in Bryansk oblast between 1986-89, while between 1990-94 inclusive 23 cases of thyroid carcinoma were reported

in children under the age of 15 at diagnosis.

A recent survey of the histological diagnosis of the thyroid cancers from Belarus found 98% agreement in 134 cases studied jointly by staff of the Pathology Institute in Belarus and the Department of Histopathology in Cambridge. In the whole series of 298 cases seen in the Institute of Pathology in Belarus between 1990-94, a total of 98% were papillary carcinomas, 1.3% were follicular carcinomas, and 0.3% medullary carcinomas.

The findings in the cases from Ukraine were remarkably similar to those from Belarus. Of the 122 cases of thyroid cancer diagnosed in children under the age of 15 at the Institute of Endocrinology in Kiev between 1990-94 inclusive, 114 cases have been studied jointly in Kiev and Cambridge, and the diagnosis agreed in over 97% of them. Of the cancers with agreed diagnosis, 94% were papillary in type, 2% were medullary, and 4% follicular carcinomas. Material from ten cases of childhood thyroid cancer in children from contaminated areas of Bryansk, Kaluga, or Tula oblasts of Russia have been studied by pathologists from the RAMS in Obninsk and Cambridge. No tumour was present in the material available for study in one case, the remaining nine cases were all papillary carcinomas, including one papillary microcarcinoma. Overall these results confirm diagnoses of thyroid malignancy made in the CIS. They also show that while the same types of childhood thyroid cancer are seen in the exposed areas as are found in an unexpected population, types other than papillary carcinoma form only a very small proportion of the cases in the exposed areas.

The results of molecular biological studies show a close link between the type of oncogene involved and the pathological type of tumour found, so that the increased frequency of thyroid carcinoma in children in areas around Chernobyl is an increase in a particular type of thyroid tumour, papillary carcinoma, associated in many cases with rearrangement in a particular oncogene, *ret*. No increase has been shown in activation of the other types of oncogenes known to be associated with thyroid carcinogenesis which were studied, the three *ras* genes, *TSHr* and *p53*.

In Belarus, the Gomel oblast, which borders Ukraine close to Chernobyl, received the highest exposure to fallout. During 1990-94, a total of 172 cases occurred in children from Gomel, with a current population of 0.37 million children, compared to 143 cases in the rest of Belarus, where 1.96 million children live. The crude rates for childhood thyroid cancer in Gomel during 1990-94 are therefore 92 per million children per year, and for the rest of Belarus 14.6 per million children per year.

Similarly in Ukraine, the northern oblasts bordering Belarus received a much higher exposure than the remainder of Ukraine. A total of 112 cases occurred during 1990-94 in the six contaminated oblasts, with a population of 2 million children, and 65 cases in the rest of the Ukraine with a population of 8.8 million children. The crude rates for the northern oblasts of Ukraine are 10.6 per million children per year, and for the rest of the Ukraine 1.5 per million children per year.

The rates in Belarus and Ukraine before Chernobyl, and the rate in England and Wales in a 30-year study, are all about 0.5 per million children per year. We can therefore conclude that there has been a very large increase in incidence of childhood thyroid carcinoma in the areas around Chernobyl and that this is correlated to the exposure to fallout.

When the cases of childhood thyroid carcinoma occurring in Belarus are divided into cohorts based on the age at exposure to the Chernobyl accident, the ratio of observed to expected number of cases was greatest in the children who were youngest at the time of Chernobyl, and dropped rapidly with increasing age at exposure. This increased sensitivity of very young children to the effects of fallout on the thyroid is consistent with observations of the increased sensitivity of young children to the carcinogenic effect of X-radiation on the thyroid. The reduction in the chance of developing thyroid

tumours with increasing age requires more observations for accurate quantification but there is a considerable difference between newborns and 10 year olds. The observations also require extension into the adolescent age group. The reduction in sensitivity with increasing age is also consistent with the lack of any carcinogenic effect of iodine-131 treatment in adults with thyrotoxicosis, although other factors are also likely to be relevant.

Several thyroid-related effects of radiation other than cancer are known to occur, of which the most obvious is the development of hypothyroidism after exposure to large amounts of either external or internal radiation. A study supported by the Sasakawa Foundation found that both nodularity and hypothyroidism were more frequent in Gomel, the area with the greatest exposure to fallout, while other conditions not related to radiation occurred at a broadly similar frequency in all five areas studied. This suggests that radiation may be linked to a high frequency of nodularity and hypothyroidism in Gomel.

The evidence presented shows clearly that there has been a major increase in histologically confirmed thyroid cancers in children in Belarus and Ukraine since the Chernobyl accident. A smaller increase has probably occurred in the Bryansk Oblast in Russia, but firm population-based evidence on the incidence of confirmed cases of childhood thyroid cancer is needed. The diagnosis of thyroid cancer has been confirmed in well over 90% of over 250 cases in both Belarus and Ukraine in an international co-operative study.

The evidence that the increase in thyroid cancer is related to isotopes of iodide present in fallout is strong but indirect. So far, no firm evidence is available of any major increase in any malignancy other than thyroid cancer in the population exposed to high levels of fallout. Increases in the incidence in a range of tumours have been reported, the scale of the increase is very much less than in the thyroid; the size of the reported increase is in the range which may make it difficult to separate a true exposure-related increase from an effect of better reporting and increased ascertainment.

It is clear that no other tumour has shown an increase in frequency comparable to that seen in the thyroid. This makes it highly likely that exposure to radioactive isotopes of iodine is responsible for the thyroid cancer increase. Radioisotopes of iodine are known to have been present in high levels in the fallout; they are very greatly concentrated in the thyroid gland, so that the radiation exposure in the gland is many times that of other tissues. Absolute proof of the causal relationship between exposure to radioiodine and the development of thyroid cancer is not available, but the circumstantial evidence is very strong, and no other plausible explanation for the increase is available.

It is not possible to predict with certainty whether the relative high risk for the development of thyroid cancer will remain at its present figure; more than five years of observation are needed. It is possible that follicular carcinomas have a longer latent period than papillary carcinomas, and that they may increase in incidence in later years. Evidence from external radiation suggests that the relative risk increases up to 20 years after exposure, then declines. But an increased risk is still present at 40 years after exposure and it would be prudent to make this assumption when considering the likely future rates of occurrence of thyroid carcinomas in the exposed population.

If the future risk is estimated on the basis of present trends in the exposed areas using a relative risk model, then the incidence of those exposed as children in Gomel will be about 200 times that of the United Kingdom. There are many uncertainties, and an exact prediction of the expected numbers of thyroid carcinomas in the future is not possible. However, it would be prudent for advance planning of screening and health care to consider that a large increase is a possible outcome.

Thyroid carcinoma in adults is in most cases a tumour of relatively low malignancy, causing death in

only a minority of cases. It is rather more aggressive in very young children, and a long follow-up period is needed. The number seen in Belarus and Ukraine constitutes a major challenge, both for treatment and for our understanding of the relationship between exposure to fallout from a nuclear accident and the subsequent development of malignancy.

The increased susceptibility of very young children to the subsequent development of thyroid carcinoma needs further study, but it may be possible to target screening to the cohorts most at risk.

---