Abstract. The effects of radiation on man have been largely based on atomic bomb studies, Chernobyl exposure differs in radiation type, dose rate and tissue distribution. This review analyses the way in which Chernobyl studies have altered our understanding of radiation and thyroid carcinoma. Latency for radiation-related thyroid carcinoma is not fixed at 10 years; the time of detection of the first cases depends on the size of the outbreak. Radiiodine is not of low carcinogenicity, it is an effective thyroid carcinogen for young children for explicable reasons. Clinical, morphological and molecular studies after Chernobyl show a correlation with tumour latency, with short latency tumours largely showing RET PTC3 rearrangements, a solid type of papillary carcinoma and an aggressive clinical behaviour. As latency increases, the pattern changes too. Interaction of radiation with the genome results particularly in double-strand DNA breaks the precursor of rearrangements. The relationship between radiation, the type of oncogene mutation and other findings are discussed. Finally, the importance of continuing to study the consequences of an accident of a type we all hope will not occur again are stressed. © 2006 Elsevier B.V. All rights reserved.

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Our understanding of the effects of radiation on man has depended to a large extent on the excellent studies that have been carried out on the population exposed to the effects of the atomic bomb in Japan. The exposure was very largely to whole body radiation for gamma rays and neutrons. About 80,000 survivors with known radiation doses are still being followed, and new consequences of radiation exposure recorded.

In contrast, the exposure after Chernobyl was very largely to beta and gamma radiation from radioactive isotopes, many millions of people have been exposed to the fallout, with a very much smaller number working in or near the reactor exposed to whole body radiation. Not only does the type of radiation exposure differ, but so do the tissue distribution and dose rate. After the atomic bomb tissue distribution was relatively uniform and the dose rate was...
very high; after exposure to fallout from Chernobyl the tissue distribution depended on the isotopes in the fallout and the dose rate was relatively low. The largest human exposure was to $^{131}\text{I}$, so that the thyroid received by far the largest dose, of the order of 500–1000 times the average non-thyroid tissue dose for iodine isotopes. The thyroid dose for those living close to the reactor was in some cases greater than the dose received by any tissue in the survivors of the atomic bomb. It follows that experience of the consequences of exposure to the atomic bombs may not apply to exposure to fallout after Chernobyl, and also that, partly because of the different types of exposure, and partly because of the much larger number of people exposed, much important information has been and will continue to be gained from the studies of the consequences of the Chernobyl accident.

The immediate consequences to the population living around the reactor were the result of fear of the unknown and distrust of government reassurances, together with the direct effect of forced evacuation for well over a hundred thousand people. The immediate consequences for those working in or immediately around the reactor while the accident was taking place and shortly afterwards were acute radiation sickness from whole body exposure in about 150 people, with 28 deaths in the short term, and about 20 more probably radiation related since that time. The first physical health consequence noted in the millions exposed to fallout in the 3 most exposed countries—Belarus, Ukraine and the Russian Federation—was a sudden increase in the numbers of thyroid carcinomas occurring in children, first noticed in 1990, 4 years after the accident. The first reaction from Europe and North America to these reports was sceptical for various reasons. It was generally felt that radiation to the thyroid from $^{131}\text{I}$ was much less carcinogenic to the thyroid than external radiation, indeed it was often assumed that it carried no significant risk for thyroid carcinogenesis in man. It was also assumed that the latent period for the development of thyroid carcinoma after radiation exposure was 10 years. These two reasons for scepticism about the reports were combined with uncertainty about the accuracy of the diagnosis, the knowledge that occult thyroid carcinoma of no clinical significance was a very common tumour, and experience of the extent of increased ascertainment that could follow greater surveillance. The reasons underlying the initial scepticism, and why it was unjustified will be discussed.

The belief that $^{131}\text{I}$ carried little carcinogenic risk was based on human and early animal studies. It had been extensively used in the treatment of thyrotoxicosis, and careful studies had shown no subsequent carcinogenic risk [1]. However, almost all the patients treated were adults, and the Chernobyl-related carcinomas were developing in those exposed as children. In addition, the dose used in treatment was usually high enough to lead to cell death—and dead cells do not give rise to tumours. Studies of the possible risk from the much smaller dose used in diagnostic studies with $^{131}\text{I}$, more often carried out in children although rarely in very young children, were equivocal [2]. Early animal observations had supported the low carcinogenicity of $^{131}\text{I}$, finding it 10 times less likely to lead to thyroid tumours than external radiation. However, these were small studies; a very much larger study concluded that both types of radiation had approximately equal carcinogenicity [3]. Findings after the Chernobyl accident show that by 1998 children under 1 year of age at exposure had developed 10 times as many thyroid tumours as those aged 10 at exposure by 11 years after the accident [4]. When the proportion of these that are likely to be spontaneous tumours is taken into account the ratio will be much greater. The belief that $^{131}\text{I}$ carried little or no carcinogenic risk in humans, still quoted in 1998 [5], was based on studies of exposures of adults with thyroid
disease, and was uncritically assumed to apply to exposures of normal children. The sensitivity of very young children to thyroid carcinogenesis after fallout exposure has important implications for future nuclear accidents.

The presumed latent period of 10 years for radiation induction of thyroid carcinoma was not derived from atomic bomb studies, but from the follow-up of children treated with external radiation to the neck area. This figure, quoted in the 1990 IAEA report on the effects of Chernobyl, was based on studies of several thousand children, for example the Rochester study of about 2500 children exposed to X rays for presumed thymic enlargement, with the subsequent development of 33 thyroid cancers [6]. In contrast, about 2 million children were exposed to fallout in Belarus alone; by 18 years after the accident over 2000 cases of thyroid cancer had occurred [7]. A metaanalysis combining several reports of thyroid carcinoma induced by external radiation of children concluded that although 2 cases had occurred within 5 years of exposure this was not significant, but there was a significant risk 5–9 years after exposure [8]. Analysis of the data in this report showed that 20% of the cancers that had occurred by 20 years after exposure were found before 10 years and 2% before 5 years, in Belarus the figures are approximately 17.5 and 3%, respectively. While the Belarus data are approximate, partly because data are provided per calendar year rather than in relation to the exposure date, the difference in scale could account for the apparent early detection of an increase. Scepticism over the reports of increases in thyroid cancer incidence only 4 years after exposure were based on the assumption that a latent period should be regarded as fixed, an idea that is difficult to sustain on biological principles. The simple explanation is that the larger the size of an outbreak, the earlier it becomes possible to detect the first increase.

Concerns about accuracy of the diagnosis were also unjustified, review of cases in Minsk and Kiev showed a very high degree of agreement, and showed that the early cases were aggressive locally invasive cancers with a high proportion of distant metastasis. This aggressiveness has not been a feature of the majority of later tumours. The problems of ascertainment were not relevant in the early cases which almost all presented clinically, and certainly did not have the characteristics of occult carcinomas. As the exposed population ages the numbers of spontaneous cases is increasing, and with increasing awareness of the problem and more sophisticated screening, greater ascertainment must be occurring.

The present position is that about 4000 thyroid cancers have occurred in those who were under 18 when exposed to fallout in the 3 countries [9]. Over half of these have occurred in Belarus, and the frequency of occurrence has been linked to the level of exposure. As has been pointed out, this makes the thyroid carcinomas that have occurred due to the Chernobyl accident the largest number of tumours of one type due to one cause on one date that has ever occurred [10]. Because the main isotope was $^{131}$I, with a physical half-life of 8.1 days, we know that the first carcinogenic event almost certainly occurred within a few weeks after April 26th 1986, allowing the latent period to be accurately determined. The age at exposure to fallout has been shown to be a critical factor in the risk of developing thyroid carcinoma after Chernobyl, with those under the age of 1 showing a very much greater risk than older children, with a rapid decline to a relatively low risk for young adults [4,11]. The likely reasons for this age-related risk include the intake of radioisotopes of iodine, the uptake of radioiodine, and biological sensitivity factors. Iodine intake is greater in young children because of the greater amount of milk in the child’s diet, and milk is the main route by which iodine isotopes from fallout are ingested. Children also have a higher uptake of radioactive iodine than adults.
Studies from the Russian Federation found that after exposure to fallout children under 1 showed a thyroid uptake of between 7- and 15-fold that in adults [12]. Similar although less marked age-related sensitivity to thyroid carcinomas occurs after exposure to external radiation [8], showing that there are age-related biological sensitivity factors.

Two main reasons for this sensitivity could be either the mitotic rate at the time of radiation exposure, or the number of cell divisions that occur in the progeny of the mutated cell, or both. As most point mutations occur during S phase, the mitotic rate at exposure is likely to be important for oncogenes activated in this way. The situation for rearrangements is more complex, it has been shown that the breakpoints for RET-PTC lie very close together in the nucleus [13], suggesting that the radiation damage occurs in interphase. Radiation is particularly effective at producing double-strand breaks in DNA, the necessary precursor to rearrangements. As the initial rearrangement is almost certainly insufficient to give a clinically significant cancer, further mutations are likely to be needed. In the absence of further radiation these are likely to be point mutations, the number of cell divisions in the clone derived from the mutated cell will then influence the risk of development of clinically significant cancer. In the thyroid the mitotic rate drops with age, to reach very low levels in adult life [14], the number of mitoses in the clone derived from the mutated cell drops even more rapidly with the age at exposure.

In sporadic papillary carcinomas in adults the great majority of cases show either a rearrangement in the RET oncogene, or a point mutation in the BRAF oncogene, with little or no overlap [15]. In the Chernobyl-related thyroid carcinomas, (so far virtually all papillary carcinomas) the early cases showed a very high proportion with RET PTC3 rearrangements [16]. Over time the proportion with RET rearrangements has declined, but RET PTC1 rearrangements are more prominent [17]. BRAF mutations occur at a low frequency in Chernobyl-related thyroid carcinomas, but they are also infrequent in thyroid carcinomas in non-exposed children [18]. It cannot be assumed that they are not radiation related; they could be associated with a longer latent period. There are, however, several reasons why at present it seems less likely that they are due to radiation than RET rearrangements. The main reason is that radiation is generally accepted to be more likely associated with double-strand breaks than point mutations. Also, although the specificity of radiation point mutations is disputed, some in vitro studies have suggested that the type of mutation that activates BRAF, a T→A transversion is one of the least likely of the point mutations to be induced by radiation. Other evidence comes from a study of thyroid carcinoma after external radiation in childhood; even in adult life the tumours are found to show a very low proportion of BRAF mutations [19]. It is also of interest that BRAF is a key gene in malignant melanoma, and unlike other skin tumours malignant melanoma did not increase in frequency after the atomic bomb exposure [20]. One case of BRAF activated by rearrangement has been found in a child with a post-Chernobyl papillary carcinoma [21], suggesting that BRAF can be linked to radiation carcinogenesis, but through rearrangement rather than point mutation.

It is now possible by combining the results of different studies to put together a coherent picture of the development of thyroid carcinoma in those exposed to fallout from the Chernobyl accident. The main source of the radiation to the thyroid was 131I in fallout, this led to DNA double-strand breaks, and probably some point mutations. Double-strand breaks giving RET rearrangement were able after the acquisition of additional mutations to lead to papillary carcinoma of the thyroid. RET PCT3 rearrangement caused more rapidly growing
tumours with shorter latency, less mature more solid morphology and more aggressive clinical behaviour. RET PCT1 rearrangement caused less rapidly growing tumours with longer latency, more mature classic papillary morphology and less aggressive clinical behaviour [17,22]. BRAF mutations have been found in only a minority of the post-Chernobyl papillary carcinomas [18], and while these could have been radiation induced, it must be remembered that with increasing time since the accident the proportion of spontaneous cases will be increasing among the exposed population. This is particularly the case in those who were older at the time of the accident. In a significant proportion of cases neither rearrangements nor BRAF mutations have been found, showing that other as yet unknown mutations are involved. Interestingly, despite all the differences between the two events, estimates of the excess relative risk per Gy for thyroid carcinoma after Chernobyl are not very different from those derived from the atomic bomb and other external radiation studies [23].

The future for thyroid malignancies is difficult to predict. If the time pattern follows that for thyroid carcinomas after external irradiation the expected total number in the most exposed areas, that is Belarus, northern Ukraine and the 4 Russian oblasts, can be calculated to be about 12,000. If the reduction in aggressiveness with increasing latency continues, the overall death rate for the post-radiation thyroid carcinomas is likely to be very low, particularly as papillary carcinomas with RET rearrangements seem less likely to progress to undifferentiated carcinoma than papillary carcinomas with BRAF mutations. However, it remains possible that papillary carcinoma with BRAF or other mutations may occur in the future, and also that follicular, medullary or undifferentiated carcinomas may occur. Follicular carcinomas are known to be associated with radiation, although to a lesser extent than papillary carcinomas; and probably with a longer latent period.

A number of challenges remain for the future study of the consequences of the Chernobyl accident. It is important to continue to document the thyroid cancers, to study the morphological types, the molecular pathology findings, and the clinical behaviour, so that these can be correlated with latency. It is important also to estimate how much of the increase is due to increased surveillance, so that the numbers of carcinomas occurring in those at risk can be divided into the cases due to radiation, the normal incidence, and the proportion of each that are due to increased surveillance. Thyroid carcinomas are associated with a particular problem in relation to surveillance, the increased sensitivity of ultrasound investigation allowing the detection of the frequently occurring papillary microcarcinomas, often a few millimetres across. There seems little doubt that the great majority of cases that occurred in those who were children both at exposure and at the time of operation were due to radiation, but it also seems likely that for those who were 17 or 18 at the time of the accident a high, and possibly very high, proportion of the cases will be due to non-Chernobyl causes, together with increased surveillance.

Finally, we should be careful to ensure that the dramatic increase in thyroid cancer does not distract attention from the need to study all other possible effects of radiation from fallout. Studies comparable with the comprehensive studies carried out after the atomic bombs are needed. Twenty years after atomic bomb exposure, significant increases in cancer were seen only in leukaemia and thyroid carcinoma. Later, significant increases in a wide range of malignant and non-malignant conditions were found. While it seems unlikely that there will be any comparable findings after Chernobyl, if careful studies are not undertaken, inappropriate claims, exaggerating or downplaying the consequences will continue to be made.
References