cer: optimisation of therapeutic dose and route. *Cancer Res* 1987, **47**, 1957–1961.
12. Goss PE, Powles TJ, Dowsett M, *et al.* Treatment of advanced postmenopausal breast cancer with an aromatase inhibitor, 4 hydroxyandrostenedione: Phase II report. *Cancer Res* 1986, **46**, 4823–4826.
13. Stein RC, Dowsett M, Hedley A, Davenport J, Coombes RC. Treatment of advanced breast cancer in postmenopausal women with 4-hydroxyandrostenedione. *Cancer Chemother Pharmacol* 1990, **26**, 75–78.
14. Lonning PE, Johannessen DC, Thorsen T. Alterations in the production rate and metabolism of oestrone and oestrone sulphate in breast cancer patients. *Br J Cancer* 1989, **60**, 107–111.
15. Jacobs S, Lonning PE, Haynes B, *et al.* Measurement of *in vivo* aromatisation by a urine technique involving HPLC for separation of oestrogen metabolites. *J Enzyme Inhibition* 1990, **4**, 315–325.
16. Lonning PE, Skulstaf R, Sunde A, *et al.* Separation of urinary metabolites of radiolabelled oestrogens in man by HPLC. *J Steroid Biochem* 1989, **32**, 91.
17. Dowsett M, Cunningham DC, Stein RC, *et al.* Dose-related endocrine effects and pharmacokinetics of oral and intramuscular 4-hydroxyandrostenedione in postmenopausal breast cancer patients. *Cancer Res* 1989, **49**, 1306–1311.
18. Lonning PE, Jacobs S, Jones A, Haynes B, Powles TJ, Dowsett M. The influences of CGS16949A on peripheral aromatisation in breast cancer patients. *Br J Cancer* 1991, **63**, 789–795.
19. Reed MJ, Lai LC, Owen AM, *et al.* Effect of treatment with 4-hydroxyandrostenedione on the peripheral conversion of androstenedione to oestrone and *in vitro* tumour aromatase activity in postmenopausal women with breast cancer. *Cancer Res* 1990, **50**, 193–196.
20. Dowsett M, Santner SJ, Santen RJ, Jeffcoate SL, Smith IE. Effective inhibits on by low dose aminoglutethemide of peripheral aromatisation in post menopausal breast cancer patients. *Br J Cancer* 1985, **52**, 31–34.

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Thyroid Function 10–18 Years after Mantle Field Irradiation for Hodgkin's Disease

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Thyroid function was measured in 81 patients who had been curatively irradiated on a mantle field for Hodgkin's disease 10–18 years ago. 47 patients (58%) had elevated levels of thyroid stimulating hormone, indicating hypofunction of the thyroid gland, compared with 4.6% of controls (hospital visitors) matched for age and sex. The mean free thyroxine index (FTI) was significantly lower in patients than in controls, but all FTI values were still normal. Age at the time of irradiation, sex, time since irradiation and administration of chemotherapy were not significant factors in the development of thyroid dysfunction. A life-long awareness of the possibility of insidiously developing myxedema in these patients is strongly advocated.
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INTRODUCTION

FOR A long time, radiation therapy has been an important treatment modality for Hodgkin's disease. One of the possible late side-effects is thyroid dysfunction. The most frequently reported late complication is hypothyroidism [1–10]. Less often, benign thyroid nodularity and thyroid carcinoma have been described [2–4, 6, 7, 11, 12].

We report on thyroid function as part of an elaborate evaluation of late sequelae from curative radiotherapy for Hodgkin's disease 10–18 years ago. Also, the influence of age at the time of treatment, sex, chemotherapy and time since irradiation were studied.

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PATIENTS AND METHODS

Between January 1990 and October 1990, thyroid function was evaluated in 190 individuals. Of these 190 individuals, 81 had received mantle field irradiation for Hodgkin's disease 10 to 18 years previously, in the Netherlands Cancer Institute. During the diagnostic work-up, all patients underwent lymphangiography. All were still free of disease at the time of the study. The limit of 18 years was chosen since, from 1972 onwards, all patients were irradiated with a linear accelerator.

The study group consisted of 42 males, aged 25–69 years, [mean (SD) 43.5 (10.0)], and 39 females, aged 29 to 72 years [mean (SD) 42.8 (11.0)]. Mean follow-up time was 14 (2.5) years. All patients had received mantle field irradiation, which included the entire thyroid gland. They received 20–40 Gy (86.2% received 40 Gy), over a 3–6 week period. 19 patients were also treated with chemotherapy after irradiation. Vinblastin was given weekly for 2 years to 5 patients; mustine, vincristine, prednisone, procarbazine (MOPP) was given to 14 patients every 4 weeks for four to six cycles.

As controls, 116 hospital visitors were carefully matched for

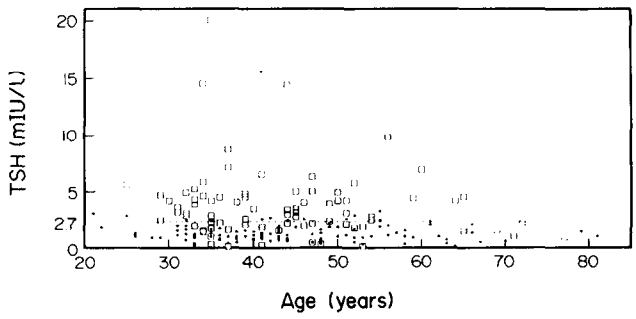

Fig. 1. Serum TSH concentrations (y-axis) vs. age (abscissa) in patients (□) and hospital-visitor controls (●). The upper normal limit of TSH (2.7 mIU/l) is indicated by a dotted horizontal line.

age (± 2 years) and sex to former patients with Hodgkin's disease. 109 hospital visitors were evaluable: 49 males in the age range 22–81 years [mean (SD) 46.6 (13.0)] and 60 females in the age range 21–67 years [mean (SD) 42.8 (10.6)].

At the time of the study, 6 patients had already been given thyroxine (T_4) treatment because of hypothyroidism; one control was on carbimazole treatment because of hyperthyroidism.

Thyroid stimulating hormone (TSH) was determined by the IMx^{tm} Ultrasensitive hTSH assay, which is based on the microparticle capture enzyme immunoassay (MEIA) technology (Abbot). T_4 andT_3 uptake were measured by IMx^{tm} immunoassays using fluorescence polarization. Multiplication of the individual T_4 by T_3 uptake/100 yielded the free thyroxine index (FTI).

TSH determinations were performed on all participants. TSH greater than 2.7 mIU/l was considered as an indication of primary hypothyroidism, as 2.7 was equal to the anti-log of the mean + 2 SD in a normal reference population (n = 94). If TSH was greater than 2.7 mIU/l, the free thyroxine index (FTI) was determined. FTI was further measured in controls matched for age and sex with patients in whom elevated TSH levels were found.

Statistical analyses were performed using SPSS PC+ V 4.0. For categorical data, contingency tables were constructed and the significance of differences assessed by means of the chi-square test. Comparisons between groups were performed by Student's t-tests on mean values. For analyses of TSH, log-transformed TSH was used, since the distribution of TSH was not normal. A paired sample t-test was performed for comparison of FTI values.

Table 2. Thyroid function parameters

	Patients	Hospital visitors	Normal range
Log TSH (mU/l)	0.44 (0.40)	0.05 (0.28)	−0.15 (0.43)
FTI	23.9 (3.06)	28.5 (5.13)	16.8 (56.0)

Values are expressed as mean (SD).

RESULTS

Figure 1 shows serum TSH levels vs. age in patients and controls. 47 of 81 patients (58%) had elevated TSH serum levels compared with only 5 of 109 controls (4.6%). 3 out of the 6 patients who were on thyroxine treatment, had elevated TSH levels, indicating inadequate hormonal replacement (Table 1). The mean log TSH level was significantly higher in the patient group than in the control group ($P < 0.001$). Correspondingly, the mean FTI in the patient group was significantly lower than in the control group ($P < 0.001$). Despite this, all FTI values were within normal range (Table 2).

Elevated TSH values were measured in 23 males (54.8%) and in 24 females (61.5%) ($P = 0.54$). Also, mean TSH values did not significantly differ between males and females. The number of patients who received less than 40 Gy was too small to study a dose–effect relationship.

Elevated TSH levels were found in 52.6% of the 19 patients who had received additional chemotherapy, compared with 62.5% of the patients who did not receive chemotherapy. Significant differences between mean values did not exist.

Of the 15 patients who were younger than 20 years of age at the time of irradiation, 80% had elevated TSH levels. Of the older patients, 53% showed elevated TSH levels ($P = 0.06$). However, neither mean values nor mean peak values (≥ 2.7 mIU/l) differed significantly. The time interval since treatment (10–18 years) had no apparent influence on the incidence of elevated TSH levels.

DISCUSSION

The incidence of thyroid dysfunction occurring after irradiation for Hodgkin's disease has varied considerably in different reports [2, 3, 7–10]. Apart from differences in radiation dose, schedule and field, the time interval since irradiation and the age at the time of treatment are factors that could explain part of this variation. In their review, Bookman and Longo reported an incidence of elevated TSH after radiation exposure

Table 1. Clinical characteristics and thyroid functions of patients who had been irradiated for Hodgkin's disease 10–18 years ago and hospital visitor controls, matched for age and sex

	n	Sex: Male	Sex: Female	Number of individuals with serum values of TSH>2.7 mU/l	Number of individuals with serum values of FTI<16.8	Number of individuals on thyroxine replacement therapy	Previous chemo-therapy after irradiation
P	81	42	39	47	0	6	19
HV	109	49	60	5	0	0	—

P = patients, HV = hospital visitors.

ranging from 31 to 78% and an incidence of clinical hypothyroidism from 6 to 25% [1]. In our study, after a mean interval since treatment of approximately 14 years, 6 patients were on thyroid replacement therapy because of clinically manifest primary hypothyroidism (7.4%), compared with none of the controls matched for age and sex. Of the other 75 patients, 44 had elevated TSH levels (58.7%) with free thyroxine index values within normal limits. Apparently, increased TSH secretion could still compensate for thyroid damage in most cases.

The relatively high rate of thyroid dysfunction in our series may be related to the fact that no attempt was made to block the thyroid during irradiation. Therefore, the whole thyroid was exposed, although a midline block to shield the cervical spinal cord was generally applied. Previous chemotherapy administration did not affect the incidence or the degree of serum TSH elevation. These findings confirm other reports [1, 2, 5, 6, 9, 13].

Since lymphangiography was performed uniformly during the diagnostic work-up before treatment, the possibility that radio-diagnostic iodine may have contributed to thyroid dysfunction [2, 9] should be considered for all cases.

Primary hypothyroidism is some seven times more common in women than in men. The fact that we observed no difference between the sexes suggests that the high incidence of hypothyroidism after irradiation is not related to the autoimmune mechanism, which is generally held responsible for ordinary myxedema mainly occurring in elderly women [14].

Literature data suggest that the thyroid in children may be more sensitive to radiation compared with older age groups [10, 15]. However, other reports on large studies of the influence of irradiation did not show a significant influence of age [7, 9, 16]. Our study included 15 patients younger than 20 years at the time of treatment, the youngest being 14 years (mean, 17.4 years). Because of small numbers, we could not make a valid interpretation of the influence of age in our material.

Observations by others [5, 16] have suggested that the time interval since irradiation is not a significant factor. Schimpff *et al.* [16] reported a maximal incidence of thyroid dysfunction reached by 6 years after irradiation. Tarbell *et al.* [10], however, reported on her experience with 590 patients who were followed for 21 years, that time of laboratory diagnosis ranged from 10 months to 14 years after radiotherapy. We found no clear relationship between the duration of follow-up and the incidence of elevated TSH, suggesting that the maximum of thyroid damage is reached prior to 10 years after irradiation. The small numbers of patients in each year of follow-up do not exclude the possibility of a gradual further increase with time.

Low-dose irradiation of the thyroid, especially during infancy and childhood, is known to be associated with a significant increase of the risk of thyroid carcinoma later in life. It is speculated that doses in excess of 20 Gy are large enough to interfere with the ability of follicular thyroidal cells to further divide [6]. Because of the relatively high dose of irradiation given to our patients, a low incidence of thyroid carcinoma would be expected [2, 4, 6, 7, 12].

In a separate study on second primary cancers in patients treated for Hodgkin's disease between 1966 and 1986 in our institute, no thyroid carcinoma has been encountered yet (F. van Leeuwen, personal communication). In a very recent paper from Stanford on 1677 patients with Hodgkin's disease (average follow-up of 9.9 years after irradiation of the thyroid), not only the risk of primary hypothyroidism but also that of Graves' disease, benign and malignant thyroid nodularity was significantly elevated [17].

We conclude that our late follow-up data are in good agreement with earlier reports, indicating a very frequent occurrence of primary hypothyroidism in both male and female patients who previously received mantle field irradiation for Hodgkin's disease. Although most patients still have subclinical hypothyroidism after 10 to 18 years, patients and physicians should remain alert as to the insidious development of myxedema in later years. Since the clinical picture of myxedema in younger individuals may be very misleading, we advocate a yearly check of serum TSH, with further measurement of the free thyroxine level in cases where TSH is elevated. Life-long thyroxine replacement therapy is indicated if free thyroxine values are abnormally low or when a goitre develops. Continued follow-up of all patients seems desirable, at least once a year, to detect thyroid abnormalities in time and to monitor the adequacy of replacement therapy, if needed.

1. Bookman MA, Longo DL. Concomitant illness in patients treated for Hodgkin's disease. *Cancer Treat Rev* 1986, **13**, 77–111.
2. Constine LS, Donaldson SS, McDougall IR, Cox RS, Link MP, Kaplan HS. Thyroid dysfunction after radiotherapy in children with Hodgkin's disease. *Cancer* 1984, **53**, 878–883.
3. Kaplan MM, Garnick MB, Gelber R, *et al.* Risk factors for thyroid abnormalities after neck irradiation for childhood cancer. *Am J Med* 1983, **74**, 272–280.
4. Kinsella TJ, Fraass BA, Glatstein E. Late effects of radiation therapy in the treatment of Hodgkin's disease. *Cancer Treat Rep* 1982, **66**, 991–1001.
5. Morgan GW, Freeman AP, McLean RG, Jarvie BH, Giles RW. Late cardiac, thyroid, and pulmonary sequelae of mantle radiotherapy for Hodgkin's disease. *Int J Radiat Oncol Biol Phys* 1985, **11**, 1925–1931.
6. Moroff SV, Fuks Z. Thyroid cancer following radiotherapy for Hodgkin's disease: a case report and review of the literature. *Med Ped Oncol* 1986, **14**, 216–220.
7. Nelson DF, Reddy KV, O'Mara RE, Rubin P. Thyroid abnormalities following neck irradiation for Hodgkin's disease. *Cancer* 1978, **42**, 2553–2562.
8. Pasqualini T, Iorcansky S, Gruneiro L, *et al.* Thyroid dysfunction in Hodgkin's disease. *Cancer* 1989, **63**, 335–339.
9. Smith RE, Adler RA, Clark P, Vrinck-Johnsen R, Tulloh ME, Colton T. Thyroid function after mantle irradiation in Hodgkin's disease. *JAMA* 1981, **245**, 46–49.
10. Tarbell NJ, Thompson L, Mauch P. Thoracic irradiation in Hodgkin's disease: disease control and long-term complications. *Int J Radiat Oncol Biol Phys* 1990, **18**, 275–281.
11. Carr RF, Livolsi VA. Morphologic changes in the thyroid after irradiation for Hodgkin's and non-Hodgkin's lymphoma. *Cancer* 1989, **64**, 825–829.
12. DeGroot L. Diagnostic approach and management of patients exposed to irradiation to the thyroid. *J Clin Endocrinol Metab* 1989, **69**, 925–928.
13. Rosenberg SA, Kaplan HS. The evolution and summary results of the Stanford randomized clinical trials of the management of Hodgkin's disease: 1962–1984. *Int J Radiat Oncol Biol Phys* 1985, **11**, 5–22.
14. Bruning P, Bonfrèr J, De Jong-Bakker M, Nooyen W, Burgers M. Primary hypothyroidism in breast cancer patients with irradiated supraclavicular lymph nodes. *Br J Cancer* 1985, **51**, 659–663.
15. Green DM, Brecher ML, Yakar D, *et al.* Thyroid function in pediatric patients after neck irradiation for Hodgkin disease. *Med Ped Oncol* 1980, **8**, 127–136.
16. Schimpff SC, Diggs CH, Wiswell JG, Salvatore PC, Wiernik PH. Radiation-related thyroid dysfunction: implications for the treatment of Hodgkin's disease. *Ann Intern Med* 1980, **92**, 91–98.
17. Hancock SL, Cox RS, McDougall IR. Thyroid diseases after treatment of Hodgkin's disease. *N Engl J Med* 1991, **325**, 599–605.