LATE HEALTH EFFECTS OF RADIATION FOR EUSTACHIAN TUBE DYSFYNCTION

LATE HEALTH EFFECTS OF RADIATION FOR EUSTACHIAN TUBE DYSFUNCTION

a non-concurrent prospective study

Lange termijneffecten op de gezondheid van bestraling voor dysfunctie van de buis van Eustachius

een historisch cohortonderzoek

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LIST OF ABBREVIATIONS

cGy centigray, one hundredth of a gray, adopted in 1977 in the International Standard of Units as the unit of absorbed radiation dose. 1 cGy = 1 rad.

CI confidence interval, an estimated range of values with a given high probability of covering the true population value.

dB decibel, a unit to express the ratio between two acoustic powers, equal to one tenth the common logarithm of the ratio of the powers. One decibel is approximately equal to the smallest difference in acoustic power that the human ear can detect.

Hz hertz, a unit of frequency equal to one cycle per second.

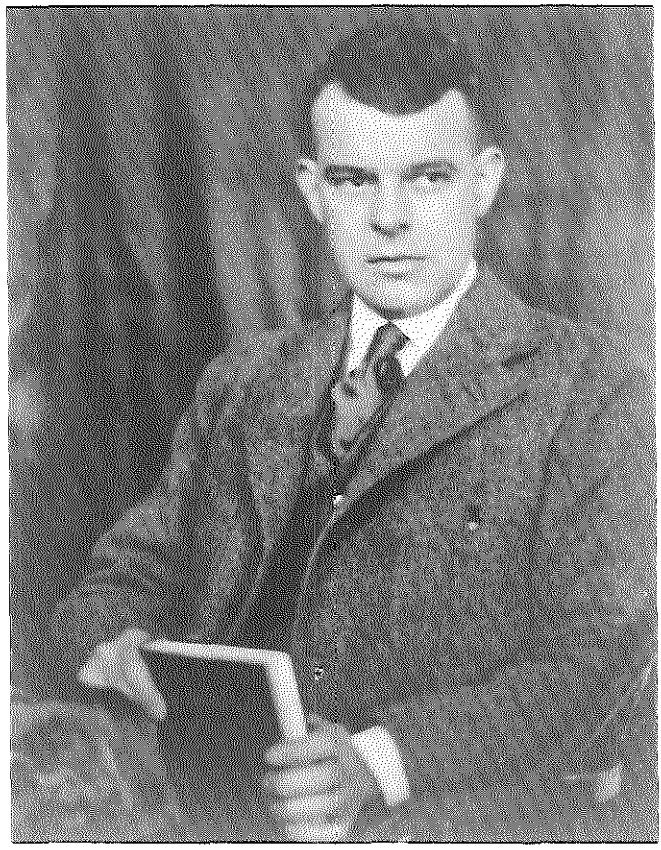
kv kilovolt, a unit of electrical pressure or electromotive force of 1000 volts.

LET linear energy transfer, the energy dissipation of ionizing radiation over a given linear distance. Highly penetrating radiations, such as röntgen and gamma rays cause low ion concentration and thus have a relatively low LET, neutrons and alpha particles have a relatively high LET.

rad radiation absorbed dose, a unit of measurement of the absorbed dose of ionizing radiation; it corresponds with an energy transfer of 100 ergs per gram of any absorbing material (including tissue). The biological effect of 1 rad varies with the kind of radiation the tissue is exposed to. 1 rad = 1 cGy.

rem rontgen-equivalent-man, the quantity of any ionizing radiation which has the same biological effect as 1 rad of X-rays; 1 rem = 1 rad × RBE (relative biological effect).

RR relative risk, the ratio between the incidence rate of disease in the exposed group and the incidence rate of disease in the non-exposed group.



Samuel James Crowe (1883-1955)

CHAPTER 1
HISTORICAL OVERVIEW AND THE GOAL OF THE STUDY

In the past nasopharyngeal irradiation was frequently used to treat children with diseases of the ear resulting from the malfunctioning of the eustachian tube. This form of treatment has all but been abandoned nowadays. What dangers threaten people who have been irradiated in this way? Are they more likely to contract tumours? Or is it so that they are more likely to run the risk of being subjected to unnecessary diagnostic procedures for the sake of identifying non-existent tumours?

At the present time there are noticeable differences in the way in which doctors approach patients with a history of radium irradiation. Some subject the patients with such an anamnesis and current complaints in the head and neck area to careful endoscopic examination based on the assumption that the problems are due to some form of tumour in this area. Others consider such a relationship to be impossible and regret that the - in their opinion - beneficial radium therapy has passed into disuse.

Shortly after the discovery of the diagnostic and therapeutic advantages of using ionising radiation in medical practice, the adverse effects also came to light. In 1896, one year after the appearance of the first X-ray films, F. Batelli, an Italian, reported the first radiation damage to human tissue and eyesight (1). Six years later Frieben described the existence of a malignant skin tumour in a worker exposed to radiation (2). In the years which followed many researchers and doctors received burns or contracted tumours and more than one hundred people died, probably as a result of exposure to irradiation.

The fact that radium - an element discovered by the Curies, among other people - possessed healing powers for tumours and infections, led to the foundation of the Radium Institute in Paris in 1906, where patients could be treated.

In the 1920s it started to become apparent that the same radium could induce tumours in people who had worked with paint containing radium (luminous paint) and in patients who had taken doses of radium for arthritis and other diseases (3). Although the damaging effects of ionising radiation were not unknown - as will be clear from the above - not only malignant diseases but also innumerable benign, often trivial, diseases were examined or treated with irradiation in the first half of this century.

The exact extent of the risk of all earlier and presently applied radiation treatments is still unknown. Some induced solid tumours arise many decades after the irradiation treatment. As the observation time increases, we gain more knowledge of the risks involved in many types of radiation therapy.

As far as the indication for radiation treatment for malignant tumours is concerned, the risks nearly always appear to be acceptable: for a life-threatening disease there is often no alternative. However, knowledge of tumour induction through the irradiation of malignant diseases has led to subtle changes in the indication criteria. In the case of a malignant tumour in a young patient with a long life expectancy,

alternative forms of treatment, such as surgery or chemotherapy, will be considered first.
Proof of harmful side effects from the irradiation of benign diseases has nearly always resulted in the abandonment of the treatment. Either the complaint was not treated any more henceforth, or there was an alternative. Differences in opinion can arise concerning the irradiation of benign diseases where little or nothing is known about the risks involved.
Nasopharyngeal irradiation treatment of the eustachian tube to improve its function was introduced by Samuel James Crowe in the U.S. in 1926. The treatment consisted of the application of two cylinders, containing 50 mg of radium sulphate, near the nasopharyngeal orifice in three sessions of 8.5 minutes. Favourable results were described in patients with barotrauma (4) and serous otitis media (5).
In the Netherlands this treatment was carried out on a large scale in the 1950s and 60s. But owing to the danger of tumour induction and the introduction of tympanic tubes the therapy became obsolete.
There are two epidemiological studies available on the long-term effects. Hazen et al. (1966) (6) published the results of a study on a group of 417 children who had been treated using 25 mg of radium (300-600 mgmin), compared with a control group of 2,746 non-exposed siblings. After a follow-up period of 14.6 years, two malignant and five benign tumours were diagnosed in the irradiated group, which did not differ from the findings in the control group.
Sandler et al. (1982) (7) described the results of a study on 904 irradiated children compared with 2,021 children treated in a different way after a follow-up period of 25 years. She reported an increased incidence of benign as well as malignant head and neck tumours in the irradiated group. There was a strikingly high number of brain tumours in the irradiated group. Another interesting finding was that there were fewer breast tumours in the irradiated women, which supports the results of Hazen et al. (1966) (6).
The present study is a non-concurrent prospective cohort study on the risks of the Crowe therapy in 2,542 subjects who underwent this treatment compared to 2,380 - similar - non-irradiated control subjects. The study population consisted of patients from five Dutch ENT clinics. The follow-up period was 25 years. This study aims to answer the following questions:

1. Does exposure to the Crowe therapy induce tumours? In this case attention is particularly focussed on the possibility of an increase in mortality and/or incidence of tumours in the head and neck region, namely nasopharyngeal and brain tumours.
2. Does the Crowe therapy have any influence on hormone dependant processes, such as growth, fertility and hormone dependant diseases, owing to the irradiation of the pituitary gland?

Additional aims of the study are:

3. To gather data in order to better determine the dose-effect relationship in the exposure range 0-50 cGy, an area in which little is known on man.
4. To study the follow-up procedures involved with non-concurrent prospective cohort studies on clinical populations in the Netherlands.

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CHAPTER 2
IRRADIATION OF THE NASOPHARYNX TO IMPROVE THE FUNCTION OF THE EUSTACHIAN TUBE

2.1 THE EUSTACHIAN TUBE

2.1.1 Anatomy

The eustachian tube connects the nasopharynx with the tympanum. In the adult the opening in the pharyngeal side of the lateral wall is localized as follows: by approximation 1 to 1.5 cm (a) under the pharyngeal roof, (b) in front of the posterior wall of the pharynx, (c) above the level of the palate and (d) behind the inferior nasal concha and the internasal septum (see Figure 2.1). The opening is bounded above and behind by the torus tubarius, an elevation produced by the cartilage of the tube. Folds of mucous membrane run from the torus tubarius to the palate - the plica salpingo-palatina - and to the lateral wall of the pharynx - the plica salpingo-pharyngea.
There is a deep recess behind the torus tubarius called the fossa of Rosenmüller. It extends posteriorly and laterally between the m. longus capitis (medially) and the m. levator veli palatini (laterally) (1). The lymphatic tissue found in the fossa of Rosenmüller has the collective name tube tonsil (2-4).
The eustachian tube in the adult runs from the orifice in a posterior, lateral and cranial direction and is three to four centimetres long. It consists for two thirds of a cartilaginous portion - the antero-medial part - and for one third of an osseous portion - the postero-lateral part. The two parts meet at a slight angle in the narrowest portion - the isthmus.
The cartilaginous portion of the eustachian tube is a cleft of the pharynx. It lies against the base of the skull in a groove between the ala major of the sphenoid bone and the pars petrosa of the temporal bone. The cartilage is of the elastic type and in transverse section it has the appearance of an upside down J. This part of the canal is completed below by connective tissue. The mucous membrane in this portion of the tube consists mainly of cylindrical ciliated epithelium. On the lateral side the tube is bounded by the m. tensor veli palatini, the n. mandibularis and the a. meningea media and on the medial side by the m. levator veli palatini and the pharyngeal recess.
The osseous portion of the eustachian tube is an anterior extension of the tympanum - the protympanum. It forms a canal through the temporal bone and can be regarded as part of the pneumatization of the temporal bone. At the base of the skull it is localized between the temporal bone and the down-sloping edge of the tegmen tympani. This part of the tube is lined by a mucoperiosteum, which normally contains squamous cell of cuboidal epithelium with fields of ciliated epithelium. On the cranial side it is bordered by the canal of the m. tensor tympani, anteriolaterally by the tympanic portion of the temporal bone and on the postero-medial side by the canal of the a. carotis (2).

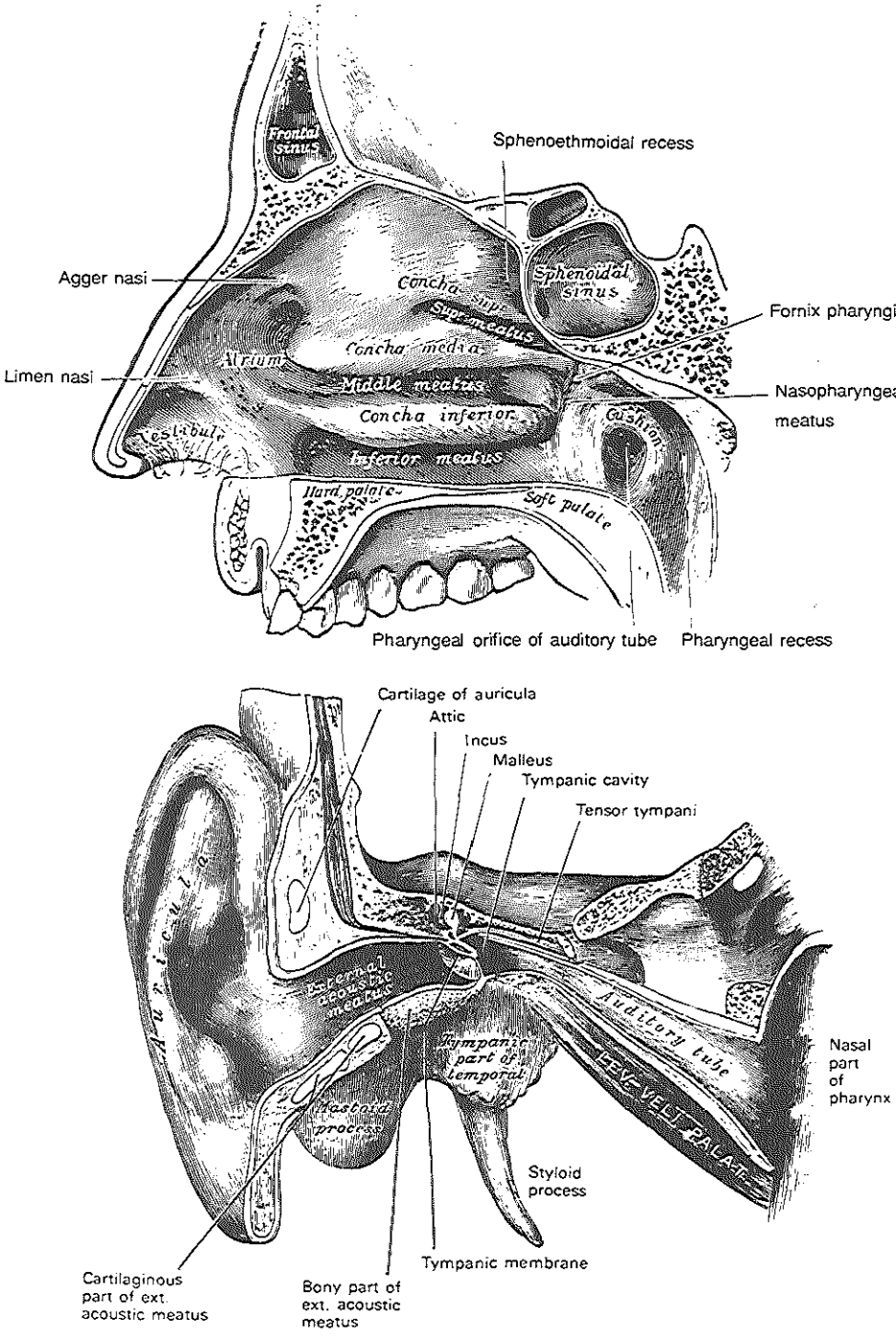

Figure 2.1 The eustachian or auditory tube in its relation to the lateral nasal wall (above) and to the middle ear (below). Gray's Anatomy.

The anatomy of the eustachian tube in newborns and young children differs considerably in some aspects from that of the adult. The tube is relatively short and wider and runs almost horizontally. The ostium pharyngeum does not have a torus tubarius and is situated further forward and more caudally than in the adult. The fossa of Rosenmüller does not develop until the second half of the infant's first year (5).

2.1.2 Lymphoid tissue in the eustachian tube

In 1875 Gerlach described the existence of lymphoid tissue in the eustachian tube and since that time 'Gerlach's tonsil' is a much discussed subject in the literature. However, it concerns a one-off observation in a child of six months, who died of otitis media duplex purulenta (6).
In her histological examination of 500 petrous bones from people of various ages, Wolff found only one with a circumscript amount of lymphoid tissue between the isthmus and the mouth of the tube, also in a child of six months old (7).
Fowler conducted a histological examination of the petrous bones of American airmen who died in England in the 1940s. In one third of the 95 specimens he found macroscopic lymphoid tissue on and in the torus tubarius. Microscopic examination revealed signs of mild salpingitis in 11 of the 16 cases. He attributed this to the flying activities or to the English climate (!). He found round cell infiltration, oedema, hyalinization of the submucosa, hyperplasia of the surface epithelium and hypersecretion of the mucous glands. He observed in some cases that the round cell infiltration took the form of a germinal centre and sometimes that of masses of lymphoid tissue with multiple germinal centres. He found abnormalities which resembled the pathological changes observed in the bronchi and sinuses of people with chronic infections (8).
Aschan, in the description of his histological examination of the eustachian tube under normal and inflammatory circumstances, observed that Fowler's patient material was exceptional: airmen exposed to barotrauma. He suggested that Fowler probably described the pathological picture of aerotitis media.
In his own examination Aschan found a striking resemblance between the histological findings of the mucosa of the middle ear and that of the eustachian tube. He established that, after birth, a moderate number of migratory cells from the reticulo-endothelial system appear in the mucous membrane of the eustachian tube in the same way as they appear at other places in the upper respiratory tract. If more cells are present it is his opinion that this is the result of otitis media. Under normal circumstances lymphoid tissue should not be found in the eustachian tube (9).
Finally, Zechner recently carried out a histological examination on the mucous membrane of the eustachian tubes in patients suffering from an obstruction. He obtained his material via biopsies during the surgical treatment of otitis media serosa. He discovered aggregations of immuno-competent cells which he called 'tube tonsil' (10).
Reviewing the literature, we can conclude that under normal circumstances only cellular components of the reticulo-endothelial system exist in the mucous membrane of the eustachian tube. Under pathological conditions an accumulation of lymphoid tissue may arise due to cell aggregation. It is advisable to make a clear

distinction between lymphoid tissue which is normally present - belonging to Waldeyer's ring - and that which is acquired - i.e. as an expression of inflammation. The term 'tube tonsil' should be reserved for the lymphoid tissue found in the fossa of Rosenmüller.

2.1.3 The physiology and dysfunction of the eustachian tube

The eustachian tube stands in close relation to the middle ear. In an eight to nine week old embryo the first visceral arch develops on either side in a lateral direction. The distal portion of the entodermal sack becomes broader and forms the primitive middle ear cavity. The proximal portion remains narrow and forms the eustachian tube (11).
Besides these fundamental anatomical relationships, there is also a physiological relationship which is maintained throughout life: a normally functioning middle ear cannot exist without a normally functioning eustachian tube.
Four functions of the eustachian tube can be distinguished:
- ventilation of the middle ear
- drainage of the middle ear
- protection against invading bacteria
- protection against piercing noises and against differences in pressure due to breathing.

The first two functions require the opening and the latter two the closing of the eustachian tube. In order to fulfil these functions the tube remains closed and only opens intermittently.
Three factors keep the tube closed:
- the elasticity of the cartilage,
- the surface tension of the mucous in the tube and
- the pressure of the peri-tubal tissue.

These processes work continuously, whereby the tube is kept constantly closed, except for when it is opened via special mechanisms. There is an active and a passive opening mechanism.
The active opening mechanism consists of the synergetic contraction of - esentially - three muscles: the m. tensor veli palatini, the m. levator veli palatini and the m. salpingo-pharyngeus. These muscles contract unconsciously during yawning or swallowing. This mechanism is disturbed in patients with a cleft palate.
Passive opening of the eustachian tube is caused by a difference in air pressure on either side of the tube. If this difference exceeds the pressure in the peri-tubular tissue by a certain degree, and subsequently overcomes the surface tension of the mucous and the elasticity of the cartilage, the tube opens. This occurs during flying and diving activities and during Valsalva and Politzer experiments.
The drainage of the tube is of particular importance in pathological situations, where debris and mucous or purulent secretions need to be drained away. Three factors are of importance to the drainage of the middle ear: active opening of the tube, mucosal ciliary activity and gravity. Active opening in itself already exerts a sucking action on the middle ear, but of more importance is the entry of air into the middle ear via this mechanism. It is only possible for material to be expelled from the middle ear if an equal volume of air replaces it.

The ciliary action also plays a major part. It caters for the transport of material through the tube and acts as protection against invading bacteria. It is possible for the ciliated epithelium to work against the force of gravity. In the middle ear cavity the epithelium is only covered in patches of cilia and this is where the third factor - gravity - takes effect. Gravity helps with the deposition of material onto the 'transport belt' in the eustachian tube. In this way drainage of the middle ear cavity is made easier if the affected ear is facing upwards (12).
Ventilation and drainage of the tube can be impeded in many ways. The tube can become narrowed due to mucosal swelling caused by viral infections of the upper respiratory tract, adenoiditis, sinusitis, allergies or malignancy. Obstructive processes in the nasopharynx can limit the function of the tube in several ways: (1) by closing off the ostium or (2) by limiting pressure changes in the nasopharynx essential for the transtubal ventilation or (3) by interfering with the mobility of the cartilage during active opening. This type of obstruction occurs in relation to adenoidal hypertrophy, tumours, nose tamponades and scars from adenotomy or accidents. Deviations of the nasal septum can result in poor functioning of the tube. This can be put right by correcting the deviation (13).
Disturbances in the active opening mechanism of the tube occur in patients with a cleft palate, owing to the absence of the connection between both m. tensores veli palatini (14). In children, insufficient correlation between the m. levator veli palatini and the tube cartilage is considered to be one of the causes of frequently recurring otitis media serosa, a result of poor tubal function (15).
Mann found a relationship between the cranio-facial morphology and the function of the tube. A more vertical out-growth of the facial bones may have a negative influence on tubal function, due to an unfavourable operational direction of the muscles (16). It is suggested that ingrowth of the muscles is the cause of otitis media serosa in the case of a very small non-obstructive carcinoma of the nasopharynx (17). Poor opening may also occur if the tube cartilage is not firm enough, whereby an otherwise normal musculature cannot open the tube (18). An increase in peritubular tissue turgor can also interfere with the opening of the eustachian tube. Turgor can increase as a result of pharmaceuticals, such as bradykinine, alpha- and beta-adrenergic agents, cardiac and renal insufficiency, hypothyroidism and menstruation (14).
From the above we can conclude that the eustachian tube has a very complicated operating mechanism. This explains the large number of different causes for disturbances in tubal function to be found in the literature. As the subject of this study - the irradiation of the nasopharynx - particularly affects lymphatic tissue, the influence of the adenoid on the function of the tubes will be discussed further.

2.1.4 The influence of the adenoid and adenotomy on tubal function

An enlarged and/or inflamed adenoid is generally considered to be the cause of impeded function of the eustachian tube. One of the first steps to be recommended in children with chronic or recurrent ear disorders is, therefore, adenotomy, possibly in combination with tonsillectomy. The adenoid cannot be removed completely because, unlike the tonsilla palatina, it is not an encapsulated anatomical unit.
In the literature, opinions on the effect of adenotomy on otitis media serosa are far

from unanimous. The cure rates vary between researchers from 20% to 90% (19-23). The variation in percentages can easily be explained by differences: in the compilation of the study groups, between the surgical methods and the judgement of the post-operative results. Selecting patients by excluding children with serious middle ear pathologies can give rise to biassed results (24).
Sadé observed that although the age at which otitis media serosa occurs most frequently (3-7 years) corresponds with the age at which the adenoid still occupies a considerable area in the nasopharynx in many children, there are still a large number of children with otitis media serosa who have had their adenoid removed (26).
Sadé mentions the following indications for adenotomy: (1) mechanical obstruction of the eustachian tube and (2) the lodging of bacteria which can penetrate the midle ear cavity. He believes that the adenoid can contribute to poor tubal function and considers adenotomy to be a useful operation. In his patient material the insertion of tympanic tubes in combination with adenotomy produced better therapeutic effects, after a follow-up period of 18 months, than the insertion of tympanic tubes alone (25).
Tos conducted a study on the improvement of the function of the eustachian tube using tympanic tubes in children with OMS. He also included the effect of adenotomy. On the grounds of his observations, he concluded that adenotomy does not immediately have any great effect on tubal function. He attributed this to the fact that, in OMS, the mucosa of the eustachian tube undergoes extensive histological changes, such as thickening and oedema, referred to as 'internal tubal dysfunction'. Although adenotomy eliminates the cause of 'external tubal dysfunction', it may take a long time before the mucosa of the tube becomes normalized (27).

2.2 THE CROWE THERAPY

Samuel James Crowe (1883-1955) studied medicine at the Johns Hopkins University in Baltimore and graduated in 1908 (28). As early as in 1912 he was asked by W.S. Halsted, surgeon and founder of the first American school of surgery (29), to set up and run an ENT clinic. A few years later he was appointed professor of the department. He became internationally known as an authority in the field of hearing impairments. In 1924 he established an otological research laboratory, with the assistance of the Rockefeller Foundation, in order to study the causes and prevention of deafness. One of the studies concerned middle ear deafness in children (30). Using a nasopharyngoscope constructed by Edgar M. Holmes, he diagnosed an excess of lymphoid tissue in the nasopharynx in many cases with this disorder.
The repeated examination of 1365 unselected school children showed that in more than 75% of those who had undergone adenotomy before puberty, the adenoid had recurred and almost 40% of the children had suffered a loss of hearing (31). In the knowledge that lymphoid tissue is pre-eminently sensitive to ionizing radiation (32), Crowe asked Curtis F. Burnam, a radiologist, to construct a needle containing radon (later radium), with which he could treat children who were hard of hearing (33). This form of therapy took root in many parts of the western world and found application for several decades.
In the 1950s other radioactive elements were examined to see whether they were

suitable for use. Cobalt-60, although cheaper than radium, was rejected owing to the greater risks involved. Radioactive phosphorus (P^{32}) had the disadvantage of a short half-life of 14 days, which made the dose calculation difficult (34). Strontium^{90}, introduced by Thullen in 1954, offered advantages over radium. It has a much shorter half-life, 28 years, and its dose fall off is steeper, so that patients and staff receive lower radiation doses (35). In the clinics where nasopharyngeal irradiation is still being applied Sr^{90} is used (36).

2.3 DOSIMETRY

In their first publications, Crowe and Burnam limited themselves to estimating the radiation doses received by tissues in the direct vicinity of the applicator, because 'surrounding tissues receive only homeopathic dosage'. They considered this to be sufficient because the amount of radiation absorbed decreases with the square of the distance between the irradiated object and the source.
Assuming that the two halves of the nasopharynx are spherical, with a diameter of two centimetres and that the radium applicator is placed in the centre of each half, they calculated a dose per treatment of 600 to 650 cGy at the wall of the nasopharynx. This was calculated for an applicator containing 50 mg radium sulphate with an exposure time of 40 minutes to both sides. They observed that the chance that the figures were inaccurate was fairly high due to size variations of the nasopharynx and the precise positioning of the applicator (37).
In order to calculate the dose received by the thyroid gland, Hazen determined the distance between the middle of the adenoid shadow in the nasopharynx and the upper lobe of the thyroid gland. He used X-ray films for this, on which he estimated the position of the thyroid gland, which is not visible on an X-ray film, in relation to the hyoid bone. By setting out 20 points, he established that the distance was 5 to 12.5 cm in patients of 4 to 14 years old. Depending on the exposure time (25 mg radium sulphate for 12 to 24 minutes) and the distance, he estimated that the pituitary gland received a dose of 8 to 36 cGy. He considered the dose received by the thyroid gland to be negligible (1).
Garsou, a radiotherapist, calculated the radiation doses received at various places in the patient's body. For a full treatment, he arrived at the following figures: 18 cGy for the lens, 4.68 cGy for the skin at the level of the thyroid gland, 0.468 cGy for the navel and 0.108 cGy for the gonads. He also estimated the dose received by the operator. During a treatment of 3 x 12 minutes in 9 weeks using 50 mg of radium, the palm of the hand received 0.047 cGy and the navel region 0.0324 cGy (see Table 2.1) (38).
Sandler estimated various tissue doses using the X-ray films of children from 2 to 16 years of age. Distances were measured between the nasopharynx and the thyroid, pituitary and salivary glands. Depending on the age of the child, she estimated these to be 4 to 13 cm for the thyroid, 2 to 4 cm for the pituitary and 5 to 8 cm for the salivary glands. According to her, the radiation dose received at the nasopharynx and the orifice of the eustachian tube was 700 cGy, at the pituitary and lower regions of the brain 78 cGy and at the thyroid gland 5 to 20 cGy. Her study group was exposed to two applicators containing 50 mg radium sulphate for a total of 36 minutes (39).

Table 2.1 Radium irradiation* dose received by the operator (cGy) compared to the ICRP** norms (38)

Body site	Dose	ICRP norms
Palm of the hand	0.047	10
Navel region or internal organs	0.0324	4

* 50 mg radium, 3 x 12 mins in 9 weeks
** International Commission on Radiological Protection (1966) maximum dose in 13 consecutive weeks

2.4 THE EFFECTS OF NASOPHARYNGEAL IRRADIATION

2.4.1 The local effect

In his experimental research into the effects of X-rays on various types of tissue, Heineke established - as early as in 1904 - that lymphatic tissue was the most sensitive (32). In the English literature, the clinical effect of irradiation of the nasopharynx is accounted for by a decrease in the adenoidal tissue, which cannot be removed surgically (8,30). Moreover, several German authors brought forward a theory of 'Gewebsumstimmung', in which ionizing radiation has a favourable influence on an inflamed mucous membrane - however, they did not fully explain this mechanism (34,35,40).

Microscopy
One month after the irradiation of the nasopharynx using 50 mg of radium for one hour, Fowler extracted tissue from the nasopharynx of a young aviator, for microscopic examination. He observed that the germinal centres had disappeared and the number of lymphocytes had decreased strongly. Many of the remaining lymphocytes had pyknotic nuclei. The capillaries in the irradiated tissue were very prominent. The endothelium of the blood vessels appeared to be thickened and the walls hyalinized. Connective tissue cells were present in greater numbers than in the control biopsy specimen taken before irradiation (8).
Westerbeek conducted a similar examination in 1949. He sent the adenoidal tissue, extracted from a six-year-old boy, who he had treated one month previously (50 mg, 36 min.), to the pathology laboratory to see whether any stuctural changes had resulted from the radium irradiation. In contrast to Fowler, he did not observe any noticeable changes (41).
Only one animal experiment is described in the literature. Microscopic examination was carried out on the effect of radium irradiation on the movement of the cilia on the mucous membrane of the eustachian tube in the horse. No adverse effects were observed after contact therapy varying from 2 mg of radium for 1 hour to 40 mg of radium for 24 hours (42).

Macroscopy
Bordley and Hardy conducted a prospective cohort study on the effect of nasopharyngeal radium irradiation on the reduction of lymphoid tissue in the nasopharynx. They subjected a group of 385 children to nasopharyngoscopy during

a followed-up period of five years, between 1948 and 1953. At the beginning of the study the average age was 8.8 years. The entry criterium for the study was a hearing loss of 15 dB or more for two frequencies in one ear or of 20 dB or more for one frequency in one ear. Half of the children (n = 193) were treated using 50 mg of radium sulphate in the nasopharynx for 8.5 minutes in three sessions at two week intervals. The other half (n = 192) were treated using a placebo applicator. This was a double blind study.
The children were examined using a nasopharyngoscope twice a year for five years - the duration of the study. In the judgement of the data obtained, attention was paid to 1) the effect of the nasopharyngeal irradiation on the adenoid and 2) the changes around the ostium of the eustachian tube as a result of the irradiation.
In the irradiated group the adenoid appeared to shrink steadily over the five year period. The greatest change took place in the first three years. The size of the adenoid in the control group also decreased but to a lesser extent than in the irradiated group. In the control group the greatest amount of change took place in the last two years, which reflected the accelerated shrinkage of the adenoid with the onset of puberty. Comparison of the two groups showed that irradiation of the nasopharynx caused the adenoid to shrink (see Figure 2.2).
The fact that moderately to large adenoids persisted in 96 of the children in the irradiated group forms enough grounds to conclude that irradiation cannot replace the surgical removal of the adenoid. In the judgement of the ostium of the eustachian tube, the extent of lymphatic 'overgrowth' was examined. Figure 2.3 shows the changes around the ostium in both groups during the five year period.

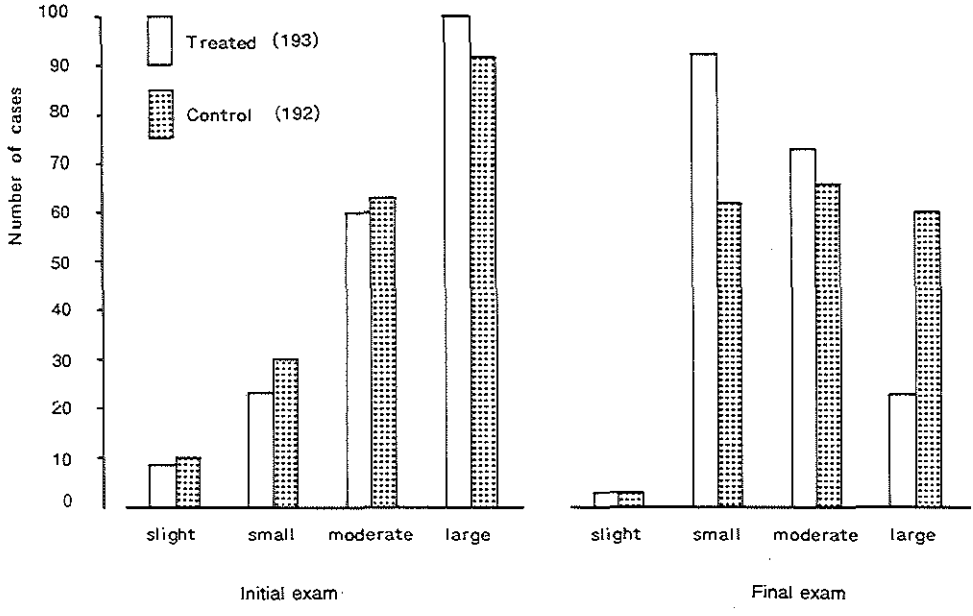

Figure 2.2 Effect of radium irradiation on the size of the adenoid (Bordley et al. 1955) (43).

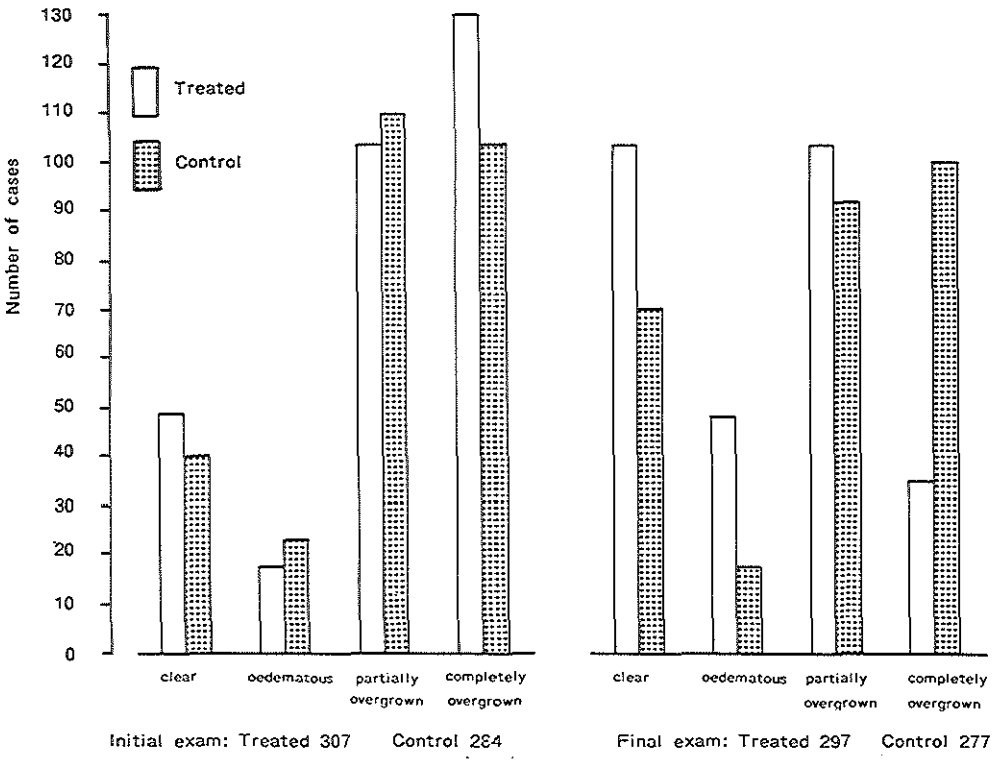

Figure 2.3 Effect of radium irradiation on the situation at the tubal orifice (Bordley et al. 1955) (43).

The decrease in the number of completely overgrown ostia from 130 to 36 and the increase in the number of clear ostia from 47 to 103 in the irradiated group clearly surpasses the results in the control group. It is striking that the decrease in size of the adenoid in the control group during the five year period did not involve a corresponding improvement around the ostium of the eustachian tube (43).
It was concluded in this double blind study that radium irradiation has a clear effect on the size of the adenoid as well as on the amount of lymphoid overgrowth around the ostium of the eustachian tube.

2.4.2 The effect on tubal function

In 1969 Beck published the results of intratubal irradiation using strontium^{90}. The indications were 1) chronic ear infections with or without perforation of the tympanic membrane, whereby surgical treatment was being considered to improve the hearing and a tubal stenosis was present and 2) chronic otitis serosa, adhaesive processes and otosclerosis with tubal dysfunction. The results were judged on the grounds of an improvement in tubal function, as measured using the 'Tuben-widerstandmessung' (TWM) according to Zöllner. This measurement consisted of

creating an increase in air pressure in the nasopharynx via the nose and subsequent measurement of the opening pressure of the eustachian tube by ausculation of the sound produced by air escaping through a perforation or by the observation of movement in the case of an intact tympanic membrane.
In Beck's study, 625 tubes were irradiated, 491 with a TWM of 30 to 80 mm Hg and 134 with a TWM of 80 mm Hg or more. In the first and second groups, the improvement rates were 88% and 36%, respectively. An improvement was considered to be a decrease in TWM value to less than 30 mm Hg (44).
One year later Siedentop published the results of a similar study and attempted to compare his results with those of Beck. His indications were 1) patients who had already undergone an unsuccessful tympanoplasty (meaning that surgery resulted in an atelectatic middle ear, perforation of the tympanic membrane or both) and 2) chronic otitis media adhaesiva. The function of the eustachian tube was measured using the aspiration method (ETF = Eustachian Tube Function), whereby the pressure in the middle ear could be varied via a manometer connected to the external auditory meatus. All the patients had an ETF of type III, IV or V. An eustachian tube with an ETF type III reduces +500 mm H_2O middle ear pressure to 0 and -250 mm H_2O to not lower than -50 mm H_2O. A type IV function reduces +500 mm H_2O to 0 but does not reduce a negative pressure. Type V does not reduce either a positive or a negative pressure. All the patients who underwent this test had a perforated tympanic membrane or a polythene drain in the tympanic membrane. A total of 27 eustachian tubes were irradiated, seven ETF type III and IV and 20 ETF type V. A positive result was considered to be an improvement in function from types III, IV and V to types I or II after eight weeks (type I reduces +500 mm H_2O and -250 mm H_2O to 0 and type II reduces +500 mm H_2O to 0 and -250 mm H_2O to a value between 0 and -50 mm H_2O. In the first group, 43% improved; in the second group 10% (see Table 2.2).

Table 2.2 Results of intratubal strontium therapy in tubal disorders, per author. Studies without a control group

Author	Ref. No.	Publ. year	N	Tubal disorders	
				Slight - Moderate	Serious
Beck	(44)	1969	625	TWM* 30-80 88%	TWM 80 or more 36%
Siedentop	(45)	1970	27	ETF** type III/IV 43%	ETF type V 10%

* Tubenwiderstandsmessung (mm Hg)
** Eustachian Tube Function

Siedentop subsequently measured the tubal function in 16 patients using the TWM as well as the ETF method in order to compare his results with Beck's. He concluded that ETF types III and IV corresponded with TWM values of 30 to 80 mm Hg and that type V corresponded with TWM values of above 80 mm Hg.
Reviewing the results, it is striking to see that Beck's were better. Despite

Siedentop's attempt to make his figures suitable for comparison, the reason for this is probably the differences between the groups of patients treated: the treatment indications were different, as were the size of the groups (45).

2.4.3 The clinical effect

The nasopharyngeal application of a radioactive substance was a popular treatment method for recurrent ear infections and otitis media serosa in children. During the Second World War the method was also frequently applied to military aviators and divers with barotraumatic disorders. Many reports have appeared on the effects of the treatment for the various indications mentioned above. However, most of the publications lacked a control group. This is a great loss with regard to the judgement of the effect of a therapy which is applied for a disorder that has a strong tendency to disappear spontaneously, such as otitis media serosa. In the discussion of the existing literature, a distinction will be made between studies with a control group and those without.

Studies without a control group

In the presentation of these studies (see Table 2.3), precise data concerning the applicator used, the dose and fractionation, will not be mentioned for every author.

Table 2.3 Literature overview: Results of nasopharyngeal irradiation using radium or strontium for otitis serosa, recurrent ear infections, and barotrauma, per author

Author	Ref. No.	Publ. year	N pat.	Cont. grp	Improvement %	Improvement Criterium	Obs. time in months
OTITIS SEROSA							
Canfield	(46)	1949	50	no	56%	'audiographic'	3->24
Krijger	(47)	1951	80	no	90%	normal hearing	12
Falbe-Hansen	(48)	1956	65	no	65%	>10 dB in speech region	>24
Flach	(34)	1966	16	no	62%		1-1.5
Riu	(49)	1966	98	no	65%	>15 dB/two frequencies	
Bourdial	(50)	1969	310	no	77%	'audiographic'	
Siedentop	(51)	1973	6	no	17%	normal hearing	>12
Bordley	(43)	1955	43	yes		(8 dB better hearing than cont. grp)	60
RECURRENT EAR INFECTIONS							
Falbe-Hansen	(48)	1956	98	no	42%	lower frequency	>24
Bourdial	(50)	1969	470	no	72%	symptom free	
BAROTRAUMA							
Riu	(49)	1966	197	no	79%	caisson test	
Fowler	(8)	1946	17	yes	76%	able to aviate	

Owing to the vast differences in compilation of the study populations and the differences in study design per author, comparison is very difficult in any case. All the studies have in common that a radiation treatment has been given to the nasopharynx or intratubally, using an applicator containing radium[226] or strontium[90].

The treatment results for *otitis serosa* show success rates of 17% to 90% (34,46-51). Although there is a large distribution between the percentages, one study in particular (17%) distinguishes itself from the rest (56%-90%) and will receive further attention.
Following intratubal irradiation using strontium^{90} in six children with otitis serosa, Siedentop observed that the therapy had not had any effect in five cases. On the grounds of sequential data analyses, he rejected the hypothesis that irradiation has a useful effect. He was dealing with a very small group of children with persistent otitis serosa, with or without atelectatic middle ear cavities.
Nasopharyngoscopy in all the children revealed abnormalities, such as narrowed, scarred or polypoid ostia. It was sometimes necessary to force the applicator into the tubes. The patients all had type V function of the eustachian tube prior to treatment, i.e. an overpressure of +500 mm H_2O, or an underpressure of -250 mm H_2O which could not be reduced transmeatally (51). The poor results of the treatment are probably connected with the selection of the children. The group had persistent tubal disorders, possibly on account of tubal stenoses.
Recurrent ear infections in children reacted to the therapy in a favourable manner in two studies, in 42% and 72% of the cases, respectively (48,50). Riu treated *barotrauma* in adults using nasopharyngeal irradiation. The therapy had a positive effect in 79% of the 197 patients, such that, after completion of treatment, a caisson test could be performed without any symptoms (49).
Comparison of the figures in Table 2.3 gives rise to difficulties, because there are differences between the compilation methods in both groups and also between the judgement criteria of the results. In many cases the duration of follow-up is not mentioned. A follow-up period of four to six weeks is certainly too short to be able to make an accurate judgement of the effect of a treatment for tubal disorders.

Studies with a control group
Two controlled double blind investigations have been described on the clinical effects of the Crowe therapy.
In 1946 Fowler published a study on 34 American aviators who he had treated on account of *barotrauma*. He had treated one half using radium and the other half using a placebo applicator. Four of the 17 aviators treated with placebo returned to work, only one was without symptoms. Of the 17 irradiated aviators, 13 returned to work and only two had mild complaints every so often (8).
In the study by Bordley & Hardy, already mentioned above, the effect of radium irradiation on the *hearing* was also examined. A group of 385 children - half of whom had been irradiated, the other half had received a placebo treatment - underwent an audiogram every six months. For further details about selection criteria etc., see page 26.
The most noticeable feature in the results is that there had been a general improvement in hearing at all frequencies in both groups. The authors give three possible explanations:
1) An age effect: as the children grow older the amount of adenoidal tissue in the nasopharynx decreases.
2) A time effect: improved hygiene, which expresses itself in more effective treatment of upper respiratory tract infections.

3) A habituation effect: the children become accustomed to the repeated audiometry and this increases their performance.

A comparison of the hearing gains in both groups showed a slight advantage in the irradiated group. The difference was small and not significant, but consistent at each measurement. The size of the relative gain certainly suffered from the fact that six children from the control group disappeared owing to a progressive loss of hearing.

The groups could be divided into three subgroups, characterized by 1) loss in the low tones, 2) loss in the high tones and 3) loss in both the high and low tones. The results in the latter group, characterized by a flat loss of hearing of 25 dB or more at two frequencies in the frequency range 125 to 1000 Hz and of 25 dB or more in the frequency range 2000 to 10,000 Hz, were the most interesting. Figure 2.4 shows the hearing gain on the last audiogram compared to the first. The irradiated group has a distinct advantage at all frequencies (43).

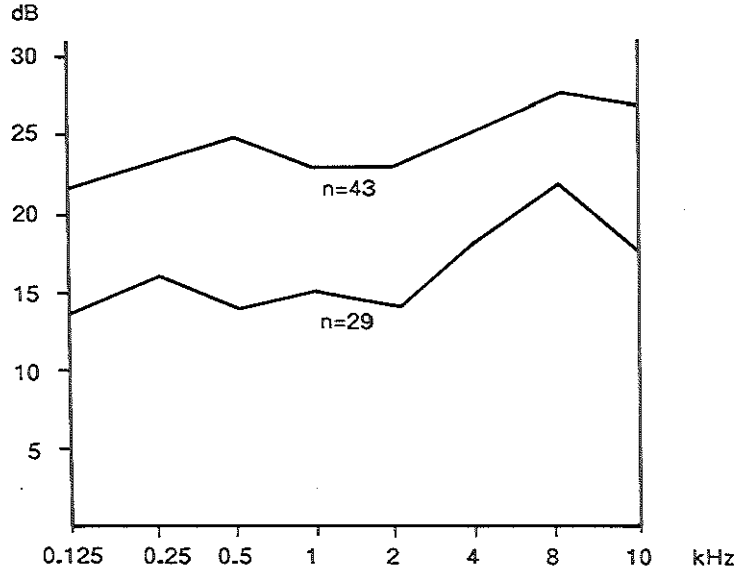

Figure 2.4 Hearing gain in the flat-hearing-loss subgroup five years after radium irradiation (n=43) and placebo (n=29) (Bordley et al. 1955) (43).

2.4.4 Distribution

Nasopharyngeal irradiation using radium was introduced in 1926 by Crowe, who was working in the Otological Research Laboratory at the Johns Hopkins university in Baltimore. The therapy experienced a striking period of flourish and an equally striking period of decline. This reversal took place in the 1950s and 60s. Remarkably, in 1955 the therapy was recommended in an 'Editorial' in the British Medical Journal, partly on account of work by Bordley and Hardy (52), while in the same year a 'Redaktionele Kanttekening' (Editorial Marginalia) in the Nederlands Tijdschrift voor Geneeskunde (Dutch Medical Journal) warned against the application of the therapy (53).

Crowe estimated that during the Second World War 25,000 treatments were carried out by military doctors in the American Air Force and at the New London Submarine Base (33). At the request of the French Institut du Cancer, Debain travelled to America in 1949 to investigate the advantages and disadvantages of the treatment. According to his reports there were 1400 applicators in use in America at that time. Medical teams with mobile clinics equipped with audiometers, nasopharyngoscopes and radium needles, visited primary schools and the children who needed treatment were dealt with on the spot. An advertisement appeared in the Saturday Evening Post: 'Will your child go deaf?... Four million American children have something wrong with their ears... But something can be done about it...' (54). Several years later a European ENT specialist accused his American colleagues of 'Kapitalisierungswünschen' (35).
Sounds of warning were also being struck in America against the unrestrained use of the therapy, pointing out the possibility of malignant degeneration (55) or an absence of therapeutic effect (34). As the use of tympanic tubes for middle ear drainage became more popular in the 1950s, the use of the Crowe therapy in America started to decline. In a survey conducted by Davison in 1965 of 100 American ENT specialists, only six of the 86 respondents were still using radium applicators. Twenty still applied external X-ray treatment to patients with lymphoid hyperplasia (49). This method is no longer in use in America (56).
In France the therapy was introduced straight after the Second World War and spread throughout the whole country (49,50,57). In 1974 favourable results were reported at the university clinic in Bordeaux (57). But the method has now been abandoned owing to external pressure (58).
In Germany nasopharyngeal irradiation made its entrance in 1951. Not only radium was used but also intratubal P^{32} and later Sr^{90} and Y^{90} (35). Intratubal irradiation is still being carried out in Würzburg using Sr^{90} for the treatment of stenoses of the eustachian tube and epipharyngitis (36).
In England nasopharyngeal irradiation using radium was conducted on a large scale during the Second World War. The method is no longer used nowadays (59,60).
Fairly recent research on the 'bétàtherapie tubaire' using Strontium^{90} has been carried out in Belgium (38,61,62). The method was introduced shortly after the Second World War and is still being used in Liège (63) and Verviers (64).
In the Netherlands the Crowe therapy was introduced in 1945 by Van Dishoeck. In 1950 he reported on his experience of using this form of radiation therapy on 200 children. His advice was to use 25 mg instead of 50 mg of radium and to examine the effect after each session in order to cut short the course of treatment if the results were favourable. In further investigations after the completion of treatment he observed that the otitis serosa had cleared up and the hearing had improved, but that there was still an under-pressure in the middle ear. He was under the impression that the source of infection had been removed with the adenoidal tissue, but that in such patients the hypertrophic mucous membrane was still responsible for the stenosis. Owing to the fact that the radium irradiation did not reach this mucous membrane effectively enough, he advised external X-ray treatment via the neck in these cases (65). In 1951 several results from the ENT clinic in Utrecht were published (47) (see Table 2.3).
A survey held in 1982 under a number of Dutch ENT specialists brought to light that the therapy had been applied on a large scale throughout the country. It passed

through its most prosperous period in the 1950s and 60s. From the data received from each respondent on the duration of practice and the numbers of patients treated per year, it can be estimated that about 24,000 patients underwent this treatment (See Appendix 1).
The fear of tumour induction through radiation, the renewed invention of tympanic tubes by Armstrong in 1954 and the activity of the inspectors from the Ministry of Health all contributed to making the method obsolete. In the Netherlands the method became extra discredited due to a notorious accident which occurred in 1958, whereby the contents of a Crowe applicator found its way into the environment (see Appendix 2).

2.5 EXTERNAL IRRADIATION OF THE NASOPHARYNX

Before the advent of applicators containing radioactive substances for use within the nasopharynx, external X-ray treatment of this area was being conducted. The first news of this came from Szàsz in 1922 (66). This form of irradiation was also applied via the mouth (67). In 1924 Witherbee compared radiotherapy with surgical treatment and spoke in favour of the former in cases where there were surgical or anaesthesical contra-indications or where complications, such as bleeding or infection, needed to be avoided (68).
On the assumption that an applicator placed in the nasopharynx could not irradiate the whole length of the eustachian tube, Dickson and McGibbon transferred to external 'deep' X-ray therapy. In 64 cases of barotrauma, 28 improved to such an extent that they were able to return to flying, without any symptoms (69).
Besides the above mentioned disadvantage of nasopharyngeal application, Baarsma and De Jong also pointed out some other drawbacks: radium irradiation did not reach the lymphatic tissue of Waldeyer's ring and the operator was exposed to high radiation doses. They applied X-ray therapy at a dosage of 3 x 150 to 200 rads, usually repeated once. In this way they treated 193 patients with a hearing loss due to tubal disorders. There were 147 patients belonging to the 4 to 16-year-old age group; in 70% the hearing became normalized. The results were not as good in the older age groups. This study did not involve a control group. They calculated the maximum exposure for several organs: nasopharynx 1150 cGy, processus zygomaticus 630 cGy and hypophysis 350 cGy (70).
Bull and McKelvie treated a small series of 19 children with otitis serosa using 220 kv. Although they did not observe a uniform effect (only five children were cured), they believed that the large-scale studies from the past should not be ignored and that the therapy was probably of use in cases where conventional therapies had failed (71).
In a German university radiotherapy institute external Telecaesium irradiation is still being applied today using a dosage of 3 x 60 cGy with two day intervals. The indication is reported to be recurrent otitis media (72).

2.6 ADVERSE EFFECTS

In 1949 Robbins and Schulz warned about the danger of malignant degeneration resulting from radium irradiation of the nasopharynx. Although they only gave

examples of complications which arose from the treatment of haemangiomas on the skin and the use of X-ray treatment, they were afraid that nasopharyngeal radium irradiation too, would lead to damage in the long-run (55).
Eighty-five patients treated by Samuel Crowe himself were subjected to a nasopharyngoscopic examination an average of 8.9 years after treatment, to inspect this area for abnormalities. Four cases of increased vascularization of the mucous membrane were observed and two cases of crustal atrophy (73).
In a non-concurrent prospective study by Hazen et al. on 417 people 14.6 years after irradiation, two malignant and five benign tumours were found, which coincided with the expected values (1).
In a similar investigation by Sandler on 904 irradiated subjects an average of 25 years after treatment, she observed significantly more brain tumours and cases of thyrotoxicosis than in a non-irradiated control group. One of the malignant head and neck tumours in the irradiated group was an undifferentiated anaplastic carcinoma of the palatum molle (39).
Fairly recently, in case studies, two different authors have reported on a cystic adenocarcinoma of the palatum durum and vomer, observed 30 and 23 years after Crowe therapy, respectively (74,75).

2.7 SUMMARY

Summarizing, it can be stated on the basis of data from the literature that irradiation of the nasopharynx using a radioactive applicator causes the lymphatic tissue to atrophy. The effect persists for many years. It is possible that this form of irradiation has a favourable effect on mucositis. In animal experiments no adverse effects on ciliary activity have been observed following contact irradiation of the mucous membrane.
Many studies have been conducted on the clinical effect of the Crowe therapy, but very few involved a control group. In the light of these investigations, the effect of the therapy on various disorders appears to have been demonstrated. Its effect is greater in cases of light and moderate tubal dysfunction than in those with serious tubal dysfunction and greater in the young than in the old. The effect seems to be dependent on the cause of the tubal dysfunction: reversible lymphoid hypertrophy and mucosal swelling.
The therapy spread widely in the 1940s, when irradiation was an accepted form of treatment, also for benign disorders. In America and Western Europe the therapy was applied on a large scale for barotrauma, otitis media serosa and recurrent ear infections.
Fear of tumour induction and greater surgical possibilities on account of the reintroduction of tympanic tubes and the appearance of the operation microscope started to drive the therapy into obsolescence as from the 1950s.

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CHAPTER 3
HEAD AND NECK TUMOURS INDUCED BY IONIZING RADIATION

3.1 INTRODUCTION

It has been known for a great many years that ionizing radiation can induce tumours after a long or short latency period. In 1902, seven years after the discovery of röntgen irradiation, Frieben described the existence of a malignant skin tumour in a worker exposed to irradiation (1). In 1929 Martland reported on an osteogenic sarcoma following radium ingestion (2).
In later years a relationship between the origination of a tumour in almost every organ in the head and neck area and previous exposure to radiation was suggested in casuistic publications (see Table 3.1) (3-12). The first one concerned an induced larynx tumour in 1936 (3).
In epidemiological studies dose-effect relationships have been demonstrated for radiation induced tumours of the thyroid gland, the brain (13) and the salivary glands (14,15).

Table 3.1 First records of radiation induced head and neck tumours

Author	Publ. year	Ref.	Organ
Lossen	1936	(3)	larynx
Kruchen	1937	(4)	pharynx
Duffy	1950	(5)	thyroid gland
Deller	1951	(6)	tongue
Aub	1952	(7)	mastoid and nasal sinuses
Mann	1953	(8)	meninges
Zülch	1956	(9)	brain
Bablik	1959	(10)	tonsil
Saenger	1960	(11)	salivary glands
Rosen	1975	(12)	parathyroid glands

3.2 MEANS OF EXPOSURE

3.2.1 Occupational

Occupational exposure, besides that mentioned by Frieben, was especially well-known in radiologists when radiation therapy was first introduced. Before radiation safety measures were enforced, leukaemia could be regarded as an occupational disease in radiologists (16).
Epidemiological studies on workers in the watch industry, where dials were painted with luminous paint, showed an increased incidence of carcinoma of the mastoid and nasal sinuses. Alpha particle radiation in the radon gas released was probably responsible for these tumours (17,18).

The examination of groups of workers in nuclear ship building and nuclear power stations did not uncover an increased tumour induction or lead to definite conclusions (quoted 16).

3.2.2 Medical

Most of our knowledge on radiation induced head and neck tumours is derived from investigations on people who have been exposed to irradiation for medical-diagnostic or therapeutic purposes.
When radiotherapy was first introduced, it was not only used for treating malignant processes but also for benign and often trivial complaints. In 1907 Friedländer propagated irradiation of the thymus gland in young children for treating malaise and breathing difficulties and to prevent cot death (19). Table 3.2 shows a number of benign disorders which were treated with radiotherapy.
In America it is estimated that, in the past, one million youngsters were irradiated for acne vulgaris (22). In two Dutch publications estimations were also made. About 100,000 Dutch people are thought to have been irradiated for benign disorders (23). Nasopharyngeal radium application was carried out on about 25,000 (usually) young people (24).
All the indications mentioned in Table 3.2 concern external irradiation using röntgen radiation. Radium, used in the form of a closed source for several different types of application, was also thought to be associated with tumours which developed at a later date. These cases consisted of skin treatment for haemangioma planum (25) and of naso-pharyngeal application for ear disorders (26).

Table 3.2 Benign disorders previously treated with radiotherapy in the head and neck region

Category	Disorder
Lymphatic system	larged thymus gland (19) hypertrophic tonsils and adenoid
Skin (20)	hirsutism acne vulgaris greasy skin and large pores haemangioma psoriasis keloid
Inflammatory/degenerative	tuberculotic lymphoma tinea capitis (21) arthrosis mastoiditis sinusitis

The internal use of iodine (I^{130}, I^{131} and I^{125}) for the treatment of thyrotoxicosis meant a particularly high radiation dose to the thyroid gland and is also associated with tumour induction (27-31).
In the first half of the century, the oral administration of radium (Ra^{224}, Ra^{226}) was recommended for many types of disorder. It was used in the form of radium drink

cures, radium bread or injections, often without the mediation of a doctor (97,18,32).
Contrast media containing thorotrast, instilled into the maxillary sinus often resulted in local or remote tumour induction (33-35). It has been reported that an extravasate of the medium, the result of a problematic carotis angiography, caused a malignancy in the neck (36).

3.2.3 Atom bomb explosions

Radiation induced head and neck tumours were also observed following exposure to radioactive dust resulting from atom bomb explosions in Hiroshima (gamma radiation and a large amount of neutron radiation) and Nagasaki (gamma radiation and a small amount of neutron radiation) and atomic tests near the Marshall Islands (gamma radiation and various isotopes) and in the deserts of Utah and Nevada.

3.3 RISK FACTORS

3.3.1 The tumour induction rate

The chance of developing a radiation induced tumour is often expressed in figures: the tumour induction rate. In the UNSCEAR report in 1977 (37), this rate was defined as the number of radiation induced tumours which developed per 10^6 persons per rad during a certain observation period ($n.10^{-6}.rad^{-1}$).
This tumour induction rate ignores a number of characteristics concerning the people exposed, such as age on exposure, sex and ethnical factors, plus a number of characteristics concerning the ionizing radiation itself, such as the type of radiation, fractionation and dose rate. It also suggests the existence of a linear relationship between the dose and the number of induced tumours as well as between the observation time and the number of induced tumours. Besides the tumour induction rate, it is also possible to establish a tumour mortality rate on the basis of the number of tumours which prove to be fatal. This value varies considerably from organ to organ (see Table 3.3).
It is important to bear these limitations in mind when employing these rates. The figures, with the exception of one or two cases, were compiled on the basis of a small

Table 3.3 Tumour induction and mortality rates for head and neck organs per 10^6 persons per cGy (UNSCEAR) (37)

Organ	Tumour induction rate	Tumour mortality rate
Thyroid gland	100	10
Brain	10-15	10-15
Salivary glands	10-15	5
Sinus mucosa	2- 5	?
Bone	2- 5	?
Skin	5	0
All other organs		100*

* All organs, including leukaemia, for doses >100 cGy

number of studies and on exposure to moderate or high radiation doses. The risks involved with exposure to low doses of radiation have been estimated by extrapolation. Longer observation times in the epidemiological studies still being conducted and future epidemiological investigations will possibly lead to alterations in these figures and produce more precise data. Tumour induction rates and tumour mortality rates are used to estimate the risks involved in radiation exposure during medical treatments and during nuclear disasters.

3.3.2 Characteristics of the exposed organism

Sex
Women appear to be more sensitive to radiation induced thyroid tumours than men. Van Daal observed a ratio of 2:1 after a thorough review of the literature (38). In the judgement of the differences, it should be borne in mind that non-radiation induced thyroid tumours are also more common in women.
In a study on survivors of the atom bomb in Hiroshima, Ohkita observed a higher incidence of salivary gland tumours in the women in a non-exposed control group and a higher incidence in men in the exposed group (39).

Age on exposure
In persons who were exposed to irradiation antenatally, it has appeared that tumours can be induced by very low doses of radiation (40). In many studies, it has been indicated that younger individuals are generally more sensitive to tumour induction via radiation than older people (41-43). In old age the sensitivity has been found to increase again (44).

Ethnical factors
In a controlled cohort study, in which 2,872 young adults who had been treated with röntgen radiation in their youth were compared with 5,005 non-irradiated family members, it appeared that radiation induced thyroid tumours occurred 3.4 times more often in Jewish children than in non-Jewish children. In the irradiated group, 24 malignant en 52 benign thyroid tumours were observed, whereas these figures in the non-irradiated group were six and nought, respectively (45).
In an American controlled cohort study on 2,200 children who had been irradiated for tinea capitis compared to a group of 1,400 non-irradiated children, it appeared that skin tumours had occurred exclusively among the white children, particularly those from Ireland, while the study group comprised 25% coloured children. In the irradiated group there were 41 people who developed one or more skin tumours, whereas in the control group only three skin tumours were observed (46).

Genetic factors
It is probably possible to designate groups of individuals who have a genetically increased chance of developing a radiation induced tumour. It has been brought forward by several authors that the high incidence of tumours which arose after irradiation in patients with multiple cases of retinoblastoma in their family, can be attributed to a radiation induced second mutation in cells which are genetically predisposed to neoplastic transformation (47,48). An increased risk is also thought to exist in patients with multiple paragangliomas (49) and in patients with the nevoid basal cell carcinoma syndrome (50).

Schneider et al. established that persons who were irradiated in their youth for benign disorders in the head and neck region and who later developed neurogenic and salivary gland tumours, ran more risk of also developing a thyroid tumour than those who did not develop such tumours. They concluded from this there were subgroups within the total irradiated population who had a different sensitivity to developing radiation induced tumours. Genetic factors, among other things, were indicated as a possible cause (42).
In their study on radiogenic skin tumours, Shore et al. also found evidence of more and less sensitive subgroups (46).

Metabolic circumstances
Irradiation of the thyroid gland causes - depending on the dose - a disturbance in the hormone balance which leads to an increase in the secretion of TSH by the pituitary gland. Animal experiments have shown that over-stimulation of the thyroid cells by TSH can induce thyroid tumours (quoted 51).
Belsky et al. were of the opinion that the origination of salivary gland tumours in survivors of the Japanese atom bomb explosions was probably assisted by the poor state of nourishment owing to the war. This was based on the suggestion that the high incidence of salivary gland tumours in Eskimos is due to a chronic vitamin A deficiency from which they suffer (52).
Finally, several authors have pointed out the possibility that radiotherapy has an increased tumour inducing effect in patients who are being treated with cytotoxic drugs at the same time (53-55).

3.3.3 Characteristics of the physical agent

Radiation type
Animal experiments have shown that in the low dose region, high LET radiation (alpha and neutron radiation) has a greated tumour inducing capacity than low LET radiation (gamma and röntgen radiation) per dose unit (56). This was also shown for the induction of leukaemia caused by the atom bomb explosions in Japan (41).

Radiation energy level
A few authors have suggested that high energy radiation, such as megavolt and cobalt radiation, carries less risk of inducing tumours than low energy radiation, such as orthovolt radiation (57,58). As possible causes they indicated the greater radiation exposure of healthy tissues, inherent of the lower energies themselves (irradiation of the skin, scatter) (57) and a greater likelihood that the patient will move due to the longer irradiation times involved with orthovolt treatment (42).
Lund et al., however, observed eight cases of secondary tumours in patients who had undergone cobalt radiotherapy, whereby the treatment data had been documented very carefully. He found five in the region which had received the highest dose and three in the periphery of the irradiated area (59). The expectation that proton radiation will carry less chance of tumour induction also seems to be unfounded (60).
The short latency times observed by Lawson et al. using megavolt irradiation compared to orthovolt radiation, which they attributed to the difference in

biological effect, are more than likely the result of the study methods used (case reports vs. cohort studies) (61).
Finally, Taylor suggested the possibility that the more modern and more effective radiotherapy methods, megavolt and cobalt radiation, will lead to a larger number of induced tumours in the long run, owing to the longer survival rates (57).

Dose rate and fractionation
Animal experiments have shown that longer radiation times for low LET radiation have a sparing effect on the origination of tumours (62). Fractionation was seen to have the same effect on the induction of pituitary tumours in animals (56). In an experiment concerning the origination of radiogenic skin tumours in animals, no difference was observed either between single or fractionated doses of radiation (63).
In man, fractionation is thought to reduce the risk of thyroid tumour induction (64). No differences were found with regard to the risk of the induction of breast tumours following fluoroscopy and the induction of leukaemia (quoted 41).

Dose
The lowest radiation doses after which induced head and neck tumours have been observed are recorded as being 6 or 7 cGy for the thyroid gland, 39 cGy for the parotid gland and 140 cGy for the brain (21,65).
On the basis of several studies, a linear dose-effect curve has been drawn up between 6 to 7 cGy and 1500 cGy for the induction of thyroid tumours (45,65-67). For this gland it is assumed that the tumour inducing capacity decreases strongly above a dose of 2000 cGy because, together with the destruction of thyroid tissue, the chance that malignant degeneration will take place becomes proportionally smaller (cell-death function) (22).
In the study on the effects of the Japanese atom bomb explosions on salivary gland tumours, a dose-effect relationship has been established in terms of: the chance of tumour induction in exposed persons increases as their distance from the hypocentre decreases (15,39).
Seydell suggested that a high dose of radiation (more than 5000 cGy), such as the dose given during the radio-therapy of malignant processes, carries a relatively smaller chance of secondary tumour induction than moderate or low doses. However, his own retrospective case-control study of the five year survival rates following the radiotherapy treatment of, among others, oropharynx tumours, which he conducted on the data at a cancer registration office, did not provide any convincing proof of this (68).

3.3.4 Latency time

The latency times, between the exposure to irradiation and the manifestation of a tumour, differ considerably. For instance, for skin tumours the shortest and the longest latency times are assumed to be 3 and 64 years, respectively (20). In the case of parotid tumours, a minimum latency period of 2 years has been proposed (69). In his study concerning radiogenic thyroid tumours, based on data from the literature, Van Daal showed that the average latency period increases as the observation time increases. This may be due to the fact that the period in which the tumours

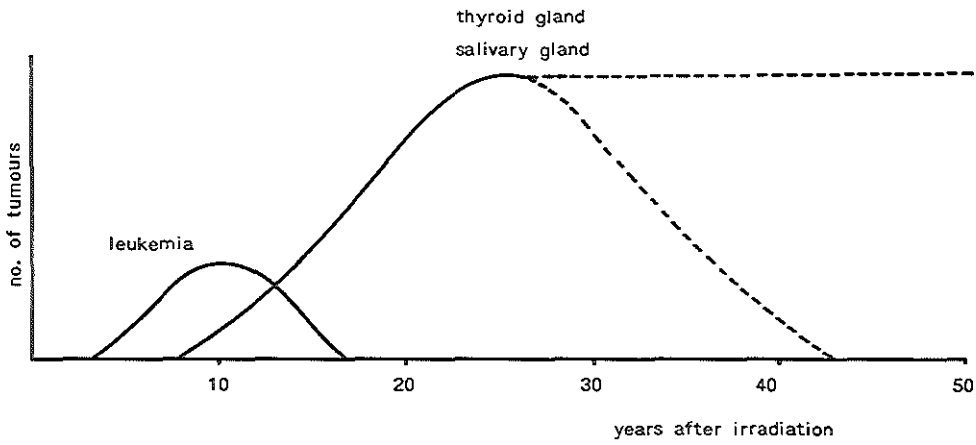

Figure 3.1 Relation between the time of exposure and the tumour manifestation time.

are likely to express themselves, after a certain minimum latency period, is unlimited (see Figure 3.1) (38).

3.3.5 Dose-response curve

In general, it is not possible to determine the exact course of the dose-response curve because epidemiologic data are lacking. An estimate can be made on the grounds of extrapolation of high to low doses and from animal to man. It can be assumed that, in the light of ionization distribution in space and time, the interaction between ionizing events in tissue in the very low dose range are negligible. The dose response at molecular and cellular level will, therefore, be linear. Although quantitative extrapolation from animal to man is unfeasible, it is possible to apply the shape of the dose-response curve from animals to man because the mechanism of cancer induction is the same for animals and human beings that have been exposed to low radiation doses (see Figure 3.2) (41).

3.3.6 Summary of the risk factors

In summarizing the risk factors, it is possible that sex may have some influence on the sensitivity of the origination of radiation induced head and neck tumours. However, we should keep in mind here, that sex can also predispose to the 'spontaneous' appearance of tumours. For instance, non-radiation induced thyroid tumours occur more frequently in women than in men.
The age on exposure, ethnical and genetic factors also seem to be of influence to radiation sensitivity. In the long run, it might become possible to indicate more groups within the population who are more at risk due to certain heredity factors, besides persons with multiple familial retinoblastomas, multiple paragangliomas and the nevoid basal cell carcinoma syndrome.
There are clear indications that the interior environment has an influence on the radiation sensitivity with regard to the induction of tumours. A high TSH level, a

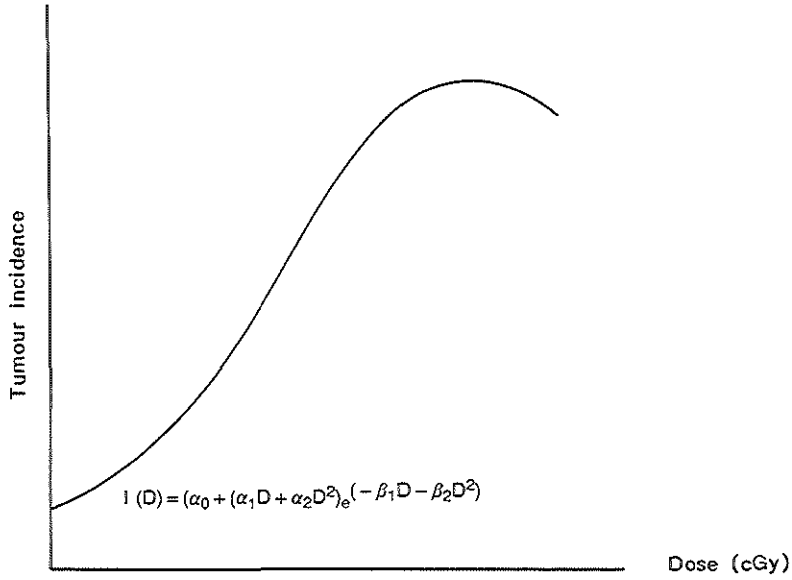

Figure 3.2 General dose-response model for radiation carcinogenesis, based on radiobiological experiments and epidemiological studies. I, tumour incidence; D, radiation dose: α_0, spontaneous incidence of tumours in the population; α_1, linear component; α_2, upward-curving quadratic component; β_1 and β_2, downward-curving components, defining cell-killing function.
According to: Fabrikant J.I. (41).

poor nutritional state and simultaneous treatment with cytotoxic drugs have been mentioned in this respect.
It has been shown that high LET radiation carries a higher tumour inducing capacity than low LET radiation. Some authors have suggested that therapeutic megavolt and cobalt radiation carries less risk of inducing tumours than orthovolt radiation. If this appears to be true, it will not be the result of the difference in energy, but to the radiation methods used: better skin sparing and less scatter. In the future, a larger number of radiation induced tumours can be expected because the modern high energy radiotherapy treatment methods will be more effective in curing the primary tumour and, therefore, the patients will live longer.
On the grounds of animal experiments and epidemiological studies, it is not possible to make a definite judgement on the influence of dose rate and fractionation. Both possibly have a sparing effect.
For every organ, the latency time of radiation induced tumours can differ considerably from person to person. The average latency time for radiation induced leukaemia is about 10 years and for solid tumours several decades. The manifestation time for radiation induced thyroid and salivary gland tumours seems to be limitless after a certain minimum latency period.
A dose-effect relationship has been established for the thyroid gland. It is assumed that there is a linear relationship for doses between 6 to 7 cGy and 1500 cGy. Above 2000 cGy the tumour inducing capacity decreases due to the destruction of thyroid tissue. A dose-effect relationship has also been demonstrated for salivary gland tumours.

3.4 STUDY DESIGNS

Initially, the relationship between the origination of tumours and prior irradiation was suggested in the light of *case histories.*
Duffy et al. (1950) established in their *case-control* study that in 28 cases of thyroid carcinoma, 9 cases had undergone irradiation of the thymus gland in their youth (5). Similar studies concerning the development of other tumours were carried out by Ju (1968) (73) on the salivary glands, by Martin et al. (1970) (20) on the skin and by Sakamoto et al. (1979) (74) on the pharynx.
The first non-concurrent *cohort study* was conducted by Simpson et al. (1950) on people who had been treated with röntgen irradiation to the thymus gland (75). Hazen et al. (1966) carried out a similar study on people who had been irradiated in their youth for abnormalities in the head and neck region (51). Modan et al. (1974) (21) examined a group of Jewish immigrants who had been irradiated on account of tinea capitis and Belsky et al. (1975) (46) investigated a group of people exposed to the Japanese atom bomb explosions.
A real health problem proved to be the radiation induced thyroid carcinoma: the 'Chicago endemic' (64). *Screening* for thyroid abnormalities was carried out by Pincus in 1967 (76).
In the 1970s, so-called Recall Clinics were set up in America, whereby people who had been irradiated in their youth were called up, examined and possibly operated on for thyroid abnormalities (77-79).
In the Netherlands follow-up investigations for thyroid abnormalities were also carried out via random sampling on people who had been irradiated in the head and neck region in their youth, in order to see whether it was necessary to examine all the people with this anamnesis (23).

3.5 SALIVARY GLANDS

Induced salivary gland tumours were observed in non-concurrent cohort studies following irradiation for benign ENT abnormalities (13,51), tinea capitis (21) and in the survivors of the Japanese atom bomb explosions (43,52).
From casuistic literature it is known that occupational exposure, I^{131} therapy for the treatment of thyroid carcinoma (80,81) and nasopharyngeal radium application to reduce hypertrophic adenoid tissue (81) have been held responsible for the induction of neoplasms of the salivary glands. Saksela et al. observed three cases of parotis carcinoma following the irradiation of benign mixed tumours of the same gland (quoted 82).
The phenomenon of increased sensitivity in younger age groups reported in Japanese research, was toned down in a later publication (43,52).
In a series of 31 possible radiation induced salivary gland tumours, Katz et al. discovered a woman-man ratio of 3:1. However, they also observed that women were exposed to radiation treatment (for keloids and I^{131} for thyroid abnormalities) more often than men (81). No differences were observed between the sexes in cohort studies on people who received external röntgen irradiation for benign ENT abnormalities (83), or in case-control studies on a group of people exposed to radioactive fall-out (14,15).

Table 3.4 Literature survey: radiation related salivary gland tumours

Author	(ref.)	Year	Study type	Type exposure	N/n*	Dose (cGy)**	Latency (yrs)**	Age exp.**	m/f	Malignant/ Benign	Localisation	Histology	Remarks
Ju	(73)	1968	case	X-ray (radium workers)	7	200-300 or more	15-25	18.5	4/3	4/2 (1 bilat.)	parotis 5 submandib. 2	mucoepiderm. ca. 2 mixed tumours 2 other 3	
Smith	(84)	1974	case	X-ray	2		25	5-10	1/1	1/1	parotis	mucoepiderm. 1 mixed tumour 1	-family history positive -father radiologist
Wiseman	(80)	1982	case	^{131}I	2	350/675 mC	3/10			2/0	parotis	non-Hodgkin lymphoma	-one case also thyroid carc.
Bacha	(53)	1983	case	X-ray (for leukemia)	1	2,400	5	12	0/1	0/1	parotis	mucoepidermoid ca.	-suggested co-factors: constitution and immunosuppression by medication
Takeichi	(14)	1976	case-control	A-bomb (Hiroshima)	36/ 211				19/17	19/17		mucoepiderm. ca. 6 malig. mix. ca. 5 other malignant 8	-benign tumours mostly mixed tumours
Walker	(69)	1981	case-control	X-ray	6/ 72	3,820	9	33	3/3	6/0	parotis	mucoepiderm. ca. 2 mixed malignant 2 other 2	-induced tumours behave like spontaneous tumours
Takeichi	(15)	1983	case-control	A-bomb (Hiroshima)	62/ 208					31/31	parotis 43 submandib. 14 other 19	mixed malig. 11 mucoepid. ca. 7 other 13	-benign mixed tumours 22 -RR = 11.0
Katz	(81)	1984	case-control	X-ray, radium, ^{131}I	31/ 275	800-1200	11-66	3-29	8/23	11/20	parotis 24 other 11	mucoepiderm. ca. 6 adenoid cyst. ca. 3 other 2	-4 patients had multiple lesions -6 patients also had thyroid tumours -1 patient had tonsillar radium treatment
Saenger	(11)	1960	cohort	X-ray	2/ 2,230	450-600	7-11	1-7	1/1	2/0		mucoepiderm. ca. 1 adenocarcinoma 1	

Hazen	(51)	1966	cohort	X-ray, radium	2 / 971	575/862	5-9	7-8	1/1		'mixed tumours'		
Belsky	(43)	1972	cohort	A-bomb (Hiroshima) (Nagasaki)	12/44,471	1->300	18	26	6/6	5/7	parotis 7 submandib. 3 minor glands 2	mucoepiderm. ca. 2 acinic cell ca. 1 other 2	-positive dose-effect relationship -younger age, higher risk
Modan	(21)	1974	cohort	X-ray	17/11,000	140	10			4/3	parotis		
Belsky	(52)	1975	cohort	A-bomb (Hiroshima) (Nagasaki)	16/41,797	1->300		26	8/8	5/11	cf Belski (1972) parotis 3 submandib. 1	cf Belski (1972) benign 4	-possible peak between '61 and '65
Shore	(110)	1976	cohort	X-ray	4/ 2,215	39	20	7	3/1	1/3	parotis	mixed tumours 2 pap. cystadeno. 1 acinic cell ca. 1	-40% excess psychiatric disorders among white exposed persons
Schneider	(83)	1977	cohort	X-ray	27/ 1,922	800	22	4.5	18/9 (in pop. 2:1)	8/19	parotis 23 submandib. 2 minor glands 2	mixed benign 17 mucoepiderm. ca. 7 other 3	-control group missing -incidence does not decline after 35 yrs
Colman	(13)	1978	cohort	X-ray	37/ 5,166	807	22	6.3		10/27	parotis 31 submandib. 4 unknown 2		-no dose-effect relationship
Schneider	(70)	1985	cohort	X-ray	67/ 5,379					16/51			-incidence does not decline

* in casuistry: number of cases
in case-control studies: irradiated cases/ total number of cases
in cohort studies: cases / total study group

** one figure indicates the absolute or mean number, otherwise the range is given

Three quarters of the salivary gland tumours are found in the parotis gland; the remaining ones are found in the submandibular or small salivary glands. One half to two thirds are malignant. In many cases multiple localizations are observed (81,84).
In 1942 Friedman discovered that the ductal epithelium of the salivary glands is very sensitive to irradiation (85). Histological examination of salivary gland tissue several months after exposure, revealed pleomorphism and atypia of the ductal epithelium (86). Other researchers succeeded in inducing a neoplastic cell line in nude mice using tissue from an irradiated human submandibular salivary gland (87).
Most of the malignant tumours are muco-epidermoid carcinomas (69). Other types which have been observed are malignant mixed tumours, adeno-cystic carcinomas, acinous cell tumours (83) and malignant lymphomas (80,81). By far the most benign induced salivary gland tumours are mixed tumours (15,43).
The latency times observed vary between 10 and 25 years (43,77). The shortest latency time recorded is 2 years (69), the longest 66 years (81).
The lowest doses to have been known to induce salivary gland tumours are 39 cGy (65) and 140 cGy (21).
There are too few data available to be able to draw up a dose-response curve. The examination of a population of Japanese who were exposed to the atom bomb explosions revealed evidence that the chance of people developing a salivary gland tumour depended on their distance from the explosion: the closer they were, the higher the risk (15,39).
Takeichi et al. carried out a case-control study on 208 patients with a histologically confirmed salivary gland tumour. Sixty-two were survivors of the atom bomb explosion in Hiroshima and 146 had not been exposed. An RR of 11.0 was established on the basis of the total number of exposed and non-exposed persons. They suggested that the incidence had reached its peak and was on the decrease, because the incidence in the five year interval, between 1967 and 1971, did not reach the same level as between 1957 and 1961 (15).
The study results per author are shown in Table 3.4.

3.6 BRAIN AND MENINGES

Irradiation of the neuro-cranium is not only likely to cause necrosis of the brain tissue but, in the long term, it can also lead to tumour induction in the brain and meninges.
These radiation induced tumours are usually the result of the medical-therapeutic treatment of malignancies, such as retinoblastoma (88), esthesioneuroblastoma (89) and pituitary adenoma (90), or of benign conditions, such as haemangioma planum of the skin (25), tubal disorders (26) and tinea capitis (91).
Also medical-diagnostic procedures, such as ventriculography using thorotrast, have been brought into association with brain tumours which developed later (92).
Recently, research has been carried out into the occurrence of brain tumours in occupationally exposed persons (93,94).
In the judgement of a second tumour, occurring after a latency period following irradiation, it is useful to note that multiple tumours arise in cases with phakomatoses, such as m. Recklinghausen. Sometimes double spontaneous brain tumours are observed, but this is very rare (95).

The most frequently observed radiation induced tumours are meningiomas (8), sarcomas (96) and astrocytomas (97).
In their report on 38 cases of radiation induced *meningiomas*, Iacono et al. made a distinction between tumours which arose following a low dose of radiation and those which appeared following a high dose. The group exposed to a high dose of radiation (2300-7200 cGy) displayed a shorter latency time (20.8 years) than the low-dose group (less than 800 cGy; 31.3 years). There also appeared to be a difference in the man-woman ratio: in the case of radiation induced meningiomas the ratio was 19:15 and in 'spontaneous' meningiomas 5:9 (98).
Modan et al. found four meningiomas in a cohort of 10,912 people who had been irradiated on account of tinea capitis and one case in a control group of equal size. These figures are too small to draw definite conclusions (21).
Animal experiments have shown that meningiomas can be induced by Co^{60} (99).
According to Powell et al., 15 cases of post-radiation *sarcoma* were described till 1977, located in or around the sella turcica in patients irradiated for brain or pituitary tumours. These tumours consisted of twelve fibrosarcomas and three osteogenic sarcomas. The radiation doses varied between 2400 and 7800 cGy and the latency times between 2.5 and 21 years (100).
Three years later Martin et al. gave an overview of 18 sarcomas: 14 fibrosarcomas, one osteosarcoma, one malignant fibrous histiocytoma and two undifferentiated sarcomas. They noted an average latency time of 10 years (101). Case reports have continued to appear since then.
Metastasising meningeal sarcomas could be induced in animal experiments by injecting the offspring of pregnant rats with Sr^{90} on the 18^{th} day of gestation (103).
Piatt et al. published a complete review of the literature on *astrocytomas* which were thought to be radiation induced. Seventeen cases were involved, the first was described by Jones in 1960 (97). Thirteen of the patients had been irradiated on account of brain tumours and four for benign disorders. The average latency time was 11.1 years, the doses varied between 400 and 6000 cGy (104).
In animal experiments it was possible to induce ependymomas in monkeys (105) and glioblastomas in monkeys (106) and rats (107).
A more unusual radiation induced tumour is the schwannoma (108-110), which has also been induced in animal experiments (107). One case of acoustic neuroma was described which arose following radiotherapy (110).
In a group of 2,215 people who had been irradiated for tinea capitis in their youth, Shore et al. found an incidence ratio of 2.8:1000 for benign and malignant brain tumours together. No such tumours were found in the control group (110). Modan et al. observed a ratio of 1.4:1000 in a group of 10,912 people treated in the same way, a significant difference with two control groups (21). In the treatment method for tinea capitis the pituitary gland received a dose of 50 cGy and the brain 120 to 140 cGy (65).
Sandler et al. found three brain tumours (two astro-cytomas and one unspecified) in a group of 904 persons who had been treated using nasopharyngeal radium (average 4.208 mgmin) after a mean follow-up period of 25 years. The incidence ratio was 3.7:1000. In a control group of 2,021 people treated in a different way no brain tumours were observed.
The difference was significant. The brain received 44 to 177 cGy in the exposed group (26).

Table 3.5 Literature survey: radiation related tumours brain and meninges

Author	(ref.)	Year	Study type	Type exposure	N/n*	Dose (cGy)**	Latency (yrs)**	Age exp.**	m/f	Malignant/ Benign	Localisation	Histology	Remarks
Beller	(91)	1972	case	X-ray tinea capitis	16		22-45	7.6	10/6	0/16	meninges	meningioma	
Gonzalez-Vitale	(90)	1976	case	X-ray pituitary tumour	1	5,000	11		1/0	1/0		malignant fibrous histiocytoma	-presents literature survey 18 fibrosarcomas after radiotherapy for brain tumours
Powell	(100)	1977	case	X-ray	1	5,000	13	52	1/0	1/0	hypophysis	fibrosarcoma	-presents literature data: doses 2400-7800 cGy latency 2.5 - 21 years
Robinson	(108)	1978	case	X-ray	3	3,400	24.5	19	2/1	2/1		astrocytoma 2 astrocytoma 1	
Sogg	(109)	1978	case	X-ray craniopharyngioma	1	6,007	5	9	0/1	1/0		astrocytoma	-radiated craniopharyngioma enhances risk for radiation-induced tumours
Coppeto	(60)	1979	case	Proton radiation acromegaly	1	10,000	7	46	1/0	1/0		fibrous histiocytoma	
Preissig	(49)	1979	case	X-ray glomus jugulare	1	4,480	8	43	1/0	1/0	cerebellum	astrocytoma	
Martin	(101)	1980	case	X-ray pituitary tumour	1	4,500	5	18	0/1	1/0	hypophysis	pituitary fibrosarcoma	-presents literature data post-irradiation pituitary sarcomas: median latency 10 years
Cohen	(95)	1981	case	X-ray medulloblastoma	1	8,000	14	4	0/1	1/0	frontal lobe	astrocytoma	
Jacono	(98)	1981	case	X-ray medulloblastoma	1	5,000	27	3	0/1	1/0	multiple lesions	meningiomas	-for post-irradiation meningiomas applies: after low-dose radiation latency is longer (30 years) than after high dose (20 years)

Pieterse	(102)	1982	case	X-ray pituitary adenoma	1		4,500	20	48	1/0	1/0	hypophysis	fibrosarcoma	
Piatt	(104)	1983	case	X-ray pituitary adenoma	1		4,900	14	38	1/0	1/0	fronto temporal bilateral	glioblastoma multiforme	-from literature data: mean latency 11.1 years
Saenger	(11)	1960	cohort	X-ray benignancies	1/	2,230	400	11	11	1/0	1/0		glioblastoma multiforme	
Modan	(21)	1974	cohort	X-ray tinea capitis	16/	11,000	140	6-21			8/8		malignant 8 benign meningioma 4 other benign 4	
Shore	(110)	1976	cohort	X-ray tinea capitis	5/	2,215	140	17	8	5/0	2/3		astrocytoma 2 meningioma 2 glioma 1 schwannoma 2	
Colman	(13)	1978	cohort	X-ray	37/	5,166	954	23	3.8		7/16			-positive dose effect relationship -incidence 32 times U.S. population incidence
Sandler	(26)	1982	cohort	radium	3/	904	44-78	15-20	11		2/	brain	astrocytoma 2	

* in casuistry: number of cases
in cohort studies : cases / total study group
** one figure indicates the absolute or mean number, otherwise the range is given

The differences in incidence ratio between these three studies can be explained by the differences in observation time.
Colman et al. conducted an investigation on 5,166 subjects who had been exposed to röntgen irradiation in their youth. Eighty per cent had been irradiated on the tonsils and adenoid. In the 3,108 people traced, 23 tumours of neural origin were observed, including nine brain tumours (a ratio of 2.9:1000 was established). The six malignant tumours found were 32 times higher than would have been expected on the grounds of the incidence in the American population. The average age on exposure was 3.8 years. After the division of the 23 tumours according to the amount of radiation received, a positive dose-effect relationship was observed. Unfortunately, this study did not involve a control group (13).
Table 3.5 shows the study results per author.

3.7 PHARYNX AND LARYNX

Radiation induced tumours of the pharynx and larynx have only been described following medical treatment with ionizing radiation. Nearly all the cases were associated with röntgen (initially orthovolt, later also megavolt) or cobalt irradiation (61). One single case has been described following internal ^{122}I application (31).
The tumour inducing irradiation was usually given for benign complaints, such as tuberculotic lymphomas (111), thyrotoxicosis (112), tubal disorders (74) and larynx papillomas (113-115).
Malignant (55,74) and benign (116) head and neck tumours formed other indications for irradiation, particularly the first stage of larynx carcinoma (57,59,61,117). The radiation treatment doses varied between 450 (118) and 1100 (119) to 20,000 (74,111) cGy.
By far the most induced tumours of the pharynx and larynx are squamous cell carcinomas. Only very few fibrosarcomas have been described (68,120,121). Sporadic tumour types, such as angiosarcoma (122), acinous cell carcinoma (123), adenocarcinoma (124) and malignant fibrous histiocytoma (116), have also been described.
In 1965 Goolden et al. published an overview of 67 pharyngeal tumours, from the literature up till then, which were thought to be radiation induced. The reasons for exposure were usually tuberculotic glands or thyrotoxicosis. In most cases the origination of the pharynx tumour was preceded by a radiation induced skin tumour in the irradiated area. The average latency time of the pharynx tumours was 30 years. The post-cricoid region appeared to be the most sensitive (125).
The fact that the hypopharynx is sensitive to radiation induced tumours is also evident in case-control studies in groups of cancer patients. In 1967 Van Dishoeck found that 8% of the patients who he had treated on account of hypopharynx tumours had a radiation treatment in their anamnesis (126). Similarly, Beekmans discovered that in a group of 328 patients with a larynx or hypopharynx tumour, 21 of them had undergone radiation treatment an average of 20 years previously owing to benign disorders in the head and neck region. Eight of these tumours were localized in the hypopharynx (quoted 127).
A study by Lawson et al., in which they examined the division of 45 post-irradiation

tumours of the larynx, pharynx and oesophagus, also provided evidence that the hypopharynx is more sensitive to radiation induced tumours than the larynx. The average latency time was 27 years. Thirty-three of the tumours appeared to be localized in the hypopharynx (61).
Sakamoto et al. supported these results in a patient-control study on 2,030 patients with a malignancy of the pharynx, larynx or thyroid gland. Seven out of the 584 pharyngeal tumours (1.20%), two out of the 1208 larynx tumours (0.17%) and six out of the 202 hypopharynx tumours (2.97%) had developed following radiation treatment. The number of hypopharynx tumours which arose following irradiation was even higher than for the thyroid gland (6 out of 238 = 2.52%)! In the epipharynx carcinoma patients, no radiation treatment was mentioned in the anamnesis. The latency time for the induced hypopharynx carcinomas was 30.2 years (74).
Goolden's finding that the post-cricoid region is predisposed to developing radiation induced tumours was supported in a recent study by Stell. He observed that 18 of the 385 patients with a hypopharynx tumour had been irradiated in the past on account of benign disorders, usually thyrotoxicosis. In 11 of these cases the process originated from the post-cricoid region. The average latency period was 35 years. The fact that 15 of the 18 tumours were found in women was explained by the observation that thyrotoxicosis and post-cricoid carcinoma are more frequent in women (119).
The relationship between the irradiation of an early stage larynx carcinoma and the origination of a second primary tumour in the irradiated area has been studied in several cohort studies. The first reports on tumour induction in the irradiated region appeared in 1955 (128).
Lawson et al. followed 535 patients for 5 to 25 years after treatment for a T1a or T1b larynx carcinoma. The treatment had consisted of surgery or radiotherapy. Thirty patients developed a second primary tumour of the larynx or hypopharynx, 9% belonged to the irradiated group and 3.9% to the surgical group. They also studied all the known cases of radiation induced tumours of the larynx or pharynx and made a striking observation. The latency period for the development of larynx or hypopharynx carcinoma following orthovolt radiotherapy, on account of benign neck disorders, appeared to be 27 years. This latency time decreased to 12 or 15 years if the radiation beam had been aimed at the larynx for the treatment of larynx papillomas and fell further, to 7 years, after megavolt radiotherapy for larynx carcinoma. On these grounds they assumed that megavolt irradiation had a higher radiobiological effect. The short latency period following megavolt therapy together with an increase in life expectancy caused them to advise against applying this treatment in persons younger than 50 years of age (61). In their comparison of the latency times, the authors did not take two factors into consideration which could influence the latency time. In the first place it is possible that the short latency time of the tumours induced following the irradiation of juvenile papillomas, was due to the young age at which the children were irradiated. Secondly, the latency times in the various studies were calculated in different ways. Case reports were used for radiation induced tumours following radiotherapy for benign neck disorders and juvenile papillomas and a cohort of persons was followed for tumours induced after radiotherapy for larynx carcinoma: if the observation time had been longer the average latency time would have probably increased.

Table 3.6 Literature survey: radiation related malignant tumours larynx and pharynx

Author	(ref.)	Year	Study type	Type exposure	N/n*	Dose (cGy)**	Latency (yrs)**	Age exp.**	m/f	Localisation	Histology	Remarks
Lossen	(3)	1936	case	X-ray lymph glands	2		10		2/0	larynx		-Patient sued radiotherapist for damages
Kruchen	(4)	1937	case	X-ray thyroid gland	1		20	45	1/0	hypopharynx	carcinoma simplex	
Den Hoed	(111)	1946	case	X-ray tuberculous glands	2	20,000	27-28	16	1/1	larynx	carcinoma	-In one patient also skin tumour
Holinger	(123)	1953	case	X-ray tuberculous glands	3		25	31	1/2	larynx 2 hypopharynx 1	carcinoma 1 fibrosarcoma 1	-Literature survey: 12 cases -3 men, 9 women -latency 16-32 years
Goolden	(125)	1965	case	X-ray thyrotoxicosis	4		40	36	0/4	oesophagus 2 hypopharynx 2	carcinomas	-Indicates post cricoid region of hypopharynx as a sensitive area
McGraw	(113)	1965	case	X-ray	3	3,000	36	17	1/2	oesophagus 1 larynx 1 laryngopharynx 1	carcinomas	-All patients also have another tumour in the irradiated field
Gerlings	(112)	1969	case	X-ray	5	3,000	33	25	2/3	larynx 3 hypopharynx 1 oesophagus 1	carcinomas	
Taylor	(57)	1977	case	X-ray larynx carcinoma	11	tumour dose	11	51	9/2	larynx	carcinomas	-Author questions course of second tumour: radiation, carcinogenic behaviour or immunologic predestination
Donaldson	(121)	1978	case	X-ray larynx carcinoma	1	5,600	11	68	1/0	larynx	fibrosarcoma	
McKillop	(31)	1978	case	X-ray thyrotoxicosis	1	2×30 mCi	8	44	0/1	larynx	sarcoma	

Reibel	(123)	1981	case	X-ray thyrotoxicosis	1		450	46	10	0/1	subglottic tracheal	acinic cell carcinoma	
Narula	(122)	1986	case	X-ray	2		5,200	21-25	16-35	2/0	nasopharynx	angiosarcoma	
Beekmans (cited 127)		1966	case control	X-ray benign diseases	21/	328		20			larynx 13 hypopharynx 8		
Sakamoto	(74)	1979	case control	X-ray	14/	2,015	6,600	28	20	4/10	pharynx 7 larynx 2 thyroid 6 (double)	carcinomas	-Epipharynx relatively resistent to radiation induced tumours
Stell	(119)	1984	case control	X-ray	18/	385	1,100-3,200	35		3/15	hypopharynx postcricoidal (1 double)	carcinomas	
Seydell	(68)	1975	cohort	X-ray malignancies	9/	611	6,800	2-32			oropharynx	epidermoidcarcinoma 8 fibrosarcoma 1	High dose radiation bears lower risk than low or medium doses
Lawson	(61)	1975	cohort	X-ray larynx carcinoma	20/	225	tumour dose	5-25			hypopharynx 2 larynx 18	carcinomas	-Literature survey: 45 cases hypopharynx 33, larynx 12, oesophagus 2 mean latency 27 years
Glanz	(117)	1976	cohort	X-ray larynx carcinoma	25/	60	tumour dose	9.9	51.3	24/ 1	larynx	carcinomas	-Ten cases were taken from other studies
Lund	(59)	1982	cohort	X-ray larynx carcinoma	10/	266	tumour dose	12		9/1	larynx 10 pharynx 1	carcinomas-	Discusses smoking habits: concludes radiation induction

* in casuistry: number of cases
in case control studies : irradiated cases/ total number of cases
in cohort studies: cases / total study group

** one figure indicates the absolute or mean number, otherwise the range is given

Glanz found 15 second primary tumours in 60 patients who had been treated successfully for T1a and T1b larynx carcinoma and survived longer than 5 years (25%). In the analysis she also added 10 patients with similar tumours from other clinics, 9 men and 1 woman. The latency times varied from 5 to 18 years, average 9.9 years. According to her, the following observations proved that these tumours were radiation induced:

- The interval matched that of a radiation induced tumour. As a rule tumour recurrence occurs within the first two years following treatment.
- The second tumour developed in the irradiated area.
- In patients treated exclusively by surgery, secondary tumours are extremely rare (1/17).
- Histological examination revealed that the second tumour originated from the irradiated surface epithelium and not from deeper lying 'nests' of tumour cells which had survived the irradiation (117).

In 450 cases of larynx and hypopharynx carcinoma, Taylor found 11 patients in whom the tumour recurred more than 5 years after irradiation. He brought forward three possible causes for the recurrence:

- The second tumour resulted from the same carcinogenic influence (smoking) as the first.
- The second tumour developed from cell groups which were not destroyed by the radiotherapy.
- The second tumour was induced by irradiation.

He also wondered whether the radiation method, orthovolt, megavolt or cobalt, had any effect on the pattern of tumour induction (57).
Finally, in their patient material, Lund et al. found 10 (3.8%) second primary tumours in 266 patients who had been irradiated on account of T1 or T2 larynx carcinoma after a mean latency time of 11.8 years. On the grounds of the observation that a second primary tumour arose just as frequently in patients who smoked as in those who did not, she concluded that the tumours had been induced by irradiation. From data in the literature, she calculated that second primary tumours developed in 5% of the cases irradiated on account of early larynx carcinoma (59).
The study data per author are shown in Table 3.6.

3.8 THYROID GLAND

The organ in the head and neck region which gained the greatest clinical meaning with regard to tumour induction is the thyroid gland. A monograph on this subject was published in 1977 (129).
Winship et al. conducted a survey on thyroid cancer in children in many hospitals throughout the world. More than 80% of the children with a thyroid malignancy appeared to have been exposed to radiation in one form or another in their very young years (130).
It has been alledged that induced thyroid carcinoma occurs twice as frequently in women as in men (38). Socio-cultural factors also appear to have some influence: Jewish children seem to be the most predisposed (45).
The portion of thyroid cells that are sublethally damaged after irradiation may give rise to malignant growth during further cell division. The hypofunction of the

thyroid gland, resulting from the irradiation, can lead to a higher production of TSH by the pituitary gland due to the feed-back mechanism. Animal experiments have shown that a raised TSH level in itself increases the chance of tumour induction (131). Moreover, there is evidence that the simultaneous exposure of the thyroid and pituitary gland involves a greater risk of tumour induction than irradiation of the thyroid gland alone (51,56).
Eighty-five per cent of induced thyroid gland tumours are of the papillary or mixed type and 15% are of the follicular type. At diagnosis 30 to 80% have already metastasised locally (38,77). The abnormality following induction is more likely to be multifocal than in non-induced carcinomas (30-50%) (38).
The average latency time, the time between irradiation and the diagnosis of the tumour, increases with the length of the observation periods. Twenty-eight years is mentioned in a fairly recent study (77). The minimum limit is given as 5 years (66).
The lowest doses thought to be responsible for thyroid tumour induction are 6.5 (21), 20 (132), 90 (13) and 150 (133) cGy. Between these values and ca. 1500 cGy there appears to be a linear relationship between dose and effect. Hempelmann et al. (45) gave the following figures for this: $2.5 \pm 0.5 \cdot 10^{-6} \cdot cGy^{-1} \cdot yr^{-1}$ and Maxon et al. (67): $4.2 \cdot 10^{-6} \cdot cGy^{-1} \cdot yr^{-1}$. The tumour inducing capacity probably decreases sharply above 2000 cGy, due to thyroid tissue destruction, which is also the case with the capacity for malignant degeneration (22). Recently, attention has been focused on the fact that high radiation doses, for abnormalities in the region of the thyroid gland, can give rise to radiation induced thyroid tumours. The amount of scatter received by the thyroid gland during treatment may well lie in the sensitive dose area for this organ (134).

3.9 SKIN

The first tumour thought to be radiation induced concerned a skin tumour in a labourer at a factory which manufactured X-ray tubes (1). Skin tumours resulting from irradiation as an occupational disease have been reported in radiologists (16) and workers in uranium mines (135). Skin tumours following medical treatment, for tinea capitis, have also been observed (46).
At the beginning of this century, when nearly all of the radiation induced skin tumours were acquired occupationally, most of the cases concerned epitheliomas of the hands. Later on, when it became the fashion to irradiate dermatoses particularly in the head and neck region (on account of over-productive sebacous glands), most of the tumours were found to be basal cell carcinomas (20). A radiation induced sarcoma has also been described (136).
The fact that radiation induced skin tumours are not mentioned in some of the studies where use has been made of death statistics or tumour registration data, is probably the result of the very small number of people who die of skin tumours and under-registration at tumour registration offices (46).
Martin et al. reviewed the files of patients at their dermatology clinic to see how many of them had an anamnesis of radiation exposure. They observed that 19% of those with a skin tumour had been exposed, against only 5% of the other patients. There was a woman : man ratio of 3:1. The chief indication for irradiation in women was hirsutism, in men acne. Haemangioma planum also formed an indica-

tion. The latency period varied from 3 to 64 years, the average was 21 years. There was a basal cell carcinoma : epithelioma ratio of 4:1. The multicentricity of the lesions and the higher tendency to metastasise than tumours from other origins was striking. The mortality rate was also higher in the tumour patients who had been exposed to irradiation, reaching 10% - of whom two thirds within 5 years. They found evidence that the chance of tumour manifestation is maintained for the whole of the patient's life (20).
Shore et al. compared a population of 2200 persons who had been irradiated on account of tinea capitis with a control group of 1400 people who had been treated in a different manner. The scalp received a dose of 300 to 600 cGy during radiotherapy. The average follow-up period was 26 years. The minimum latency period was 20 years, the average was 32.2 years. In the irradiated group 41 patients were found to have a skin tumour, some of them had multiple lesions. Only three cases were observed in the control group. All the tumours were basal cell carcinomas.
It was thought that ultraviolet light from sunlight was a contributing factor because:
- The tumours were chiefly localized in areas of the head and neck which were exposed to sunlight.
- The tumours were particularly common in people with fair skin.
- Tumours were only found in white people, although 25% of the study group comprised coloured people.

The fact that an increased skin tumour incidence has not been observed in survivors of the Japanese atom bomb explosions is attributed to the high level of skin pigmentation in Japanese people. The authors concluded that the estimations of skin sensitivity to radiation induced tumours up till then had been too low and they recommended that the ICRP norm (50 rem/year) be reduced (46).
Howell observed that the latency period in people with a certain disposition to developing skin tumours (the nevoid basal cell carcinoma syndrome) was considerably shorter (0.5 to 3 years) than in 'normal' irradiated people. He concluded from this that the mechanism of carcinogenesis in these basal cell carcinomas takes place in at least two stages (50).
Van Daal et al. recently published the results of a cohort study on 605 persons who had been irradiated 16 to 46 years previously for benign disorders in the head and neck region. A clinical examination was carried out on 257 people, in whom 20 skin tumours (one epithelioma, the remainder were all basal cell carcinomas) and 7 thyroid tumours were found. In the light of the figures expected according to the UNSCEAR scale, these results meant a higher incidence of skin tumours (factor 7) and a lower incidence of thyroid tumours (factor 4). Possible causes were stated as being differences in patient selection, study methods and treatment time (137). Reanalysis of the study data revealed a tumour induction rate of 40 skin cancers per 10^6 persons per cGy. On account of these late radiation effects they concluded that benign skin disorders should not be treated by radiotherapy (138).

3.10 PARATHYROID GLANDS

In 1975 Rosen et al. described a parathyroid adenoma which had developed 40 years after irradiation for hirsutism (12).

Several years later a report appeared on 27 operations which had been performed for hyperparathyroidism in people who had been irradiated in their youth for benign disorders in the head and neck region. In 13 cases a parathyroid adenoma was observed. In 4 cases additional malignant and in 6 cases additional benign thyroid tumours were found (139).
In 1979 Russ et al. brought out a report of a retrospective investigation in which the anamneses of 74 patients with a histologically confirmed diagnosis of parathyroid adenoma were examined for radiation exposure. Medical-diagnostic or therapeutic irradiation appeared in 25% of the cases, as opposed to 7.9% in a control group. The average age on exposure was 16 years. The interval between exposure and surgical removal of the adenoma was 24 to 47 years, the mean latency was 30 years. The major portion of the irradiated patients with parathyroid adenomas also developed other induced tumours, for example of the thyroid, breast, parotis and skin (140).
Van Daal et al. found a clear relationship between irradiation in the head and neck region and the development of functional or morphological abnormalities (adenomas) of the parathyroid glands in their study on 257 previously irradiated persons. They advise preoperative screening for hyperparathyroidism and extensive exploration of all parathyroid glands in patients who are to undergo surgery for radiation related thyroid nodules (141).
Tumours of the parathyroid glands have also been induced by ionizing radiation in animal experiments (142).

3.11 MASTOID AND NASAL SINUSES

In 1952 Aub et al. described three epidermoid carcinomas of the nasal sinuses and petrous bone in people who had been exposed to internal irradiation, via radioactive substances a few decades earlier. The people (usually women), had either been employed in the watch-making industry where they had used paint containing radium, in laboratories, or had been given oral or intravenous radioactive substances as medicine (7).
In a group of 5058 people who had been exposed in this manner, 21 mastoid carcinomas and 11 malignant tumours of the nasal sinuses were found. The latency time varied between 20 and 50 years, with an average of 33 years. More than a third of the malignancies were mucoepidermoid tumours, which are very rarely observed among non-radiation induced tumours of the mastoid and nasal sinuses. The lowest dose calculated was 605 cGy. Thirteen per cent of the people who had been exposed to more than 1000 cGy developed a malignant mastoid or paranasal sinus tumour. The predisposition of the mastoid and nasal sinuses for developing radiation induced tumours was explained through the observation that radon gas - a daughter product of radium - accumulates in poorly ventilated body cavities (17,18).
Mastoid tumours have not only been observed following internal exposure to radioactive substances but also following external irradiation for the treatment of recurrent cerebellar astrocytoma (143) and thyroid carcinoma (144).
It has been reported that carcinoma of the maxillary sinus can develop after a latency period of 12 to 24 years following thorotrast instillation. Since 1980, 18 such tumours have been mentioned in case reports (33,35).

One case of ethmoid adenocarcinoma has been described, 30 years after exposure to a high dose of radiotherapy on account of a bilateral retinoblastoma (145).

3.12 OTHER HEAD AND NECK ORGANS

The first osteogenic sarcoma was described by Cahan et al. in 1948. It had developed following radiotherapy for retinoblastoma (4). Such tumours have also been discovered in the orbita (146), os temporale (147) and the brain (see brain sarcoma). Sixty-two secondary tumours of varying natures were observed recently in a group of 693 patients, an average of 10.4 years after irradiation for bilateral retinoblastoma (48).
In a case report, a patient with fibrosarcoma of the mandibula was described who had also undergone radiotherapy for retinoblastoma (148).
The following more or less well documented tumours have also been described: dumb-bell sarcoma of the foramen jugulare (149), carcinoma of a sebaceous gland on the eyelid (150), odontoma of the jaw (151), several malignancies of the tongue (6,152), sarcoma of the lip (153) and neoplastic lymphangitis (154).

3.13 MULTICENTRICITY AND PLURALITY

On the basis of the physical properties of ionizing radiation, it is possible for a number of tumours to develop simultaneously at various locations in the irradiated tissue. In an organ this manifests itself in the form of multicentricity and in an organ system in plurality.
A genetically determined increased sensitivity to developing radiation induced tumours may play a part here (42,46).
In 1946 Den Hoed described a patient who had developed a basal cell carcinoma of the skin and a larynx carcinoma, 25 years after radiation treatment for tuberculotic lymphomas (111). Since then, several - chiefly casuistic - publications have appeared on multiple radiation induced tumours (74,77,109).
Triple radiation induced tumours - a 'hattrick' - have been described in the head and neck region (113,156).
Multiple tumours have also been revealed in retrospective case-report (140) and cohort (42) studies.
Animal experiments have proved that it is possible to induce double tumours (103).
Scanlon stated that if a radiation induced tumour appears in a gland, the risk of other glands developing tumours in the irradiated region is significantly increased. He called this 'polyglandular neoplastic potential' (77).

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CHAPTER 4
THE DESIGN OF THE STUDY

4.1 INTRODUCTION

The most important question in this study concerned the long-term influence of nasopharyngeal radium irradiation on people's health. The principal considerations were tumour induction in the head and neck region and disturbances in processes which are influenced by hormones. In view of the possibility that these effects are relatively rare and for the sake of the statistical evidential value, we endeavoured to identify as many people as possible who have been treated using nasopharyngeal radium irradiation in the past.
Owing to the fact that the latency time of solid tumours can be several decades or more, it was necessary to allow a fair period of time to elapse between the treatment and the person's participation in the present study.
With the goal of, among other things, tracing a suitable study population, a questionnaire was sent to ENT specialists in the summer of 1982. Members of the Dutch Ear Nose and Throat Society were invited to take part in the survey, but bearing in mind the period in which the therapy was applied, only those who had become members before or in 1960 and whose names appeared in the annual report of 1980 received a request. This involved 110 ENT specialists (see Appendix 1).
On the basis of the results of the questionnaire, ENT specialists in the Netherlands and Belgium were approached by letter or telephone with a number of specific questions.
In order to find out whether the data in patients' records formed a suitable source of information, a study was carried out in the archives of eight ENT clinics and one radiotherapy department. Assessments were made of the possibility of finding sufficiently large numbers of irradiated persons as well as non-irradiated control subjects. Obviously, factors such as time, manpower and cost played a part in this. It was finally decided that the records in five Dutch ENT archives were suitable for study purposes.
See Table 4.1 for a chronological presentation of the data collected.

Table 4.1 Data collection in chronological rank order

Collection method	Period
Survey of 110 ENT specialists	Summer 1982
Study group from 5 ENT archives	Sept. '82 -June '83
Controls from 5 ENT archives	Jan.'83 -Dec'83
Follow-up of 500 non-selected subjects	July'83- Dec. '83
Follow-up whole group of 4922 persons	July'84- Feb. '85
Health surveys of 4457 subjects	Feb.'85- Aug. '85
Asking patient's permission to verify 644 'tumours'	Jan.'86- Mar. '86
Verification of 505 'tumours' via the specialist concerned	Apr.'86- Aug. '86

4.2 THE STUDY GROUP

People born between 1910 and 1965 were eligible for inclusion in the study.
The tracing of data in the records of irradiated and control subjects was carried out by the secretarial staff of the ENT clinics concerned. The diagnosis was always taken from the record cards by the same ENT specialist - the author.

4.2.1 The irradiated group

The record cards of the irradiated subjects were traced systematically. The following data were noted: surname, christian name(s), address, date of birth or age, type of health insurance, date of first consultation, diagnosis, data when the irradiation took place, the number of exposures and the duration of treatment. Where possible, the name of the patient's g.p. at that time was also noted. Each irradiated person was given an identification and clinic number (see Appendix 3).
For the purpose of compiling a control group, the data per clinic were expressed according to the year of birth (5 year groups) and the year of the first consultation (5 year groups).

4.2.2 Control persons

The control group was compiled on the basis of the data collected on the irradiated group per clinic. At each ENT clinic the records of random potential control persons were taken from the archives. If it appeared that their sex and years of birth and treatment matched those of a person in the irradiated group they were included in the control group. This process was repeated until the control group was complete. An example of the way in which a control group was compiled (clinic 2) is shown in Appendix 4.
The same data was noted for the control persons as for the irradiated persons. The groups only differed with regard to whether or not they had been exposed to radiation and the diagnosis.

4.2.3 Results

In three clinics the subject's sex could only be deduced on the grounds of the christian name. As the christian names did not always give a definite answer, a number have been noted as 'sex unknown'. Erroneously, the irradiated subjects in whom the sex was unknown were not included in the rendering of the irradiated groups, so a deficit arose in the control groups from three clinics. See Table 4.2 for the results of the compilation of the study group.

4.3 FOLLOW-UP

Follow-up methods were tested in 500 persons - about one tenth of the total study group - from clinic 3 as from July 1983. For each person, a request was made to the Registry of Births, Deaths and Marriages in the municipality mentioned on the record card, in order to acquire the following information:

Table 4.2 The number of exposed and non-exposed study subjects per sex and clinic

	Males		Females		Total	
Clinic	Exp	NExp	Exp	NExp	Exp	NExp
1	723	648	477	463	1200	1111
2	188	184	140	142	328	326
3	388	373	346	333	734	706
4	83	85	60	59	143	144
5	88	58	49	35	137	93
Total	1470	1348	1072	1032	2542	2380

- Is the person still living at the same address?
- If the person has moved, what is the new address?
- If the patient is deceased, what is the date of death and the death certificate number?

The form and accompanying letter used for this purpose are shown in Appendix 5. If the person had moved, the new municipality/municipalities was/were approached until the new address was found or it was discovered that the person was deceased. In many cases the forms were forwarded automatically by the record offices.
As the results of this test were considered to be satisfactory, it was decided to conduct the follow-up for the total study group in this manner. The procedure was started in July 1984.

4.3.1 Emigrated

When previously emigrated Dutch people return to the Netherlands, this event is recorded at the Government Inspection Department of the Public Registry Offices for Births, Deaths and Marriages in The Hague. In order to persue the follow-up in cases where the people had remigrated, the data of 241 emigrated persons were sent to this registry office. In this way it was possible to trace 46 of the emigrated people for follow-up.

4.3.2 Moved, present whereabouts unknown

A number of people appeared to have moved without the record office in the municipality concerned knowing the new address. However, it was possible to persue the follow-up in the case of 45 out of the 175 'untraceables'. The new addresses of 43 people were found in the archives of the Ministry of Defence. Two people had died, which was revealed by the Central Bureau of Genealogy.
Attempts to find untraceable people via the general patient archives of the hospital where the patient was treated at that time, produced little result. It was only possible to track down one of the 25 untraceables from clinic 2.

4.3.3 Deceased

In the event that study subjects were found to have died, information about the cause of death was requested and obtained from the Central Statistical Office (CSO). The applications went via the chief medical officer. In 144 out of the 150 deceased (96%) it was possible to find out the cause of death. In five cases this was not possible because the people had died abroad; in one case the information could not be found.

4.3.4 Results

At the end of the follow-up phase in February 1985, it appeared that from the total study group of 4922 persons 4607 (93.6%) had been traced. See Table 4.3 for a summary of the follow-up.

Table 4.3 Follow-up status study group

Status	Number	(%)
Traced	4607	93.6
Alive, of whom	4457	90.6
Respondents	3855	78.3
Non-respondents	602	12.2
Deceased	150	3.0
Untraceable, of whom	315	6.4
Emigrated	196	4.0
Lost	119	2.4
Total	4922	100.0

4.4 THE QUESTIONNAIRE

In February 1985 a health questionnaire and accompanying letter was sent to 4457 study subjects (see Appendix 6) whose current address was known. In several dozen cases the people concerned were living in Belgium or Germany, very close to the treatment district of clinic 1. In the address, only the initials and surname were used; in the case of married women only the maiden name.
After three weeks the 2167 non-respondents (48.6%) were sent a reminder consisting of the same health survey and an accompanying letter. After this reminder the follow-up was continued with the assistance of the Institute for Social Scientific Research in Tilburg.
Interviewers from this institute were informed about the aim and design of the study. The 1178 remaining non-respondents (26.4%) were approached by telephone or if they were not on the telephone were visited at home. (A small number of people living in remote places and without a telephone were not followed-up). In 576 of the cases it proved possible to obtain answers which were suitable for processing. The final non-response consisted of 602 persons (13.5%).

The interviewers noted the reason for non-response for 555 non-respondents (92%). It usually comprised a refusal without motives being given. Quite often the people concerned could not be contacted owing to an unlisted telephone number, or were always out or did not answer the door. Promises to still send back the form or announcements that the form was already on its way were heard frequently. In a few cases the people did not respond as a matter of principle or for reasons of privacy. Further grounds for non-response were mental deficiency, psychiatric treatment or long trips abroad. See Table 4.4 for a detailed list of reasons for non-response.

Table 4.4 Reasons for non-response (N = 602)

Reason	N
Flat refusal	211
Form already sent back	90
Moved	51
Never home	47
Promise to return the form	42
Address unknown	19
Unreachable by phone	18
Reasons of privacy	16
No telephone, lives remotely	12
Unlisted address/telephone number	11
Opposed in principle	6
Personal details incorrect	5
Long trips abroad	5
Ill at home	4
Did not answer the door	4
Undergoing psychiatric treatment	4
Admitted to hospital	3
Mentally deficient	2
Divorced, moved away	2
Died recently	1
Drug addiction	1
In prison	1
Reason unknown	47
Total	602

During the survey it appeared that a number of health questionnaires had not been filled in by the study person intended but by a relative with the same name. This was partly the result of the brief data used in the address. After comparing the date of birth which had been filled in on the questionnaire with that of the intended study subject it appeared that this had taken place in 177 cases.
The study subjects were approached once again, with an adapted version of the accompanying letter and using a more detailed address (including the date of birth). This method proved to be successful in 141 (79.7%) of the cases, sometimes following a reminder per telephone or post.

4.4.1 Results

A total of 3855 completed questionnaires were returned (86.5% of those sent), see Table 4.3.

4.5 VERIFICATION OF A POSITIVE TUMOUR ANAMNESIS

In January 1986 a start was made to verify the positive tumour anamneses suspected on the grounds of the answers filled in on the health questionnaires. No verification was carried out in cases where it - almost - certainly concerned a benign complaint. In order to limit the number of cases requiring verification, those in whom it was likely that a hysterectomy had been performed on account of menometrorrhagia and those in whom cervix cytology had taken place, were not followed-up. (See Chapter 5 Coding questionnaire information).

4.5.1 Asking the study subjects for permission

In the 644 suspected cases of neoplastic disorders, an attempt was made to acquire the person's original clinical or pathological diagnosis from the specialist who had treated the patient at that time.
These members of the study group were sent a letter in which we requested their permission to approach the specialist concerned. An appropriate text was chosen, depending on whether the suspicion was based on the answer to question 2,4 or 5 of the health questionnaire (see Appendix 7). A copy of the person's answer to the question was enclosed. Specific questions were asked about the hospital, the specialist and the year in which the treatment had taken place.
People in whom multiple tumours were suspected received a request for each suspected tumour. In this way it was possible for the people to make their own choice as to whether they wished to give their permission for one tumour but not for another. Non-respondents were approached three weeks later by telephone and asked if they would proceed with their answers.

4.5.2 The request to the doctor who treated the patient

The letters of request were provided with a sticker on which the clinical or pathological diagnosis could be written. They were sent with an accompanying letter (see Appendix 8) to the doctor whose name had been written on the request form by the study subjects. If it appeared from the Medical Address List 1985-1986 that the specialist concerned was no longer working at the hospital mentioned by the study person, the letter was sent to another doctor at the same department. If the specialist's name was unknown, the request was sent to a doctor at a department thought to be most suitable for the complaint concerned. The non-respondents were approached three weeks later by telephone.

4.5.3 Results

Only 68 (11%) of the 644 written requests sent out were not answered (see Figure 4.1).

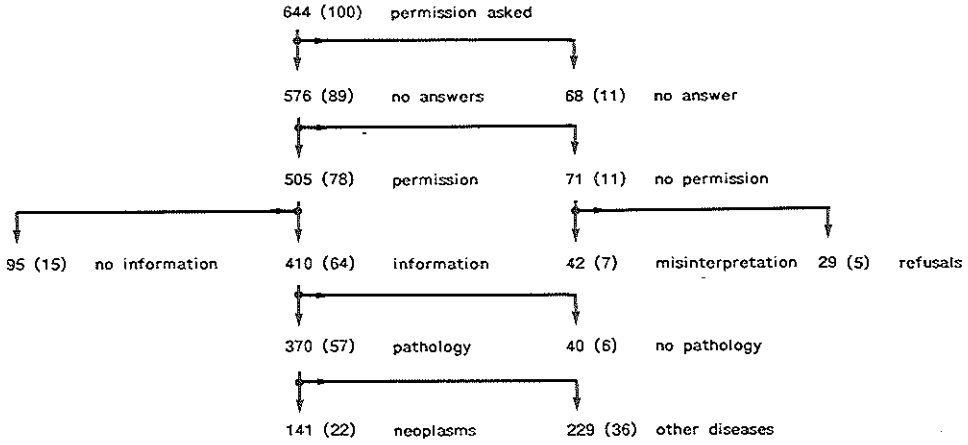

Figure 4.1 Results verification procedure. Verification was carried out when, on the basis of inquiry, a neoplastic disease was suspected. Percentages in brackets.

Permission could not be obtained from 71 (11%) of the 576 people who answered the request. In 42 the coder had misinterpreted the answer on the questionnaire: either there never had been a tumour or the 'suspicion of a tumour' had been based on a symptom or it had healed spontaneously.
There were also reports that the patient had not visited the doctor for that particular complaint or that there had been a mistake. In the remaining 29 cases (5%) it was a matter of flat refusal.
The specialists who had treated the 505 cases (78%), from whom we received permission, were approached for information concerning these study subjects. No information was available on 95 patients (15%). The reason was usually related to the long period of time which had elapsed since the presentation of symptoms: the records had been lost, or the hospital had been closed, or the specialist was unknown, retired or deceased.
Forty (6%) of the 410 cases of suspected tumours (64%) on which we did obtain information, did not appear to involve a pathology, or involved only the examination of symptoms or normal findings (biopsy of the stomach mucosa, liver puncture).
The remaining 370 (57%) comprised diagnoses of 141 neoplasms (22%) and 229 (36%) other disorders.

CHAPTER 5
DATA COLLECTION

5.1 DOSIMETRY

The radiation doses received by the pituitary gland, the thyroid gland and the parotid gland were calculated for the three different radium applicators used for treatment at the five ENT clinics which participated in this study. Depending on the age and treatment method, which varied per clinic with regard to the applicator and treatment duration, the following doses were calculated: 10-36 cGy for the pituitary gland, 2-7 cGy for the thyroid gland and 4-19 cGy for the parotid gland. The doses received by the tissues in immediate contact with the needle were much higher: 3,500-23,000 cGy. See Appendix 9 for a detailed calculation. Reviewing the dose values calculated in our own study, it has been established that the relationships between the doses absorbed by the various organs are in agreement with those mentioned in the literature. In the Netherlands the doses per organ are generally lower than those calculated by other authors because lower activity radium applicators were used (10 mg and 25 mg) as well as 50 mg radium applicators, and the treatment duration was usually shorter (see Chapter 2 'Dosimetry').

5.2 THE DATA FORM

A data form was filled in for every person in the study group. (See Appendix 3). The first page, on which the christian and surname, address, date of birth, identification (ID) and clinic numbers - necessary for the status vitalis - were noted, was used for follow-up purposes.
On the second page the data necessary for establishing and classifying the study groups were recorded. These included the ID and clinic number, sex, date of birth and the type of health insurance. The date of the first contact with the patient was also set down in order to be able to select a control group later on. Finally, the diagnosis and radiation therapy data were noted.

5.2.1 Coding

Copying the data from the record cards gave rise to some amount of difficulty on account of the brief notations which had been used. This was the result of the fact that the specialists involved had set up the filing system purely for their own use. Very often the information was limited to one word or abbreviation which summarized the ENT examination, diagnosis or treatment.
Each person was given an ID number, beginning with number 0001. The members of the irradiated group were numbered first, followed by the control group. It was possible to ascertain the sex in most cases, but if the christian name was fitting for both sexes or if the study person was referred to as 'child' the person was coded as 'sex unknown'.

The date of birth had been recorded for practically everyone, but sometimes only the age in years had been noted. In the latter case the age and corresponding year were coded. If possible the type of health insurance was also recorded. The clinic number indicated which of the five archives the patient had been selected from. The date of the first consultation was regarded as the first contact with the study person. The following rules were used in the coding of the diagnosis:

1) *Otitis media serosa* (OMS) included all possible synonyms, such as 'glue ears' and 'tubal catarrh'. Also the finding 'withdrawn tympanic membranes' and the notation 'deaf' followed by treatment for OMS, were included in this category.
2) *Recurrent ear infection* included acute otitis, chronic otitis, mastoiditis, status after mastoidectomy or radicalization and 'ear ache'.
3) *Other tubal dysfunction* was usually used in the case of adults. These included tinnitus (without loss of perception) and 'crackling noises in the ears'.
4) *Adeno-tonsillectomy* also referred to as hypertrophic tonsils, hypertrophic adenoid or adenotomy and 'blocked nose'.
5) *Sinusitis* included rhinitis and allergic rhinopathy.
6) *Perceptive hearing loss*
8) *Other disorders*
9) *Diagnosis unknown*

5.3 THE HEALTH SURVEY

In the health survey (see Appendix 6) questions were asked which, on the grounds of data in the literature, were known or assumed to be relevant to the topic: the effects of ionizing radiation on man. Suffering from cancer or having suffered from cancer in the past formed the central theme. Every effort was made to reduce the chance of missing a positive tumour anamnesis by formulating the questions in different ways. Questions: 2 (admissions to hospital), 4 (tumours) and 5 (biopsies) were formulated with this goal in mind.
Questions were also asked about hormone regulated disturbances. These were aimed at detecting possible abnormalities related to the influence of radiation on the function of the pituitary gland. Questions 3 and 6 dealt specifically with totally or partially hormone regulated disorders or their medical treatment, such as diabetes, anaemia, dysfunction of the thyroid gland and hypertension. Questions 10 and 11 on fertility, were also asked with a view to detecting hormonal disturbances resulting from the influence of the pituitary gland. Question 1 concerning height and weight was asked in association with possible growth disturbances.
The answers to questions 7 and 8 provided information on radiation exposure other than nasopharyngeal radium irradiation; and 8 and 9 on other carcinogens. Finally, the date of birth was requested in question 1 as a means of checking that the correct person had filled in the form. See Table 5.1 for an overview of the topics included in the health survey.

5.3.1 Coding questionnaire information

A data-input form was used to code the answers given in the health survey (see Appendix 10). The answers to questions 2,4 and 5 concerning the tumour anamnesis

Table 5.1 Overview of the topics in the health survey

Topic	Question(s)
Tumour induction	2,4,and 5
Hormone balance	1,3,6,10 and 11
Other radiation effects	3
Exposure to other irradiation	7 and 8
Exposure to other carcinogens	8 and 9

were coded by an ENT specialist (the author) with the cooperation of an internist-oncologist. All the other answers were coded by three fifth-year medical students; a quality control was also carried out.

Tumours

A positive tumour anamnesis, suspected on the grounds of the answers to questions 2, 4 and 5, was coded according to its localization and nature (see Table 5.2 and 5.3).

Table 5.2 Coding of the tumour anamnesis on the grounds of questions 2, 4 and 5, according to localization

01 brain	18 bone head & neck region
02 thyroid gland	19 bone unspecified
03 parathyroid glands	20 leukaemia
04 pituitary gland	21 breast
05 salivary glands	22 penis
06 oesophagus	23 prostate
07 lip	24 testes
08 mouth	25 vagina
09 paranasal sinuses	26 uterus
10 throat	27 ovary
11 ear	28 lungs
12 vocal cords	29 adrenal gland
13 eye	30 other abdominal organs
14 lymph glands head & neck	31 other head & neck region
15 lymph glands unspecified	32 other unspecified
16 skin head & neck region	33 head & neck surgery indicating possible tumour
17 skin unspecified	

A maximum of three possible tumours per study person could be coded. See Appendix 11 for examples of coding according to localization and nature.

Table 5.3 Coding of the tumour anamnesis on the grounds of questions 2, 4 and 5, according to nature

1	definitely benign
2	probably benign
3	possibly benign - possibly malignant
4	probably malignant
5	definitely malignant
6	unknown, no classification possible

Carcinogens
The answers to question 8 concerning occupational exposure to carcinogens were coded according to a list of poisonous substances from occupation, according to Verberk and Zielhuis (Appendix 12) (1).
Three groups were classified: 'none', '(probably) very little' and 'a great deal'. Respondents who had been employed for less or more than 10 years in an occupation involving risk, were classified under '(probably) very little' and 'a great deal', respectively.

5.4 CAUSES OF DEATH

It was possible to trace the cause of death in 144 of the 150 people (96%) who had died. The causes of death were obtained from the Central Statistical Office and coded according to the Revision of the Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death, valid for the year of death. Due to the fact that considerable differences can exist between the various Revisions with regard to the coding of diseases, injuries and causes of death, all the codes for the causes of death were compared with, and where necessary made to conform with, the SMR edition of the 'Classificatie van Ziekten 1980' (2). The causes of death are presented in Chapter 7.

5.5 CAUSES OF DISEASE

On the grounds of the study subject's answers to questions 2, 4 and 5 of the health survey, which gave rise to 644 suspected tumours, we tried to obtain supplementary information from the former specialist. In this way it was possible to verify the diagnoses in 370 cases: 141 were related to neoplasms and 229 to other complaints. All 370 diagnoses were coded according to the 'Classificatie van Ziekten 1980'. These codes were divided into a number of groups of interest. These are presented, together with the causes of death in Chapter 8.

REFERENCES CHAPTER 5

(1) Verberk, M.M., Zielhuis, R.L. (1980): Giftige stoffen uit het beroep. Stafleu pp 52-53 Table II 'Beroepen met een verhoogd kankerrisico'.
(2) Anonymous (1980): Classificatie van Ziekten 1980. SMR-uitgave, based on the International Classification of Diseases, 9th Revision, Clinical Modificaton (ICD-9-CM).

CHAPTER 6
DESCRIPTION OF THE STUDY POPULATION ACCORDING TO CHARACTERISTICS

The control group is slightly smaller than the irradiated group. This is due to the fact that no control persons were selected for irradiated persons classified under 'sex unknown' in the first phase of the study (see Chapter 4 'The study group').

6.1 AGE

The average age of the study subjects at the time of treatment was 10.1 years. The majority were between six and ten years old (see Table 6.1).

Table 6.1 Mean age at the start of treatment per clinic. Irradiated group only

Age	Clinic						
	1	2	3	4	5	all	%
0-5	345	28	102	4	26	505	20.4
6-10	609	187	365	69	43	1273	51.3
11-15	125	61	116	23	25	350	14.1
16-20	22	20	45	3	16	106	4.3
21-25	12	5	32	3	6	58	2.3
26-30	8	4	24	2	4	42	1.7
31-35	19	11	20	2	6	58	2.3
36-40	11	0	13	6	4	34	1.4
41-75	20	2	2	28	2	54	2.2
Total	1171	318	719	140	132	2480	100.0

Missing observations: 62

In our study group it appeared that children with otitis media serosa, the most frequent indication for naso-pharyngeal irradiation, consulted an ENT specialist for treatment at this age, which corresponds with the ages reported in the literature. A random survey of the population showed that the most common age for otitis serosa is slightly lower: between three and six years (1).

6.2 SEX

There were more males than females in the study group (57.3% vs 42.7%, see Chapter 4 Table 4.2). This is in agreement with expectations because the most frequent indication for irradiation, otitis media serosa, is diagnosed more often in boys than in girls. In a study conducted by Kokko, a group of children with otitis serosa was described with a boy:girl ratio of 59:41 (quoted 1). Lildholdt found a

similar relationship (56.7% vs 43.3%), however, this difference was not significant after comparison with the male:female ratio in the local population (51.3% vs 48.7%) (2).

6.3 CLINIC

Control patients were only selected for irradiated patients in whom the sex was known. Therefore, a small deficit has arisen in the control group (see Chapter 4, Table 4.2).

6.4 DIAGNOSIS

In the irradiated group otitis serosa, recurrent otitis and 'other tubal disorders' formed the diagnoses in 93.7%. These were also the most important indications for irradiation. The control group consisted mainly of children who had undergone an adeno-tonsillectomy (42.1%) and sufferers from recurrent otitis (27.2%). The indications for irradiation differed between clinics: in clinic 2 a hypertrophic adenoid was a frequent indication for radium treatment (see Table 6.2).

Table 6.2 Diagnostic indications per clinic for exposed and non-exposed subjects

Diagnosis	Clinic													
	1		2		3		4		5		All			
	Exp	NExp	Exp	NExp	Exp	NExp	Exp	NExp	Exp	NExp	Exp	%	NExp	%
Serous otitis	706	57	208	15	468	40	89	6	53	2	1524	60.5	120	5.0
Recurrent otitis	457	473	54	47	223	101	16	19	66	7	816	32.4	647	27.2
Tubal dysfunct.	4	-	3	-	6	2	6	-	-	2	19	0.8	4	0.2
Adenotonsillect.	10	280	53	233	1	381	-	54	13	53	77	3.1	1001	42.1
Rhinosinusitis	4	82	6	17	8	13	3	36	3	6	24	1.0	154	6.5
Perceptive loss	-	18	-	-	1	8	-	3	-	2	1	0.0	31	1.3
Other	3	196	2	15	4	158	1	26	-	21	10	0.4	416	17.5
Unknown	13	3	2	-	4	1	27	-	2	-	48	1.9	4	0.2
Total	1197	1109	328	327	715	704	142	144	137	93	2519	100	2377	100

Missing observations: 26

6.5 RADIUM TREATMENT

Depending on the clinic and age of the patient, the radiation doses varied between 250 and 4000 mgmin. The average was 1197.8 mgmin and the standard deviation was 718.4 mgmin. In Figure 6.1 the number of exposed subjects (N is $\geqq$ 10) have been set out against the dose received.

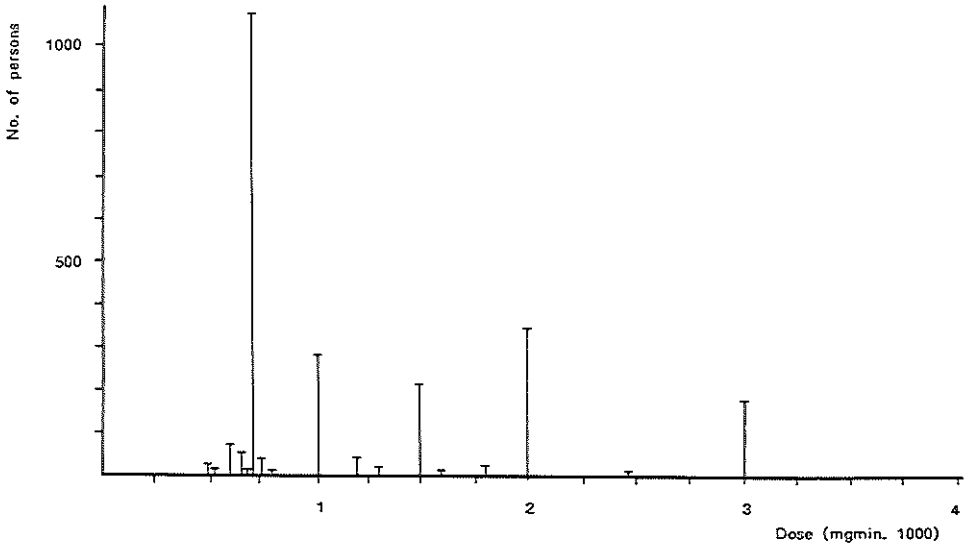

Figure 6.1 Number of subjects exposed to nasopharyngeal radium irradiation, per dose (mgmin x 1000). Only groups of at least ten are recorded, accounting for 2,458 persons. Groups of less than ten accounted for 79 persons. In five persons the radiation dose was unknown.

6.6 EXPOSURE TO IRRADIATION

Question 7a of the health survey, concerning exposure to irradiation during diagnostic X-ray examination, did not show any clear differences between the irradiated and control groups. However, question 7b, regarding possible 'other' exposure, gave rise to a number of different and interesting answers (see Table 6.3).

Table 6.3 Exposure to 'other' irradiation per clinic for exposed and non-exposed subjects

Radiation	Clinic													
	1		2		3		4		5		All			
	Exp	NExp	Exp	NExp	Exp	NExp	Exp	NExp	Exp	NExp	Exp	%	NExp	%
Cobalt	45	7	8	-	19	1	1	-	2	-	75	3.9	8	0.5
Röntgen	62	86	14	21	36	38	8	6	2	5	122	6.4	156	9.2
Radium	236	5	48	4	151	3	30	1	22	-	487	25.6	13	0.8
Diverse	43	5	7	-	13	1	6	1	4	1	73	3.8	8	0.5
Unknown	111	40	18	10	35	20	5	2	12	-	181	9.5	72	4.2
None	477	746	137	193	274	389	38	72	40	46	966	50.7	1446	84.9
Total	974	889	232	228	528	452	88	82	82	52	1904	100	1702	100

The exposed group expressed in their answers that they were very much aware of the radium irradiation in their past. A quarter of the respondents could even remember the name radium; also the name cobalt, various and unknown were often mentioned.

6.7 EXPOSURE TO CARCINOGENS

The coding of exposure to occupational irradiation gave rise to such a small number of positive answers that a meaningful comparison was not possible (see Table 6.4). The coding of occupational exposure to other carcinogens showed no differences between the irradiated and non-irradiated persons at clinics 1,2 and 3 (see Table 6.4). The number of subjects in clinics 4 and 5 were too small to draw conclusions. When the populations at the various clinics were compared, a striking difference was observed between clinic 1 (situated in the south of the province Limburg) and clinic 2 (situated in the province Drenthe). In the area surrounding clinic 1, where there is a large amount of petrochemical industry, exposure to carcinogens (other than ionizing radiation) was coded in 20.9%, whereas for clinic 2, in an area with considerably less industry, this was only 15.5%.

Table 6.4 Occupational exposure to radiation and carcinogenic substances per clinic for exposed and non-exposed subjects

Exposure	Clinic											
	1		2		3		4		5		All	
	Exp	NExp	Exp	NExp	Exp	NExp	Exp	NExp	Exp	NExp	Epx	NExp
Radiation												
none	947	888	235	222	522	445	82	85	85	52	1871	1692
little	73	-	1	-	1	1	-	2	-	10	5	
much	2	-	-	1	1	-	-	-	-	-	3	1
Carcinogens												
none	761	700	200	188	425	361	74	82	63	41	1523	1372
little	130	124	17	20	53	46	8	2	7	4	215	196
much	65	67	18	16	45	39	1	1	17	7	146	130

6.8 ALCOHOL AND TOBACCO

No differences were found between the irradiated and non-irradiated groups with regard to the use of alcohol and tobacco. However, it appeared that people from the southern clinics (1 and 3) drank more beer; and the men generally smoked more cigarettes than the women (see Table 6.5).

Table 6.5 Use of stimulants per clinic and sex for exposed and non-exposed subjects

Stimulant	Clinic																			
	1				2				3				4				5			
	Exp		NExp		Exp		NExp		Exp		NExp		Exp		NExp		Exp		NExp	
	m	f	m	f	m	f	m	f	m	f	m	f	m	f	m	f	m	f	m	f
Beer weekly	11.3	3.4	12.8	2.9	10.3	0.4	8.1	1.8	10.4	1.0	12.5	1.2	8.0	0.6	9.5	1.2	9.9	1.1	8.5	0.9
Wine weekly	1.3	3.4	1.3	3.6	1.4	6.0	1.3	4.4	2.4	6.8	2.0	5.5	4.0	5.8	5.0	6.0	1.7	5.6	1.4	4.2
Dutch gin weekly	1.1	0.5	1.1	0.5	2.3	1.3	3.3	1.2	2.7	1.3	2.7	0.9	3.3	0.8	4.2	0.2	4.4	0.7	4.6	1.1
Cigarettes daily	14.5	13.7	16.2	13.7	14.7	12.8	15.1	13.6	15.6	13.3	17.3	13.4	13.9	11.4	13.8	10.7	14.0	11.6	15.7	12.8
Pipe daily	0.2	0.1	0.2	0.0	0.3	0.0	0.3	0.0	0.2	0.1	0.2	0.0	0.6	0.0	0.9	0.1	0.8	0.0	0.9	0.0
Cigars daily	0.4	0.2	0.3	0.1	0.5	1.0	0.4	0.0	0.6	0.1	0.6	0.2	0.7	0.0	2.0	0.5	0.7	0.0	1.6	0.0

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CHAPTER 7
MORTALITY AFTER NASOPHARYNGEAL RADIUM IRRADIATION TREATMENT

7.1 INTRODUCTION

Nasopharyngeal irradiation using radium^{226} was introduced by Samuel Crowe in 1924 (1). This therapy was designed to improve the function of the eustachian tube by shrinking lymphoid tissue in and around the tubal orifice. It has appeared to be effective in children suffering from secretory otitis media (2) and in airmen suffering from barotrauma (3).
Nasopharyngeal radium irradiation became routine medical practice in America and Europe in the 1940s and 50s. The therapy was made practically obsolete as a result of the realization that radiation treatment involved a potential cancer risk (4) and through the availability of other forms of treatment (5).
Two studies conducted in America on small groups of people (6,7) confirmed that children treated for various conditions using the nasopharyngeal application of radium^{226} run the risk of developing cancer in the long-term. Owing to the interest in studies on subjects exposed to low-dose irradiation, we carried out the present study on a large group of Dutch people who had been treated using nasopharyngeal radium^{226} irradiation in their youth.

7.2 MATERIALS AND METHODS

7.2.1 Study population

A group of 2,542 persons who were born after 1909 and treated using nasopharyngeal radium irradiation between 1945 and 1965 were selected from the medical records of five ENT clinics in the Netherlands. These people comprised the exposed group. The large majority (92.9%) had been treated for secretory otitis media (60.4%) or recurrent otitis (32.5%).
A group of control subjects were also selected at random from the same medical records until equal numbers of exposed and non-exposed people had been assembled for each clinic, matched for sex, year of birth (5 year age groups) and year of first contact (5 year intervals). The non-exposed group had been treated without the use of radium for a variety of ENT disorders, including hypertrophic tonsils and adenoids (42.1%), recurrent otitis (27.2%), rhinosinusitis (6.5%), secretory otitis media (5.0%) and perceptive deafness (1.3%). The non-exposed group consisted of 2,380 subjects. The number of exposed and non-exposed persons per clinic are shown in Table 7.1.

To the reader:
Chapter 7 has been accepted for publication in the Annals of ORL, in a modified form. The sections 'Introduction' through 'Follow-up' have been presented in the previous chapters. The section 'Dosimetry' has been dealt with extensively in Appendix 9.

Table 7.1 The number of exposed and non-exposed study subjects per sex and clinic

Clinic	Males		Females		Total	
	Exp	NExp	Exp	NExp	Exp	NExp
1	723	648	477	463	1200	1111
2	188	184	140	142	328	326
3	388	373	346	333	734	706
4	83	85	60	59	143	144
5	88	58	49	35	137	93
Total	1470	1348	1072	1032	2542	2380

At clinics 1,3 and 5 the sex of the patient was not specified on the records and was subsequently defined on the basis of the christian name. In cases where the christian name was not gender specific, the subject was coded as sex unknown. As the result of an oversight, no control subjects were selected for the exposed persons classified under sex unknown. This is the reason why the exposed and non-exposed groups are of unequal size. In the course of the follow-up the sex of all the exposed persons became known. In Table 7.2 the numbers of exposed and non-exposed subjects are shown according to age, sex and year of first contact. The numbers of exposed and non-exposed persons are fairly well balanced with regard to age and sex.

Table 7.2 Number of exposed and non-exposed individuals according to year of first contact*, age* and sex

Year of first contact	Sex	Age**											
		0-5		6-10		11-15		16-25		26-75		Total	
		Exp	NExp	Exp	Nexp	Exp	NExp	Exp	NExp	Exp	NExp	Exp	NExp
1946-50	M	64	56	54	49	15	15	19	13	10	7	162	140
	F	70	52	51	43	14	9	15	9	8	13	158	126
1951-55	M	177	170	127	117	27	26	29	29	41	33	401	375
	F	132	128	104	108	38	35	24	27	17	15	315	313
1956-60	M	241	210	127	108	47	47	8	22	29	30	452	417
	F	175	159	100	84	31	32	13	18	12	15	331	308
1961-65	M	151	137	136	136	24	52	19	20	39	40	369	385
	F	80	91	93	90	28	47	7	14	16	17	224	259
Total	M	633	573	444	410	113	140	75	84	119	110	1384	1317
	F	457	430	348	325	111	123	59	68	53	60	1028	1006

* Age or year of first contact unknown for 130 exposed and 57 non-exposed persons.
** Age at the time of first contact

7.2.2 Follow-up

The cohort was followed from the time of the first contact until death, emigration or, for those still alive and resident in the Netherlands, until 1 February 1985. The subjects were traced by various means, for example via municipal and state registry offices, conscription files and telephone directories. A separate search was made for

Table 7.3 Follow-up status of the total study population 1 February 1985

Status	Exposed		Non-exposed		Total	
	n	(%)	n	(%)	n	(%)
Located	2390	94.0	2217	93.2	4607	93.6
Alive	2315	91.1	2142	90.0	4457	90.6
Deceased	75	2.9	75	3.2	150	3.0
Not located	152	6.0	163	6.8	315	6.4
Emigrated	98	3.9	98	4.1	196	4.0
Untraceable	54	2.1	65	2.7	119	2.4
Total	2542	100	2380	100	4922	100

the untraceables in the death registry files at the Central Bureau of Genealogy. A summary of the follow-up status is shown in Table 7.3. In total it was possible to trace 94.0% of the exposed (male 93.3%, female 94.2%) and 93% of the non-exposed persons (male 94.1%, female 92%). Of the 6.4% lost to follow-up, 4% were known to have emigrated and 2.4% could not be traced.

Information concerning the deceased was obtained from the Chief Inspector of Public Health. It was possible to establish the cause of death in 144 of the 150 persons known to have died (96%). For five people who had died outside the Netherlands the cause of death could not be determined and in one subject the death certificate could not be found.

7.2.3 Dosimetry*

The radiotherapy treatment was carried out in a similar way to that described by Crowe (1). A cylinder containing radium sulphate was inserted into the nostril and positioned close to the orifice of the eustachian tube. It was then left in place for several minutes. The type of applicator used (mg radium) and the number and duration of the applications differed for each ENT clinic. These data had been carefully recorded for every irradiated subject (see Table 7.4.). The subjects from clinic 1 (n = 1200) were irradiated using a nickel-alloy applicator containing 25 mg in four sessions. The treatment time for subjects under 16 years of age was seven minutes, for those over 16, fifteen minutes. The radiation doses received by the tissues in the head and neck region depended on the distance from the radiation source, the size of the subject at the time of treatment and the position of the applicator. Dose estimations were made for selected sites in each age group using the isodose curve for the applicator employed and the 'average' measurements per age group as taken from the skull films of 25 individuals between three and sixteen years of age. The dose rates (in cGy/h) were estimated for the thyroid, parotid and pituitary glands for all the applicators used at the five ENT clinics. Depending on the clinic and age of the subject, the absorbed doses were estimated to be between 2 and 7 cGy for

* This part of the study was executed under the supervision of A.G. Visser, PhD, radiophysicist of the Rotterdam Radiotherapeutic Institute.

Table 7.4 Radiation treatment methods per clinic and estimated doses (cGy) received at different anatomical sites

Clinic	n	Treatment parameters			Estimated dose (cGy)			
		mg Ra	Time (min)*	Sessions	Thyroid	Parotid	Pituitary	Adjacent tissue
1	1200	25	28- 60	4	2-3	6- 8	12-14	4,480- 9,600
2	328	50	36- 72	3	5-7	14-19	29-36	11,520-23,040
3	734	25	40- 80	4	3-4	8-11	16-20	6,400-12,800
4	143	10	60-240	1-4	2-3	4-13	11-18	3,555-14,220
5	137	25	26- 52	3	2-3	5- 7	10-13	4,160- 8,320
All	2542	10-50	26-240	1-4	2-7	4-19	10-36	4,160-23,040

* Total exposure time age dependent

the thyroid gland, between 4 and 19 cGy for the parotid gland and between 10 and 36 cGy for the pituitary gland. The doses estimated to have been absorbed by the adjacent tissues at the orifice of the eustachian tube and by the nasopharyngeal mucosa are considerably higher (see Table 7.4).

7.2.4 Method of analysis

The mortality rates per 10,000 person years for the exposed and non-exposed groups and for males and females separately were compared per cause of death.
For the calculation of follow-up periods, the date of first treatment (exposed) or of first consult (non-exposed) were taken as the start of follow-up. However, in several cases this data was unknown. Our study population also comprised patients whose first consultation took place before the period in which treatments were applied at the clinics. These subjects were excluded from the study, leaving 2,510 exposed and 2,199 non-exposed persons for analysis (see Table 7.5). The end of the period of follow-up for all cases was either the date of death or loss to follow-up or 1 February 1985.
The statistics presented in the next sections of this chapter concern these selected populations. Confidence intervals for the risks were calculated (8).

Table 7.5 Selection of subjects for whom period of follow-up is exactly known, per sex for exposed and non-exposed subjects

	Male		Female		Total	
	Exp	nexp	exp	nexp	exp	nexp
Study subjects with known period of follow-up	1448	1257	1062	942	2510	2199
Study subjects with unknown period of follow-up	22	91	10	90	32	181
Total no. subjects	1470	1348	1072	1032	2542	2380

7.3 RESULTS

As shown in Table 7.6, the mortality rate for all causes for both sexes combined was almost equal in the exposed group ($11.5/10^4$ person years) and in the non-exposed group ($11.0/10^4$ person years). For males the rate in the exposed ($15.4/10^4$ person years) is about 118% of the rate in the non-exposed ($13.1/10^4$ persons years), whereas for females the rate in the exposed ($6.3/10^4$ person years) is about 75% of that in the non-exposed ($8.3/10^4$ person years).
There were no remarkable differences between the exposed and non-exposed groups for causes of death other than cancer. In the exposed group three times as many males died of cancer (at all sites) than in the non-exposed group; for exposed females about half the number of the non-exposed were found. However, neither of these findings are statistically significant.
In Table 7.7 the number of deaths per specific cancer site are shown. The numbers for any one site are small, thus limiting the conclusions which can be drawn. In four exposed males lymphatic or haematopoietic tumours were found (two were leukaemia), whereas none were found in non-exposed males. The 95% confidence interval (8) showed no significant difference between groups, however. In females there were fewer deaths from cancer in the exposed group than in the non-exposed group.
These malignancies did not appear to be concentrated at any particular site. Smaller numbers of brain, breast, lymphatic and haematopoietic malignancies were found in the exposed females compared to non-exposed females. Only one death due to brain cancer of unspecified nature was found in the exposed group, whereas two were found in the non-exposed group. None of these differences are statistically significant. Twenty-four malignancies were classified under 'other' sites. These included four cases of cancer of the lung (only males, two had been exposed), eight of the digestive tract and six of the urogenital system.

7.4 DISCUSSION

Irradiation of the head in persons suffering from tinea capitis has been associated with an increased risk of their developing leukaemia (9,10). This observation is consistent with findings after larger portions of the bone marrow have been exposed to radiation, such as is the case during radiotherapy of the spine for ankylosing spondylitis in adults and following irradiation of the chest in children (11). It has also been reported that children who have been irradiated on account of tinea capitis run an increased risk of developing tumours of the central nervous system (9,10) and persons who have frequently been subjected to full-mouth dental X-ray examinations run an increased risk of developing meningiomas (12). The radiation exposures thought to be associated with an increased risk of developing leukaemia or tumours of the central nervous system in these studies were 30 and 150 cGy, respectively. The risks were generally two to three and a half times higher than expected. However, in the study by Ron et al. (10) the increase in risk for leukaemia only reached marginal levels of significance.
During nasopharyngeal radium therapy, the tissues immediately adjacent to the applicator receive very high doses of radiation due to beta and gamma irradiation.

Table 7.6 The number (n) of deaths, the cumulative mortality rate (per 10,000 person years, 1945-1985) for exposed and non-exposed subjects, the relative risks (RR) and confidence intervals (95%) associated with exposure, per sex.

	Male						Female						Total					
	exposed		non-exp				exposed		non-exp				exposed		non-exp			
	n	rate	n	rate	RR	95%CI	n	rate	n	rate	RR	95%CI	n	rate	n	rate	RR	95%CI
Total (all causes)	56	15.4	44	13.1	1.18	(.77-1.80)	17	6.3	21	8.3	0.75	(.37-1.52)	73	11.5	65	11.0	1.04	(.73-1.51)
Cancer	15	4.1	5	1.5	2.78	(.96-9.36)	6	2.2	10	4.0	0.56	(.17-1.69)	21	3.3	15	2.5	1.30	(.64-2.71)
Cardiovascular	12	3.3	15	4.5	0.74	(.32-1.72)	4	1.5	3	1.2	1.24	(.22-8.38)	16	2.5	18	3.1	0.82	(.19-1.72)
Accidents/Suicide	17	4.7	15	4.5	1.05	(.49-2.21)	3	1.1	2	0.8	1.40	(.16-17.7)	20	3.2	17	2.9	1.09	(.55-2.22)
Other	9	2.5	7	2.1	1.19	(.40-3.70)	4	1.5	6	2.4	0.62	(.13-2.65)	13	2.0	13	2.2	0.93	(.40-2.17)
Unknown	3	0.8	2	0.6	1.39	(.16-17.6)	0	-	0	-	*	*	3	0.5	2	0.3	1.39	(.16-17.6)
N in group	1448		1257				1062		942				2510		2199			
person years	36387		33680				27048		25202				63435		58882			

* impossible value (not defined)

Table 7.7 The number (n) of cancer deaths, the cumulative mortality rate (per 10,000 person years, 1945-1985) for exposed and non-exposed subjects, the relative risks (RR) and confidence intervals (95%) associated with exposure, per sex.

	Male						Female						Total					
	exposed		non-exp				exposed		non-exp				exposed		non-exp			
	n	rate	n	rate	RR	95%CI	n	rate	n	rate	RR	95%CI	n	rate	n	rate	RR	95%CI
Total (all sites)	15	4.1	5	1.5	2.78	(.96-9.36)	6	2.2	10	4.0	0.56	(.17-1.69)	21	3.3	15	2.5	1.30	(.64-2.71)
Brain	1	0.3	0	-	*	*	0	-	2	0.8	0	(0 -4.96)	1	0.2	2	0.3	0.46	(.01-8.73)
Head and Neck	0	-	0	-	*	*	0	-	0	-	*	*	0	-	0	-	*	*
L/H[+]	4	1.1	0	-	*	(.61- *)	1	0.4	2	0.8	0.47	(.01-8.77)	5	0.8	2	0.3	2.32	(.38-23.5)
Breast	0	-	0	-	*	*	0	-	2	0.8	0	(0 -4.96)	0	-	2	0.3	0	(0 -4.94)
Other	10	2.7	5	1.5	1.86	(.58-7.12)	5	1.8	4	1.6	1.16	(.25-5.72)	15	2.4	9	1.5	1.55	(.63-4.09)
N in group	1448		1257				1062		942				2510		2199			
person years	36387		33680				27048		25202				63435		58882			

* impossible value (not defined or infinitely high)
[+] Lymphatic and hematopoietic system

Tissues further than one cm away from the source are only exposed to gamma radiation, the intensity of which decreases inversely with the square of the distance (see Table 7.4) (13).
Two prior studies on subjects who have been treated using radium applicators for ENT conditions have been carried out. Hazen et al. (1966) followed-up 417 children - who had been treated with a 25 mg radium applicator (usual dose per treatment 300-600 mgmin) - for an average of 14.6 years. Only two malignant and five benign neoplasms were identified in the exposed group compared to 10 and 23, respectively, in 2,746 siblings. No increased risk was found in this small study group (6).
More recently, Sandler et al. (1982) followed-up 904 persons - who had been treated using a 50 mg radium applicator (usual dose 4,208 mgmin) - for 18 to 35 years. She compared the subsequent incidence of cancer to that in 2,021 non-exposed persons. Three brain tumours and an anaplastic tumour of the soft palate were observed in the exposed group, whereas no cases of cancer in the head and neck region were found in the non-exposed group ($p < .05$). No other areas showed an increased risk (7).
The present study was similar in design to that of Sandler et al. (1982). Our study group was, however, considerably larger (2,542 exposed, 2,380 non-exposed) and the average dose was lower (average 1,198 mgmin). In the Netherlands, unilateral irradiation was the standard treatment procedure, whereas in Sandler et al.'s study (1980) the population had been subjected to bilateral treatment (14).
For each exposed person on our study group the probability that he/she would still be alive at the end of the study period was calculated, using age, sex and period specific death rates for the Netherlands. This led to an expected number of deaths: 51 males and 18 females out of 2287 persons. These figures are very close to the 56 males and 17 females we observed in our population (Table 7.6).
Therefore, the conclusion can be drawn that the death rate in the exposed and non-exposed groups is comparable to the death rate in the Dutch population as a whole.
There were five persons in our study group for whom we could not establish the cause of death. Table 7.6 shows 15 deaths from cancer out of a total of 56. This leads to the assumption that at least one of these five subjects can be expected to have died of cancer as well.
In the present study no overall significant increase in mortality due to cancer was found. When the study population was examined according to sex, no notable differences in mortality due to all causes or causes other than cancer were found between the exposed and non-exposed persons. In the case of mortality due to cancer, a marginal increase was noted for lymphatic and haematopoietic malignancies in males only.
However, it is not justified to conclude that there is a causal relationship between malignancies of the lymphatic and haematopoietic system and radiation here, because of the small numbers of tumours observed, the inconsistencies in the incidence of tumours between men and women and the much longer latency periods (see Table 7.8) than are usually observed for radiation associated malignancies of the lymphatic and haematopoietic system. We did not find an increased incidence of brain cancer in this group. Considerable statistical variability resulted from the low incidences, therefore, the observation of an increased incidence of cancer in some areas in exposed males and a decrease in exposed females does not lead to a ready interpretation. We are continuing our follow-up efforts to identify subjects who are still alive, which may help to clarify our results.

Table 7.8 Individual data of deaths due to tumours of lymphatic and haematopoietic system and brain per sex for exposed and non-exposed subjects

Sex	Exposure status		ICD9	Diagnosis	Yr birth	Dose	Yr I/C*	Yr death	Latency (yrs)
Male	Exposed	L/H**	202.8	Malignant lymphoma	1953	700	1963	1980	17
			205.1	Chron. myeloid leukemia	1934	1500	1956	1976	20
			205.0	Acute myeloid leukemia	1947	750	1953	1977	24
			202.1	Mycosis fungoides	1917	1200	1954	1963	9
		Brain	239.6	Non-specified brain tum.	1913	1500	1962	1971	9
	Non-exposed	L/H							
		Brain							
Female	Exposed	L/H	205.1	Chron. myeloid leukemia	1943	1500	1955	1983	28
		Brain							
	Non-exposed	L/H	205.0	Acute myeloid leukemia	1947		1951	1978	27
			206.0	Acute monocytic leukemia	1915		1962	1980	18
		Brain	191.6	Malig. tumour cerebellum	1958		1959	1982	23
			191.9	Malig. brain tumour	1950		1953	1981	28

* Year of irradiation or first contact
** Lymphatic and haematopoietic system

In the exposed group no deaths as a result of breast cancer were observed, whereas there were two cases in the non-exposed group. Hazen et al. (6) found no cases in their exposed subjects and three in the siblings. Sandler et al. (7) suggested that the decreased incidence of breast cancer in their population might be related to alterations in pituitary function following nasopharyngeal radium treatment. The present study findings agree with this suggestion.
Summarizing, no increased incidence of cancer at any site associated with the Crowe therapy was observed in the present study. Sandler et al.'s (1982) (7) findings relating to an increased incidence of cancers in the head and neck region were not confirmed in our study. The average radiation exposures were lower in the Netherlands, which may have contributed to this finding. Also, the small incidence, even in our relatively large study group, makes precise comparisons between studies difficult.

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CHAPTER 8
TUMOUR INCIDENCE AFTER NASOPHARYNGEAL RADIUM IRRADIATION

8.1 INTRODUCTION

In 1896, one year after the appearance of the first X-ray films, radiation damage to various human tissues and to vision was mentioned by the Italian F. Batelli (1). The first report of a malignancy was published in 1902 by Frieben: a skin cancer in a radiation worker (2). Since then the tumour inducing properties of ionizing radiation have been well established (3).
Almost all tissues in the head and neck region have been shown capable of developing neoplasms after radiation exposure. Particularly sensitive organs are the thyroid gland (4), the salivary glands (5), the brain (6) and the hypopharynx (7). The tendency of radiation related neoplasms to show multicentricity and plurality is in concurrence with the physical properties of radiation (8). Irradiation of the head and neck region has also given rise to non-neoplastic disease, such as necrosis of brain tissue, cataracts and thyreotoxicosis. Psychiatric disorders were suggested to be radiation related in a study concerning children irradiated for tinea capitis (9). Irradiation therapy was in common practice between 1920 and 1960 for benign conditions, such as hypertrophic tonsils and adenoids, thymus enlargement, acne, tinea capitis, thyreotoxicosis, keloid and haemangioma planum.

In 1926 Crowe introduced irradiation of the nasopharynx as a treatment for diseases of the ear caused by malfunction of the eustachian tube (10). The treatment consisted of the application of a cylinder containing radium sulphate near the nasopharyngeal orifice. This therapy was carried out on a large scale in school children suffering from serous otitis media (11) and in airmen suffering from barotrauma (12). Fear of cancer induction (13) and the availability of alternative therapies (14) have made the therapy practically obsolete.
Two authors described an adenocystic carcinoma of the palatum durum and vomer 30 and 23 years after the Crowe therapy, respectively (15,16).
Sandler et al. (1982) reported the results of a U.S. non-concurrent prospective study in which 904 persons who had been exposed to nasopharyngeal irradiation were compared to 2,021 non-exposed control subjects. The person-years of observation were 22,500 and the mean individual radiation dose was 4,208 mgmin. A significantly higher incidence of brain tumours and thyreotoxicosis was reported in the exposed subjects. One of the malignant head and neck tumours in the exposed group was an undifferentiated anaplastic carcinoma of the palatum molle (17).
We selected a large population of 2,542 persons who had been treated using the Crowe therapy from the records in Ear, Nose and Throat clinics in the Netherlands.

To the reader:
Chapter 8, in modified form, has been submitted for publication. The sections 'Introduction' through 'Follow-up' have been presented in the previous chapters; the section 'Dosimetry' is presented extensively in Appendix 9.

The mean individual radiation dose was approximately half of that reported by Sandler et al. (1982). The morbidity in this group and in a non-exposed control group are described below.

8.2 MATERIALS AND METHODS

8.2.1 Study population

The exposed population consists of all the subjects (2,542) selected from the files at five Dutch ENT clinics who were born after 1909 and treated in the years 1945-1965 using nasopharyngeal radium irradiation. The reasons for radiation therapy were primarily secretory otitis media and recurrent otitis, together accounting for 92.9% of the indications in the exposed study subjects.
The control population (n = 2,380) was selected from the records at the same clinics in such a way as to correspond with the exposed subjects with respect to clinic, sex, birth year (5 year age groups) and the year of first contact (5 year time periods). The non-exposed subjects had been treated without the use of radium for a variety of ENT disorders, including hypertrophic tonsils and adenoids (42.1%), recurrent otitis (27.2%), rhinosinusitis (6.5%), secretory otitis media (5.0%) and perceptive deafness (1.3%). Persons with a previous history of malignant disease were excluded from the study.

8.2.2 Follow-up

The entire cohort of exposed and non-exposed subjects was followed-up until death, emigration or February 1 1985. Tracing efforts were carried out by various means, including searches in municipal registries, state registries, conscription files and telephone books. For those lost to follow-up a search was made in the death registry files of the Central Bureau of Genealogy. A summary of the follow-up is presented in Table 8.1.
Each individual traced received an explanatory letter and a questionnaire to be completed by the subject. The questionnaires were identical for the exposed and non-exposed persons, without any indication of prior irradiation.

Table 8.1 Study population. Follow-up status up till February 1985

Status	Exposed (%)	Non-exposed (%)	Total (%)
Located	2390 (94.0)	2217 (93.2)	4607 (93.6)
Alive	2315 (91.1)	2142 (90.0)	4457 (90.6)
Survey yes	2022 (79.6)	1833 (77.0)	3855 (78.3)
no	293 (11.5)	309 (13.0)	602 (12.2)
Deceased	75 (2.9)	75 (3.2)	150 (3.0)
Not located	152 (6.0)	163 (6.8)	315 (6.4)
Emigrated	98 (3.9)	98 (4.1)	196 (4.0)
Lost	54 (2.1)	65 (2.7)	119 (2.4)
Tot. populat.	2542 (100%)	2380 (100%)	4922 (100%)

Five main topics were emphasized in the questionnaire: tumour history, conditions potentially related to pituitary gland function, radiation history, occupational exposure to carcinogens and smoking and drinking habits.
Non-respondents were sent a second questionnaire. Persons who did not return a questionnaire were approached by an interviewer who obtained the data over the telephone. Interviewers were not informed of the exposure status of the study subjects. Except in cases where prohibitive efforts would be required, non-respondents were visited at home when telephone interviews were not possible. For deceased persons the data on the death certificate were obtained from the Chief Inspector of Public Health in order to determine the cause of death.
Tumours or suspected tumours reported in the questionnaires were classified into one of five categories according to their assumed nature, (certainly benign, probably benign, possibly benign/possibly malignant, probably malignant, certainly malignant) or classified as 'nature of tumour unknown'. Categories 1 (certainly benign) and 2 (probably benign) were not followed-up. Owing to the large number of uterus extirpations reported (over 100), which were probably mainly performed for menometrorrhagia, follow-up for this organ was only carried out for categories 4 (probably malignant) and 5 (certainly malignant).
An attempt was made to obtain a clinical or histological diagnosis from the physician who treated the subject at the time, in the case of suspected malignant disease. We asked the study persons for permission to verify the suspected disease. The questions concerned hospitalization, year of treatment and the name of the physician who had treated the subject. When more than one malignant disease was suspected, requests were made for each of the diseases. So it could happen that permission was given to verify only one out of several suspected malignancies.
Requests for clinical or histological diagnosis were sent to the physician, with an explanatory letter and the written permission of the subject. If the physician had retired or no longer worked in the hospital, the information was requested via a physician of the same discipline. If the name of the physician was unknown, the information was requested via a representative of the most appropriate discipline. This part of the study was impeded because some hospital files had been disposed of and some of the hospitals had closed down. Pathology specimens were not reviewed. In order to minimize reporting bias, only illnesses diagnosed to the date of the first study letter were included in the analysis.

8.2.3 Dosimetry*

The study group was selected from five different ENT clinics. The radium source, number of sessions and exposure times differed between clinics, but these parameters had been recorded accurately for every irradiated individual (Table 8.2). Estimates for various tissue doses were made for 'average persons' in each group. Measurements were taken from skull films of individuals, not in the study population, aged between three and sixteen years of age. The dose rate was measured in cGy/h for all applicators employed as a function of age, for target organs such as the thyroid, parotid and pituitary glands.

* This part of the study was executed under the supervision of A.G. Visser, PhD, radiophysicist of the Rotterdam Radiotherapeutic Institute.

Table 8.2 Radiation methods and estimated radiation doses (cGy) received at different anatomical sites for each of the five participating clinics

Clinic		Treatment parameters			Estimated dose (cGy)			
	n	mg Ra	Time (min)*	Sessions	Thyroid	Parotid	Hypophysis	Adj. tissue
1	1200	25	28- 60	4	2-3	6- 8	12-14	4,480- 9,600
2	328	50	36- 72	3	5-7	14-19	29-36	11,520-23,040
3	734	25	40- 80	4	3-4	8-11	16-20	6,400-12,800
4	143	10	60-240	1-4	2-3	4-13	11-18	3,555-14,220
5	137	25	26- 52	3	2-3	5- 7	10-13	4,160- 8,320
All	2542	10-50	26-240	1-4	2-7	4-19	10-36	4,160-23,040

* Total exposure time age dependent

The absorbed doses for the entire irradiated population, depending on clinic and age, varied from 2-7 cGy for the thyroid, from 4-19 cGy for the parotid and from 10-36 cGy for the pituitary gland. The doses absorbed by the nasopharyngeal mucosa and the immediately adjacent tissues were considerably higher.

8.2.4 Methods of analysis

The cumulative incidence rates per 10,000 person years and for males and females separately were compared per tumour site. For the calculation of follow-up periods, the date of first treatment (exposed) or of first consult (non-exposed) were taken as the start of follow-up. However, in several cases this data was unknown. Our study population also comprised subjects whose first consultation took place before the period in which treatments were applied at the clinics.
These persons were excluded from the study, which left 2,510 exposed and 2,199 non-exposed subjects for analysis (see Table 8.3). The end of the period of follow-up for all cases was the date of death or loss to follow-up or 1 February 1985. The statistics presented in the following sections concern these selected populations. Confidence intervals for the risks were calculated (18).
Practically every case of cancer was registered in the mortality data. However, data on incidence are incomplete due to non-response to the questionnaire or in the verification procedures. To correct for both deficits, we derived correction factors based on the assumption that the non-response group (either questionnaire or verification) would have shown the same cancer rates.

Table 8.3 Selection of subjects for whom period of follow-up is exactly known, per sex for exposed and non-exposed subjects

	Male		Female		Total	
	Exp	nexp	exp	nexp	exp	nexp
Study subjects with known period of follow-up	1448	1257	1062	942	2510	2199
Study subjects with unknown period of follow-up	22	91	10	90	32	181
Total no. subjects	1470	1348	1072	1032	2542	2380

8.3 RESULTS

We were able to locate 91% of the entire study population and ascertain 3% to be dead (Table 8.1). Tracing efforts were equally successful for exposed and non-exposed persons. Located individuals were similar to those not located with respect to age at first contact, year of birth, sex and diagnosis. The total number of person years of follow-up was 63,435. Exposed subjects were followed-up for an average of 25.3 years, non-exposed subjects for an average of 26.8 years (see Table 8.4). This difference is the consequence of the different starting points of the follow-up periods between both groups.
Of the study subjects who were located alive, 86.5% completed a questionnaire, either by mail, telephone or via home interviews; 60% of the completed questionnaires were returned after the first request and 23% after the second and in 17% data was obtained by telephone and home interview. A slightly greater portion of the exposed group completed the questionnaire (87.3%) than the non-exposed group (85.6%) (Table 8.1).

Permission for verification of suspected malignant diseases was obtained for 78.4% of the requests. Information from the physician or hospital records revealed the true nature of the disease in 81.2% of the requests.

Table 8.4 Characteristics of the study population, only subjects with known period of follow-up

	Male		Female		Total	
Characteristics	Exp	nexp	exp	nexp	exp	nexp
No. of subjects	1448	1257	1062	942	2510	2199
Mean no. person-years follow-up	25.1	26.8	25.5	26.8	25.3	26.8
No. of respondents only	1125	988	870	737	1995	1725
Mean No. person-years follow-up respond. only	26.0	26.7	26.4	27.1	26.1	26.9

8.3.1 Malignancies

As shown in Table 8.5, there were some differences in total cancer mortality. In the exposed group three times as many males died of cancer (of all sites) than in the non-exposed group; for exposed females about half the number of the non-exposed was found.
Lymphatic or haematopoietic tumours were found in four exposed males (two were leukemias), whereas none were found in non-exposed males.
In exposed females, no deaths as a result of breast cancer were observed, whereas there were two in the non-exposed group. These findings have been discussed in more detail in Chapter 7.
Differences were noted in total cancer incidence between the respondents to the questionnaire. In the exposed group twice as many verified malignant tumours were found as in the non-exposed group. A striking difference was found in the occur-

Table 8.5 Number of deaths and incident cases of malignant tumours for exposed and non-exposed study subjects, per sex.
Incidence based on verification of suspected malignant disease .

Cancer site	Mortality						Incidence*					
	Male		Female		Total		Male		Female		Total	
	Exp	Nexp	Exp	Nexp	Exp	Nexp	Exp	Nexp	Exp	Nexp	Exp	Nexp
Total (all sites)	15	5	6	10	21	15	11	6	10	4	21	10
Brain**	1	0	0	2	1	2	2	1	0	1	2	2
Head and neck	0	0	0	0	0	0	4	1	2	0	6	1
L/H***	4	0	1	2	5	2	1	2	0	0	1	2
Breast	0	0	0	2	0	2	0	0	4	2	4	2
Other	10	5	5	4	15	9	4	2	4	1	8	3

* Non respondents excluded
** Histologically benign brain tumours (one fatal) included
*** Lymphatic and haematopoietic system

rence of head and neck tumours: six in the exposed, only one in the non-exposed group.
In Table 8.6 a specification of the head and neck cancer incidence is presented. Three organs in the head and neck region showed an increased tumour incidence in the exposed: the larynx, the thyroid and the skin. However, the numbers were very small.

Two laryngeal carcinomas and three head and neck skin carcinomas were found in exposed males, whereas only one head and neck skin carcinoma was found in non-exposed males. In exposed females, two thyroid carcinomas were observed, against none in non-exposed females.
In Table 8.7 the mortality and incidence data have been combined to produce a cumulative incidence.

The only confidence interval that does not include the value 1.00 is that for the relative risk for all malignant tumours combined and for both sexes (CI 1.01-2.83). The excess risk is mainly caused by 'head and neck tumours' and 'other tumours' (lung, digestive tract and urogenital system). However, if taken separately, there is no significant excess risk for any of these tumour sites in the exposed group.

Table 8.6 Malignant head and neck tumour incidence for exposed and non-exposed study subjects, per sex. Based on verification of suspected malignant disease

Cancer site (ICD)	Male		Female		Total	
	Exp	N-exp	Exp	N-exp	Exp	N-exp
Larynx (161)	2	0	0	0	2	0
Skin (173.0-4)	2	1	0	0	2	1
Thyroid (193)	0	0	2	0	2	0
Total	4	1	2	0	6	1

Table 8.7 Cumulative incidence^ and cumulative incidence rates (per 10,000 years, 1945-1985) per cancer site for exposed and non-exposed subjects, the relative risks (RR) and confidence intervals (95%) associated with exposure, per sex.

	Male						Female						Total					
	exposed		non-exp				exposed		non-exp				exposed		non-exp			
	n	rate	n	rate	RR	95%CI	n	rate	n	rate	RR	95%CI	n	rate	n	rate	RR	95%CI
Total (all sites)	36.8	10.1	18.9	5.0	2.01	(.96-4.44)	23.7	8.8	16.3	6.5	1.35	(.79-3.19)	60.5	9.5	33.2	5.6	1.69	(1.01-2.83)
Brain	5.0	1.4	2.0	0.6	2.32	(.25-57.1)	0.0	-	3.6	1.4	*	(0 -2.28)	5.0	0.8	5.6	1.0	0.83	(.23-10.6)
Head and neck	7.9	2.2	2.0	0.6	3.68	(.36-40.9)	3.5	-	0.0	-	*	(.20- *)	11.4	1.8	2.0	0.3	5.29	(.61- 109)
Larynx	*4.0*	*1.1*	*0.0*	-	*	*(.20- *)*	*0.0*	-	*0.0*	-	*	*	*4.0*	*0.6*	*0.0*	-	*	*(.20- *)*
Skin	*4.0*	*1.1*	*2.0*	*0.6*	*1.86*	*(.11- 125)*	*0.0*	-	*0.0*	-	*	*	*4.0*	*0.6*	*2.0*	*0.3*	*1.85*	*(.11- 125)*
Thyroid	*0.0*	-	*0.0*	-	*	*	*3.5*	*1.3*	*0.0*	-	*	*(.20- *)*	*3.5*	*0.6*	*0.0*	-	*	*(.20- *)*
L/H**	6.0	1.7	4.0	1.2	1.39	(.23-5.77)	1.0	0.4	2.0	0.8	0.46	(.01-9.35)	7.0	1.1	6.0	1.0	1.08	(.26-5.13)
Breast	0.0	-	0.0	-	*	*	7.1	2.6	5.2	2.1	1.26	(.15-4.15)	7.1	1.1	5.2	0.9	1.26	(.15-4.15)
Other	17.9	4.9	9.0	2.7	1.84	(.69-5.42)	12.1	4.5	5.6	2.2	2.00	(.58-8.14)	30.0	4.7	14.6	2.5	1.91	(.93-4.13)
Correction factor (due to response+/ verifications++)	1.978 (1.23/ 1.60)		1.990 (1.25/ 1.59)				1.770 (1.20/ 1.47)		1.582 (1.27/ 125)									
N in study group	1448		1257				1062		942				2510		2199			
person-years	36387		33680				27048		25202				63435		58882			

^ Cumulative incidence is mortality plus corrected incidence among survivors
* impossible value (not defined or infinitely high)
** lymphatic and hematopoietic system
+ first part of the correction factor: 1/(response on questionnaire); for male exposed: 1.23.
++ second part of the correction factor: requested number of verifications/received number of verifications; for male exposed: 1.60
Total correction factor is the product; for male exposed: 1.23 x 1.60 = 1.978
all CI's are calculated with (18)

The differences in mortality from lymphatic or haematopoietic tumours in males (see Table 8.5) were almost compensated for by the incidences in the part of the population that was still alive. In females, differences in breast cancer mortality were almost nullified when incidence data were added.

8.3.2 Benign tumours

In comparing benign tumour incidence, overall and for specific sites (Table 8.8), no differences were noted between exposed and non-exposed groups. Striking was the almost threefold over-reporting of benign tumours by the female population irrespective of the state of exposure.

Table 8.8 Benign tumour incidence for exposed and non-exposed study subjects, per sex

	Male		Female		Total	
Tumours (ICD)	Exp	Nexp	Exp	Nexp	Exp	Nexp
Digestive tract (211)	0	1	0	2	0	3
Skin (214,216)*	5	6	17	11	22	17
Breast (214.1;217)	3	3	19	12	22	15
Head and neck	1	2	2	5	3	7
Lips, mouth, pharynx (210)	0	2	1	2	1	4
Skin (214.0;216.0-4)	1	0	0	2	1	2
Thyroid (226)	0	0	1	1	1	1
UG tract (218-23)	2	0	3	3	5	3
Other + Haemangioma (228-9)	3	2	0	1	3	3
Total	14	14	41	34	55	48

8.4 DISCUSSION

In the 1977 report of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), tumour induction rates are given for different head and neck organs (3). The rate is defined as the number of induced tumours appearing in one million persons exposed to one cGy. A median latency is assumed of about 25 years, so that the total number of cancers diagnosed within this time, after exposure to radiation, may represent about half of all cancers likely to have been induced. This rate does not take variables such as age at exposure, sex or the kind of radiation into account and assumes a linear relationship between dose and the number of induced tumours. Based on these assumptions, the expected number of induced tumours at selected sites in our study group have been estimated and are shown in Table 8.9. The estimation of one expected induced tumour per site is only exceeded for the thyroid gland and the brain.
In our study an excess of two malignant thyroid tumours and a deficit of one brain tumour was observed in the exposed group.

In 1952 Loch and Fischer reported the first follow-up study of 85 persons who had been irradiated by Crowe a mean of 8.9 years before. Five persons showed enlarged

Table 8.9 Expected number of induced and observed malignancies of parotid gland, thyroid gland and brain in a population (n = 2,500) exposed to nasopharyngeal irradiation

Organ	Induction rate*		Number of tumours	
	$.10^{-6}.cGy^{-1}$	Dose (cGy)	Expected	Observed
Parotid	20	4-19	0.2-0.95	0
Thyroid	100	2- 7	0.5-1.75	2
Brain	20	10-36	0.5-1.8	-1

* As given by UNSCEAR (1977) (3)

blood vessels and two persons showed slight crusting (19). In a non-concurrent study of 417 persons by Hazen et al., a mean of 14.6 years after irradiation, two malignant and five benign tumours were found, which did not differ from the expected values (20). In both investigations the follow-up period was short and control groups were either lacking (19) or difficult to assess (20).

More recently, Sandler et al. (1982) carried out a study on 904 persons who had been treated with a 50 mg radium applicator, with a follow-up period of 18 to 35 years (usual dose 4,208 mgmin) and compared the subsequent cancer occurrence to that in a group of 2,021 non-exposed subjects. Three brain tumours and an anaplastic cancer of the soft palate were identified in the exposed group, whereas no cancers of the head and neck were found in the non-exposed group ($p<.05$). No other increased incidences of cancer risk were found. A nearly significant reduction in breast cancer in exposed females was noted (17).

The present study was similar in design to that of Sandler et al. (1982). The study group was, however, considerably larger (2,542 exposed, 2,380 non-exposed) and the average dose was lower (average 1,198 mgmin). In the Netherlands unilateral irradiation had been the standard form of treatment, whereas the Sandler et al. (1980) population had been exposed to bilateral treatment (21).

In the present study we will have missed several types of cancer. We have already noticed deficits due to non-response to the questionnaire or verification procedure. Correction factors have been introduced to compensate for this (see Table 8.7). However, these factors may be too high because existing incidences will have been reported more frequently than lacking incidences, i.e. the frequency of cancer cases in the non-respondents may have been lower. On the other hand, the number of people with cancer in the deceased group might have been higher than reported due to cancer being present in subjects who died of other causes and in the five missing observations (Table 7.6). The incidence of cancer among the survivors will have been too low owing to misrecollection in these subjects. We did not find significant differences between subjects in the exposed group who remembered being treated with the Crowe therapy and those who did not; this might lead to the conclusion that there was no over-reporting by subjects who remembered the radiation treatment.

There is no reason to suppose that these possible causes of under or over-reporting are any different in the exposed and non-exposed groups. In other words we expect the relative risks to be unbiased.

Small but significant increases in the cancer incidence were found in the exposed

group. This was mainly the result of cancer in the head and neck region and at 'other' sites remote from the irradiated area. The relative risk for these sites was not significantly different from 1.00. Small differences in mortality from cancer of the lymphatic or haematopoietic system in males and from breast cancer in females disappeared when the incidences were added.

The two laryngeal carcinomas and two skin carcinomas in the head and neck region cannot easily be brought into connection with the low radiation doses received via nasopharyngeal radium irradiation. As regards the two thyroid carcinomas in exposed females, a relationship with previous irradiation is more obvious in view of the tendency of the thyroid gland towards radiation carcinogenesis.

Although no statistically significant increases in cancer incidence in the head and neck region were established and although it would be hard to find an explanation for the (non-significant) higher cancer rates at other sites, we cannot ignore the increased overall cancer rate in exposed subjects.

In our investigation of benign tumour incidence, women appeared to report three times as many benign tumours as men, irrespective of whether or not they had been exposed to irradiation.

Contrary to Sandler et al. (1982), we were unable to find a higher brain tumour incidence in the exposed group. Our breast cancer mortality did agree with their findings, but our cumulative breast cancer incidence did not; the latter incidence also disagreed with the findings in the population studied by Hazen et al. (1966), in which pituitary irradiation had taken place (19).

Summarizing, our study does corroborate the hypothesis that there is some risk of tumour induction involved with nasopharyngeal radium irradiation at the dose level applied to this population.

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CHAPTER 9
HORMONAL AND OTHER EFFECTS OF NASOPHARYNGEAL RADIUM IRRADIATION

In order to examine the possible induction effects of nasopharyngeal radium irradiation on hormone balance, resulting from the inclusion of the pituitary gland in the treatment field, a number of specific questions were asked in the questionnaire. These questions were formulated with the aim of detecting hormonal disease as well as hormone-influenced processes, such as growth and fertility. The statistics in this chapter concern selected populations, as mentioned in Chapter 7 under 'Methods of analysis'.

9.1 HORMONAL DISEASE

Differences were observed with regard to hormonal disease between the exposed and non-exposed groups. This was also the case for the use of medications corresponding to hormonal disease. It was striking that both thyroid disease (1.9% vs 1.2%) and thyroid medication (1.3% vs 0.8%) were more frequent in the irradiated group. This was also true for diabetes mellitus (1.8% vs 1.1%) and antidiabetic medication. The fact that subjects were aware that they had been irradiated did not account for the larger number of reports (see Table 9.1).

Table 9.1 Hormone-related disease and medication for exposed and non-exposed subjects.

Hormone related:	Exposed			Non-exposed		
	N	%	rate	N	%	rate
Disease						
Diabetes	36	1.8	7.3	19	1.1	4.2
Anaemia	348	17.7	70.1	287	17.1	63.7
Thyroid disease	38	1.9	7.7	21	1.2	4.7
Hypophyseal	5	0.2	1.0	4	0.2	0.9
Hormonal disease	58	3.0	11.7	48	2.9	10.7
Medication						
Oral antidiabetics	12	0.6	2.4	8	0.5	1.8
Insulin	23	1.2	4.6	16	1.0	3.6
Antihypertensives	126	6.6	25.4	101	6.2	22.4
Hormones	155	8.1	31.2	125	7.6	27.8
Thyroid medication	25	1.3	5.0	14	0.8	3.1

9.2. HORMONE-INFLUENCED BODY FUNCTION

The irradiation of the head and neck region did not have any clear effect on height or weight. Height was 174 ± 10 cm and weight was 71.3 ± 13 kg for the exposed group compared to 173 ± 11 cm and 71.2 ± 13 kg for the non-exposed group, respectively.
There were no differences between the groups concerning the marital status (79.5% vs 78.1%) and fertility, expressed in relation to the number of children. Parents in the exposed group had an average of 2.16 ± 1.01 children and in the non-exposed group 2.12 ± 1.06 children. Involuntary infertility occurred in 2.8% of the exposed and in 2.4% of the non-exposed subjects. No differences were observed with regard to the age of menarche, the regularity of the menses, the number of miscarriages and the age of menopause in the female respondents.

9.3 OTHER HEALTH EFFECTS

9.3.1 Hearing disorders

As shown in Table 9.2, there is a higher incidence of hearing disorders and people with hearing aids in the exposed group. This is to be expected, because the most important reason for irradiating patients (otitis serosa) carries a risk of late hearing impediment which, even with optimum medical care, cannot be completely prevented. On the basis of similar findings in the population of Sandler et al., which consisted solely of people who had been treated for hearing disorders in their youth, (see Chapter 7, 'Discussion') the assumption was made that nasopharyngeal radium therapy does not have any long-term effect on the prevention of deafness (1). However, it is possible that particularly the persistent cases of otitis serosa underwent the treatment and in this way gave rise to a selection.

Table 9.2 Other diseases of exposed and non-exposed subjects.

Disease	Exposed		Non-exposed	
	N	%	N	%
Hearing disorder	823	42.1	256	15.2
Hearing aid	133	6.8	37	2.2
Cataract	18	0.9	15	0.9
Epilepsy	22	1.1	22	1.3
Mental depression	249	12.7	192	11.4
Psychiatric treatment	159	8.1	111	6.6

9.3.2 Visual disorders

The incidence of cataracts was the same in both groups. This is also unremarkable because the lens only becomes affected at higher radiation doses (200-600 cGy) (2).

9.3.3 Psychiatric disorders

In the study conducted by Shore et al. (3), mentioned above (see Chapter 3, 'Brain and meninges') an increased incidence of - treated - psychiatric disorders (40%) was observed among white people in the irradiated group. Although the dose received by the brain in his study was much larger (70-170 cGy) than in our study, we still included questions concerning depression and treatment by psychologists or psychiatrists in our questionnaire. The incidence of treatment by the latter appeared to be higher (8.1% vs 6.6%) in the exposed group. It seems that this difference is related to the higher incidence of hearing deficits among the exposed subjects. (See Table 9.3).

Table 9.3 Occurrence of mental disorders compared to state of hearing. Number and percentage of total respondents.

Mental disorder	Hearing disorder					
	no	(%)	yes	(%)	total	(%)
Depression	260	(10.2)	180	(16.7)	440	(12.1)
Psych. treatment	157	(6.2)	113	(10.5)	270	(7.4)
Total respondents	2551	(100)	1075	(100)	3626	(100)

9.4 DISCUSSION

The radiation dose received by the pituitary gland during nasopharyngeal radium treatment was small (10-36 cGy). From radiotherapy practice it is known that disorders in pituitary function normally manifest themselves following much higher radiation doses. Moreover, the questions in our questionnaire were too broad to detect small function deficits of the pituitary gland which express themselves in the form of hormone imbalance.
In conclusion, small differences were found with relation to hormonal disorders and hormone-influenced processes. The distinctly higher number of psychiatric disorders seems to be related to the greater number of hearing deficits in the exposed group.

REFERENCES CHAPTER 9

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CHAPTER 10
DISCUSSION AND CONCLUSIONS

10.1 DISCUSSION

The motivation to carry out this study lay in the very great contrast of views which clinicians seem to have regarding the Crowe therapy, its effectiveness and its late side-effects.
Despite the fact that some physicians are rather sceptical about the tumour inducing capacity of this therapy and others think that the chance of tumour induction is small, they will all still be inclined to carry out very careful examinations of patients - with an anamnesis of Crowe therapy - for tumours, 'just to be on the safe side'. With the additional realization that a diversity of opinions exist on the therapeutic effect of the Crowe therapy, our curiosity was more than sufficiently provoked. After all, wouldn't it be all the more regrettable if people ran an increased risk throughout their lives of developing cancer as the result of a treatment during their youth which appeared to be ineffective afterwards?
A prospective non-concurrent design was chosen for the execution of this study, involving about 2,500 persons who had been exposed to irradiation. The population could have been larger if more funds had been available and if there had been more cooperation between colleagues. Some researchers in the field of radiation might think that, in view of the low radiation doses received by several of the organs, a study population of 2,500 subjects is too small. The number of radiation induced tumours which - on theoretical grounds - may occur in our population, is indeed not very large (see Chapter 8, Table 8.9). However, the dose received by the pituitary gland (10-36 cGy) was substantial and the dose received by the nasopharynx (3,500-23,000 cGy) was considerable. Moreover, the possible negative results can be used to establish the lower limit of the risk.
The number of A-bomb and nuclear disaster victims (Chernobyl) and people who have been exposed to irradiation, via their occupation or for medical reasons, is small. But due to the prohibition to experiment on people, we are obliged to use such populations for research purposes. Comparisons of the results in similar studies can strengthen or weaken the meaning of the observed risks, even if they are not statistically significant in the separate studies. Moreover, one of the advantages in our study was that the radiation doses received by the various head and neck organs could be calculated accurately, which is not always the case with medical exposure and mostly impossible with regard to the A-bomb and nuclear disasters.
In a similar study to ours, by Sandler et al. (1982) (see Chapter 7, 'Discussion') an increased incidence of RES tumours and a decreased incidence of breast tumours were found in the exposed group, which were not statistically significant. Our results regarding mortality support these findings. In Sandler et al.'s study a statistically significant higher incidence of head and neck tumours and thyrotoxicosis was found in the exposed group.
In our study on the cause of death no corresponding indications were found. However, on the basis of the answers in the questionnaire regarding the incidence

of disease, there appeared to be a higher (but not statistically significant) incidence in the total number of head and neck tumours. A higher incidence of thyroid disease was also noted. Contrary to the findings in Sandler et al.'s study, the higher all-cancer incidence in our exposed group reached statistical significance.
Owing to the fact that the radiation dose received by the larynx (≦ 7 cGy) and skin (≦ 20 cGY) was much lower in our study than is usually the case for radiation induced tumours, it is not easy to establish a relationship between the origination of these tumours and the previous nasopharyngeal irradiation.
The thyroid gland is very sensitive to irradiation. Radiation-induced carcinomas of this organ have been seen to develop after low radiation doses, such as those received by our study group (≦ 7 cGy).
It is notable that the high radiation exposure of the mucosal lining of the nasopharynx, in our study 3,500-23,000 cGy, did not result in the origination of radiation-induced nasopharyngeal tumours. This finding is in agreement with the results of Sandler et al.'s study.
The results in our study do corroborate the hypothesis that some risk of tumour induction is involved with nasopharyngeal radium irradiation, although its validity is restricted due to the limited number of study subjects and the limited number of tumours found.
What are the consequences of the results of this study regarding our judgement of the nasopharyngeal radium irradiation (Crowe therapy) as a medical treatment? Although it is very probable, on the basis of data from the literature, that irradiation has a therapeutic effect on disorders resulting from dysfunction of the eustachian tube, it seems best to leave the therapy in its obsolete state. Physicians who are still practicing the Crowe therapy should reconsider possible alternative therapies for patients presenting with tubal problems.
In the first place, there is probably some risk of tumour induction on the grounds of the results from this and other studies. Furthermore, we must remember that some radiation-induced tumours may manifest themselves after a longer latency time (30 or 40 years) than the observation period in our study, which adds to the risk.
Those who wish to reserve the treatment for very persistent cases of tubal dysfunction would do well to remember that scarred eustachian tubes do not respond to irradiation. What are the consequences of the results of this study regarding the physician's attitude towards patients with nasopharyngeal radium treatment in their anamnesis?
The risk of tumour induction is too small to justify exhaustive examination of symptom-free persons. Extensive diagnostic measures are unnecessary and alarming and should therefore not be carried out.
For the same reasons, recalling these persons and screening them for existing tumours should not be considered. The following conclusions are formulated as answers to the questions posed in Chapter 1:

10.2 CONCLUSIONS

(1) During an observation period of a mean of 25.3 years in 2,542 persons who had been treated using Crowe's nasopharyngeal radiation method as applied in the

Netherlands, no increased mortality due to cancer was observed. However, a statistically significant increase in the cumulative incidence of all malignant tumours combined was found. Separation of the individual tumour sites did not produce a significant excess. No increased incidence of nasopharyngeal or brain cancer was found.

(2) There were some indications that the Crowe therapy had affected hormone-influenced processes.

(3) Through comparisons with a similar American study (Sandler et al.), indications regarding the possibility of tumour induction in man in the exposure range 0-50 cGy were strengthened. No data were obtained for establishing a dose-effect relationship.

(4) Owing to the efficient registration of births, deaths and marriages in the Netherlands, it is possible to conduct successful epidemiological follow-up procedures (in this study 93.6% of the population could be followed-up).

SUMMARY

The Crowe therapy - nasopharyngeal irradiation by means of radium application - was a very popular form of treatment for ear disorders in children and for barotrauma in adults between about 1925 and 1975 in America and Europe. Nowadays this treatment has more or less been abandoned owing to the fear of tumour induction and replacement treatments. It is necessary for a physician who is confronted with a patient who has been irradiated using the Crowe therapy in the past, to know the nature and degree of the risks. In this thesis a non-concurrent cohort study is described in which the effects of the Crowe therapy were examined with regard to the health of a population of persons who were irradiated in their youth.

In Chapter 1 the aims of the study are formulated. The most important question is whether the Crowe therapy leads to the origination of tumours. Most of the attention is focussed on the head and neck region. The second question concerns the possible influence of the Crowe therapy on hormone balance, as a result of the pituitary gland being in the treatment field. Further, it is investigated whether information can be obtained regarding dose-effect relationships in a dose range (0-50 cGy) for which little is known in man. Finally, the study method - involving the follow-up procedures relevant to a non-concurrent cohort study in the Netherlands - forms a topic of investigation.

Chapter 2 deals with the Crowe therapy in greater detail. Some attention is paid to the anatomy and physiology of the eustachian tube, as it is the ultimate goal of the Crowe therapy to improve the function of this organ. Owing to the fact that lymphoid tissue is pre-eminently sensitive to irradiation, the distribution of this tissue in and around the eustachian tube is described. Under normal circumstances there is no lymphoid tissue in the eustachian tube. The adenoid can have a negative effect on tubal function and adenotomy can have a positive one.
Double blind controlled research has shown that the Crowe therapy affects the size of the adenoid as well as the degree of lymphoid overgrowth at the tubal orifice. Most studies on the effect of tubal function and the effect of the various clinical expressions of poor tubal function lack a control group. Effectiveness has been shown via double blind controlled research with regard to flat hearing loss, such as occurs in children with otitis serosa and with regard to adults with barotrauma.

Chapter 3 gives an overview of the present state of knowledge on - ionizing - radiation induced tumours in the head and neck region. Besides occupational exposure to radiation and exposure for medical reasons, a great deal of knowledge has been acquired on radiation induced tumours from the Japanese atom bomb explosion victims. The chance of a radiation induced tumour developing depends on many factors. These are associated with the characteristics of the individual and of the physical agent.
Women are more sensitive to radiation induced thyroid tumours than men. Exposure at a young age and particularly antenatally leads to an increased risk of developing radiation induced tumours.

Ethnical factors also appear to be of influence. In one study Jews were found to be more predisposed to developing thyroid tumours and in another study white people were found to be more predisposed to developing radiation induced skin tumours than coloured people.
Various studies have shown the existence of genetically determined sensitivity to radiation induced tumours. This was observed in patients with multiple familial retinoblastomas and in patients with the nevoid basal cell carcinoma syndrome.
The patient's metabolic situation also appears to play a part. For example, a high TSH level, malnutrician and the use of cytotoxic drugs were found to involve an increased risk.
The risk of developing a radiation induced tumour depends on the type of radiation. High LET radiation (alpha and neutron irradiation) has a higher tumour inducing capacity than low LET radiation (gamma and röntgen radiation) per dose unit. Moreover, it is possible that the energy level, dose rate and fractionation also influence the origination of radiation induced tumours.
The lowest dose thought to have induced a tumour is 6 cGy. The risk increases with the dose to a certain level (2000 cGy for thyroid tumours) and decreases at higher levels because the number of cells which can become malignant decreases (cell death function). The minimum latency period is a few years, the maximum latency period appears to be unlimited. A description of tumour induction due to irradiation is given for a number of organs in the head and neck region.
The salivary glands are receiving increasing attention as a site where radiation induced tumours can arise. In a population of people exposed to the atom bomb explosions in Japan, it was established that the chance of developing a salivary gland tumour increases as the distance of the exposed person from the explosion site decreases.
Radiation induced salivary gland tumours can be malignant or benign and can have all kinds of histologies. Radiation induced tumours of the brain and meninges are particularly well known as 'second primary tumours' following the irradiation of retinoblastomas or pituitary adenomas. It is also believed that tumour induction is possible after low radiation doses, such as 120-140 cGy, given for tinea capitis.
The first radiation induced tumours to be described in the head and neck region were localized in the pharynx and larynx. They are reported exclusively following medical treatment using ionizing irradiation. The fact that cohort studies have proved that 5% of the people who have been irradiated for an early stage larynx carcinoma develop a second primary tumour, has clear clinical implications. The thyroid gland is the most sensitive organ in the human body for radiation induced tumours. For this reason, most of the knowledge on the relationship between radiation and cancer has been acquired via studies on radiation induced thyroid tumours.
The skin is also very radiation sensitive. Basal cell carcinomas have been described following radiation for dermatoses (acne) on the face. The degree of skin pigmentation is an important risk factor. The clinical significance of radiation induced skin tumours is small: as a rule they can be treated adequately.
The most striking forms of radiation induced tumours are those which develop at several different places in the same organ (multicentric) and those which develop in several different tissues simultaneously (pluritissular). This is associated with the physical nature of the ionizing radiation.

In Chapter 4 the design of the study is described. The exposed group, comprising 2,542 persons, was selected from the records at five ENT clinics. The control group was selected on the basis of the characteristics of the subjects in the exposed group, i.e. the year of birth, the year of first contact and sex. During follow-up we tried to find out how many subjects were still alive and how many had died. This was accomplished in 93.6% of the cases. The cause of death was established for the deceased and the subjects who were still alive were surveyed with questions concerning their health. The response to the survey was 86.5%. If it was suspected on the grounds of the questionnaire that a subject was suffering from or had suffered from a tumour, their specialist - at that time - was approached for verification of the diagnosis.
The method of collecting data is described in Chapter 5. The radiation doses were calculated with the aid of antero-posterior and lateral skull X-ray films of children of various ages with a placebo applicator in situ. In this way it was possible to determine the doses received by each organ in the head and neck region. The details are presented in Appendix 9. Depending on the age and clinic, the doses for the pituitary gland varied from 10-36 cGy, for the thyroid from 2-7 cGy, for the parotis from 4-19 cGy and for the nasopharynx 3,500-23,000 cGy.
All the necessary data for the follow-up examination were obtained from the records at the five ENT clinics, including sex, insurance, date of first contact, diagnosis and radiotherapy treatment data.
The health survey comprised questions concerning potential tumours, problems with hormone balance and other possible effects that the irradiation of the head and neck region might have had on the health of the subject. Finally, the way in which the various data were coded is described.

In Chapter 6 a number of characteristics of the study population are presented. The average age of the subjects at the beginning of follow-up and the slight predominance of males (57:43) corresponds with the pre-eminent age and sex at which otitis serosa is usually treated. Otitis serosa was the most frequent indication for the Crowe therapy.

The mortality of the exposed group is compared to that of the non-exposed group in Chapter 7. No significant differences were observed with regard to the total mortality, deaths due to cancer or deaths due to cancer of specific organs. Four cases of lymphatic or haematopoietic tumours, two of which were leukemias, were identified as the cause of death in males in the exposed group, whereas none were observed in the non-exposed group). One brain tumour was found in the exposed group, against two in the non-exposed group.

In Chapter 8 the cumulative tumour incidence is compared in exposed and non-exposed subjects. Six head and neck tumours were observed in the exposed group, whereas only one was found in the non-exposed group. This difference is not statistically significant. For all cancers a significantly higher cumulative incidence was found in the exposed group. This significance is mainly caused by 'head and neck tumours' and 'other tumours' (lung, digestive tract and urogenital system). No differences were found between the exposed and non-exposed groups with regard to benign tumour incidence.

Chapter 9 deals with the influence of irradiation on the occurrence of hormonal disorders, such as diabetes mellitus and thyroid disorders and hormone-influenced processes, such as growth and fertility. Small differences were observed to the disadvantage of the exposed group. Notably, more reports of thyroid disease were found in the exposed group. The higher incidence of mental depression and treatment by psychologists or psychiatrists seems to be related to the higher incidence of hearing deficits among exposed subjects.

In conclusion, the results of our study show that some risk of tumour induction is involved with nasopharyngeal radium irradiation. No increased mortality due to cancer was observed. However, a statistically significant increase in the cumulative incidence for all cancers combined was observed. Separation of the individual tumour sites did not produce a significant excess.
There were some indications that the Crowe therapy had affected hormone-influenced processes.
Indications regarding the possibility of tumour induction in man in the exposure range 0-50 cGy were strengthened. This study has shown that it is possible to conduct successful epidemiological follow-up procedures in the Netherlands owing to the efficient registration of births, deaths and marriages.
The Crowe therapy, as a medical treatment, should be left in its obsolete state.
In view of the small risk of tumour induction that irradiatied persons run, we consider that it is not necessary to pay special attention to symptom-free patients or to recall exposed persons for screening.

SAMENVATTING

De therapie volgens Crowe, nasofaryngeale bestraling door middel van radium-applicatie, werd veelvuldig toegepast tussen ±1925 en ±1975 in de V.S. en in Europa voor ooraandoeningen bij kinderen en barotrauma bij volwassenen.
Thans is deze therapie vrijwel verlaten wegens angst voor tumorinductie en de beschikbaarheid van vervangende therapieën. Voor de medicus die geconfronteerd wordt met een patiënt die in het verleden volgens Crowe bestraald werd is het nodig te weten welke de aard en de mate van de risico's zijn.
In dit proefschrift wordt een historisch cohort-onderzoek beschreven waarin de effecten van de Crowe-therapie op de gezondheid van een in het verleden bestraalde populatie worden nagegaan.

In Hoofdstuk 1 worden de vraagstellingen geformuleerd. De belangrijkste is of de Crowe therapie leidt tot het ontstaan van gezwellen. De meeste aandacht heeft hierbij de hoofd-halsregio. De tweede vraagstelling betreft de eventuele invloed van de Crowe therapie op de hormoonhuishouding door het meebestraald zijn van de hypofyse. Vervolgens wordt in dit onderzoek nagegaan of informatie kan worden verkregen over dosis-effectrelaties in een dosisgebied (0-50 cGy) waarover bij de mens nog weinig bekend is. Tenslotte is de methode van onderzoek, de follow-up procedures bij een historisch prospectief cohortonderzoek in Nederland, onderwerp van studie.

In Hoofdstuk 2 wordt nader ingegaan op de Crowe therapie. Enige beschouwingen worden gewijd aan anatomie en fysiologie van de buis van Eustachius welks functieverbetering doel is van de Crowe therapie. Omdat lymfoid weefsel bij uitstek gevoelig is voor straling wordt de verdeling van dit weefsel in en rond de buis van Eustachius besproken. Onder normale omstandigheden bevindt zich geen lymfoid weefsel in de buis van Eustachius. Het adenoid kan een negatieve en de adenotomie een positieve invloed hebben op de tubafunctie. In dubbelblind gecontroleerd onderzoek werd aangetoond dat Crowe bestraling effect heeft zowel op de grootte van het adenoid als op de mate van lymfoïde 'overgroei'van de mond van de buis van Eustachius. De meeste onderzoeken naar het effect op de tubafunctie en het effect op de verschillende klinische uitingen van een slechte tubafunctie ontberen een controlegroep. Ten aanzien van vlakke gehoorverliezen bij kinderen, zoals gezien wordt bij otitis serosa en ten aanzien van barotrauma bij volwassenen werd in dubbelblind gecontroleerd onderzoek de werkzaamheid aangetoond.

Hoofdstuk 3 geeft een overzicht van de bestaande kennis over door ioniserende straling geïnduceerde hoofd-halstumoren. Behalve door blootstelling aan straling in het beroep en om medische redenen, is veel kennis over tumorinductie vergaard door blootstelling aan straling van slachtoffers van de atoombomexplosies in Japan. De kans op het krijgen van een stralengeïnduceerde tumor is van vele factoren afhankelijk. Deze betreffen zowel kenmerken van het blootgestelde organisme als kenmerken van het fysisch agens.
Vrouwen zijn gevoeliger voor stralengeïnduceerde schildkliertumoren dan mannen.

Expositie op jeugdige leeftijd en vooral antenatale expositie leidt tot een hoger risico op het ontstaan van stralengeïnduceerde tumoren.
Ook etnische factoren bleken van invloed. In een onderzoek predisponeerde joods-zijn tot het krijgen van stralengeïnduceerde schildkliertumoren en in een ander onderzoek predisponeerde blank-zijn tot het krijgen van stralengeïnduceerde huid-tumoren.
In verschillend onderzoeken bleek een genetisch bepaalde gevoeligheid voor stralengeïnduceerde tumoren te bestaan. Dit werd o.a. gezien bij patienten met multipele familiaire retinoblastomen en patienten met het nevoid basal cell carcinoma syndrome. Ook bleek de metabole toestand een rol te spelen. Zo werden een hoog TSH-gehalte, ondervoeding en gebruik van cytostatica als risicoverhogend aangewezen. Het risico op het ontstaan van stralengeïnduceerde tumoren is afhankelijk van de soort straling. Hoge LET-straling (alfa- en neutronenstraling) heeft een hoger tumorinducerend effect dan lage LET-straling (gamma- en röntgenstraling) per dosiseenheid. Daarnaast is het mogelijk dat het energieniveau van de straling, het dosistempo en het fractioneren van de dosis van invloed zijn op het ontstaan van stralengeïnduceerde tumoren.
De laagste dosis waarna tumorinductie werd aangenomen bedraagt 6 cGy. Het risico neemt toe met de dosis tot een bepaald niveau (2000 cGy bij schildkliertumoren) en neemt bij hogere niveaus weer af doordat het aantal cellen dat maligne kan transformeren steeds kleiner wordt (celdoodfunctie). De minimum latentietijd bedraagt enkele jaren, de maximum latentietijd lijkt onbegrensd. Voor een aantal hoofd-halsorganen afzonderlijk wordt de tumorinductie door straling beschreven. De speekselklieren krijgen in toenemende mate aandacht als plaats waar stralengeïn-duceerde tumoren kunnen optreden. In een aan een japanse atoombomexplosie blootgestelde populatie werd vastgesteld dat de kans op speekselkliertumoren groter werd naarmate de geëxponeerde zich dichter bij de plaats van explosie bevond. Geïnduceerde speekselkliertumoren kunnen goed- of kwaadaardig zijn en van velerlei histologische aard.
Stralengeïnduceerde tumoren van hersenen en hersenvliezen zijn vooral bekend als 'tweede primaire tumoren' na bestraling voor retinoblastoom of hypofyseadenoom. Ook voor lagere stralingsdoses, zoals 120-140 cGy gegeven voor tinea capitis, wordt de mogelijkheid van tumorinductie aangenomen.
De eerste beschreven stralengeïnduceerde hoofd-halstumoren waren gelocaliseerd in farynx en larynx. Zij zijn uitsluitend vermeld na medische behandeling met ioniserende straling. Omdat in cohort-onderzoek is aangetoond dat zich bij personen die bestraald zijn voor een klein larynxcarcinoom in 5% der gevallen in het bestraalde gebied een tweede primaire tumor ontwikkelt, heeft dit een duidelijke klinische betekenis.
De schildklier is voor tumorinductie door straling het gevoeligste orgaan van het menselijk lichaam. Om die reden is de meeste kennis over de relatie straling en kanker vergaard door bestudering van de stralengeïnduceerde schildkliertumor.
De huid is eveneens een gevoelig orgaan. Basaliomen werden beschreven na bestraling voor dermatosen (acné) in het gelaat. De mate van huidpigmentatie is een belangrijke risicofactor. De klinische betekenis van stralengeïnduceerde huid-tumoren is gering: in de regel zijn zij goed behandelbaar.
De meest treffende vorm van tumorinductie door straling is het op meerdere plaatsen (multicentrisch) of het in meerdere organen tegelijkertijd (meervoudig)

ontstaan van de afwijking. Dit hangt samen met de fysische eigenschappen van ioniserende straling.

In Hoofdstuk 4 wordt de opzet van het onderzoek beschreven. De bestraalde groep, 2542 personen, werd uit vijf KNO-archieven geselecteerd. De controlegroep werd samengesteld uit dezelfde archieven op grond van een weergave van de bestraalde groep, overeenkomend in geboortejaar, jaar van eerste contact en geslacht. Bij de follow-up werd nagegaan of de personen uit beide groepen nog in leven waren of overleden waren. Dit gelukte in 93,6% van de gevallen. Van de overledenen werd de doodsoorzaak opgespoord en de nog levenden werden geënquêteerd met vragen betreffende de gezondheid. De respons op de enquête bedroeg 86,5%. Indien op grond van de enquête vermoed werd dat de betreffende respondent aan een gezwelziekte leed of geleden had, werd getracht de diagnose bij de destijds behandelende arts te verifiëren.

In Hoofdstuk 5 wordt besproken op welke wijze de gegevens verzameld werden. Met behulp van voorachterwaartse en dwarse schedelfoto's met een placeboapplicator in situ werden dosisberekeningen uitgevoerd bij kinderen van verschillende leeftijden. Voor elk hoofd-halsorgaan konden zo ontvangen doses berekend worden. In Appendix 9 worden de details hiervan gepresenteerd. Afhankelijk van leeftijd en kliniek varieerde de dosis voor de hypofyse van 10-36 cGy, voor de schildklier van 2-7 cGy, voor de gl. parotis van 4-19 cGy en voor de nasofarynx van 3.500 tot 23.000 cGy.
Uit de archieven van de verschillend KNO-klinieken werden de personalia en andere gegevens benodigd voor de follow-up overgenomen alsmede geslacht, verzekeringsvorm, datum eerste contact, diagnose en bestralingsgegevens.
De gezondheidsvragenlijst, gebruikt bij de enquete, bevatte vragen over mogelijke gezwelziekten, vragen betrekking hebbend op de hormoonhuishouding en enige vragen betreffende andere mogelijke effecten op de gezondheid van bestraling van het hoofd-halsgebied. Tenslotte wordt in dit hoofdstuk de wijze van codering van de verschillende gegevens besproken.

In Hoofdstuk 6 worden enkele kenmerken van de onderzoeks-populatie gepresenteerd. De gemiddelde leeftijd bij het begin van de follow-up en het in geringe mate overwegen van het mannelijk geslacht (57:43) komt overeen met de voorkeursleeftijd en het geslacht waarbij otitis serosa wordt behandeld. Otitis serosa was de belangrijkste indicatie voor de Crowe therapie.

In Hoofdstuk 7 wordt de sterfte van de bestraalde groep vergeleken met die van de controlegroep. Geen significante verschillen werden aangetoond in totale sterfte, sterfte aan kanker of sterfte aan kanker van bepaalde organen. Vier gevallen van lymfatische of haematopoietische tumoren, waarvan twee leukamie, werden bij bestraalde mannen als doodsoorzaak vastgesteld, terwijl er geen bij de niet bestraalde groep werden gevonden. In de bestraalde groep werd één hersentumor gevonden, tegen twee in de niet-bestraalde groep.

In Hoofdstuk 8 is het voorkomen van tumoren tussen bestraalde en niet bestraalde personen vergeleken. Zes maligne hoofd-hals tumoren werden bij de bestraalde

groep gevonden, terwijl er bij de niet bestraalde groep slechts een werd ontdekt. Dit verschil is statistisch niet significant. Voor alle maligne tumoren tesamen, werd een statistisch significant verhoogde cumulatieve incidentie vastgesteld in de bestraalde groep. Dit verschil werd vooral bepaald door 'hoofd-halstumoren en 'andere tumoren' (long, maag-darm-stelsel en tractus urogenitalis). Met betrekking tot het optreden van benigne tumoren werden er geen verschillen gevonden tussen de bestraalde en de niet bestraalde groepen.

In Hoofdstuk 9 wordt de invloed van de bestraling nagegaan op het voorkomen van hormonale aandoeningen zoals diabetes mellitus en schildklieraandoeningen en hormonaal beïnvloedbare processen zoals groei en vruchtbaarheid. Er werden kleine verschillen vastgesteld ten nadele van de bestraalde groep. Met name werden vermeldingen van schildklieraandoeningen vaker waargenomen. De hogere incidentie depressies en psychologische of psychiatrische behandeling lijken in verband te staan met de hogere incidentie van gehoorstoornissen onder bestraalde personen.

Op grond van deze studie mogen we concluderen dat er enig risico van tumorinductie bestaat door nasofaryngeale radiumbestraling. Een verhoogde sterfte aan kanker werd niet waargenomen. Wel kon een statistisch significante verhoging van de cumulatieve incidentie van alle maligne tumoren tesamen worden vastgesteld. Gekeken naar de afzonderlijke organen, werden geen significante verschillen gezien. Er werden enige aanwijzingen gevonden dat de therapie volgens Crowe invloed heeft op het voorkomen van hormonaal bepaalde aandoeningen.
Bestaande aanwijzingen dat ioniserende straling in het dosisgebied 0-50 cGy bij de mens tumoren kan induceren werden bevestigd.
Deze studie heeft aangetoond dat een historisch cohortonderzoek in Nederland met succes kan worden uitgevoerd dankzij de efficiënte gemeentelijke registratie van geboorte, huwelijk en overlijden.
Op grond van het voorgaande lijkt het beter de Crowe therapie niet meer toe te passen.
Vanwege het kleine risico dat bestraalde personen lopen op het krijgen van een stralengeïnduceerde tumor concluderen wij dat het niet noodzakelijk is om speciale aandacht te besteden aan patienten die vrij van symptomen zijn of om bestraalde patienten op te roepen voor screeningsonderzoek.

DANKWOORD

Overeenkomstig de aard van het onderzoek hebben velen bijgedragen aan het tot stand komen van dit proefschrift. In het bijzonder gaat mijn dank uit naar:
De duizenden ex-patiënten van de vijf deelnemende KNO-klinieken, die de moeite namen de gezondheidsvragenlijst in te vullen.
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CURRICULUM VITAE

De schrijver van dit proefschrift werd geboren op 15 november 1948 te Haarlem. In 1968 behaalde hij het diploma HBS-B aan het lyceum 'Marnix van St. Aldegonde' te Haarlem. De studie medicijnen werd aangevangen aan de Rijksuniversiteit te Utrecht (1968-1970) en afgesloten aan de Vrije Universiteit te Amsterdam in 1975.
De dienstplicht werd vervuld bij de Koninklijke Marine als assistent neurologie/psychiatrie in het Marine Hospitaal te Overveen.
Van 1977 tot 1981 werd hij opgeleid tot keel-, neus- en oorarts door Prof. Dr. P.E. Hoeksema aan de Rijksuniversiteit te Groningen. Sinds 1981 is hij als zodanig werkzaam in het Maaslandziekenhuis te Sittard. De auteur is gehuwd en is vader van vier kinderen.

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APPENDIX 1
QUESTIONNAIRE: THE APPLICATION OF THE CROWE THERAPY IN THE NETHERLANDS

A.1.1 INTRODUCTION

In order to form an impression of the way and degree to which the Crowe Therapy was applied in the Netherlands, a questionnaire was sent to a number of ENT specialists in the middle of 1982. An additional aim of the survey was to gain an insight into the results and side effects of the therapy. The data obtained in this way were used to track down clinics with records suitable for the epidemiological study, to be carried out later, on the relationship between the Crowe Therapy and tumour induction.

A.1.2 METHODS

A questionnaire, with an accompanying letter and stamped addressed envelope, was sent to all 110 members of the Dutch Society of Ear, Nose and Throat Specialists who had joined the society in or after 1960 and whose name appeared in the society's annual report of 1980. Moreover, four surveys were conducted on the telephone with non-members of the society who, on the basis of the written questionnaires or via other means, were known to have applied the Crowe therapy.

A.1.3 RESULTS

Answers were received from 66 of the 110 ENT specialists approached (60%). One colleague appeared to have died shortly before and two answers did not supply any information. This left 63 reactions for processing (57%). A summary of the answers will be presented per question.

Question 1. Have you applied the Crowe therapy yourself or had it applied in your own or someone else's practice?

This question was answered in the affirmative by 35 respondents (56%). Eight did not give any further information: seven had only applied the therapy during their training and one had referred patients, who were considered to be candidates for the Crowe Therapy, to a colleague.
Twenty-eight respondents said no to this question. They were only questioned further with regard to possible observations of tumour induction due to radium irradiation (question 11). The positive answers of 27 respondents to questions 2 to 10 are shown in Table A1.1, together with the answers from the four surveys conducted per telephone.

Table A1.1 Results of the survey on the application of the Crowe therapy in the Netherlands

No.	City/town	Years	Pat/yr	Mg	Dose	Indication*	Results	Complications
1	Assen	53-55	1-2	25		SOM	good	
2	Unknown	55-65			10[1]	SOM	v. satisfactory	
3	Leiden	48-73	200-250	12.5	30[1]	SOM	v. good	
4	Sluiskil	55-64	20-30			SOM	good	
5	Tiel	54-67	50	50	3.12[1]	SOM + RO	favourable	
6	Alkmaar	52-58	15			SOM	v. good	
7	Utrecht	50-58	40-60	50	2.8[1]	SOM	good	palat necrosis
8	Utrecht	50-58	dozens	50	5[1]-15[1]	SOM	no def. concl.	radium ulcer, atlas necrosis, epipharyngitis sicca
9	Den Bosch	51-68	50-100	25	4.10[1]	SOM + M	v. favourable	
10	The Hague	64-76	20	50	3.10[1]	SOM	favourable	
11	Amsterdam	46-60	100-150	50	3.(1-3)[1]	SOM	often succes.	
12	Amsterdam	58-68	0-20	50	3.3	SOM	good	
13	Zaandam	53-63	50			SOM	good	
14	Sneek	51-65		50	2.(4,5-8)[1]	SOM	favourable	
15	Haarlem**	53-69	many	25	3.(8,5-12)[1]	SOM	good	
16	Zutphen	50-51	25	25		SOM		
17	The Hague	57-60	sporadic			SOM	result of anaes.	
18	Groningen	48-65	20	25		SOM	not spectacular	
19	Groningen	50-		25		SOM		
20	Utrecht	53		50		SOM	good	cylinder broken from needle
21	The Hague	1950s	10-20	25		SOM		
22	Enschede	50-55	4			SOM	v. satisfactory	
23	Amsterdam	48-70	150	50		SOM + PN	good-excellent	
24	Den Helder	55-64	5-10			SOM		
25	The Hague**	to 70				SOM		
26	Den Bosch	50-62	5-8	15		SOM	good	
27	Bussum	56-70	25	25	3.10[1]	SOM	good fairly often	
28	Sittard	54-81	120	25	4.(7-15)[1]	SOM	v. good	
29	Haarlem	46-69	50	10	(1-3).60	SOM	good	
30	Assen	46-70	50	50	3.20[1]	SOM	good	
31	Amsterdam	55-62	50			SOM	not very effective	

* SOM = otitis serosa; RO = persistent otitis; M = mastoiditis; PN = polyposis nasi
** in cooperation with radiologist/radiotherapist

Question 2. In which hospital/practice did this therapy take place?

The names of 27 hospitals/practices were mentioned, 24 in the written questionnaire and three on the telephone. This figure is smaller than the number of specialists who applied the therapy. This is the result of succession and of cooperation within one practice (see Figure A1.1).

Figure A1.1 Application of nasopharyngeal radium treatment in the Netherlands. Clinics in which treatment was given: Alkmaar, Amsterdam (4x), Assen, Bussum, Enschede, 's-Gravenhage (4x), Groningen, Haarlem (2x), Den Helder, 's-Hertogenbosch (2x), Leiden (2x), Sittard, Sluiskil, Sneek, Tiel, Utrecht, Zaandam, Zutphen.
Δ Information obtained by written enquiry.
* Information obtained by verbal communication.

Question 3. In what period was the therapy conducted?

The period of application of the therapy varied from a few years to twenty or so years. It was introduced in the Netherlands by Van Dishoeck in 1945 and was at its peak in the 1950s and at the beginning of the 1960s. The therapy was applied until the 1970s at five clinics. It has more or less been abandoned nowadays (see Figure A1.2).

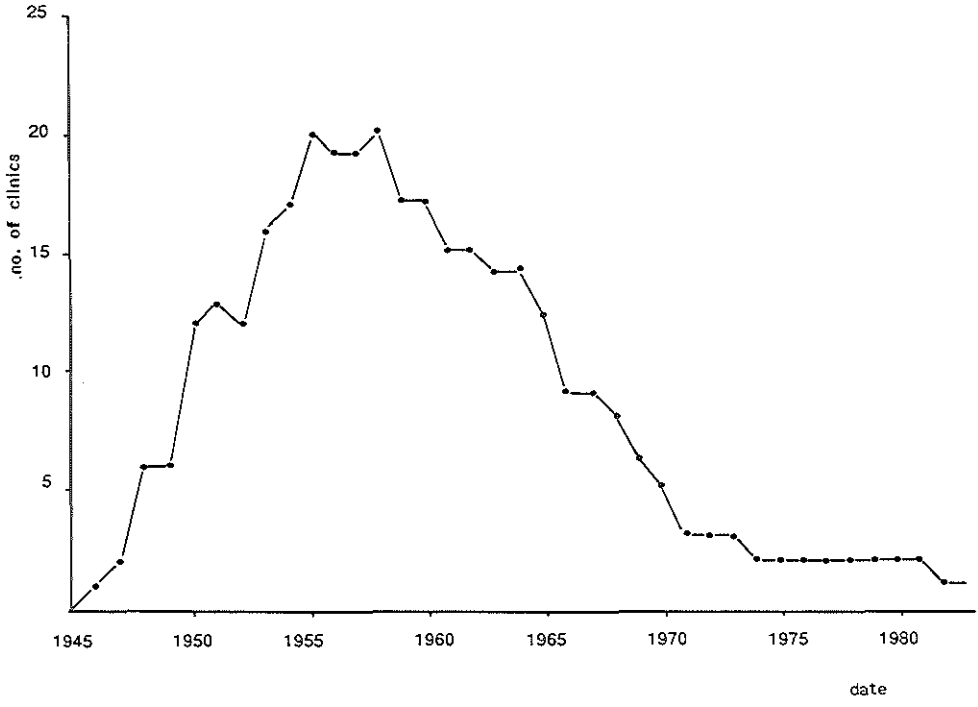

Figure A1.2 Application of nasopharyngeal radium treatment in the Netherlands. Number of clinics, per date.

Question 4. Approximately how many patients were treated per year using radium?

Exact answers were given to this question, varying from 1.5 to 225. The average was about 50 patients per year. With the aid of the answers to question 5, an estimation was made of the number of people who had been treated in this way: approximately 24,500. We were careful not to count the answers of specialists who had been working at the same clinic during the same period more than once.

Question 5. How much radium sulphate did the needle contain?

In eight cases 25 mg was mentioned and in ten, 50 mg. Other quantities were only mentioned once: 12.5 mg, 15 mg and 25 mg (radon).

Question 6. What was the dose applied per age of the patients?

This question produced a great diversity of answers, varying from 1 to 4 sessions of 1 to 30 minutes duration.

Question 7. What were the treatment indications?

By far the most respondents gave otitis serosa or a synonym as the indication for treatment. Recurrent otitis, polyposis nasi and inflammation following radical mastoidectomy were also mentioned.

Question 8. What were the general results of the therapy for the various indications?

A therapeutic effect was mentioned by 19 respondents. They chose one of the following classifications to describe the effect: 'good', 'very good', 'favourable', 'very satisfactory', 'often successful', 'good to excellent' and 'good, fairly often'. Two respondents considered the results to be 'very mediocre'. Other responses which were encountered once each were: 'no definitive conclusion', 'no spectacular results', 'not very effective' and 'the effect was possibly the result of the anaesthetic used (procaine)'.

Question 9. Has an accident with a radium source ever taken place at your practice?

This question only produced the report of an accident which was already known: the breakage of a needle and ingestion of the radium-containing cylinder, SAZU, 1958.

Question 10. Did you ever observe harmful side-effects in the short-term?

Several respondents mentioned the consequences of too long applications, such as epipharyngitis sicca, radium ulcer and necrosis of the palate. Also, necrosis of the atlas was thought to have been observed.

Question 11. Have you ever found a benign or malignant tumour in the head and neck region of a patient who had been exposed to radium irradiation?

This question was presented to everybody, either in the questionnaire or on the telephone. It was answered twice in the affirmative. One of the respondents reported to have seen such a tumour during his training in Leiden (1949-1952). The other thought he had seen one or two such tumours in his own practice since 1960. Both respondents had given a negative answer to Question 1, therefore, they had not conducted the treatment themselves.

A.1.4 DISCUSSION

Only a few general conclusions can be drawn from the data acquired via the questionnaire. The response rate of 60% is not high enough to be able to make a more precise estimation of the application of the therapy in the Netherlands. For many respondents, the Crowe therapy was a treatment from the past. Many had already stopped practising by the time the survey was held and the majority who had applied the Crowe therapy had abandoned the method twenty or so years earlier. Moreover, the figures and treatment results estimated by the therapists themselves are not always completely reliable. It is possible that personal feelings and/or the general regard of the therapy led to under or over estimations. The fact that not all the clinics where the Crowe therapy was applied are known, is a distorting factor in the estimation of the number of people who were irradiated.
Reviewing the results of the questionnaire, it appears that there were supporters and opponents of the Crowe therapy. The supporters treated many patients, observed good results and no side-effects. Those who saw side-effects had not carried out the treatment themselves. The most important result of the questionnaire was finding a number of clinics with records suitable for the epidemiological study to be conducted in continuation at a later date.

A.1.5 CONCLUSIONS

It can be concluded that, for many years, the Crowe therapy was a generally accepted form of treatment by ENT specialists throughout the Netherlands and was - sometimes - applied in cooperation with radiologists or radiotherapists. An estimation of the number of Dutch people who had been treated using the Crowe therapy since the Second World War, based on the information gained from specialists who had applied the therapy, gave rise to a figure of at least 24,500 people. When asked about the effects of the therapy, the majority of the respondents gave a positive answer. No judgements can be made on the side-effects of the treatment on the strength of this questionnaire.

APPENDIX 2
THE LOST RADIUM NEEDLE, PUTTEN 1958

A2.1 INTRODUCTION

In the past, when radium application was a popular way of treating tumours, it was not unusual for radium needles or seeds to become mislayed. Such needles or seeds could, for instance, find their way into dustbins, sewers, a crevice in the floor, rubbish dumps or could be stolen.
In the head and neck region, radium seeds from an inplant sometimes migrated via the soft tissues or via the arterial or venous blood-vessels to other parts of the body. This migration within the body was probably caused by the effect of the irradiation itself: as the tumour started to shrink the seeds took up different positions, or, if the wall of a large blood-vessel became necrotic the seeds could enter the circulation (quoted 1).
Due to a particularly unfortunate coincidence, the radio-active contents of a radium needle became deposited in the environment. The following account of the accident is mainly based on a Report from the Director-General of Public Health to the Minister for Social Services and Public Health which appeared on 23 June 1958 (2).

A2.2 THE FACTS OF THE ACCIDENT

On 15 January, a six-year-old girl attended the ENT policlinic at the University Hospital in Utrecht, accompanied by her father. She had already undergone adenotonsillectomy on account of tubal deafness at an earlier stage, but the operation had not produced the required results.
After an examination of the patient, it was decided to treat her using nasopharyngeal radium applicaton, via a series of eight-minute sessions. A translation of the Dutch Report is as follows:
'The doctor at the policlinic who had examined the girl proceeded to the treatment area with the child and her father at approximately 11.30 a.m. While passing through an adjoining room, he invited a younger colleague who was working there and had never seen the treatment, to come and watch.
In the treatment room, he took the needle from a lead box, placed it in the patient's right nostril and set the alarm clock to go off in eight minutes. The young assistant entered the room after the radium needle had been inserted. Both assistants then left the treatment room. When the alarm went off eight minutes later, the older assistant went back to the patient, removed the radium needle, placed it in the left nostril and reset the alarm clock for eight minutes. After this he proceeded to his own office somewhere else in the building. When the alarm went off for the second time, the young assistant entered the treatment room, removed the radium needle and put it back into the lead box.
As the girl and her father were leaving the treatment room at approximately 11.50

a.m., they met the older assistant who asked them to come back for a check-up two weeks later.
After leaving the hospital, the girl and her father walked around the city for some time before proceeding to the station. At the station the girl was said to have sneezed and shown signs of nausea without actually vomiting. She vomited later that evening at home, after she had gone to bed. The vomit was collected in a newspaper by her father and incinerated in the living room fire'. As far as this with the translation of the Report.
The next morning during an inspection of the needle, the senior consultant discovered that the cylinder containing the radium, at the end of the needle, was missing. After a thorough search of the policlinic without any result, the conclusion was drawn that the cylinder had probably become lodged in the girl's nostril. After informing the police in Putten, the girl and her parents were asked to return to the hospital as quickly as possible for further investigation at the policlinic.
Monitoring the child using Geiger counters and via X-ray examinations, showed that the cylinder was not in the girl's body. A further thorough search, the next day, of the policlinic, the surrounding area and the rubbish tip did not produce any results.
In the afternoon of 17 January, a search was started in Putten, the child's place of residence. Radioactivity was discovered there, close to the living-room fire and in the garden where the fire ashes had been deposited.
The provincial and national governments were informed and a series of activities followed to prevent any further radio-active contamination from taking place and to clear up the existing contamination. That same evening the inhabitants evacuated the house. The patient and her family were taken to the SAZU the next day and remained there until 26 February 1958. By that time the house had been decontaminated and restored and the family could move back in.

A2.3 THE CLEANING-UP PROCEDURE

It was thought that the missing cylinder containing radium had broken as a result of the high temperature in the fire and in this way had become partly deposited in the fire and partly in the ashes in the garden. It was, therefore, no longer a matter of a closed source but of an open one. The ash was thought to have spread outside the garden via the wind. It was almost certain that the living room had been contaminated by the radioactive ashes. Not only was the house evacuated but also a nearby nursery school and the contaminated area was cordoned off.
When the definitive clearing-up procedure was started on 21 January 1958, many organizations were called in to assist, such as the N.V. KEMA, the Public Health Department, the Medical-Biological Laboratory of the State Defence Department TNO (the Dutch Organization for Applied Scientific Research) and the Royal Dutch Navy.
The activities consisted of decontaminating the area, the house and the chimney - which was demolished later - and removing the fire and the contaminated material. Also for psychological reasons, the clearing-up of the contaminated material was carried out as thoroughly as possible.
On 10 February, 28 crates and drums of contaminated material, which had been

filled up and sealed with concrete, were transported to Den Helder on two lorries. From there, on 11 February, they were loaded onboard the cruiser HMS 'De Zeven Provinciën' and dumped into the Atlantic Ocean at a depth of about 500 metres. On 14 February the house was declared fit for inhabitance by the Chief Inspector of Pharmaceuticals and on 26 February the family returned to their fully restored and largely refurnished home.

A2.4 THE AFTERMATH

This accident, with all the consequences, was a news topic in the Netherlands and abroad for some while. The events were covered very thoroughly in the newspapers. In editorial articles the question of blame was raised and the sense of the family's stay at the SAZU was a subject of discussion.
Within a few weeks of the accident a 'medical committee', which had been appointed by the medical faculty of the University of Utrecht, came to the conclusion that no mistakes had been made during the treatment. For this reason no disciplinary measures were taken against the doctors involved. Besides this, an investigation was also set up by the judicial authorities. It was the opinion of the senior officer at that time that there was no law under which the activities or possible acts of negligence could be brought (3).
Undoubtedly, this incident and the negative publicity which the radium irradiation treatment gained in this country, formed part of the reason for abandoning the Crowe therapy.
And what happened to the little girl - the 'victim' of the accident? All went well. She got married and has two healthy children.

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APPENDIX 3
THE DATA FORM

THE DATA FORM

ID number:___ ___ ___ ___
CLINIC :___ ___

NAME :_____ _____
sirname christian name(s)

ADDRESS :_____ ___ _____
street no. place

DATE OF BIRTH:___ ___ ___ ___ ___ ___
day month year

REGISTER OF POPULATION

MUNICIPALITY	SENT	RECEIVED	NEW ADDRESS PATIENT
1. _____	___/___/___	___/___/___	_____
2. _____	___/___/___	___/___/___	_____
3. _____	___/___/___	___/___/___	_____
4. _____	___/___/___	___/___/___	_____

GENERAL PRACTITIONER	SENT	RECEIVED	NEW ADDRESS PATIENT
1._____	___/___/___	___/___/___	_____
name			
_____			_____
address			
2._____	___/___/___	___/___/___	_____
name			
_____			
address			

QUESTIONNAIRE		SENT	RECEIVED
	1.	___/___/___	___/___/___
TELEPHONE	2.	___/___/___	___/___/___

MEDICAL DATA	SENT 1	TELEPHONE/ SENT 2	RECEIVED
1. _____	___/___/___	___/___/___	___/___/___
_____			
2. _____	___/___/___	___/___/___	___/___/___
_____			
3. _____	___/___/___	___/___/___	___/___/___
_____			

PUNCH CARDS ↓↓↓

ID ____

SEX ____
1. male
2. female
9. unknown

DATE OF BIRTH ____ ____ ____
day month year

OR

AGE ____ in ____
age year

INSURANCE ____
1. national health
2. private
9. unknown

CLINIC ____

DATE 1st CONSULT ____ ____ ____
day month year

DIAGNOSIS/INDICATIONS ____
1. glue ears
2. recurrent otitis
3. other tubal dysfunction
4. A + T
5. sinusitis (i.d.)
6. perceptive hearing loss
8. other (please specify)

_____

_____

9. unknown

PUNCH CARDS ↓↓↓

RADIUM TREATMENT ____
1. yes
2. no
9. unknown

1st TREATMENT DATE ____ ____ ____
day month year

____ ____
minutes

2nd TREATMENT DATE ____ ____ ____
day month year

____ ____
minutes

3rd TREATMENT DATE ____ ____ ____
day month year

____ ____
minutes

4th TREATMENT DATE ____ ____ ____
day month year

____ ____
minutes

5th TREATMENT DATE ____ ____ ____
day month year

____ ____
minutes

OTHER RADIUM TREATMENTS WHICH DO NOT FIT IN THIS DIAGRAM: _____

_____

_____

APPENDIX 4
WORK METHOD FOR THE COMPILATION OF A CONTROL GROUP, CLINIC 2

It is the object to choose the control group in such a way that it matches the irradiated group as far as possible. Both groups should have the following characteristics in common: 1) size, 2) man:woman ratio, 3) age distribution, 4) time of first consultation.
It is permitted, on statistical grounds, to bundle the latter two characteristics in five-year groups.
The accompanying table of the irradiated group contains 47 figures. Each figure represents the size of a subgroup that must be selected from the records and placed into the corresponding envelope.

Here is a step by step account of the procedure:

1) The same records must be used as for the selection of the irradiated persons, i.e. 52 index boxes A to Z mixed Sick Fund/Private patients.

2) All the index boxes must be given a number 1 to 52, starting with A.

3) The index boxes must be worked through according to the accompanying list of random numbers, i.e. first index box 11, followed by 48, 40, etc,.
If all 52 boxes have been gone through and the control group still is not full, start again at box 11.

4) In order to obtain 326 control persons, 6 cards must be taken from 38 boxes and 7 from 14 boxes.

5) A card must be taken from each box, about 5 cm from the front. Check to see whether the sex, year of birth (5 years) and the date of first consultation fit one of the envelopes, if they do, put the card inside and write the score on the envelope.

6) If the card does not fit into any of the envelopes because it does not match or the envelope is full, take the card immediately next to it instead.

7) If the card does fit into an envelope, the next control subject must be selected 1 cm farther back. (This is to prevent selections with the same surname).

8) In the beginning, finding suitable records will be quick and easy, but later on it will become more and more difficult.

List of random numbers, between 1 and 52

11 48 40 31 33 44 52 43 02 04 47 21 13 09 45 50 35 29
36 37 05 14 06 46 17 16 20 39 51 19 23 30 07 01 12 24
22 27 34 28 38 42 25 08 10 49 26 32 15 41 03 18

Table A4.1 Number of exposed subjects according to year of first contact, age and sex. Clinic 2

Birth year	Year of first contact											
	<1945		1945-49		1950-54		1955-59		1960-64		1965	
	M	F	M	F	M	F	M	F	M	F	M	F
1910-29			7	6	1		2		1	1		
1930-34			5	2		2			3			
1935-39			10	3	3	3						
1940-44			22	25	5	7	3	2	4		1	
1945-49			12	8	34	23	9	4	1	2	1	
1950-54					3	7	17	19	13	8	1	1
1955-59							2	5	21	10	3	1
1960-64									1		2	
65												
Total			56	44	47	41	33	30	44	21	8	2

APPENDIX 5
SEARCH FORM, FOR THE REGISTRY OF BIRTHS DEATHS AND MARRIAGES

Chief Inspector
Registry of Births, Deaths and Marriages
(of a particular municipality)

Dear Sir or Madam,

I would like to draw your attention to the following.

In the 1940s to 60s children with ear disorders were often treated using radium. This treatment consisted of the insertion of a radium needle into the nasopharynx. About 25,000 children have been treated in this way and have thereby been exposed to irradiation.

In cooperation with the Capacity Group Epidemiology of the State University in Maastricht (the Netherlands) and with a subsidy from the Queen Wilhelmina Fund (Dutch Organization for Cancer-Control), we are conducting an epidemiological study at our department, on the long-term effects of the treatment on the health of approximately 2,500 children who have been treated.

In order to be able to carry out this study, it will be necessary for us to establish the present status of these persons (the study population), dead or alive, the present addresses and if any have died, the cause of death. For the latter we have obtained permission from the Chief Inspector of Public Health in Leidschendam.

May we kindly request you to furnish us with the information mentioned above for the persons who lived in your municipality. Please would you tell us whether:
a. the person is still alive in your municipality,
b. the person has moved house,
c. the person has died while living in your municipality.
Would you also fill in the date when you complete the forms. We are enclosing forms on which you can record the details.

If you have any questions concerning this study, please do not hesitate to contact me or my research assistant. We are reachable by telephone between 9.00 and 13.00 on all week days. The number is: 04490-18666, ext. 2184.

Yours sincerely,

P.G. Verduijn
ENT Specialist

Please send the completed forms to:
P.G. Verduijn, ENT Specialist
Ziekenhuis 'De Goddelijke Voorzienigheid'
Walramstraat 23
6131 BK Sittard

Enclosures

Search form for the registry of births, deaths and marriages

SEARCH FORM FOR THE REGISTRY OF BIRTHS, DEATHS AND MARRIAGES

Christian name(s), Sir name, date of birth and address at that time

1. What has happened to this person?
(Circle answer A, B or C and fill in the details)

A. still alive in the municipality mentioned above
present address (if different from above):

street :_____ no. _____

B. moved to another municipality
address :

street :_____ no. _____

municipality:_____

country :_____

date of move:___ ___ ___ ___ ___ ___ date of completion of form:___ ___ ___ ___ ___ ___

day month year day month year

A. still alive in the municipality mentioned above
present address (if different from above):

street :_____ no. _____

B. moved to another municipality
address :

street :_____ no. _____

municipality:_____

country :_____

date of move:___ ___ ___ ___ ___ ___ date of completion of form:___ ___ ___ ___ ___ ___

day month year day month year

C. deceased
date of death:___ ___ ___ ___ ___ ___

day month year

in municipality :_____

death certificate no.:_____

date of completion of form:___ ___ ___ ___ ___ ___

day month year

February 1985

Dear Sir or Madam,

Via newspapers, magazines and television, you will most likely have become aware that some factors in our environment probably play a part in the development of various diseases. These factors can be present, for instance, in our living or working environment and cause sickness in the long-term. The notion exists that certain medical treatments, such as radiotherapy or the application of certain medicatons, can have this effect.

As a doctor who has specialized in the field of ear, nose and throat diseases, I would like to study this phenomenon in people who have been treated in the past for diseases of these organs.

I have enclosed a health-questionnaire form and stamped addressed envelope, as it appears that you were treated some years ago at the ENT clinic in one of the following hospitals:

- 'De Goddelijke Voorzienigheid' Hospital in Sittard,
- Wilhelmina Hospital in Assen
- Carolus Hospital in 's-Hertogenbosch
- Elisabeth's Hospice in Harlem
- University Hospital in Groningen

I would appreciate it very much if you could spare a half hour of your time to fill in the form as fully as possible and return it to us in the envelope.

We are not only interested in your general state of health, but also particularly in disorders which are concerned with fertility and the possible occurrence of tumours. We have also included a number of questions about the use of stimulants. In order for our study to be successful, it is very important that you answer all the questions. We can assure you that the information will be treated strictly confidentially and processed anonymously.

If you have any questions regarding this letter or the form, please do not hesitate to phone me or my research assistant. Our telephone number is: 04490-18666, ext. 2184.

Yours sincerely,

P.G. Verduijn
ENT Specialist

Enclosures

ZIEKENHUIS "DE GODDELIJKE VOORZIENIGHEID"
Afd. Klinische Epidemiologie
Walramstraat 23, 6131 BK SITTARD.

februari 1985

Zeer geachte Heer, Mevrouw,

Via de kranten, tijdschriften en televisie zal het u bekend zijn, dat factoren in onze omgeving een rol kunnen spelen bij de ontwikkeling van verschillende ziekten. Men denkt bijvoorbeeld aan factoren in het woon- en werkmilieu, die vaak over langere termijn ziekten kunnen veroorzaken. Het vermoeden bestaat, dat ook bepaalde medische behandelingen zoals bestraling of toediening van bepaalde medicijnen deze effecten kunnen hebben.
Als arts, gespecialiseerd op het gebied van keel, neus en oren wil ik dit onderzoeken bij mensen die jaren geleden behandeld werden voor ziekten van die organen.
Ik stuur u bijgaand formulier omdat u lange tijd geleden onder behandeling bent geweest op de KNO-afdeling van één van de volgende vijf ziekenhuizen:

- Ziekenhuis "De Goddelijke Voorzienigheid" te Sittard
- Wilhelminaziekenhuis te Assen
- Carolusziekenhuis te 's-Hertogenbosch
- Elisabeth's Gasthuis te Haarlem
- Academisch Ziekenhuis te Groningen.

Ik zou graag een half uur van uw tijd willen vragen om het formulier zo nauwkeurig mogelijk in te vullen en in bijgevoegde enveloppe aan ons te retourneren.
Behalve naar de algemene gezondheidstoestand, gaat onze interesse vooral uit naar stoornissen betreffende vruchtbaarheid en mogelijk ontstaan van gezwellen. Ook zijn enkele vragen gesteld over het gebruik van genotmiddelen. Ongeacht uw huidige gezondheidstoestand is het van groot belang voor het slagen van dit onderzoek dat u de vragen beantwoordt. Ik kan u verzekeren dat uw gegevens vertrouwelijk zullen blijven en anoniem zullen worden bewerkt.
Als dit schrijven of het formulier nog vragen bij u oproept kunt u mij of mijn research-assistent bellen onder tel. nr. 04490-18666 tst. 2184.
Bij voorbaat dank ik u hartelijk voor uw medewerking.

Hoogachtend,

P.G. Verduijn, KNO-arts.

APPENDIX 6
THE HEALTH SURVEY

HEALTH QUESTIONNAIRE

1. First we would like some background information:

Date of birth ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋
day month year

Height ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ Weight ⌊_⌋⌊_⌋
m cm kg

2. Have you ever been admitted to hospital for more than one night (except with regard to childbirth)? Please mark the relevant box: Yes or No with a X.

	YES	NO
	☐	☐

If you have anwered yes, for what reason and when were you admitted?

Reason	Year
a	.....
b	.....
c	.....
d	.....
e	.....

3. Have you ever had any of the following diseases or complaints? Please mark the relevant boxes with a X.

	YES	NO
diabetes	☐	☐
anaemia	☐	☐
thyroid disease	☐	☐
hearing disorder	☐	☐
you wear a hearing aid	☐	☐
cataract	☐	☐
epilepsy	☐	☐
pituitary disease	☐	☐
hormonal disorder	☐	☐
depression	☐	☐
treatment by psychologist or psychiatrist	☐	☐

ZIEKENHUIS
"DE GODDELIJKE VOORZIENIGHEID"
04490 - 16666 tst. 2184

GEZONDHEIDSVRAGENLIJST

1. Eerst willen we enkele achtergrondgegevens van u vragen:

Geboortedatum ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋
dag maand jaar

Lengte ⌊_⌋ ⌊_⌋⌊_⌋ Gewicht ⌊_⌋⌊_⌋
m cm kg

2. Bent u ooit langer dan één nacht in een ziekenhuis opgenomen geweest (behalve voor een eventuele bevalling)? Zet dan a.u.b. een kruisje ☒ in het op u van toepassing zijnde hokje: JA of NEE.

JA	NEE
☐	☐

Zo ja, waarvoor en wanneer?

waarvoor:	jaar
a	
b	
c	
d	
e	

3. Heeft u de volgende ZIEKTEN of KLACHTEN gehad? Zet a.u.b. een kruisje ☒ in het op u van toepassing zijnde hokje.

	JA	NEE
suikerziekte	☐	☐
bloedarmoede	☐	☐
schildklierziekte	☐	☐
gehoorstoornis	☐	☐
dragen van een gehoorapparaat	☐	☐
oogtenstroebeling (staar)	☐	☐
epilepsie (vallende ziekte)	☐	☐
ziekte van de hypofyse (hersenaanhangsel)	☐	☐
hormonale stoornis	☐	☐
depressieve stemming	☐	☐
behandeling door psycholoog of psychiater	☐	☐

4. Has a tumour (benign or malignant), swelling, cancer or growth ever been diagnosed in or on your: (please mark the relevent box(es)

	YES	NO
skin	☐	☐
thyroid gland	☐	☐
pituitary gland	☐	☐
salivary glands	☐	☐
breast(s)	☐	☐
leukaemia	☐	☐
lymph glands	☐	☐
oesophagus	☐	☐
lip(s)	☐	☐
in your mouth	☐	☐
nose	☐	☐
throat	☐	☐
other organs	☐	☐

If so, please specify the organ(s) .....

.....

5. Have you ever had tissue removed for a biopsy?

YES ☐ NO ☐

If so, from which organ and when was that?

Organ or region	Year
a	
b	
c	

6. Have you ever used any of the following medications?

	YES	NO
tablets for diabetes	☐	☐
insuline	☐	☐
tablets for high blood pressure	☐	☐
hormones	☐	☐
thyroid medication	☐	☐
diuretics	☐	☐

4. Is bij u ooit een tumor (goedaardig of kwaadaardig), gezwel, kanker of groeisel vastgesteld van de: (ook weer een kruisje ☒ zetten in het hokje van uw keuze).

	JA	NEE
huid	☐	☐
schildklier	☐	☐
hypofyse (hersenaanhangsel)	☐	☐
speekselklieren	☐	☐
borst(en)	☐	☐
bloedkanker (leukemie)	☐	☐
(lymfe)klieren	☐	☐
slokdarm	☐	☐
lip	☐	☐
in de mond	☐	☐
neus	☐	☐
keel	☐	☐
andere organen	☐	☐

Zo ja, welke? .....

.....

5. Is er bij u ooit weefsel weggenomen voor onderzoek? (biopsie)

JA ☐ NEE ☐

Zo ja, van welk orgaan of plek en wanneer?

orgaan of plek	jaar
a	
b	
c	

6. Heeft u ooit de volgende medicijnen gebruikt?

	JA	NEE
tabletten voor suikerziekte	☐	☐
insuline	☐	☐
tabletten tegen hoge bloeddruk	☐	☐
hormonen	☐	☐
schildklierpreparaten	☐	☐
plaspillen	☐	☐

7. The questions below are concerned with possible exposure to irradiation.

a. Have you ever been X-rayed for: (and if so, how often)

	YES	NO
broken bone(s)	☐ ___ times	☐
fitting shoes	☐ ___ times	☐
breast screening	☐ ___ times	☐
dental examination	☐ ___ times	☐
screening (t.b.)	☐ ___ times	☐

b. Have you ever been irradiated in a different manner?

YES ☐ NO ☐

If so, was that with cobalt ☐, röntgen ☐ or radium ☐ ?

8. What three occupations have you conducted for the longest amount of time and for how long?

Occupation	Type of company	Number of years
1		
2		
3		

9. The questions below are concerned with stimulants.

a. How many glasses -on average- do you drink per day or per week of the following:

	PER DAY	PER WEEK
beer	_____	_____
wine, sherry, port etc.	_____	_____
gin, cognac, liqueur etc.	_____	_____

b. Have you ever smoked?
☐ no (go on to question 10)
☐ yes and still do
☐ yes, in the past, but not now

c. How old were you when you started smoking?
_____ years old

d. If you have stopped, how old were you when you stopped?
_____ years old

e. How many did/do you smoke per day?

cigarettes (or rolling tobacco)	pipe	cigars
_____ number	_____ number	_____ number

7. Hieronder volgen enkele vragen over mogelijke blootstelling aan straling.

a. Zijn er bij u ooit röntgenfoto's gemaakt voor: (en zo ja, hoe vaak)

	JA	NEE
botbreuk	☐ ___ keer	☐
schoenen passen	☐ ___ keer	☐
borstonderzoek	☐ ___ keer	☐
tanden/kiezen	☐ ___ keer	☐
doorlichting (t.b.c.)	☐ ___ keer	☐

b. Bent u ooit op een andere manier bestraald?

JA ☐ NEE ☐

Zo ja, was dat met cobalt ☐, röntgen ☐ of radium ☐ ?

8. Welke drie beroepen heeft u het langste uitgeoefend, en hoe lang?

Beroep	Soort bedrijf	Aantal jaren
1		
2		
3		

9. Hieronder volgen enkele vragen over het gebruik van genotmiddelen.

a. Hoeveel glazen of glaasjes drinkt u gemiddeld per dag of per week van het volgende:

	PER DAG	PER WEEK
bier	_____	_____
wijn, sherry, port e.d.	_____	_____
jenever, cognac, likeur e.d.	_____	_____

b. Heeft u ooit gerookt?
☐ nee (ga naar vraag 10)
☐ ja, nu nog
☐ ja, vroeger wel, nu niet meer

c. Hoe oud was u toen u begon met roken?
_____ jaar oud

d. Indien u bent gestopt, hoe oud was u toen u stopte?
_____ jaar oud

e. Hoeveel rookt(e) u meestal per dag?

sigaretten (of shag)	pijp	sigaren
_____ stuks	_____ stuks	_____ stuks

10. Are you married or have you been married?

YES ☐ NO ☐

How many live babies did you have in total? (not including adopted children) number _____

Have you been troubled with involuntary infertility? (you could not have children) YES ☐ NO ☐

11. ONLY FOR WOMEN

The following questions concern your menstruation and (possible) pregnancies. Please mark the relevent box.

a. Have you ever menstruated? YES ☐ NO ☐

If so, how old were you when it first started? _____ years old

b. Was/is your menstruation regular ☐ irregular ☐

c. Have you ever had a miscarriage? YES ☐ NO ☐

If so, how often have you had a miscarriage? _____ times

d. Have you reached the meropauze? YES ☐ NO ☐ not applicable ☐

If so, how old were you when it occurred? _____ years old

Please will you return the completed questionnaire to us in the stamped addressed envelope (enclosed).

We thank you very much for your cooperation!

10. Bent u gehuwd of gehuwd geweest?

JA ☐ NEE ☐

Hoeveel levend geboren kinderen kreeg u in totaal? (geadopteerde kinderen niet meegerekend) aantal _____

Is er bij u sprake van onvrijwillige onvruchtbaarheid? (geen kinderen kunnen krijgen) JA ☐ NEE ☐

11. ALLEEN VOOR VROUWEN

Hier volgen enkele vragen over uw menstruatie en eventuele zwangerschappen. Zet u a.u.b. een kruisje ☒ bij het juiste antwoord.

a. Heeft u ooit gemenstrueerd? JA ☐ NEE ☐

Zo ja, hoe oud was u toen u de eerste menstruatie kreeg? _____ jaar oud

b. Hoe is/was uw menstruatie? regelmatig ☐ niet regelmatig ☐

c. Heeft u ooit één of meer miskramen gehad? JA ☐ NEE ☐

Zo ja, hoe vaak had u een miskraam? _____ aantal

d. Heeft u de menopauze al bereikt? JA ☐ NEE ☐ niet van toepassing ☐

Zo ja, hoe oud was u toen? _____ jaar oud

Wilt u deze vragenlijst terugzenden in bijgevoegde antwoordenveloppe? Dit kan zonder postzegel.
Wij danken u hartelijk voor uw medewerking!

APPENDIX 7

REQUEST FOR VERIFICATION OF (PREVIOUSLY GIVEN) PERMISSION

January 1986

Dear Sir or Madam,

At the begining of last year I sent you a health questionnaire. May I take this opportunity to thank you for returning the completed form to me.
I would like to ask you for your cooperation once again. This time just for a few minutes. In your answer to question 2 you mentioned that you had been admitted to hospital for a certain disorder. I have enclosed a copy of the question. The answer I am referring to has been underlined in red. This piece of information may be of great importance to my study. In order to establish the exact nature of the disorder, I would appreciate it very much if you could answer the following questions.

1. To which hospital were you admitted for the disorder?
2. In which year did this admission take place?
3. What was the name of the specialist who treated you?
4. Would you have any objections to our approaching this specialist for the purpose of gaining further information concerning the diagnosis?

As was also the case with the first form, your answers will be treated with the strictest of confidence and processed anonymously. Please will you return the completed form to me. A stamped addressed envelope has been enclosed.
If you have any questions regarding this letter or the form, please do not hesitate to phone me or my research assistant. Our telephone number is: 04490-18666, ext. 2184.

Yours sincerely,

P.G. Verduijn
ENT specialist

Enclosures

ZIEKENHUIS "DE GODDELIJKE VOORZIENIGHEID"
Afd. Klinische Epidemiologie
Walramstraat 23, 6131 BK SITTARD.

Zeer geachte Heer, Mevrouw, januari 1986

Begin vorig jaar zond ik U een gezondheidsvragenlijst. Bij deze wil ik U hartelijk danken dat ik deze lijst ingevuld van U mocht terugontvangen.

Graag zou ik nogmaals Uw medewerking willen vragen. Ditmaal slechts enkele minuten. Het gaat om het volgende.

U heeft bij vraag 2 opgegeven dat U in een ziekenhuis opgenomen bent geweest voor een bepaalde ziekte of aandoening. Een copie van die vraag is bijgevoegd. Het gaat om het met rood onderstreepte antwoord. Dit gegeven kan van belang zijn voor mijn onderzoek. Om de precieze aard van de aandoening te kunnen achterhalen wil ik U graag de volgende vragen stellen.

1. In welk ziekenhuis werd U voor bedoelde aandoening opgenomen? .....
   .....
2. In welk jaar gebeurde dat? .....
3. Hoe heette de behandelend specialist? .....
4. Vindt U het goed dat ik deze specialist om nadere inlichtingen over de diagnose vraag? .....

Ook voor deze gegevens blijft gelden dat ze vertrouwelijk zullen worden behandeld en anoniem worden bewerkt.

Zoudt U, na beantwoording van de vragen, alles in bijgevoegde antwoordenveloppe aan mij willen terugsturen?
Voor eventuele vragen kunt U mij bellen onder telefoonnr. 04490-18666 tst. 2184.
Bij voorbaat dank ik U hartelijk voor Uw medewerking.

Hoogachtend,

P.G. Verduijn, KNO-arts

January 1986

Dear Sir or Madam,

At the begining of last year I sent you a health questionnaire. May I take this opportunity to thank you for returning the completed form to me.
I would like to ask you for your cooperation once again. This time just for a few minutes.
In your answer to question 4 you mentioned that a tumour had been found. I have enclosed a copy of the question. The answer I am referring to has been underlined in red. This piece of information may be of great importance to my study. In order to establish the exact nature of the disorder, I would appreciate it very much if you could answer the following questions.

1. To which hospital were you admitted for the disorder?
2. In which year did this admission take place?
3. What was the name of the specialist who treated you?
4. Would you have any objections to our approaching this specialist for the purpose of gaining further information concerning the diagnosis?

As was also the case with the first form, your answers will be treated with the strictest of confidence and processed anonymously. Please will you return the completed form to me. A stamped addressed envelope has been enclosed.
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Yours sincerely,

P.G. Verduijn
ENT specialist

Enclosures

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Walramstraat 23, 6131 BK SITTARD.

Zeer geachte Heer, Mevrouw, januari 1986

Begin vorig jaar zond ik U een gezondheidsvragenlijst. Bij deze wil ik U hartelijk danken dat ik deze lijst ingevuld van U mocht terugontvangen.

Graag zou ik nogmaals Uw medewerking willen vragen. Ditmaal slechts enkele minuten. Het gaat om het volgende.

U heeft bij vraag 4 opgegeven dat bij U ooit een tumor of gezwel is vastgesteld. Een copie van die vraag is bijgevoegd. Het gaat om het met rood onderstreepte antwoord. Dit gegeven kan van belang zijn voor mijn onderzoek. Om de precieze aard van de tumor te kunnen achterhalen wil ik U graag de volgende vragen stellen.

1. In welk ziekenhuis werd de tumor vastgesteld? .....
   .....
2. In welk jaar gebeurde dat? .....
3. Hoe heette de behandelend specialist? .....
4. Vindt U het goed dat ik deze specialist om nadere inlichtingen over de diagnose vraag? .....

Ook voor deze gegevens blijft gelden dat ze vertrouwelijk zullen worden behandeld en anoniem worden bewerkt.

Zoudt U deze brief na beantwoording van de vragen in bijgevoegde enveloppe aan mij willen retourneren.
Voor eventuele vragen kunt U mij bellen onder telefoonnr. 04490-18666 tst. 2184.
Bij voorbaat dank ik U hartelijk voor Uw medewerking.

Hoogachtend,

P.G. Verduijn, KNO-arts

January 1986

Dear Sir or Madam,

At the begining of last year I sent you a health questionnaire. May I take this opportunity to thank you for returning the completed form to me.
I would like to ask you for your cooperation once again. This time just for a few minutes.
In your answer to question 5 you mentioned that some tissue had been removed for examination. I have enclosed a copy of the question. The answer I am referring to has been underlined in red. This piece of information may be of great importance to my study. In order to establish the exact nature of the tissue, I would appreciate it very much if you could answer the following questions.

1. To which hospital were you admitted for the disorder?
2. In which year did this admission take place?
3. What was the name of the specialist who treated you?
4. Would you have any objections to our approaching this specialist for the purpose of gaining further information concerning the diagnosis?

As was also the case with the first form, your answers will be treated with the strictest of confidence and processed anonymously. Please will you return the completed form to me. A stamped addressed envelope has been enclosed.
If you have any questions regarding this letter or the form, please do not hesitate to phone me or my research assistant. Our telephone number is: 04490-18666, ext. 2184.

Yours sincerely,

P.G. Verduijn
ENT specialist

Enclosures

ZIEKENHUIS "DE GODDELIJKE VOORZIENIGHEID"
Afd. Klinische Epidemiologie
Walramstraat 23, 6131 BK SITTARD.

Zeer geachte Heer, Mevrouw, januari 1986

Begin vorig jaar zond ik U een gezondheidsvragenlijst. Bij deze wil ik U hartelijk danken dat ik deze lijst ingevuld van U mocht terugontvangen.

Graag zou ik nogmaals Uw medewerking willen vragen. Ditmaal slechts enkele minuten. Het gaat om het volgende.

U heeft bij vraag 5 opgegeven dat bij U ooit weefsel is weggenomen voor onderzoek. Een copie van die vraag is bijgevoegd. Het gaat om het met rood onderstreepte antwoord. Dit gegeven kan van belang zijn voor mijn onderzoek. Om de precieze aard van het weefsel te kunnen achterhalen wil ik U graag de volgende vragen stellen.

1. In welk ziekenhuis werd het weefsel weggenomen? .....
   .....
2. In welk jaar gebeurde dat? .....
3. Hoe heette de behandelend specialist? .....
4. Vindt U het goed dat ik deze specialist om nadere inlichtingen over de diagnose vraag . .....

Ook voor deze gegevens blijft gelden dat ze vertrouwelijk zullen worden behandeld en anoniem worden bewerkt.

Zoudt U, na beantwoording van de vragen, alles in bijgevoegde antwoordenveloppe aan mij willen terugsturen?
Voor eventuele vragen kunt U mij bellen onder telefoonnr. 04490-18666 tst. 2184.
Bij voorbaat dank ik U hartelijk voor Uw medewerking.

Hoogachtend,

P.G. Verduijn, KNO-arts

APPENDIX 8
ACCOMPANYING LETTER TO THE DOCTOR CONCERNED

Dear Colleague,

For the last few years I have been conducting a study on the relationship between irradiation and the origination of tumours.
The treatment I am interested in concerns the irradiation of the nasopharynx of people with otitis serosa, using radium. This therapy was applied very frequently by ENT specialists and radiologists in the 1950s and 60s.

Recently, tumour induction has been suggested by several authors but never demonstrated convincingly.

The study involves approximately 2,500 persons who have been treated in the past and a control group of comparable size. It is being conducted in cooperation with the Institute of Social Health of the Erasmus University in Rotterdam (Prof.Dr. P.J. van der Maas and Dr.Ir. J.D.F. Habbema). In a survey held at the beginning of last year among the 5000 study persons, it appeared that many of the respondents had either suffered from a tumour or had been subjected to an operation indicative of such a disorder.

Would it be possible for you to spare some time to help with the collection of study data, by verifying the diagnoses given by the respondents. In the accompanying letter, which also contains the subjects' permission, a space has been reserved for your pathological diagnosis. A stamped addressed envelope has been enclosed. It is possible that the married women have been filed under their maiden names.

Unfortunately, it is not possible for me to offer you any payment for your time, but your cooperation would be greatly appreciated. When the study has been completed, I will be pleased to send you a summary of the results.

Yours sincerely,

P.G. Verduijn
ENT specialist

Enclosures

ZIEKENHUIS "DE GODDELIJKE VOORZIENIGHEID"
Afd. Klinische Epidemiologie
Walramstraat 23, 6131 BK SITTARD.

Zeer geachte collega,

Ik ben reeds enige jaren bezig met een onderzoek naar de relatie tussen bestraling met radium en het ontstaan van tumoren.
Het gaat om bestraling met radium in de neus-keelholte ter behandeling van otitis serosa. Deze therapie werd in de jaren vijftig en zestig algemeen toegepast door KNO-arts en radioloog.

Tumorinductie werd recent door verschillende auteurs gesuggereerd maar nooit overtuigend aangetoond.

Bij het onderzoek zijn plm. 2500 destijds behandelde personen en een even groot aantal controles betrokken. Het onderzoek geschiedt onder meer in samenwerking met het Instituut Maatschappelijke Gezondheidszorg van de Erasmus Universiteit te Rotterdam (Prof.Dr. P.J. van der Maas en Dr. Ir. J.D.F. Habbema).
Bij een begin vorig jaar gehouden enquete onder de genoemde 5000 personen werd door vele respondenten opgegeven ooit aan een gezwelziekte te hebben geleden of een operatie te hebben ondergaan die op een dergelijke ziekte kan wijzen.

Hierbij wil ik Uw medewerking vragen bij het verifiëren van de opgegeven diagnose. Op bijgaande brief, waarop ook de toestemming van de patiënt is vermeld, is een gedeelte gereserveerd voor Uw PA-diagnose.

Helaas is het niet mogelijk U voor deze inspanning te honoreren. U zult het moeten doen met mijn dank. Wel zal ik U te zijner tijd het resultaat van mijn onderzoek toesturen.

Met collegiale hoogachting,

P.G. Verduijn, KNO-arts

PS: bijgaand een gefrankeerde retourenvelop.
PPS: de gegevens van gehuwde vrouwen zijn mogelijk onder hun meisjesnaam in Uw archief te vinden.

APPENDIX 9
DOSIMETRY*

A9.1 THE RADIUM APPLICATOR

The radium applicator constructed by Crowe and Burnam, which was to become the most popular design with other users, consisted of a cylinder of 21.5 mm length and an external diameter of 2.3 mm. The thickness of the wall, made of nickel alloy (Ni 63%, Cu 28-34%, Fe 2.5% max., Mn 2% max. and Si 0.5% max.), was 0.3 mm. The cylinder was filled with radium sulphate. (Figure A9.1).

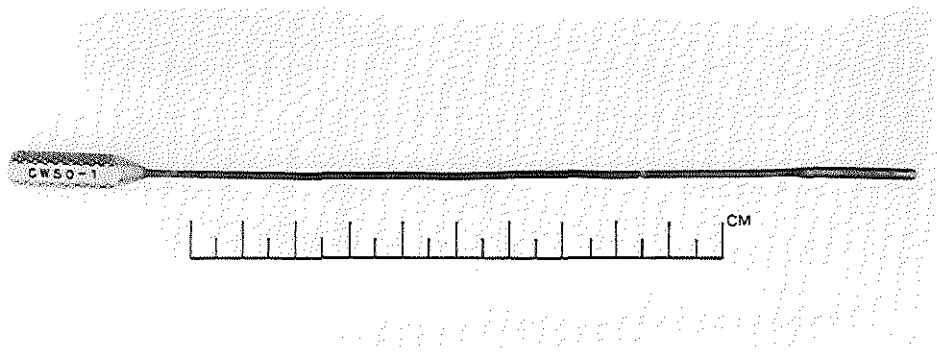

Figure A9.1 Radium applicator which was used at Clinic 2. On the right: the cylinder filled with radium sulphate. On the left: the handle.

Radium^{226} has a half live of 1600 years. In the disintegration to the stable end product, Pb^{206}, a spectrum of alpha, beta and gamma radiation is emitted.
The nickel alloy cylinder absorbs all the alpha particles and allows all the gamma radiation to escape without absorbtion. The low energy beta particles (up to 0.74 Mev) are also absorbed by the nickel alloy, but the higher energy particles (0.74-3.17 Mev emitted by RaC) pass through. The maximum depth of penetration in water and soft tissue is 13 mm. At a distance of more than 13 mm from the needle, at which distance the parotis, thyroid and pituitary gland are situated, it is only necessary to take the gamma radiation dose into consideration. Moreover, the fact that only gamma radiation plays a part, means that the influence of inhomogenity will be small, thus, bone and air cavities will not lead to serious changes in the dose distribution. Platinum absorbs considerably more beta radiation and also reduces the gamma radiation to some extent. Therefore, a correction factor had to be employed in the calculation. In Table A9.1 the applicators used and data concerning the duration of radiation treatment and interval are shown per clinic.

* This part of the study was executed under the supervision of A.G. Visser, PhD, radiophysicist of the Rotterdam Radiotherapeutic Institute.

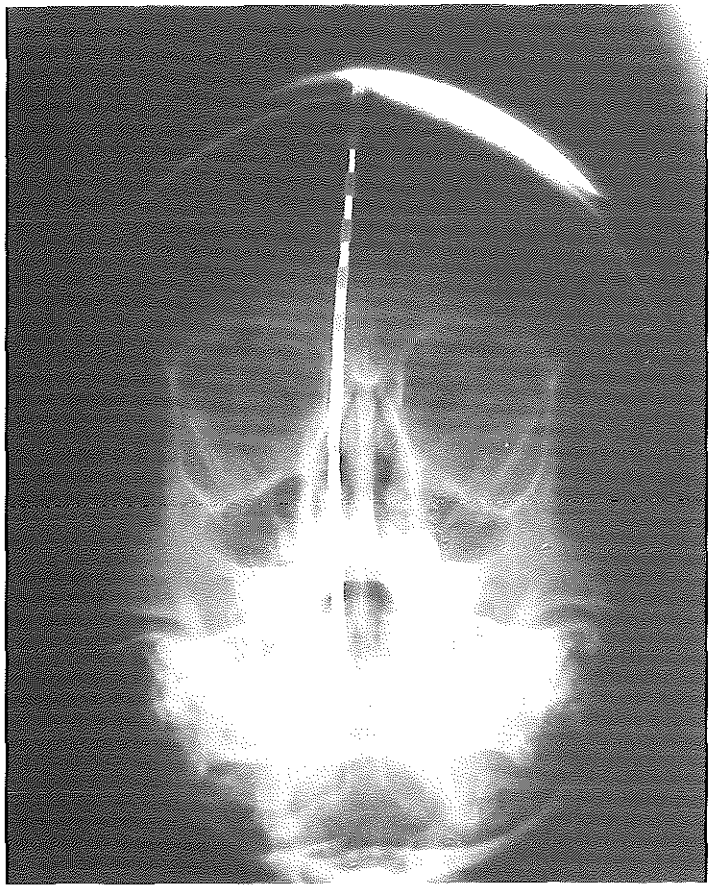

Figure A9.2 Antero-posterior skull X-ray with calibrated placebo applicator in situ (f, 4.75 yr).

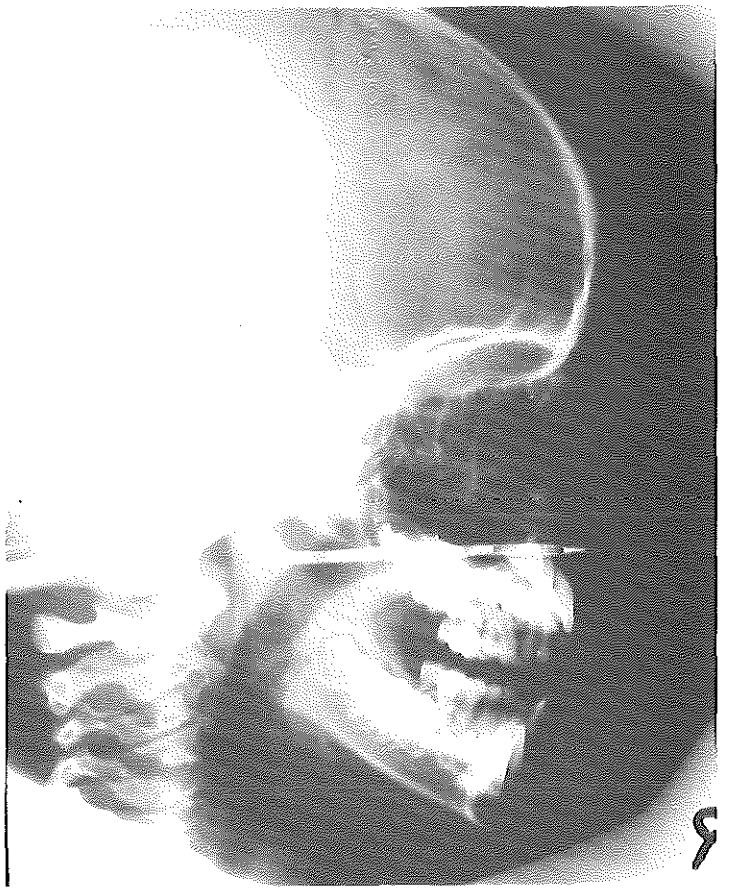

Figure A9.3 Lateral skull X-ray with calibrated placebo applicator in situ (m, 5.1 yr).

Table A9.1 Radium applicators and radiotherapy data, per clinic

Clinic	Applicator		Radiotherapy data		
	radium (mg)	wall (mm)	duration (min)*	N sessions	interval
1	25	nickel alloy 0.3	28-60	4	1 week
2	50	nickel alloy 0.3	36-72	3	2-4 wks
3	25	nickel alloy 0.3	40-80	4	1 week
4	10	Pt 0.1	60-240	1-4	to 1 yr
5	25	nickel alloy 0.1	26-52	3	1-2 wks

* Total exposure time dependent on age

A9.2 DOSE CALCULATION PROCEDURE

Antero-posterior and lateral skull X-ray films were taken of 25 children, 12 girls and 13 boys, with a calibrated placebo applicator in situ (see Figures A9.2 and A9.3). The magnification factor was calculated on seven lateral films. In Figure A9.4 this is set out against the age of the child. It appeared that the same magnification factor could be applied to the lateral films for the whole age range. A magnification factor of 1.1 was chosen. The actual magnification factors lay within 2% of this figure, which was negligible as far as the dose calculatons were concerned.
The dose distribution was calculated for the applicator used at clinic 1. Keeping in mind the magnification factor for the lateral films, a dose distribution was obtained which was valid in the medial sagittal plane (see Figure A9.5). The dose distribution calculated for the applicators at clinic 1, was also valid for the applicators used at clinics 2,3 and 5, on the understanding that the doses found for clinic 2 were multiplied by two. For clinic 4 the dose should be divided by a factor 2.7 (10 mg Ra; Pt cylinder).
The dose rate for the pituitary and thyroid gland were calculated using this dose distribution. This was not directly possible for the parotis because it is not situated on the medial line. The total distance between the centre of the needle and the parotis was determined with the aid of Pythagorus' Theorem, from the distance between the medial line (on the film) and the distance of the parotis from the medial sagittal plane (3.8 cm).

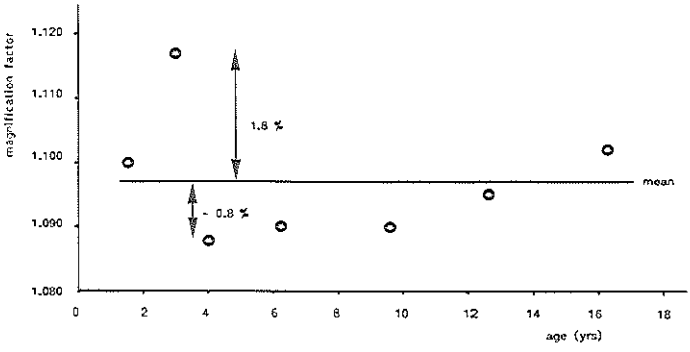

Figure A9.4 Magnification factor of lateral X-ray films, per age.

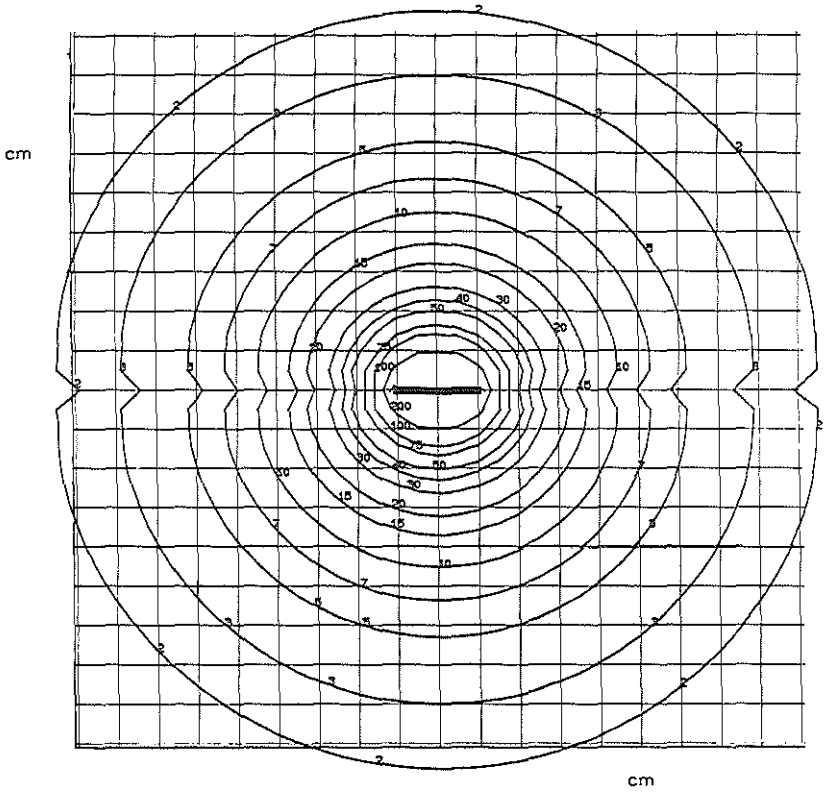

Figure A9.5 Dose distribution 24.77 mg radium sulphate in 0.3 mm Monel applicator. Isodose curves are given in cGy/h. A transparent of this dose distribution on a scale of 1.1 : 1 was used to calculate organ doses.

The sella turcica, which was easily visible on all the lateral films, was used as the measurement point for the pituitary gland. The position of the thyroid gland was established via a point in the middle of the tracheal shadow, at the level of the fifth cervical vertebra. It was determined that the parotis gland lay on the dorsal side of the ramus mandibulae, close to the angulus mandibulae.

A9.3 RESULTS

In Figure A9.6 the dose rates in cGy/h at the pituitary gland, parotis and thyroid gland are set out for the 25 mg radium applicator for the various age groups. The curve drawn through the points on the graph, shows the dose rate as a function of age. By applying the duration of radiation, which varied per clinic and per age category, the dose received by the organs in the head and neck region could be calculated.
The dose received by the tissues in direct contact with the applicator could also be calculated using these data, given the dose rate on the surface of the applicator (for 25 mg 160 cGy/min (1)) (see Table A9.2).

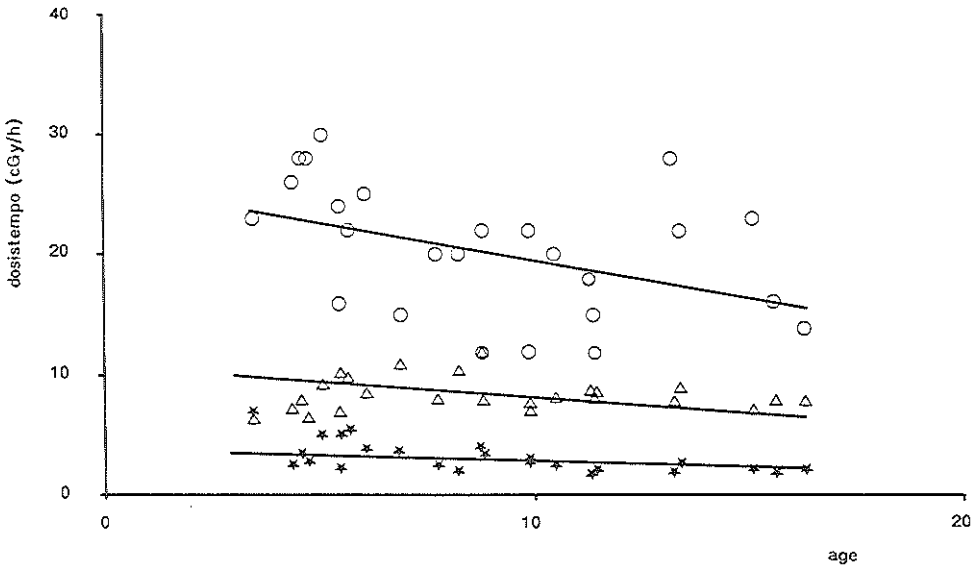

Figure A9.6 Dose rate (cGy/h) for some head and neck organs, per age, for 24.77 mg radium sulphate in 0.3 mm Monel applicator.
* thyroid, Δ parotid gland, ○ pituitary gland.

Table A9.2 Dose received (cGy) depending on age, per organ and per clinic

Clinic	Thyroid gland	Parotid gland	Pituitary gland	Tissue contact
1	2-3	6- 8	12-14	4480- 9600
2	5-7	14-19	29-36	11520-23040
3	3-4	8-11	16-20	6400-12800
4	2-3	4-13	11-18	3555-14222
5	2-3	5- 7	10-13	4160- 8320

REFERENCES APPENDIX 9

(1) Garsou, J., Boniver, R. (1971): A propos de la répartition du debit de dose absorbée autour de la sonde de Crowe. Proposition d'un nouveau schema d'utilisation therapeutique. J. Belge. Radiol. 54: 701-8

APPENDIX 10

THE DATA-INPUT FORM

ANSWERS TO HEALTH QUESTIONNAIRE

THE DATA-INPUT FORM
ANSWERS TO HEALTH QUESTIONNAIRE

Coding

Unless a different coding is specified, the following codes are valid:

y = yes
n = no

Do not fill anything in if it appears from the context that a question did not need to be answered because it was not applicable, or was not filled in.

	Beginning of record
Questionnaire No.	01(_|_|_|_|_|_)06
Patient ID	07(_|_|_|_)10
1. BACKGROUND INFORMATION (Question 1)	
1.1 Date of birth (day/month/year)	11(_|_|_|_|_|_)16
1.2 Height in cm	17(_|_|_)19
1.3 Weight in kg	20(_|_|_)22
2 DISEASES AND/OR COMPLAINTS (Question 3)	
2.01 Diabetes	23(_)
2.02 Anaemia	24(_)
2.03 Thyroid disease	25(_)
2.04 Hearing disorder	26(_)
2.04.1 If so, does the person wear a hearing aid?	27(_)
2.05 Cataract	28(_)
2.06 Epilepsy	29(_)
2.07 Pituitary disease	30(_)
2.08 Hormonal disorder	31(_)
2.09 Depression	32(_)
2.10 Treatment by psychologist or psychiatrist	33(_)

3. TUMOURS (Questions 2,4 and 5)	
3.1 Do the answers to questions 2, 4 and 5 indicate the existence of one or more benign or malignant tumours?	34(_)
If so, specify a maximum of 3 tumours:	
3.1.1. What is the code with regard to the organ or location of the tumour? (See the coding list)	35(_|_)36
3.1.2. Was the tumour benign / malignant? 1 = definitely benign 2 = probably benign 3 = possibly benign, possibly malignant 4 = probably malignant 5 = definitely malignant 6 = unknown, no judgement possible	37(_)
3.2.1. What is the code with regard to the organ or location of the tumour?	38(_|_)39
3.2.2. Was the tumour benign / malignant?	40(_)
3.3.1. What is the code with regard to the organ or location of the tumour?	41(_|_)42
3.3.2. Was the tumour benign / malignant?	43(_)
4. USE OF MEDICATION (Question 6)	
4.1 Tablets for diabetes	44(_)
4.2 Insuline	45(_)
4.3 Tablets for high blood pressure	46(_)
4.4 Hormones	47(_)
4.5 Thyroid medication	48(_)
4.6 Diuretics	49(_)

5 EXPOSURE TO IRRADIATION (Question 7)

5.1 No. of X-rays for

5.1.1 Broken bone(s) 50(_)

5.1.2 Fitting shoes 51(_)

5.1.3 Breast screening 52(_)

5.1.4 Dental examination 53(_)

5.1.5 Screening for TB 54(_)

5.2 Exposure to other irradiation? 55(_)
n = no 1 = yes, with cobalt
2 = yes, with röntgen 3 = yes, with radium
4 = yes, with various 5 = yes, unknown

6. OCCUPATION RISK (Question 8)

From the occupations listed,the one involving the greatest risk should be coded, see the coding list.

6.1 Exposure to irradiation 56(_)
1 = none/negligable
2 = a little
3 = a great deal

6.2 Contact with carcinogenic substances 57(_)
1 = none/negligable
2 = a little
3 = a great deal

7. USE OF STIMULANTS (Question 9)

7.1 Does the respondent drink alcohol? 58(_)

If so, how many glasses -on average- per week of

7.1.1 Beer 59(_|_)60

7.1.2 Wine, sherry, port etc. 61(_|_)62

7.1.3 Gin, cognac, liqueur etc. 63(_|_)64

7.2 Has the respondent ever smoked? 65(_)

7.2.1 If so, at what age did he/she start? 66(_|_)67

7.2.2 Does the respondent still smoke? 68(_)

7.2.2.1 If not, at what age did he/she stop? 69(_|_)70

7.2.3 How many did/does the respondent smoke?

7.2.3.1 Number of cigarettes per day (rolling tobacco) 71(_|_)72

7.2.3.2 Number of pipes per day 73(_|_)74

7.2.3.3 Number of cigars per day 75(_|_)76

8. MARRIAGE AND/OR CHILDREN (Question 10)

8.1 Is the respondent married or has he/she been married? 77(_)

8.2 How many live babies did the respondent have? (Not including adopted children, > 9 children = 9) 78(_)

8.3 Has the respondent been troubled with involuntary infertility (could not have any children)? 79(_)

9 ONLY FOR WOMEN (Vraag 11)

9.1 Has the respondent ever menstruated? 80(_)

9.1.1 If so, how old was she when it started? 81(_|_)82

9.1.2 Is/was the menstruation regular? 83(_)

9.2 Has the respondent had one or more miscarriages and if so, how many? 84(_)
n = no, figure = yes, and the number (figure 9 = 9 or more)

9.3 Has the respondent reached the menopause? 85(_)

9.3.1 If so, at what age? 86(_|_)87

End of record

APPENDIX 11
EXAMPLES OF CODING ACCORDING TO LOCATION AND NATURE FOR ANSWERS TO QUESTIONS 2, 4, AND 5 OF THE HEALTH SURVEY

Answers		Code	
Respondent's description	Question No.	Location	Nature
Lump on hand, benign	4	32	2
Uterus	4	26	6
Birth mark, since birth	4	17	2
Lymph nodes, according to stomatologist benign	4	14	2
Breasts	4	21	6
Fallopian tube and ovary	4	27	6
Skin	4	17	6
Thyroid gland	4	02	6
Nose	4	09	6
Salivary glands	4	05	6
Lymph nodes	4	15	6
Popliteal space	4	32	6
Piece of muscle removed	4	32	6
Liver puncture	5	30	3
Lungs	4	28	6
Fluid from nipple	4	21	6
Lip	4	07	6
In the mouth	4	08	6
Birth marks on head	4	17	3
Knee bursa	4	32	1
Stomach	4	30	6
Leg	5	32	3
Skin on back, 15 yrs ago	5	17	2
Tumour ear lobe, 1983	4	16	2
Atheromatous cyst	4	17	2
Hodgkin's disease (neck)	4	14	5
Lipoma on back	4	17	2
Abdomen, 1968	5	17	2
Lump on vocal cords	4	12	2
Uterus, examined, no abnormalities found	5	26	3
Growth on finger	4	32	3
Intestines	5	30	3
Uterus, fibroid	4	26	3
Lipoma on head	4	31	2
Ganglion	4	32	1
Osgood Schlatter	4	32	1
Wart on bottom, 1984	4	17	2
Uterus	5	26	3
Wart	4	17	2
Cyst in pancreas	4	30	2
Fibroid in uterine wall	4	26	3
Throat	4	10	6

Sternum puncture	5	32	6
Rectoscopy rectum, 1975	5	30	3
Bone marrow puncture	5	not coded	
Uterus, fertility probl.	5	26	2
Intestines, inflam.	5	30	2
Cervical polyp	2	26	6
Kidneys, 1977	5	30	3
Large intestine, 1978	5	30	3
Cyst throat	4	10	2
Bartholin's cyst	4	26	2
Cyst/polyp vagina	4	25	3
Appendix and r. ovary	4	30	2
Sinuses	5	09	3
Throat cyst removed	4	31	3
Kidney cyst, 1972	4	30	2
Wart on penis	4	22	3
2/3 of stomach removed	2	30	3
Leukoplakia in mouth	4	08	3
Prostate, benign	2	23	3

APPENDIX 12
OCCUPATIONS WITH AN INCREASED RISK FOR CANCER

Occupations with an increased risk for cancer

Localization	Suspicious materials and factors	Occupations
Bladder	Coal products, aromatic amines, (benzidine, auramine, 2-naphtylamine, 4-aminobiphenyl)	producers of arom. amines, colouring industry, pigment and paint manuf., rubber and cable manuf., textile dye and print, gas indust., tar and petrol worker, leather worker, fireman, hair-dresser, tailor, printer, engineer, coal miner, cable layer, cook.
Prostate	cadmium*	battery manuf., etc.
Kidney	cadmium*	battery manuf., etc.
Scrotum	polycyclic hydrocarbons, soot	chimneysweep, metal worker, weaver
Skin (squamous cell ca.)	arsenic, polycyclic hydrocarbons (also: UV light, e.g. sunlight, ionizing radiat.)	welder, road worker, farmer, fisherman, radiologist
Skin (malig. melanoma)	PCBs (polychlorebiphenyls)*	PCB production
Lip	? tar products	fisherman
Bone	radium, thorium, plutonium	watch maker using radioactive paint
Pancreas		chemist, printer
Brain	vinylchloride*	chemical and rubber industry
Stomach	nickel, asbestos	nickel worker, coal miner, rubber industry, asbestos worker
Liver (incl. angiosarc)	aflatoxine, vinylchloride industry	ground-nut worker, chemical
Leukemia, malig. lymphoma, M. Hodgkin	benzine, ionizing radiation, vinylchloride, various chemicals, (also infection)*	chemical and nuclear industry, rubber industry, radiologist, cobbler, painter, glue worker, carpenter, chemist, teacher, radiologist, pathologist.
Nose and sinuses (adenocarcinoma)	wood, leather, nickel, isopropyloil*	carpenter etc., leather industry, cobbler, nickel industry, petro-chemical industry, isopropyl alcohol manuf. according to conc. acid process

Lung	arsenic, chrome, nickel, ionizing radiation, asbestos, polycyclic hydrocarbons, mustard gas, isopropyloil +, bis(chlor methyl)-ether, chlormethylmethyl ether, epichlorhydrin, acrylon	metal industry, moulding, steel indust. radiologist, nuclear worker, paper/petrol/transport industry, printer, uranium miner, professional chaufeur, isopropylalcohol manuf. according to conc. acid process.
Pleura, peritoneum, (mesothelioma)	asbestos	isolator, shipbuilder, asbestos manuf., asbestos cement, wearer of asbestos protective clothing (firemen), others with indirect asbestos contact: relatives of workers, laundry worker.
Tumours in children	hydrocarbons*, anaesthetic gasses	children of painters, mechanics, petrol pump assistants, hosp. theatre personnel

* Based on casuistic data or once-off systematic research without convincing results.