FROM RADIUMHEMMET (DIRECTOR: PROF. J. EINHORN), THE DEPARTMENT OF OPHTHALMOLOGY (DIRECTOR: PROF. G. KARPE), KAROLINSKA SJUKHUSET, AND THE DEPARTMENT OF CLINICAL RADIOPHYSICS (DIRECTOR: PROF. R. WALSTAM), NATIONAL INSTITUTE OF RADIATION PROTECTION, STOCKHOLM, SWEDEN.

OPHTHALMOLOGIC OBSERVATIONS ON LONG-TERM SURVIVORS AFTER RADIOTHERAPY FOR NASOPHARYNGEAL TUMOURS

by

A. DE SCHRYVER, LILLEMOR WACHTMEISTER and I. BÅRYD

The late radiation effects on a variety of anatomic structures, both intra- and extracranial, may be evaluated in long-term survivors after radiation treatment for malignant nasopharyngeal tumours. Because of the position of the nasopharynx practically at the centre of the head, it is impossible for the therapist completely to avoid neighbouring structures, such as the eye or the medulla. Moreover, because of the tendency for these tumours to invade the base of the skull it is customary to include the floor of the middle cranial fossa in the target area; indeed it may be expected that several structures at the base of the brain, such as the lower part of the temporal lobes, some of the anterior cranial nerves, the chiasma and the pituitary gland, will be exposed to considerable doses of radiation.

An evaluation of the tolerance of these tissues to ionizing radiation in man presents a complex problem when radiotherapy has been given for primary intracranial disease, for example pituitary adenoma or intracranial tumour. It may

Submitted for publication 30 April 1970.

be difficult, if not impossible in such cases, to tell whether any changes are attributable to the underlying condition or to late effects of radiation.

The aim of the present investigation was to examine the possibility of late radiation induced lesions of the optic nerve. However, because of the vicinity of the eyeball itself to the radiation focus in the nasopharynx and hence the likelihood of significant exposure, the lens and the choroidoretinal tunic were also included in the examination. This was in spite of the fact that as a result of protective measures, the doses were expected to be low and postirradiation changes of the lens have been well documented (3, 5, 8, 11, 17, 18, 23).

Material and Methods

During the 25-year period 1937—1962 approximately 650 cases of malignant nasopharyngeal tumours (mainly poorly differentiated carcinomas and reticulum cell sarcomas) were treated by full-course radiotherapy. All the patients were followed up at least once a year, indefinitely. The crude 5-year survival rate was about 30 % for the tumour group as a whole. Among those living at the time of the present investigation were 80 patients who had survived for at least 5 years, including 58 who had lived for 10 years or more. Of this latter group 50 patients were called for special ophthalmologic control, the remaining 8 patients being either too old or in poor general condition. Twenty-nine of the 50 patients presented for examination; one patient with a survival of only 7 years was also included, making a total of 30 (9 women and 21 men). Their ages at the time of the investigation ranged from 43 to 77, mean 61, years and at the time of treatment from 16 to 59, mean 42, years. As regards the representativeness of the group, one of the most frequent reasons given for not attending the examination was that the patient was doing well and working. Admission to hospital for about a week (other tests were run simultaneously) would in some instances have resulted in financial loss. Most of the patients with any complaints at all were eager to be examined. It would therefore seem that there was no overrepresentation of normal or symptom-free subjects in the material.

Of the patients examined, 5 had a history of hypertension. None had diabetes mellitus, nor had any of them ever been treated with steroids or miotics. Eight patients had a history of ophthalmologic disease: corneal ulcer in 3, iritis in 2, contusions in 2 and possible vitreous haemorrhage in 1 patient. In none of these patients was there a time relationship between the eye condition and the radiation treatment; in fact, in most of them an obvious, purely ophthalmologic cause existed.

The treatment method used was basically the same for all the patients and may briefly be described as a 4-field technique with two lateral and two anterior malar

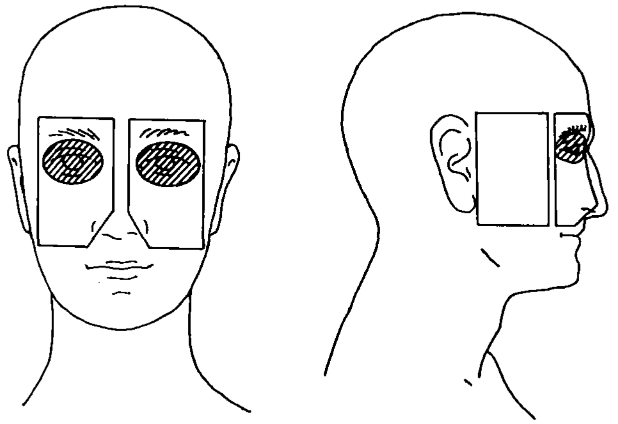

Fig. 1. The limits of the anterior and lateral fields.

fields, the latter deflected about 15° inwards. The radiation energy was approximately 190 kVp with a HVL of 1 mm Cu, the FSD being 50 cm. The field limits were as follows (Fig. 1): (1) Lateral field: Superior limit corresponding to the upper border of the pinna; posterior limit immediately anterior to the tragus; anterior limit about 1 cm behind the lateral border of the orbit; inferior limit about 1 cm above the angle of the mandible. (2) Anterior field: Superior limit including the eyebrow (which, however, was shielded); inferior limit middle of upper lip; medial limit included the ala nasi; lateral limit the lateral border of the orbit. The eye was protected by an oval lead shield measuring about $45 \times 30 \times 3$ mm.

The target always included the base of the skull, the immediately contiguous parts of the brain stem in the middle cranial fossa, and the lower part of the temporal lobes. The exposure in most of the patients was between 2 400 and 3 000 R per field (skin exposure), depending on the pathology and the regression of the tumour during the treatment. The entire course was given in 20 to 40 days, the estimated tumour dose ranging roughly from 5 000 to 6 000 rad. If the tumour was still visible or possibly had not completely disappeared 6 to 8 weeks after completion of the roentgen course, a 50 mg radium source, filtered by 4 mm Al, was applied locally for between 3 and 8 hours. If treatment had to be given to both sides of the nasopharyngeal cavity, an application was made on 2 consecutive days.

This investigation was not concerned with the value of the treatment method as such. All but one of the patients were treated at least 10 years ago, since when supervoltage techniques have been introduced for nasopharyngeal tumours.

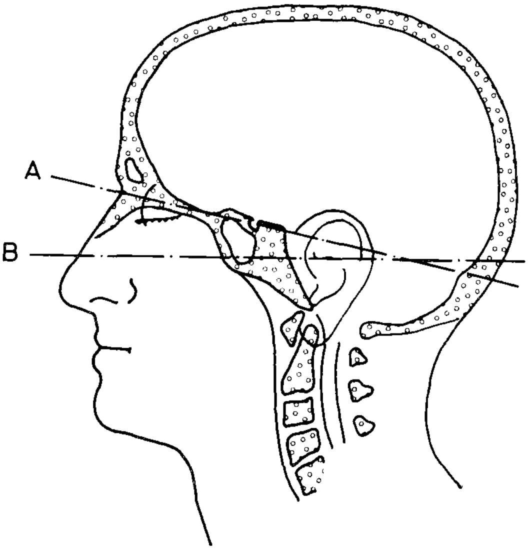

Fig. 2. Sagittal section. A the plane of the isodose plotting and B the approximate direction of the a. p. beams.

Estimation of the absorbed radiation dose

Theoretical reconstruction of dose distribution. When a preliminary series of 10 patients had been examined an attempt was made in all the subsequent 20 patients to reconstruct the dose distribution for each patient. An anatomic contour that intersected the base of the skull approximately at the sella turcica was obtained at eye level (Fig. 2). Epilation and skin atrophy often enabled the fields to be easily reproduced and photographs of the patient taken during treatment and showing the skin reaction were sometimes available. Simulator roentgenograms of all the fields, that enabled the actual treatment conditions to be reconstructed and the exposed structures to be located exactly, were obtained for all the patients. Films for the anterior fields were obtained both with and without an eye-shield. It proved that the chiasma had always been included in the lateral beams and usually in the a.p. beams as well. The site of the optic chiasma on the sphenoid body was evident in the simulator films near the inner limit of the field, close to the border of the eye-shield.

The following values for certain anatomic measurements were assumed for the purpose of this investigation: thickness of the eyelid 2 mm (mean of authors' measurements), cornea 0.6 mm (WOLFF 1961), anterior chamber 3.5 to 4 mm (JANSSON 1963) and lens 3.5 to 4.2 mm (JANSSON); the axial diameter of the eyeball 23 mm (females) and 24 mm (males) (JANSSON). The distance between the surface of the closed eyelid to the lens equator plane was thus about 8 to 9 mm. The distance to the posterior pole of the retina was approximately 24 mm.

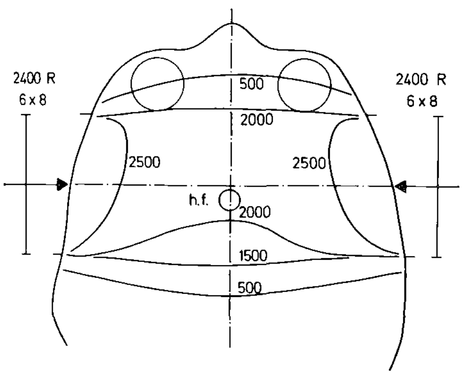

Fig. 3.

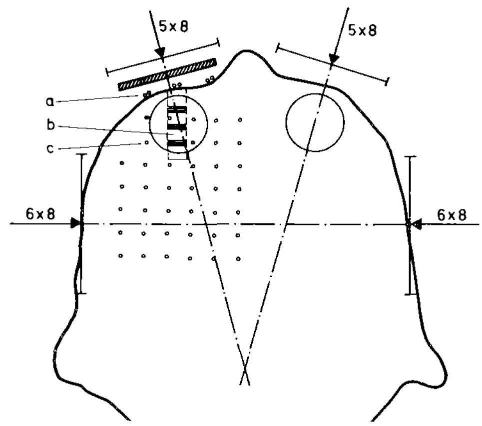

Fig. 4.

Fig. 3. Example of computed dose distribution in plane A (lateral field contributions only). h. f. = hypophyseal fossa.

Fig. 4. Cross-section through the skull phantom in plane A. a) LiF rods on surface immediately below lead shield. b) Cylindrical cavity containing 3 sets of 4 to 5 LiF disks each. Residual space filled with perspex blocks. c) Holes for TLD rods.

In each case a dose distribution was computed at eye-level, using standard isodose diagrams corresponding to a HVL of 1.0 mm Cu (FSD = 50 cm). As the optic chiasma and the eyeball are situated at this level, lying either entirely within (for the latter) or close to (for the former) the region of protection produced by the lead eye-shields, the isodose plotting was greatly complicated. To simplify the situation only the dose delivered by the lateral, unshielded fields (Fig. 3) was considered and to this was added a theoretical fraction of the anterior surface dose, based on phantom measurements behind lead (see below). It was assumed that both the eye and the optic chiasma were entirely shielded but, as stated above, this was not in fact so. The irradiation at that time was, however, performed without any head-immobilizing device, and slight movements might have brought the chiasma within the cone of protection produced by the eye-shield. It was therefore considered that the above assumption would provide a lower limit for the chiasma dose.

The total contribution of the two anterior fields was for the lens approximately 14 %, for the posterior pole of the eyeball 17 % and for the chiasma 25 % of the surface dose. All the tissue doses are expressed in rad. Corrections of — 7 % each were made for bone absorption (4 mm) for the lateral fields.

Phantom measurements. Measurements were made in a water and in an anatomic skull phantom. The dose measurements in the water-filled perspex tank

Table 1

Approximative cumulative depth doses (as percentage of nominal surface dose) in lens and retina

Field	Depth dose	
	Lens	Retina
Anterior	14 %	17 %
Lateral	20 %	60 %

(30 × 30 × 40 cm) were recorded with a Siemens Sondenfingerhutkammer with a Philips ionization chamber as monitoring instrument. Some measurements required a small chamber with an external diameter of only 7 mm (BENNER et coll. 1959). The anatomic phantom consisted of a natural skull on which the external soft-tissue structures were modelled in Mix D, a tissue-equivalent compound (JONES & RAINE 1949); it has been demonstrated by, among others, DAHL & VIKTERLÖF (1958) that this paraffin mixture has a satisfactory radiophysic water equivalence. The intracranial cavity was filled with the same material, in which narrow holes could easily be drilled to receive either small Sievert condenser chambers (SIEVERT 1932) or three types of thermoluminescence dosimeters (TLD), namely, lithium borate ($Li_2B_4O_7$:Mn) and lithium fluoride (LiF) teflon rods measuring 1 × 6 mm, and lithium fluoride disks measuring 0.5 × 8 mm.

The thermoluminescence dosimeters were calibrated against ^{60}Co gamma radiation, and their energy dependence for the relevant roentgen energy (190 kV) was determined. Before reading (on an instrument manufactured by Controls for Radiation, Inc.), the lithium fluoride dosimeters were brought to zero by exposing them for 15 minutes at 300° C, followed by 24 hours at 80° C. The lithium borate rods needed only 30 minutes at 300° C.

The irradiation conditions were similar to those for the clinical treatments (190 kV roentgen rays, 0.5 mm Cu + 1.0 mm Al filtration, HVL 1 mm Cu, FSD 50 cm). The field sizes, 5 × 8 cm and 6 × 8 cm for the anterior and lateral fields, respectively, matched the above mentioned anatomic landmarks. The positions of the beams were checked on the simulator. The 'eye' was protected by an oval, 3 mm thick lead shield during irradiation of the anterior fields. The doses were measured and computed in a plane passing through the eyeballs and the sella turcica (Fig. 2, plane A). The estimated dose contributions from the radium applicators to the target areas probably never exceeded 50 rad

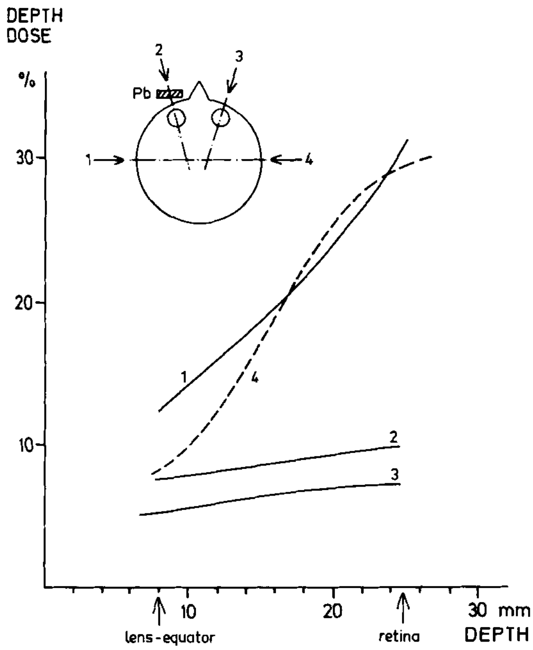

Fig. 5. Contributions of the 4 fields to one eye as measured in an anatomic phantom by TL dosimetry. The lens is at about 8—9 mm depth, the retina at about 25 mm.

to the lens and the retina and 100 rad to the optic nerves, and were regarded as negligible. They are not included in the dose figures recorded in this paper.

LiF rods were placed on the surface of the anatomic phantom immediately behind the shield, and LiF disks at progressive depths along the axis of the lens in order to determine the dose gradient in the first 30 mm behind the eye-shield (Fig. 4). The total doses contributed by the two anterior fields to each lens and retina were approximately 14 and 17 % of the nominal surface dose (Table 1 and Fig. 5).

The largest contribution to the retina came from the lateral field, the projection of its anterior margin being almost tangential to the posterior pole of the eye. The calculated dose distributions in plane A (Fig. 3) were, moreover, verified by LiF rod measurements at a number of points.

Estimation of the radiation dose at the level of the optic chiasma was particularly delicate because of its proximity to the borders of the region of protection produced by the eye-shields. As these shields covered almost the entire width of the anterior field (Fig. 1), straightforward 4-field isodose plotting was considered unpractical and, instead, direct phantom measurements were regarded as being the only method likely to give dependable figures for the anterior field contributions. (Measurements of depth doses for the lateral field indicated acceptable agreement with the values obtained diagrammatically.)

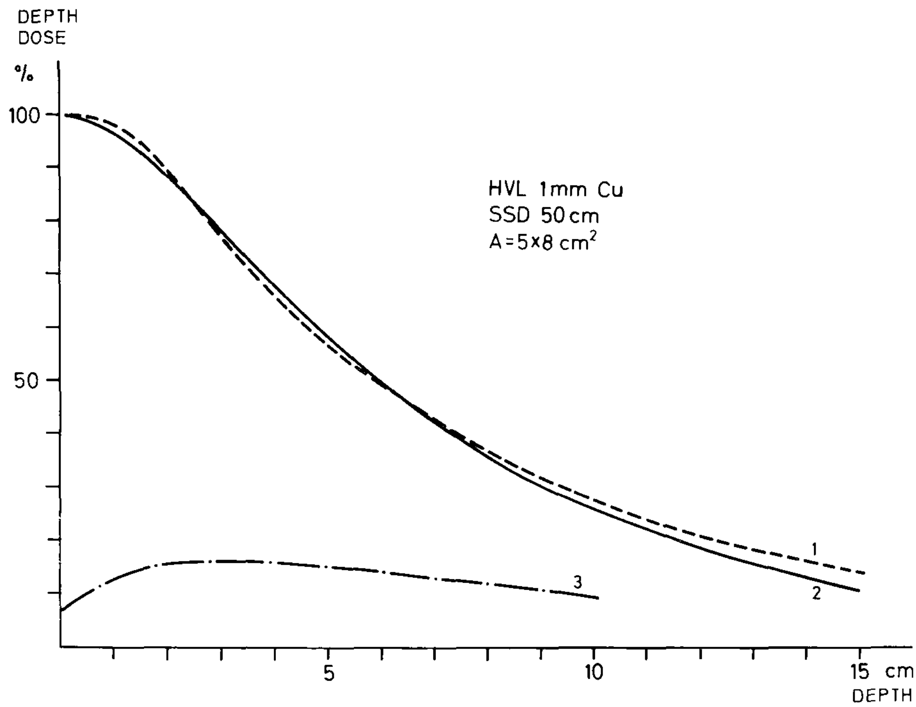

Fig. 6. Depth dose curve (3) behind the centre of a 3 mm lead eye-shield in a water phantom. Normal curves (1) (authors' measurement) and (2) (according to Brit. J. Radiol., Suppl. No. 10) given for comparison.

The first step was to determine in a water phantom the depth-dose curve behind the typical lead eye-shield with a Siemens Sondenfingerhutkammer. As the dose was fairly constant over a wide range (Fig. 6) the depth of the shielded structure relative to the anterior surface of the skull was of minor importance. However, since the simulator films indicated that the chiasma lay situated mostly outside the protected zone, more important were the depth dose variations in a plane perpendicular to the beam axis at the approximate depth of the chiasma. This was examined in a water phantom in which a small ionization chamber (Benner et coll. 1959) coupled to an X—Y registering device automatically scanned the radiation intensity perpendicular to the incident beam. Measurements were performed at three depths (5, 6 and 7 cm) and in two perpendicular directions (AB and CD in Fig. 7). Measurements were made with (curve a) and without (curve b) a lead shield. An example of a measurement recorded at a depth of 6 cm appears in Fig. 7. The dose was relatively constant over most

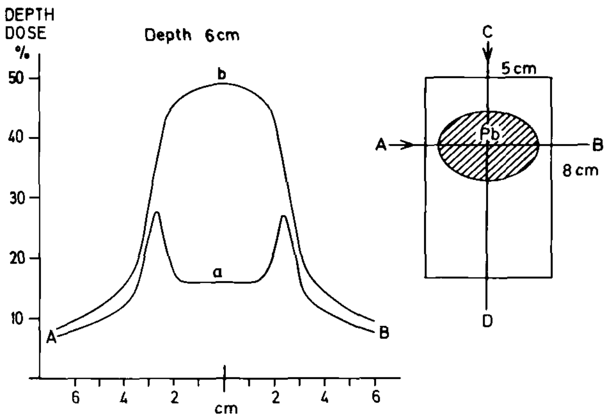

Fig. 7. Recording of the radiation intensity (percentage of surface value) at 6 cm depth as a function of chamber position (movement direction: AB).

of the protected zone but rose sharply to a maximum as the chamber moved over the boundary (from 16 to 27 % in the example given).

As these results indicate, the absorbed doses were subject to important variations in the marginal zone of the cone of protection produced by the eye-shield, and it was therefore decided to accept as a lower limit the minimum dose obtained during the measurements behind the lead protector, i.e. 12.5 % $\times$ 2 = 25 % (Table 2). In each case this value was added to the lateral field contribution determined from the isodose reconstructions, to obtain the minimum doses. The estimated maxima were obtained by adding to the same lateral field contributions a fraction indicated by curve b in Fig. 7 for each case where the chiasma region could be seen outside the lead shield (the vast majority). Although these computed maxima were often considerably higher, they were probably closer to the true doses than were the minimum figures.

Ophthalmologic examination

Three distinctive anatomic and functional units associated with the sense of vision are to some degree exposed to radiation in the treatment of malignant nasopharyngeal tumours by the above mentioned technique; these are the optical media of the eye, the receptor system in the retina and the afferent pathway of the optic nerve. (The quadrigeminal and occipital centres are normally not included in the radiation zone.) The patients in this investigation were therefore examined for possible damage at the three above-mentioned levels: the media, the choroidoretinal tunic and the optic nerve.

The following examinations were carried out in all patients. Visual acuity, tonometry according to Schiötz, slit-lamp microscopy, transillumination of the

Table 2

Relative depth dose in the region of the optic chiasma

Field	Relative depth dose values			
	Condenser chamber	TLD	Siemens chamber	Isodose diagram*
Anterior**	13 %	12 %	12.5 %	—
Lateral	43 %	44 %	—	42 %

* Corrected for bone absorption.

** It is assumed that the region of the chiasma is completely shielded.

optic media, and ophthalmoscopy after dilating the pupil with Mydriacyl, perimetry according to Goldman and colour vision tests with pseudoisochromatic plates according to Boström & Kugelberg and Boström II (4,15). ERG was recorded by the Karpe method (14) in one patient and an adaptation curve was obtained; in a few other cases photographs of the lens (direct transillumination) and fundus were taken.

Dose calculations are not available for 10 of the patients. However, as they did not constitute a selected group, either clinically or as regards the treatment technique, their data were included in the investigation.

Results

Estimated absorbed radiation doses

Lens and retina. The doses calculated and checked by the techniques described above ranged for the lens from 600 rad in 5 weeks to 1 100 rad in 4 weeks. The figures were of course higher for the posterior pole of the eye, corresponding to the central part of the retina. Moreover, at this level an attempt was made to determine a dose range; not unexpectedly these ranges varied quite widely — from 100 to 1 800 rad. Among the lowest figures recorded lie 1 300 to 1 800 rad, and among the highest ones, 3 200 to 3 500 rad.

Optic chiasma. The minimum values ranged from 1 800 to 4 300 rad, and the maximum ones from 2 000 to 4 900 rad. Moreover, at least 3 cases had maximum doses of between 4 400 and 4 900 rad.

Ophthalmologic data

The media. Pathologic changes of some sort were observed in one or both lenses in 25 of the 30 patients. Ten had opacities in the posterior subcapsular region, and 7 in the perinuclear subcapsular region. Purely cortical opacities (granulae and 'spokes') were observed in 6 patients, 2 of whom also displayed posterior subcapsular changes, one with perinuclear subcapsular changes and the other with anterior subcapsular vacuoles and posterior subcapsular opacities. One patient had anterior, and another posterior subcapsular vacuoles.

The fundi. The lenses were so opacified in one patient that finer details could not be seen at ophthalmoscopy. In another patient the left lens was opacified to such a degree that ophthalmoscopy of only the right eye was possible. Of the remaining 29 patients, including this last one, 5 presented retinal changes characterized by small round haemorrhages and micro-aneurysms, mainly in the macula. Two of these 5 patients were, or had been, suffering from hypertension. Extensive haemorrhage, exudate and pigmentation were present in one patient who had been suffering from hypertension but whose blood pressure had fallen without any treatment within normal limits. Fundus hypertonicus I and II was evident in 4, arteriosclerotic changes in 7 and peripapillary atrophy (without myopia) in 3 patients. The maculae were stippled with fine glistering dots and small yellowish atrophic patches in 14 patients.

The perimetry. No changes characteristic of optic nerve lesions were present. A bilateral concentrically contracted visual field without hemianopsy or central scotoma was evident in one patient. The patient had moderate myopia (—8.0) with impaired vision (right eye = 0.4 and left eye = 0.5 after correction) and collaborated poorly. Another patient presented with a concentric contraction of the left visual field, but even here vision was impaired (left eye = 0.7 after correction) and collaboration poor. In another four patients there was relative contraction of the upper part of the fields, tested with a small and dimly lit object (0.33 : 0.10 : 1/4 mm^2), as in vascular conditions. Both eyes were affected in two of them and left eye only in the other two.

Vision. Twenty-two of the 30 patients examined had normal visual acuity after correction of any refractive errors, and in 8 patients vision was impaired. Of these one patient presented with corneal scars of traumatic origin and another had hyperopia and in childhood probably strabismus. In the remaining 6 patients the impaired vision was due to lens opacity — 2 with cortical, 2 with posterior subcapsular, 1 with posterior and peripheral cortical (in this patient, however, a moderate myopia may have been a contributing cause), and 1 with perinuclear subcapsular opacity.

Intra-ocular pressure. This was normal in all but one of the 30 patients (a moderately increased pressure was recorded in this patient and bilateral glaucoma simplex was subsequently treated).

Colour perception. — Eight of the 30 patients, including one female, had defective colour perception — congenital in 3 and of obscure origin in 3; the remaining 2 patients, including the woman, collaborated poorly owing to advanced age.

An electroretinogram (KARPE 1945), recorded in one patient with extensive fundus lesions, presented normal values. The adaptation curve was also normal.

Discussion

As in all such investigations, the dosimetry was based on reconstructions that are inevitably in some measure artificial. While it is probably safe to say that the figures for the doses administered are accurate to within 10 %, the margin of error for the relevant geometric factors cannot be so exactly determined. Slight day-to-day variations in the positioning of the patient may have resulted in a depth-dose distribution somewhat different from the reconstructed one. As the structures investigated were situated in zones where relatively steep dose gradients might be expected, the doses may have been significantly influenced by small variations. Account was taken of this whenever possible by specifying an estimated dose range instead of a single value. All the calculations were made without knowledge of the clinical findings.

Lens. The radiosensitivity of the lens is well established, both experimentally and clinically, and comprehensive reviews of the literature on the subject have been given by POPPE (1942), HAM (1953) and PISTOLESI (1959). It is now generally accepted that 400 R can be considered as a threshold dose, at least in the adult and for roentgen rays, and when fractionated over three or more weeks while 1 200 R will invariably induce some degree of radiation cataract (MERRIAM & FOCHT 1957). Although this investigation was not primarily concerned with radiation induced lens changes, they were none the less carefully studied. Radiation cataract has been extensively investigated both in animals and clinically. Initially, small opacities appear subcapsularly in the region of the posterior horizontal suture; these eventually acquire a 'doughnut' form, evident in the slit-lamp beam as a bivalve configuration. Large vacuoles and polychromatic cysts located subcapsularly in the posterior cortex as well as thin granular and feather-like formations may develop. Gradually, a dense discoid opacity is formed in the posterior pole. An anterior subcapsular haze may appear, eventually together with vacuoles. Finally, the lens is completely opacified (18).

Lens changes of some sort were discovered in 25 of the 30 patients. CINOTTI & PATTI (1968) in an examination of a 'normal' population of 177 persons with about the same median age as the present group of patients and with no history of diabetes, glaucoma or congenital lens-opacity observed posterior subcapsular opacities in about 19 %. There were no sex differences.

Ten of the present 25 patients presented posterior subcapsular opacities of the type associated with radiation cataract (COGAN et coll. 1952); this would be almost twice as many as would be expected in a 'normal' population with the approximate age distribution of the present series. A further 7 patients had disseminated small punctiform opacities with a perinuclear subcapsular distribution, such as have been reported in radiation cataract (8). This type of opacity, which was not mentioned by CINOTTI & PATTI (1968), can be differentiated clinically from the flocculent, whitish nuclear or subcapsular changes, located for the most part posteriorly, evident in diabetes. Finally, 2 patients had anterior subcapsular vacuoles such as those observed by AXELSSON & HOLMBERG (1966) after treatment with miotics; however, none of the patients had received such drugs and moreover this type of change has been known to develop after radiation (8). In summary, 19 of the 30 patients presented with alterations consistent with radiation induced cataract, and it would thus seem likely that a number of the changes discovered in their lenses were, in fact, due to the irradiation treatment. This is the more probable as the calculated lens doses (600 to 1 100 rad) all fall within a range known to be potentially cataractogenic (MERRIAM & FOCHT 1957). However, to judge from the results of CINOTTI & PATTI (1968), the alterations in some of these 19 patients might well have been of a purely senile type.

Functionally, almost all the observed lens changes consistent with radiation induced cataract were benign in that they were small, stationary and affected vision only slightly, if at all. This is in agreement with the observations of several other investigators (QVIST & ZACHAU-CHRISTIANSEN 1959, MERRIAM & FOCHT 1957, MILLER et coll. 1967). According to MERRIAM & FOCHT progressive cataracts resulting in complete opacification of the lens and corresponding loss of vision would be expected mainly with doses above 1 000 rad, although might occasionally occur at lower dose levels. In this series, with none of the estimated lens doses exceeding 1 100 rad, only one patient had lens changes of the radiation induced type (a dense posterior subcapsular discoid opacity) that had resulted in markedly impaired vision (0.3 to 0.4 for the more affected eye). The dose absorbed by the lens was estimated at 1 100 rad. Two further patients in this series presented with a considerable loss of vision (0.5 or less) but the lens changes were of a more senile type. Moreover moderately severe myopia (— 8) may have contributed to the loss of vision in one of them.

Cataracts occurred in about 61 % of the patients with estimated lens exposures of 550 to 1 150 R in the series of MERRIAM & FOCHT (1957). The corresponding figure for the present series with ophthalmologic appearances as in radiation cataract was 63 % for estimated lens doses of 600 to 1 100 rad.

The choroidoretinal tunic. Although the retina is more radio-resistant than the lens a number of experimental observations have indicated that at least some elements of the retina may be seriously damaged by relatively moderate doses in the range of 2 000 rad (CIBIS et coll. 1955). Recent investigations in the rabbit carried out by DEVI et coll. (1968) and LOMMATZSCH et coll. (1968) have disclosed the effect of different radiation doses on the electroretinogram (ERG) in experiments covering a few days up to three weeks.

The conditions under which many of these observations were made preclude them being always directly applicable to clinical situations (where large single doses of radiation are the exception rather than the rule). It is however evident that the possibility of radiation induced damage to the retina should be borne in mind whenever this has been exposed to more than 2 000 rad.

Both the macula and the retinal vessels were entirely normal in 11 patients of this series. At least one type of change (microaneurysm, haemorrhage, atrophy, the presence of small, glistering dots) was present in 18 patients. Refined ophthalmoscopy was impossible in one patient. To examine whether these alterations might be in any way related to the amount of absorbed radiation, the group of 20 patients where dose reconstructions were available was divided roughly and quite arbitrarily into those receiving less and those receiving more than 2 500 rad on the posterior third of the eyeball (6 and 14 patients, respectively). In the 'low dose' group the findings were quite normal in 4 out of 6 patients, they were difficult to assess in one but no gross changes were evident, while in one atrophic changes were present in both maculae. In the other 14 patients the maximum dose to the retina was estimated to be higher than 2 500 rad, and all with abnormal findings except one belonged to this 'high dose' group (11 out of 14).

The extent to which the changes observed may be ascribed to radiation is difficult to decide. As PERRERS-TAYLOR et coll. (1965) stated, all types of radiation induced alterations in the choroid and retina may occasionally occur in the elderly as purely senile changes. It was therefore impossible to attribute the changes observed to the radiation exposure with any degree of confidence and in the hypertensive patients they may have had a purely vascular origin. However, as all but one of the changes were observed above a certain dose level, the radiation was probably of etiologic importance. Furthermore, one of the patients in whom the retina was apparently exposed to one of the highest doses (3 400 rad), presented the most intense pathologic changes (haemorrhage, exudate and pigmentation). The fact that the electroretinographic response and adaptation curve were normal does not exclude the possibility that the lesions were due to radiation damage. In a recent experimental investigation of the rabbit retina, LOMMATZSCH et coll. (1968) reported that less than 5 000 rad ^{60}Co gamma radiation in one single dose would not produce appreciable lasting changes in the ERG, at least in short-term observations. Similar findings were reported by DEVI et coll. (1968) who, moreover, concluded from their clinical data that 'the radiosensitivity of the human retina was comparable to that of the rabbit retina'. Only after single doses of at least 5 000 rad may serious and probably irreversible damage of the receptor and bipolar cells of the retina be expected. Admittedly these findings have no bearing on possible late secondary changes resulting from radiation induced vascular damage, as indeed were most of the changes in the present series. Even in the more severe cases vision would hardly be affected. The human retina would appear to tolerate doses up to 3 000 to 3 500 rad if fractionated over 4 to 5 weeks, and although hypertensive vascular changes were sometimes present.

The optic nerve. Little is known about the radiosensitivity of the optic nerve. As reported by BIEGEL, the results of earlier investigations (before the thirties) are conflicting, probably owing, at least in some degree, to dosimetry problems. In this author's more recent experimental work (1955) in the rabbit, exposure of the optic nerve to 23 MeV roentgen rays in doses of up to 4 500 R and to the same doses of 17 and 19 MeV electrons failed to produce histologic evidence of radiation damage. Despite the general agreement on the relative radio-resistance of the optic nerve (3, 22) actual data in man are scarce. CLAUS et coll. (1968) described optic nerve damage in 8 out of 25 irradiated cases. However, the total dose to the nerves was 6 000 to 8 000 R and, moreover, in at least 5 of the cases other local factors, such as tumour growth or ocular complications (glaucoma, inflammation), were either wholly or at least partially responsible for the observed optical atrophy.

No damage to the optic nerves detectable by perimetry was recorded in any case of the present series although in at least 3 the dose was not less than 4 400 rad, that is if it assumed that the upper limit of the calculated dose ranges is the more realistic. In none of the cases with impaired vision, was this due to an optic nerve lesion, but to changes in the media (plus one patient of hyperopia and probably strabismus in childhood). Even the 3 patients which chiasma doses of 4 400 rad or more had both normal vision and normal visual fields.

The figure of 8 out of 30 patients for defective colour perception is more than three times the expected frequency (about 8 % in males and 1 % in females). The history in 3 patients proved the anomaly to be congenital, and in 2 the situation was dubious because of poor collaboration from the elderly patients. In 2 of the remaining 3 patients the absorbed dose in the chiasma was estimated at about 4 400 rad and in the third patient it was unknown. While defective colour perception cannot confidently be ascribed to the absorbed radiation it would seem no less difficult to rule out some form of damage to the optic nerve.

Acknowledgements

The location of the optic chiasma, in particular, was carefully reviewed by Curt Lagergren and Paul Edholm, both at the Department of Diagnostic Radiology, Karolinska Sjukhuset, to whom the authors wish to express their gratitude.

SUMMARY

Thirty patients who had received radiotherapy seven to thirty years previously for nasopharyngeal tumours were examined ophthalmologically for late radiation changes. Opacities in the lens were present in 25 of the patients; in 19 with characteristics similar to those in radiation cataract. Choroidoretinal changes were evident in 1 of the 6 patients for whom the estimated absorbed dose had been less than 2 500 rad over 3 to 5 weeks and in 11 of the 14 patients in whom the dose had been higher. None of the patients sustained obvious damage to the optic nerve.

ZUSAMMENFASSUNG

Dreissig Patienten, die 7 bis 30 Jahre zuvor mit Tiefenbestrahlung wegen eines Tumors des Nasenrachenraumes behandelt worden waren, wurden ophthalmologisch auf Strahlenschädigung des Auges untersucht. Trübungen der Linse wurden in 25 Patienten gefunden, in 19 zeigten sich die typischen Formen eines Strahlenkataraktes. Retinochorioidale Schädigungen zeigten sich in einem von 6 Fällen, in denen die absorbierte Strahlendosis weniger als 2500 rad in 3 bis 5 Wochen gewesen war und in 11 von 14 Patienten in denen die Dosis höher gewesen war. In keinem Falle konnte eine Schädigung des Nervus opticus mit Sicherheit nachgewiesen werden.

RÉSUMÉ

Les auteurs ont fait un examen ophtalmologique pour rechercher des lésions tardives à 30 malades qui avaient été traités par radiothérapie de 7 à 30 ans auparavant pour des tumeurs naso-pharyngiennes. Vingt-cinq de ces malades avaient des opacités dans le cristallin; chez 19 ces opacités avaient des caractéristiques semblables à celles de la cataracte due aux radiations. Il y avait des lésions choroïdo-rétiniennes évidentes chez un des 6 patients chez lesquels la dose absorbée estimée avait été inférieure à 2 500 rad en 3 à 5 semaines et chez 11 des 14 malades chez lesquels la dose avait été supérieure. Aucun des malades n'avait subi de lésion certaine du nerf optique.

REFERENCES

1. Axelsson U. and Holmberg Å.: The frequency of cataract after miotic therapy. Acta ophthal. 44 (1966), 421.
2. Benner S., Ragnhult I. and Gebert G.: Miniature ionization chambers for measurements in body cavities. Phys. in Med. Biol. 4 (1959), 26.
3. Biegel A. C.: Experimental ocular effects of high-voltage radiation from the betatron. Arch. Ophthal. 54 (1955), 392.

4. Boström C. G.: Färgsinneskontrollens organisation. (In Swedish.) Svenska Läk.-Tidn. 41 (1944), 2885.
5. Cibis P. A., Noell W. K. and Eichel B.: Ocular effects produced by high-intensity X-radiation. Arch. Ophthal. 53 (1955), 651.
6. Cinotti A. A. and Patti J. C.: Lens abnormalities in an aging population of nonglaucomatous patients. Amer. J. Ophthal. 65 (1968), 25.
7. Claus H.-G., Diethelm L. und Cullmann B.: Der Einfluss einer hochdosierten Gammastrahlung auf das menschliche Auge. Strahlentherapie 136 (1968), 395.
8. Cogan D. G., Donaldson D. D. and Reese A. B.: Clinical and pathological characteristics of radiation cataract. Arch. Ophthal. 47 (1952), 55.
9. Dahl O. and Vikterlöf K. J.: Dose distributions in arc therapy in the 200 to 250 kV range. Acta radiol. (1958) Suppl. No. 171.
10. Devi S. K., Riley E. F. and Burns C. A.: Electroretinographic responses of the rabbit after x-irradiation. Invest. Ophthal. 7 (1968), 219.
11. Ham Jr W. T.: Radiation cataract; a review. Arch. Ophthal. 50 (1953), 618.
12. Jansson F.: Measurements of intraocular distances by ultrasound. Acta ophthal. (1963) Suppl. No. 74.
13. Jones D. E. A. and Raine H. C.: Letter to the Editor. Brit. J. Radiol. 22 (1949), 549.
14. Karpe G.: The basis of clinical electroretinography. Acta ophthal. (1945) Suppl. No. 24.
15. Kugelberg I.: De nya svenska färgsinnestavlorna. (In Swedish.) Svenska Läk.-Tidn. 41 (1944), 2898.
16. Lommatzsch P., Fürst G. und Ulrich W. D.: Vergleichende morphologische und funktionelle (ERG) Untersuchungen an der Retina des Kaninchens nach Einwirkung von Gammastrahlen (^{60}Co) und hochenergetischen Elektronen. Albrecht v. Graefes Arch. Ophthal. 175 (1968), 34.
17. Merriam Jr G. R. and Focht E. F.: A clinical study of radiation cataracts and the relationship to dose. Amer. J. Roentgenol. 77 (1957), 759.
18. — — Clinical and experimental study of effect of single and divided doses of radiation on cataract production. Trans. Amer. ophthal. Soc. 60 (1962), 35.
19. Miller R. J., Fujmo T. and Nefzger M.: Lens findings in atomic bomb survivors. Arch. Ophthal. 78 (1967), 697.
20. Notter G., Walstam R. and Wikholm L.: Radiation induced cataracts after radium therapy in children. *In:* Proceedings of the first Nordic Radiation Protection Conference. Acta radiol. (1966) Suppl. No. 254, p. 87.
21. Perrers-Taylor M., Brinkley D. and Reynolds T.: Choroido-retinal damage as a complication of radiotherapy. Acta radiol. Ther. Phys. Biol. 3 (1965), 431.
22. Pistolesi G. F.: Radiation injury of ocular structures: comprehensive review. Quad. Radiol. 24 (1959), 471.
23. Poppe E.: Experimental investigations of the effects of roentgenrays on the eye. Jacob Dybwad, Oslo 1942.
24. Qvist C. F. and Zachau-Christiansen B.: Radiation cataract following fractionated radium therapy in childhood. Acta radiol. 51 (1959), 207.
25. Sievert R. M.: Eine Methode zur Messung von Röntgen-, Radium- und Ultrastrahlung nebst einige Untersuchungen über die Anwendbarkeit derselben in der Physik und der Medizin. Acta radiol. (1932) Suppl. No. 14.
26. Wolff A.: Pathology of the eye. Cassel & Co., London 1961.