Radiation Toxicity To the Visual System

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This issue of the Journal of Neuro-Ophthalmology includes several articles regarding radiation-induced injury to the visual system, including one by Monheit et al (1) describing visual field loss due to occipital lobe necrosis. Although the latter type of injury has apparently not been previously reported, its occurrence is hardly surprising. One would predict a very high risk of necrosis of any central nervous system site after exposure to approximately 60 Gy of fractionated irradiation, followed by re-irradiation with a single high dose (32 Gy) fraction. Although nine years had passed since the first course of radiation therapy (RT) in Monheit et al's patient, some degree of latent neural and vascular damage from the first course of RT no doubt persisted. Intensive hypofractionated (single fraction or a few high-dose fractions) treatment of any human tissue is accompanied by an increased risk of necrosis compared with fractionated treatment, and residual toxic damage further compounds the risk. Unfortunately, the site of this patient's necrosis involved a highly eloquent part of the brain. This case is not, however, indicative of any particular sensitivity of the occipital lobes to radiation toxicity.

On the other hand, the report by van den Bergh et al (2) is an important confirmation of the low risk of optic neuropathy following RT for nonfunctioning pituitary adenomas. Using doses of 45–50.4 Gy, van den Bergh et al reported no injuries. Given the lack of a significant dose response above 45 Gy in 25 fractions, most centers now do not exceed that regimen. Probably because of pre-existing opticochiasmatic compression, the optic nerves in patients with nonfunctioning pituitary adenomas are somewhat more susceptible to injury after RT than the optic nerves in patients without pre-existing compression. As noted in the authors' Table 2 (2), even 45 Gy in 25 fractions has been responsible for injury in a few reported patients. In the University of Florida pituitary adenoma series (3), two patients whose optic nerves received 50 Gy in 30 fractions at 1.67 Gy per fraction also developed neuropathy. Injury after treatment with either of these dose fractionation schemes in non-pituitary patients would be extraordinarily unusual, and I am unaware of any such reports.

Until the 1960s and early 1970s, it was thought that the retina and optic nerve were relatively resistant to the effects of RT. The sparse literature that existed at that time considerably overestimated the tolerance of these structures, suggesting that 68 Gy in 30 fractions at 2.27 Gy per fraction was within retinal tolerance (4). The last 25 years have brought considerable understanding of the types of injury that RT can induce (5).

If the orbital contents are irradiated, there is a risk of injury to the lacrimal tissue. In the University of Florida series (5,6), patients who suffered significant injury to lacrimal tissue were usually symptomatic within one month of completion of RT, and were noted to have severe corneal opacification and vascularization by nine to ten months. Corneal reactions included edema, ulceration, bacterial infection, vascularization, opacification, perforation of the globe, symblepharon, and phthisis bulbi. Enucleation or evisceration because of continued pain or perforation of the globe was required in half of the patients. Radiation dose response is not an all or none phenomenon. The shape of the dose response curve is
If it is possible to shield enough lacrimal tissue to prevent dry eye syndrome, then at higher doses one risks radiation retinopathy, which usually develops two to three years after RT and has many characteristics of diabetic retinopathy (5,7,8). Approximately half of the patients with severe radiation retinopathy develop ruberosis iridis or neovascular glaucoma. The risk of radiation retinopathy increases steeply above 45 Gy to external beam portals that include the majority of the retina. Pan-retinal laser photocoagulation may offer some benefit in preventing progression to neovascular glaucoma (7). There is increased risk of retinopathy in those treated with fraction sizes ≥1.9 Gy, in those who have received chemotherapy, in older patients, and in those with diabetes mellitus.

If the patient does not experience retinal injury, blindness may still result from optic nerve or chiasm injury (5,8,9). These structures have approximately the same radiation sensitivity as the spinal cord, the risk of injury increases steeply above 55 Gy. Among nerves that received ≥60 Gy, dose per fraction has been more important than total dose (8). In an earlier study (8), the 15-year actuarial risk of optic neuropathy after ≥60 Gy was 11% with <1.9 Gy per fraction as compared with 47% with ≥1.9 Gy per fraction. There was also a greater risk with increasing age. There is no effective treatment of optic neuropathy; although hyperbaric oxygen and corticosteroids are worth trying, most patients do not respond favorably.

Vision loss after RT is most often unilateral, but bilateral blindness may also occur. The most common scenario leading to bilateral blindness includes ipsilateral radiation retinopathy (which is often "expected" when there is extensive orbital involvement by paranasal sinus cancer), and contralateral optic neuropathy. Bilateral optic neuropathy or chiasm injury may also occur. Better target definition as well as three-dimensional conformal and intensity-modulated techniques and stereotactically aided treatment setups are all useful in limiting the dose to these vital structures (see the article by Pan and Hayman [10] in this issue). These techniques allow optimal patient positioning and field reproducibility, unconventional angles of beam entry, geometric shaping of the radiation beam so that it corresponds to the "beam's-eye" view of the target, and geometric shaping of the isodose distribution by altering beam intensity (fluence). These features allow deliberate inhomogeneity across target and avoidance areas. The radiation oncologist must pay careful attention to time–dose parameters (fractionation) and carefully calculate total dose and fraction size to each vital structure and attempt to limit the volume of tissue receiving that dose.

Despite the greatest attention to detail, the most sophisticated protocols, and the best equipment, optic neuropathy and retinopathy will still occasionally be seen when attempting to control advanced cancers with high-dose RT. This is because many large tumors occur in close proximity to or engulf healthy tissues in such a manner that no amount of careful planning can avoid their receiving a toxic dose.

REFERENCES

Radionecrosis of the Inferior Occipital Lobes With Altitudinal Visual Field Loss After Gamma Knife Radiosurgery

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Abstract: A patient had bilateral superior altitudinal visual field defects because of radionecrosis of the inferior occipital lobes after gamma knife radiosurgery for a recurrent atypical cerebellar meningioma. Although radionecrosis of the anterior visual pathway has been well-documented, this is the first report of visual field loss associated with occipital lobe radionecrosis. The treatment dose this patient received is within the range of predicted tolerable radiosurgical dosing, although this patient was at increased risk for radionecrosis secondary to previous external beam radiotherapy. By offering an effective, noninvasive treatment, radiosurgery has changed the management of intracranial lesions. Radiosurgery targets a discrete volume of tissue and relatively spares the surrounding normal tissue. Radiation injury, or radionecrosis, is the only significant complication of radiosurgery (1). We present a case of bilateral occipital lobe radionecrosis after gamma knife surgery that resulted in bilateral superior altitudinal defects.

CASE REPORT

In September 2001, a 48-year-old woman was referred for neuro-ophthalmologic evaluation of sudden visual field loss present for two days and preceded by several months of intense headaches.

An atypical cerebellar meningioma involving the straight sinus had been resected in 1992. A postoperative magnetic resonance imaging (MRI) showed no residual tumor. However, after resection she had received external beam radiotherapy of 1.8 Gy in 33 fractions totaling 59.4 Gy. She had undergone an ophthalmologic examination in 1993 with visual acuities of 20/15 OU and normal threshold automated visual fields.

In July 2000, a routine surveillance MRI scan demonstrated tumor recurrence (Fig. 1), and in August 2000 the patient underwent a single gamma knife treatment of 16 Gy at the 50% isodose line.

In September 2001, our examination disclosed that the patient had corrected acuities of 20/25 OU. All other aspects of the ophthalmologic examination were normal except that Swedish Interactive Threshold Algorithms standard 24-2 automated visual fields showed dense superior altitudinal defects (Fig. 2).

An MRI in September 2001 showed increased enhancement of the occipital lobes bilaterally, left more than right, when compared with the scan before gamma knife treatment (Fig. 3). A single photon emission computed tomography (SPECT) scan illustrated reduced blood flow in the areas of occipital enhancement, consistent with radionecrosis. A review of the gamma knife treatment planning scan disclosed that the occipital lobes beneath the calcarine fissure had received radiosurgical doses near the minimum treatment dose of 16 Gy (Fig. 4).

The patient was placed on dexamethasone with no apparent improvement in the visual field defects at one-year follow-up.

DISCUSSION

This case is, to our knowledge, the first to report occipital lobe radionecrosis with dense superior altitudinal defects after gamma knife radiosurgery.

Lars Leksell, a Swedish neurosurgeon, pioneered radiosurgery, which aimed to direct a high dose of radiation to a discrete tissue volume and to spare surrounding healthy tissue. Along with radiobiologist Borje Larsson, Leksell de-
FIG. 1. Enhanced T1-weighted axial MRI scan performed in 2000, eight years after tumor extirpation and external beam radiotherapy. It shows a mass projecting from the left side of the tentorium superiorly into the supratentorial region. The patient received stereotactic radiosurgery (16 Gy by gamma knife at the 50% isodose line).

veloped the first gamma knife unit in the 1960s (2). The gamma knife uses 201 cobalt sources to deliver ionizing radiation to a target volume. Its beams are collimated and convergent and may be blocked selectively to adjust the shape and volume of the tissue to be treated. The outer rim of the tumor typically receives 50% of the maximum dose ("minimal tumor dose"), which represents the 50% isodose line on the planning scan (1). After a stereotactic frame is placed, the patient undergoes a MRI treatment planning scan. Specialized computer software creates the plan by reconstructing the two-dimensional images into three-dimensional target volumes to be treated. The stereotactic frame serves as a reference for the coordinate system, the X-, Y-, and Z-axes, and creates the stereotactic space (3).

There are several proposed mechanisms for radiation injury. One is damage to cellular DNA. Tumor cells have poor cell repair mechanisms and are, relative to normal cells, unable to recover from the radiation. Normal cells may be damaged if the dose they receive is too high (4). Tandon et al (5) believe that injury is based in the vascular endothelium; radiation increases the production of coagulative factors that cause vascular thrombosis. At the same time, the cell cycle of the endothelium is disrupted, which causes a large number of abnormally functioning endothelial cells to be produced, with subsequent breakdown in the blood-brain barrier. Other studies have examined the role of cytokines in radiation injury. Kureshi et al (6) found interleukin-1, tumor necrosis factor alpha, and interleukin-6 expressed by infiltrating macrophages during radionecrosis of cerebral tissue.

Damage to healthy tissue surrounding the treated lesion may appear months to years after focal brain irradiation (2). The presenting symptom is usually a headache, focal or generalized seizures, or hemiparesis. MRI reveals a hypointense mass, sometimes with contrast enhancement, which is not readily distinguishable from malignant tissue. Biopsy is diagnostic, demonstrating coagulative necrosis of white matter, telangiectasia, fibrinoid necrosis of blood vessels, thrombus formation, glial cell proliferation, and multinucleated giant astrocytes. When biopsy is not possible, SPECT or positron emission tomography scan with radio-labeled glucose will show decreased metabolism in the area of interest, which suggests radionecrosis rather than recurrent malignancy (7).

Visual field defects have been well described after the use of conventional external beam therapy to lesions near the anterior visual pathway, including pituitary tumors, craniopharyngiomas, parasellar meningiomas, and optic nerve meningiomas (8-12). The defects generally occur one or more years after radiation treatment. On MRI, there is optic nerve swelling and enhancement (13). Radiation optic neuropathy after gamma knife therapy has been less
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FIG. 3. MRI performed at the time of detection of superior altitudinal visual field loss. Enhanced axial T1-weighted scans (A, B, C) demonstrate enhancement of the white matter of the occipital lobes, left more than right. Axial T2-weighted scans (D, E, F) show high signal in the occipital white matter. Reduced blood flow on the SPECT scan in this region confirmed the impression of radionecrosis.

often reported perhaps because patients with lesions near the optic structures are less often treated with single fraction radiotherapy. Yet, a 1997 series reported 2400 patients treated by gamma knife for lesions around the anterior visual pathway, (2) and only four (0.2%) had visual loss up to 30 months later. Delivery of more than 8 Gy was associated with a higher incidence of tissue injury. Additional risk factors for developing radiation damage included previous external beam radiotherapy and visual dysfunction before treatment (2). In a series of patients treated for cavernous sinus lesions with single fraction stereotactic radiation, Leber et al (23) found the incidence of optic neuropathy to be zero in patients exposed to 10 Gy or less. Doses greater than 10 Gy resulted in dramatic increases in optic neuropathies, with 15 Gy having a 77.8% incidence. In contrast, the oculomotor and trigeminal nerves were much more tolerant to the same doses (23). In another series of 66 patients who had cavernous sinus and petroclival area lesions treated by gamma knife (14), the optic nerves, chiasm, or tract received between 1 and 16 Gy, with a median of 10 Gy. In 59 (89%) of cases, the dose was greater than 8 Gy, yet there was no visual loss after a two-year follow up. The authors postulated that the anterior visual pathway may tolerate a dose of 12 to 16 Gy provided there are no factors that would predispose the patient to radionecrosis, including previous dysfunction or previous radiosurgery at the same site (14).

Guidelines to estimate the risk of cortical radionecrosis after gamma knife treatment have been actively pursued. The foundation of radiosurgical prescription dosing today is based on work performed by Raymond Kjellberg in 1983 (15). His study centered on the dose of Gy delivered to a tissue volume as the predictor of radionecrosis. He formulated a curve of volume of tissue treated versus dose of Gy that would predict a 1% chance of radionecrosis (15). Chin et al (1) suggest a dose of 10 Gy given to a volume of tissue 10 mm$^3$ or more is associated with a higher risk of radionecrosis (1). Flickinger et al (16,18) found that the risk of radionecrosis after gamma knife radiosurgery in patients with arteriovenous malformations varied dramatically with location within the brain and volume of tissue receiving 12 Gy. Other studies suggest that “conformity,” the ability of the treatment to spare surrounding normal tissue, is an important predictor in radiation injury. The ratio of prescription volume (total treated volume) to target volume (treated tumor volume) is the conformity index. In radiosurgery, this index should be less than two (17).

The studies on the risk of radionecrosis from radiosurgery have reached the following conclusions: 1) the most important predictors of radionecrosis are tumor vol-
volume, treated volume, total dose, and conformity (see below); and 2) a subset of “vulnerable” patients develop radionecrosis at much lower levels than normally observed (1,18). Ongoing research is aimed at identifying these vulnerable patients to appropriately modify treatment (19).

Our patient had external beam radiotherapy (EBRT) before her gamma knife treatment, which increased her risk for radionecrosis. This variable is not included in the aforementioned studies. Stafford et al (24) evaluated the tolerance of the optic apparatus to gamma knife after stereotactic radiosurgery. Among 215 patients with benign tumors adjacent to the anterior optic apparatus treated with gamma knife radiosurgery, 23 had had previous EBRT with a mean dose of 50.2 Gy. One patient had EBRT in conjunction with radiosurgery. Three of the four patients who had radionecrosis after gamma knife radiosurgery had previous EBRT or concurrent EBRT. The authors concluded that the risk of radionecrosis in patients receiving a point dose of 12 Gy or less is 1%, but that the risk increases to 13% if the patient has had previous EBRT (24). Shaw et al (25) studied maximum tolerated doses of single fraction radiosurgery in patients with recurrent, previously irradiated primary brain tumors and metastases. In that study, 156 patients had received a median dose of 60 Gy from previous fractionated radiation therapy and were later treated with stereotactic radiosurgery. The patients were divided by tumor size: 1) small (less than 20 mm diameter with a median volume of 3.6 ml); 2) medium (21–30 mm diameter with median volume of 6 ml); and 3) large (31–40 mm diameter with median volume of 17.9 ml). The authors found that the maximum tolerable doses of single fraction radiosurgery in patients with previously irradiated tumors to be 24 Gy in small tumors, 18 Gy in medium-sized tumors, and 15 Gy in large tumors. These doses were prescribed to the 50% to 90% isoline, which encompassed the entire enhancing tumor volume. Patients with medium-sized tumors (21–30 mm) had 7.3-fold higher risk and those with large tumors (31–40 mm) had a 16-fold higher risk for unacceptable central nervous system toxicity than patients with small tumors (<20 mm) (25).

In our patient, the treatment plan (Fig. 4) covered the enhancing margins of the meningioma with 16 Gy at the 50% isoline. The maximum dose was 32 Gy, delivered to the center of the lesion, and the 25% isoline, which encompassed the occipital lobes, was 8 Gy. The tumor volume treated was 7.9 cm³; the perilesional tissue treated was 7.6 cm³. Thus, the total volume of tissue treated was 15.5 cm³. This volume received greater than or equal to 16 Gy. With
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a tumor volume of 7.9 mL, our patient would be included in the medium-sized tumor group of Shaw et al (25). By their calculations, the maximum tolerable dose would be 18 Gy to the 50% isoline, greater than the estimated 16 Gy dose she received. Thus, she received a “tolerable” dose as predicted by the aforementioned study. She did have, however, a 7.3-fold higher risk for radionecrosis than a patient with a smaller tumor.

At this time, there is no proven treatment of radionecrosis. There are several classes of drugs, all of which have been used with variable response. Corticosteroids have been used to decrease cerebral edema (1) and the production of cytokine release after radiation, but have not proven to change the clinical course of radionecrosis. Lazaroids (21-aminosteriods) are effective in animal models (5), but human data do not exist. Hyperbaric oxygen therapy is thought to be helpful by raising the tissue PO2 and initiating a cellular and vascular repair. One study based in Austria by Leber et al (20) evaluated the effects of hyperbaric oxygen therapy on two patients with signs of radionecrosis after gamma knife treatment. The two patients were treated by breathing 100% oxygen at 2.5 atm absolute for one hour each day, 40 times in cycles of 10 sessions. In this study, one patient had resolution of the radiographic findings of tissue injury, whereas the other had a reduction in the size of the damaged area. No corticosteroids were given to these patients (20). The efficacy of hyperbaric oxygen has been questioned by Brown et al (21) and Roden et al (22).

In summary, we present a case of radionecrosis of the occipital cortex resulting in visual field loss after gamma knife radiosurgery to a recurrent cerebellar tumor. We have reviewed the radiosurgical literature and applied predictive models to our patient to retrospectively assess her risk of this complication. The radiosurgical dose she received was within the predicted tolerable range but she carried a 7.3-fold increased risk of radionecrosis with this dose than that of a patient with a smaller tumor.

REFERENCES

Lack of Radiation Optic Neuropathy in 72 Patients Treated for Pituitary Adenoma

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Abstract: The incidence of radiation optic neuropathy (RON) after external photon beam radiation therapy for nonfunctioning pituitary adenoma (NFA) is not well-studied. Retrospective review of ophthalmological and imaging data in 72 patients with NFA treated between 1985 and 1998 with external beam radiation therapy after surgery. Clinical follow-up after radiation therapy had to be at least 18 months. RON was defined as a sudden and profound irreversible visual loss affecting the optic nerve or chiasm. A review of previously published cases of RON was then performed. In our cohort, no patient had RON. A total of 11 adequately documented series reports of RON were found in the medical literature on radiation-treated NFAs. The incidence of RON in NFA from these series is 0.53% (95% CI, 0.26%-0.96%). An additional 14 single RON cases have been reported, bringing the total of adequately documented RON cases to 25. RON is a rare complication after external beam radiation therapy for NFA.

(Pituitary adenomas account for at least 12% of all intracranial neoplasms (1). Their incidence is estimated to be 20 to 30 per million (2). Approximately 25% to 30% of patients with pituitary adenomas do not have a classic hypersecretory syndrome such as acromegaly, Cushing disease, or prolactinoma. Tumors that do not appear to secrete hormones are called nonfunctioning adenomas (NFA) (3). NFAs often present with signs of mass effect, such as visual changes, and symptoms of pituitary insufficiency (4).

Radiation therapy plays an important role in the treatment of NFAs. In the past, radiation therapy alone was the treatment of choice unless there were large visual deficits, in which case a craniotomy was performed to decompress the optic nerves and chiasm. With improving microsurgical techniques, the preferred treatment became neurosurgery followed by radiation therapy for extensive bulky lesions, histologically invasive adenomas, or incomplete excision (5). The routine use of postoperative radiation therapy in case of residual tumor is controversial (6–9); its use prevents regrowth of residual tumor in most cases, but it may cause such side effects as radiation optic neuropathy (RON) (10,11). The incidence of RON after external beam radiation therapy for NFA has not been well-documented. There is also debate as to whether patients with NFA are less likely to have RON develop after radiation therapy than those with growth hormone-secreting or adrenocorticotropic hormone-secreting pituitary adenoma (12–17).

The aim of this retrospective study was to discover the incidence of RON in a cohort of irradiated patients with NFA. Also, a review of previously published series and individual case reports is presented, from which an estimation of the incidence of RON in irradiated NFA can be deduced.

METHODS

In 2001, we conducted a retrospective investigation of the ophthalmological, neurosurgical, and radiation therapy records of 77 patients who had undergone surgery and external beam radiation treatment of NFA from 1985 to 1998 at the University Hospital, Groningen, The Netherlands (n = 52) and four regional institutions with equivalent radiation therapy protocols (n = 20).

The median age of our cohort at the start of radiation therapy was 52 years. The sex distribution was 41 males (57%) and 31 females (43%). All 72 patients were treated with a combination of surgery and radiation therapy. Sixty patients had one, ten patients had two, and one patient had four operations before radiation therapy. One patient had a second operation for tumor recurrence after operation and radiation therapy. Median ophthalmological follow-up time after radiation therapy was 51 months (range, 19–171 months). Total radiation dose ranged from 45 to 55.8 Gy.

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The daily radiation fraction size varied from 1.8 to 2 Gy. Median overall treatment time was 35 days (range, 30–42 days). The radiation fractionation schemes used were 45 Gy in 25 daily fractions \((n = 49, 68\%)\), 50 Gy in 25 daily fractions \((n = 9, 13\%)\), 50.4 Gy in 28 daily fractions \((n = 7, 10\%)\), 46 Gy in 23 daily fractions \((n = 6, 8\%)\), and 55.8 Gy in 31 daily fractions \((n = 1, 1\%)\). All radiation treatment fields were applied daily.

Patients were treated with linear accelerators with 4-MV photons \((n = 5)\), 6-MV photons \((n = 45)\), 8-MV photons \((n = 11)\), 10-MV photons \((n = 5)\), and 16- to 18-MV photons \((n = 6)\). A two-field opposed lateral technique was used in 10 patients, a three-field technique in 30 patients, a five-field technique in 20 patients, and a combination of these techniques in 22 patients. The most frequent combination was opposed lateral fields, followed by a three-field \((n = 13)\) or a five-field technique \((n = 5)\). In the time period 1985 to 1990, the radiation dose to the tumor was prescribed at the tumor encompassing isodose, and from 1991 to 1998 it was prescribed at a central point in the tumor according to the recommendations of the International Commission on Radiation Units and Measurements (ICRU) \((20)\).

Ophthalmological follow-up, defined as the period between the first day of irradiation and the last ophthalmological examination, had to be at least 18 months. Five patients were excluded because they were lost to follow-up before 18 months, reducing the cohort to 72.

Visual fields were obtained with Goldmann kinetic perimetry. The visual field data of all patients at diagnosis, after neurosurgery, radiation therapy, and in follow-up were reviewed by one neuro-ophthalmologist (J.-W.R.P.).

The diagnosis of RON was based on the criteria of Kline et al \((18)\) and Parsons et al \((19)\): 1) irreversible visual loss with visual field defects of optic nerve or chiasmal origin; 2) absence of visual pathway compression caused by recurrence or progression of tumor, radiation-induced neoplasm, arachnoidal adhesions around the chiasm, radiation retinopathy, or other ophthalmologic disease; 3) absence of optic edema; 4) optic disc pallor noted within six to eight weeks after onset of symptoms. The diagnosis of RON was also based on review of visual fields, visual acuity, and fundoscopic examinations in combination with brain imaging.

For our review of the published literature on RON, we performed a search of Medline between 1966 and May 2003 and a search of Embase between 1989 and May 2003. Key words were radiation optic neuropathy, nonfunctioning pituitary adenoma, and radiotherapy. All articles that included patients with NFA were checked for vision loss caused by radiation therapy. The references retrieved by Medline and Embase were screened for other references not found using the aforementioned key words.

To estimate the incidence of RON in NFA, we included only cohort series of patients in whom RON was studied. In reports that included functioning and nonfunctioning pituitary adenomas, we included only those in which the number of NFA and RON cases was reported. To evaluate risk factors for RON, we included only those cases from series and case reports in which radiation treatment data were available. Our calculations include our own series as well as previous reports. The 95% confidence interval was calculated assuming a binomial distribution.

RESULTS

In our cohort, no patient in the current study had RON diagnosed. One of 72 irradiated patients had spiraling isopters on Goldmann perimetry without visual acuity loss as late as 11 years after radiation therapy. Because of her unusual visual fields, Goldmann perimetry was repeated five times over a time period of 17 months with consistent spiraling. Funduscopic examination of both eyes revealed normal optic discs. Gadolinium-enhanced magnetic resonance imaging showed no pertinent abnormalities, such as high signal in the optic nerves or chiasm \((21)\). Visual-evoked potentials showed no amplitude reduction or latency increase with pattern stimulation. Two years later, the spiraling had disappeared and visual acuity remained normal. Although she was initially considered to have atypical RON \((22)\), this diagnosis was rejected when visual field defects normalized.

As shown in Table 1, we found 27 pertinent series of patients in whom the development of RON was considered. From these series, we calculated that 11 of 2,063 patients had RON, yielding an incidence of 0.53% \((95\% CI, 0.26\%–0.96\%)\). We found an additional 14 RON single-case reports in the literature, making a total of 25 cases.

In 16 of these cases, visual acuity loss was reported (Table 2). It was bilateral in nine patients \((56\%)\) and unilateral in seven patients \((44\%)\). Of the 25 eyes affected, 13 eyes \((52\%)\) had no light perception; two eyes \((8\%)\) had light perception; two eyes \((8\%)\) had hand movements; four eyes \((16\%)\) had a visual acuity between 20/800 and 20/100; and four eyes \((16\%)\) had a visual acuity better than 20/100.

In the 23 RON cases in which data were available, the peak latency between radiation therapy and the development of RON was between 12 and 18 months \((18)\) (Table 2). The median latency time was 11 months \((range, 2–54 months)\). Four patients \((16\%)\) had a latency period longer than 18 months.

In the 21 RON cases in which total radiation dose and radiation fraction size data were available, 14 patients \((67\%)\) received a total dose of more than 50 Gy and/or a daily fraction size more than 2 Gy. Of note, seven patients \((33\%)\) who had visual loss caused by RON were treated with a supposedly safe daily radiation fraction size and total radiation dose. Information was not available in most reports with respect to the ICRU 50/62 recommended \((20)\)
TABLE 1. Incidence of radiation optic neuropathy (RON) in reported series of irradiated patients with nonfunctioning pituitary adenomas

<table>
<thead>
<tr>
<th>Ref</th>
<th>Number of patients</th>
<th>Total radiation dose (Gray)</th>
<th>Fraction size (Gray)</th>
<th>Number of RON cases</th>
<th>Treatment period</th>
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<tr>
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<td>127</td>
<td>35</td>
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<td>0</td>
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<td>35–45</td>
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<td>0</td>
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<td>112</td>
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<td>120</td>
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<td>Sasak, 2000 (50)</td>
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<td>44–70</td>
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<td>Total</td>
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NA, not available.

minimum (95% of the prescribed dose) and maximum radiation doses (107% of the prescribed dose) to the optic system. In the 20 RON cases in which patient age or gender was reported, the median patient age was 54 years (with 12 patients being older than 50 years), and 12 (60%) cases were in women (95% CI, 36%–81%).

**DISCUSSION**

Based on the review of our cohort of 72 cases and the published literature, RON is a rare complication after external beam radiation therapy in patients with NFA. We found no case of RON in our cohort. Our literature review found a total of 11 adequately documented cases of RON in series reports of radiation-treated NFA patients for an overall incidence of 0.53%. This is significantly lower than the 1.36% incidence of RON in acromegalic patients (23) ($P = 0.01$; odds ratio 2.56; 95% CI, 1.26–5.22). One possible determinant contributing to the relatively increased incidence of RON in GH-secreting pituitary adenomas compared with NFAs is the occurrence of more microvascular damage in association with GH excess (12).

An additional 14 RON cases emerged from single case reports. Reviewing the total of 25 cases, we found that RON usually occurred between 12 and 18 months after radiation treatment but could occur after a considerably longer latency period. Previous reports do indicate that a
<table>
<thead>
<tr>
<th>Author (year or publication)</th>
<th>Gender</th>
<th>Age at diagnosis of RON (y)</th>
<th>Surgery</th>
<th>Total dose (Gy)</th>
<th>Fraction size (Gy)</th>
<th>Treatment time (d)</th>
<th>Latency of RON (mo)</th>
<th>Visual status to RON attributable</th>
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<tr>
<td>Crompton, 1961 (52)</td>
<td>F</td>
<td>56</td>
<td>Y</td>
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<td>F</td>
<td>41</td>
<td>N</td>
<td>45</td>
<td>2.25</td>
<td>32</td>
<td>6</td>
<td>OD: NFP</td>
</tr>
<tr>
<td>Harris, 1976 (24)*</td>
<td>M</td>
<td>62</td>
<td>Y</td>
<td>45</td>
<td>2.5</td>
<td>26</td>
<td>15</td>
<td>OD: NLP</td>
</tr>
<tr>
<td>Harris, 1976 (24)*</td>
<td>M</td>
<td>66</td>
<td>N</td>
<td>45</td>
<td>2.5</td>
<td>26</td>
<td>6</td>
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<td>Aristizabal, 1977 (12)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>2</td>
<td>OD: NLP</td>
<td></td>
</tr>
<tr>
<td>Martins, 1977 (53)</td>
<td>F</td>
<td>61</td>
<td>Y</td>
<td>67</td>
<td>2.25</td>
<td>37</td>
<td>33</td>
<td>OD: LP</td>
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<td>44</td>
<td>Y</td>
<td>65.8</td>
<td>2.2</td>
<td>46</td>
<td>13</td>
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<td>F</td>
<td>28</td>
<td>N</td>
<td>50</td>
<td>NA</td>
<td>35</td>
<td>14</td>
<td>OD: 20/20</td>
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<tr>
<td>Fitzgerald, 1981 (22)</td>
<td>F</td>
<td>65</td>
<td>N</td>
<td>50</td>
<td>NA</td>
<td>42</td>
<td>13</td>
<td>OD: 20/20</td>
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<tr>
<td>Fukamach, 1982 (55)</td>
<td>F</td>
<td>49</td>
<td>Y</td>
<td>50</td>
<td>2</td>
<td>35</td>
<td>10</td>
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<tr>
<td>Hammer, 1983 (15)</td>
<td>F</td>
<td>52</td>
<td>Y</td>
<td>42.5</td>
<td>2.8</td>
<td>21</td>
<td>13</td>
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<td>Kline, 1985 (18)</td>
<td>M</td>
<td>73</td>
<td>Y</td>
<td>50</td>
<td>2</td>
<td>38</td>
<td>12</td>
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<td>Kundra, 1990 (56)</td>
<td>M</td>
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<td>Y</td>
<td>55</td>
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<tr>
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<td>M</td>
<td>46</td>
<td>Y</td>
<td>55</td>
<td>2.2</td>
<td>NA</td>
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<td>Zimmerman, 1990 (57)</td>
<td>M</td>
<td>64</td>
<td>Y</td>
<td>50.4</td>
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<td>28</td>
<td>14</td>
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<td>F</td>
<td>56</td>
<td>Y</td>
<td>45</td>
<td>1.8</td>
<td>35</td>
<td>10</td>
<td>OD: NLP</td>
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<tr>
<td>Guy, 1991 (21)</td>
<td>M</td>
<td>51</td>
<td>Y</td>
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<td>2</td>
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<td>30</td>
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<td>Hudgins, 1992 (59)</td>
<td>F</td>
<td>75</td>
<td>Y</td>
<td>54</td>
<td>1.8</td>
<td>NA</td>
<td>35</td>
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<td>Saltel, 1992 (60)</td>
<td>F</td>
<td>40</td>
<td>Y</td>
<td>30</td>
<td>NA</td>
<td>NA</td>
<td>8</td>
<td>OD: 20/20</td>
</tr>
<tr>
<td>Hughes, 1993 (61)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>50</td>
<td>2.5</td>
<td>N/A</td>
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<td>Hughes, 1993 (61)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>50</td>
<td>2.5</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>McClellan, 1995 (62)</td>
<td>M</td>
<td>67</td>
<td>Y</td>
<td>45</td>
<td>1.8</td>
<td>36</td>
<td>3</td>
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<tr>
<td>Colao, 1998 (47)*</td>
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<td>N/A</td>
<td>Y</td>
<td>45</td>
<td>1.8</td>
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<td>Brezn, 1998 (48)*</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>50</td>
<td>2</td>
<td>N/A</td>
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</table>

Bold rows indicate patients in whom RON developed with "safe" radiation regimens.
F, female; M, male; Y, yes; N, no; VA, visual acuity; N/A, data not available.
*These references are also included in Table 1, because patient and treatment characteristics were available.
In some cases, visual acuity was documented as "normal," or when not normal, as attributable to a cause other than RON; for simplicity, 20/20 has been used in all such cases.
total radiation dose greater than 50 Gy and/or a daily radiation fraction size greater than 2 Gy are risk factors for developing RON (19,24), although RON can occur at lower doses (14,19).

In as many as 33% of reported cases, we could identify no risk factors related to radiation therapy. Older age has been touted as a possible risk factor for RON (25), but our series suggests that age is not a strong risk factor for developing RON in NFA, given the median age of 52 years at the start of radiation therapy among our patients. Our review also found no major gender predominance for the development of RON.

Based on these results, the current dose-fractionation policy in our department is 45 Gy in 1.8-Gy fractions for all pituitary adenomas. According to McCollough et al (26), there is no benefit in applying a higher total dose.

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   mophobe adenomas with megavoltage irradiation. Cancer 1973:35:
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Ophthalmic Artery Occlusion Secondary to Radiation-Induced Vasculopathy

Rita Singh, MD, Jonathan D. Trobe, MD, James A. Hayman, MD, and John P. Deveikis, MD

Abstract: A 35-year-old man with neurofibromatosis type 1 (NF1) had a left ophthalmic artery occlusion that caused no light perception OS 28 years after having been treated with external beam radiation therapy for a presumed glioma of the right optic nerve and chiasm. Clinical and imaging findings were consistent with radiation-induced cerebral vasculopathy. This ophthalmic complication has never been reported, despite the common occurrence of severe carotid–ophthalmic artery junction stenosis after radiation in NF1 patients. Even though modern radiation techniques limit collateral damage, this modality should be used with discretion in NF1 patients, given the vulnerability of their immature cerebral vasculature to radiation.

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CASE REPORT

A 35-year-old man had sudden painless visual loss OS. At age seven, NF1 and glioma of the right optic nerve and chiasm were diagnosed. He was treated with cobalt-60 external beam radiation to a minimal dose of 50 Gy in 2 Gy fractions over 33 days using right and left 5x5 cm retroorbital opposed lateral fields encompassing both optic nerves and the chiasm. His medical history included essential hypertension, well-controlled on an angiotensin-converting enzyme inhibitor. He had no other risk factors for arteriosclerosis.

Three days before his sudden visual loss OS, he had undergone a routine ophthalmic examination that had disclosed best-corrected visual acuities of 20/200 OD, 20/20 OS with an afferent pupil defect OD, and pale optic discs OU.

Three days after his acute visual loss OS, our examination disclosed a visual acuity of 20/200 OD and no light perception OS. An afferent pupil defect was present OS. Fundus examination of the OD showed a pale optic disc.
Fundus examination of the OS disclosed a diffusely cloudy white retina with a cherry red spot and "box-car" blood flow within the arterioles and veins (Fig. 1). His head had the "hour glass" deformity associated with hypoplasia of temporal bones because of treatment with radiation at a young age (Fig. 2). Neurological examination was normal.

Blood tests were negative for a hypercoagulability state. Magnetic resonance imaging (MRI) revealed enlargement of the right optic nerve (Fig. 3A) and chiasm (Fig. 3B), as well as focal increase in fluid attenuated inversion recovery (FLAIR) signal in the white matter of left temporal (Fig. 3C) and right basal frontal (Fig. 3D) lobes. Magnetic resonance angiography (MRA) suggested irregularities of the paracloïd carotid arteries and severe stenosis or occlusion of the left posterior cerebral artery, ambient segment. Catheter cerebral angiography (Fig. 4) confirmed that the right paracloïd internal carotid artery was 25% narrowed and that the left paracloïd internal carotid artery was 50% narrowed at the take-off of the ophthalmic artery. Both ophthalmic arteries were patent. There was abrupt occlusion of the left posterior cerebral artery. The right pericallosal artery was occluded and filled retrograde from leptomeningeal collaterals.

These angiographic abnormalities are compatible with radiation-induced vasculopathy. The patient was placed briefly on intravenous heparin and chronically on oral warfarin. Re-examination three months later revealed no change in visual function.

**DISCUSSION**

Twenty-eight years after conventional cobalt-60 external beam radiation for an anterior visual pathway glioma, our patient had complete loss of vision from ophthalmic artery occlusion in his only sighted eye. Given the angiographic findings, we presume that the primary cause is radiation-induced vasculopathy, with secondary contributions from his underlying NF1 and essential hypertension. This case is distinctive not only because of the extremely long interval between radiation and stroke but also because no such ophthalmic complication has been previously reported.

Radiation-induced cerebral vasculopathy has been documented in more than 50 reported cases (14-16). The majority of cases follow irradiation of tumors at the base of the middle cranial fossa in children aged younger than seven years. Angiographically, radiation-induced vasculopathy appears as steno-occlusive abnormalities of large intracranial vessels within the radiation field. In some cases, a rete of leptomeningeal collaterals bypasses the occluded trunk vessels to deliver blood to convexity cerebral arteries ("moya moya" pattern). Pathologically, radiation-induced vasculopathy appears as fibrous thickening of the intima with endothelial proliferation (17). Although many patients have acute, local neurologic deficits, others may not have stroke, their vascular abnormalities discovered on routine follow-up of their tumors or in the investigation of chronic cognitive deficits. Patients who have the "moya moya" pattern may be better-protected against stroke because they have collateral channels. Vasculopathy, transient ischemic attack, and stroke occur as early as five months and as late as 15 years after radiation, with 36
FIG. 3. The T1-weighted enhanced axial MRI shows thickened right optic nerve (A) and chiasm (B), consistent with anterior visual pathway glioma. There is a focal increase in fluid attenuated inversion recovery (FLAIR) signal in the white matter of the left temporal (C) and right basal frontal (D) lobes, consistent with radiation injury (arrows).

months being an average latency. Our case is a stand-out in that it occurred 28 years later. His systemic hypertension may have added to his vulnerability, but previous reports have not documented systemic hypertension as a risk factor for vascular complications of cranial radiation in NF1.

Nearly 50% of cases of radiation-induced vasculopathy occur in children irradiated for AVPGs. Perhaps this is because so many patients with AVPG also have NF1, which is associated with a greatly increased likelihood of this complication. Nonirradiated NF1 patients may have identical angiographic and pathologic vascular abnormalities (18), but they are far less common or severe than those in NF1 patients who have been irradiated. The presence of NF1 not only increases the likelihood of vasculopathy, it reduces the radiation dose needed to produce it (19,20).

Is this complication less likely to occur with modern imaging and radiation treatment planning and delivery methods, which can more accurately define the target lesion and limit the dose of radiation to surrounding critical structures? Older treatment machines and techniques, which account for most of the reported vascular complications, delivered a high dose of radiation to the carotid siphon. Because the energy of the radiation emitted by cobalt-60 is lower than the beams generated by modern linear accelerators, we would expect a lower dose to be delivered to the surrounding vasculature with modern methods. Proton beam therapy is ideally suited for this disease, given the relatively the discrete nature of the lesion and the ability to deposit a dose over a very short range because of the Bragg peak effect. The availability of MRI and software to accurately fuse computed tomography and MRI data sets now allows radiation oncologists to target the glioma itself,

FIG. 4. Cerebral angiogram. Lateral projections of right (A) and left (B) internal carotid injections show focal stenosis of paraclinoid segments of the internal carotid arteries (large arrows), which is worse on the left. The ophthalmic arteries (small arrows) are patent. There is occlusion of the ambient segment of the left posterior cerebral artery (*). Leptomeningeal collaterals from the right posterior cerebral artery reconstitute an occluded left pericallosal artery (C).
rather than a region encompassing the entire anterior visual pathway as was performed in this case. Improvements in hardware and software have also led to the use of three-dimensional conformal treatment techniques and optimized treatment plans that use intensity-modulated radiation therapy, both of which can achieve lower doses of radiation to surrounding normal structures (Fig. 5).

Given these advances in technique, the risk of a vascular complication would be significantly lower if such a patient were to undergo radiation treatment today. However, because of the proximity of these tumors to the vasculature and the possibility that even very low doses of radiation may cause vasculopathy (14,20), it is likely that the risk of such a complication in patients with NF1 will always exist. Chemotherapy should thus be used in place of radiation when young patients demonstrate growth of an AVPG or visual decline attributable to it (1). Radiation should be delayed as long as possible.

REFERENCES
Bilateral Anterior Ischemic Optic Neuropathy After Liposuction

Rod Foroozan, MD and Joseph Varon, MD, FACP, FCCP, FCCM

Abstract: A 30-year-old woman had bilateral anterior ischemic optic neuropathy after undergoing large-volume liposuction. Visual function remained stable over a four-month follow-up, with decreased visual acuity and marked constriction of the visual fields. To our knowledge, this is the second reported case of ischemic optic neuropathy in this setting.

(L Neuro-Ophthalmol 2004;24: 211–213)

Liposuction is one of the most commonly performed cosmetic procedures in the United States and is generally considered a safe procedure. However, serious complications, including fatalities, have been reported (1,2). We report a patient in whom visual loss from bilateral anterior ischemic optic neuropathy (AION) developed after liposuction. This is the second reported case of AION after liposuction.

CASE REPORT

A 30-year-old woman with a history of obesity (218 lbs [99 Kg], body mass index >35%) and hypothyroidism underwent high-volume tumescent liposuction and abdominoplasty. Preoperative blood pressure had been 121/77 mm Hg, pulse 79/min, and hemoglobin 13.9 g/dL.

The 4.5-hour procedure was performed under general endotracheal anesthesia, during which 22,000 mL of fat was removed. Her postoperative weight loss was 65 pounds (29.5 kg). The intra-operative blood pressure was 120/50 mm Hg for nearly the entire procedure. She was given 12,100 mL of tumescent fluid, which included 3 mL of epinephrine 1:1000 and 75 mL of 1% lidocaine, and 6700 mL of crystalloid fluid intravenously.

In the recovery room, she reported blurred vision, attributed to the effects of general anesthesia. At the time of her visual symptom, blood pressure was 90/56 mm Hg, and pulse was 116/min and regular. Vital signs remained essentially unchanged for the next 60 minutes. Systolic blood pressure remained between 100 and 110 mm Hg and diastolic blood pressure between 50 and 70 mm Hg for the remainder of the 24-hour hospital stay.

Four days later, she developed headaches and dyspnea; six days after that, she came to the emergency department. Blood pressure was 110/60 mm Hg, pulse was 100/min and regular, and respirations were 20/min. Spiral computed tomography of the chest revealed multiple pulmonary emboli. Duplex ultrasonography of the lower extremities revealed no venous abnormalities. She had thrombocytopenia (platelets 42,000/mm³) and anemia (hemoglobin 7.0 g/dL, hematocrit 21.6%). She was transfused with 2 units of packed red blood cells and transferred to the critical care service, where anticoagulation with heparin was initiated for the pulmonary emboli.

Ophthalmic examination revealed a near visual acuity of 20/70 OU. Pupils measured 8 mm in dim illumination and reacted sluggishly to light, with a left relative afferent pupillary defect. She was unable to identify any of the Ishihara pseudoisochromatic color plates with either eye and had inferior altitudinal visual field defects to confrontation. Bilateral pallid optic disc edema and hemorrhages were present within the retinal nerve fiber layer (Fig. 1). The remainder of the fundus examination was normal.

Magnetic resonance imaging and magnetic resonance venography of the brain revealed thrombosis of the right internal jugular vein, as well as the right transverse and sigmoid sinuses (Fig. 2). Hemoglobin was 9.5 g/dL and she received an additional 2 units of packed red blood cells. Lumbar puncture was not performed because of thrombocytopenia and the anticoagulation. Because of a concern that increased intracranial pressure might be present, she was started on acetazolamide, 500 mg twice daily.

One week later, distance visual acuity was 20/60 OU and pupils still showed a left relative afferent pupillary defect. Automated perimetry revealed dense inferior altitudinal and superior arcuate visual field defects OU. Two weeks later, visual acuity was 20/40 OU with sectoral pallor of the inferior portions of the optic discs OU. Visual fields were unchanged.
FIG. 1. Bilateral pallid optic disc edema and nerve fiber layer hemorrhages associated with bilateral visual loss 11 days after high-volume liposuction.

Four months after her initial examination, visual acuity was 20/50 OD and 20/60 OS with sluggishly reactive pupils and a left relative afferent pupillary defect. Automated perimetry revealed inferior altitudinal and superior arcuate visual field defects bilaterally (Fig. 3). Both optic discs were pale.

DISCUSSION

High-volume liposuction (>1500 mL of fat aspirated), as performed in this case, may be associated with a relatively high rate of morbidity and mortality (3). Pulmonary embolism, as occurred in our patient, is estimated to occur in 1:2000 patients undergoing liposuction and has been implicated in 20% of fatalities (2). Other complications have included viscus perforation, fat embolism, cardiopulmonary failure, deep venous thrombosis, infection, and hemorrhage (2,3).

Visual loss after liposuction is rare, with only one previous report (4). In that case, unilateral hypotensive anterior ischemic optic neuropathy occurred in a 47-year-old woman who underwent liposuction of the abdomen, thighs, and arms, and developed postoperative hypotension, tachycardia, and anemia (4). Visual loss developed OD on the second postoperative day and progressed to no light perception over the ensuing two days. Pallid optic disc edema was noted in the OD and the vision remained unchanged despite transfusion of 2 units of packed red blood cells. Magnetic resonance imaging and magnetic resonance angiography of the head were normal.

Bilateral visual loss from AION after high-volume liposuction developed in our patient in association with pulmonary embolism and dural venous sinus thrombosis. The timing of her visual symptoms, decreased visual acuity, dyschromatopsia, visual field defects, and the appearance of the pallid swelling of the optic discs were characteristic of the perioperative optic nerve infarction that occurs in the setting of anemia and hypotension (5). Venous sinus thrombosis also developed, a complication not previously reported in this setting. The pulmonary embolism and dural venous sinus thrombosis may have resulted from rapid and severe dehydration.

Although the earliest reports of liposuction recommended removal of no more than 1500 mL of fat, the introduction of epinephrine-containing wetting solutions has allowed larger volumes of fat to be aspirated. Removal of these larger volumes has generally been thought to be associated with an increased rate of complications, including fluid overload, pulmonary edema, lidocaine toxicity, deep venous thrombosis, and pulmonary embolism (6). Our patient underwent a large-volume removal of 22,000 mL of fat.

FIG. 2. Axial fluid attenuated inversion recovery (FLAIR) magnetic resonance imaging of the brain (A) reveals thrombosis within the right transverse sinus (arrow). Coronal contrast-enhanced T1-weighted magnetic resonance imaging (B) shows clot within the right transverse sinus resulting in the "empty delta sign" (arrow). Magnetic resonance venography (C) shows reduced or absent signal within the right internal jugular vein and the right transverse and sigmoid sinuses.
and was given 12,100 mL of tumescent fluid and 6700 mL of crystalloid fluid. These changes likely contributed to the ensuing hypotension and anemia that precipitated the bilateral AION.

REFERENCES

Evidence for a Probable Causal Relationship Between Tretinoin, Acitretin, and Etretinate and Intracranial Hypertension

Frederick W. Fraunfelder, MD and Frederick T. Fraunfelder, MD

Abstract: With the recognition that vitamin A and isotretinoin may cause intracranial hypertension, the authors reviewed 331 case reports of ocular side effects associated with the three other marketed retinoids: tretinoin, acitretin, and etretinate. The reports were drawn from the National Registry of Drug-Induced Ocular Side Effects, the World Health Organization (WHO), the Food and Drug Administration, and medical journals between 1979 and 2003. There were 21 cases of intracranial hypertension associated with these three retinoids, leading to an inference that they are probably causally related to intracranial hypertension by WHO criteria. The lack of positive rechallenge data precludes the inference of a definite causal relationship to intracranial hypertension by WHO criteria. The inference of an independent causal role of these retinoids is further cautioned by the fact that six patients were concurrently using tetracycline or minocycline. Even so, the data suggest that all retinoids may, in rare instances, cause intracranial hypertension.

In 2003, isotretinoin was placed in the World Health Organization (WHO) "certain" category for inducing intracranial hypertension (IH) because of positive rechallenge data, a characteristic pattern of rapid IH onset after exposure, and the fact that this agent is a degradative product of all-trans retinoic acid (ATRA; vitamin A), a known contributor to IH (2-6). Because ATRA and isotretinoin are now recognized as agents that can cause IH, we reviewed the case reports of ophthalmic side effects of other retinoids to ascertain if they too might cause IH. We selected all retinoids marketed in the United States for treatment of acne, as well as tretinoin, which is used to induce remission of leukemia. Only acitretin, tretinoin, and etretinate had complete case reports of associated IH.

METHODS

We hunted for case reports of ocular side effects related to retinoid therapy among reports submitted by physicians between 1979 and 2003 to the National Registry of Drug-Induced Ocular Side Effects (Portland, OR), WHO (Uppsala, Sweden), and the Food and Drug Administration (FDA; Rockville, MD). National Registry reports were sent spontaneously from physicians to the website (www.eyedrugregistry.com) or via mail to the Casey Eye Institute. WHO data were available to the authors, who were acting as WHO consultants. FDA reports were available through the Freedom of Information Act. We also reviewed medical journals for reports of retinoid-associated ophthalmic side effects over the past 20 years by searching Medline using the retinoid generic name and either "intracranial hypertension" or "pseudotumor cerebri" as keywords. Reports related to ATRA (vitamin A) and isotretinoin were not included.

We encountered 331 reports of ocular side effects and analyzed them for an association with IH. Tretinoin, acitretin, and etretinate were the only medications found to have an association with IH. We noted the age and gender of the patient, duration of therapy, dose of the retinoid, concurrent use of other medications, positive dechallenge (IH abated...
Intracranial Hypertension

when the retinoid was discontinued), and positive rechallenge data (IH recurred when the retinoid was restarted).

RESULTS

There were 21 case reports of retinoid-associated IH (Table 1). For acitretin, one case report came from the WHO and two from the FDA. For tretinoin, two reports came from the WHO and nine from the FDA. Etretinate had one case report submitted to the National Registry, one to the WHO, two to the FDA, and three from the medical journal literature. These data suggest that, in rare instances, retinoids may cause IH when used at prescribed therapeutic doses. Onset of symptoms (blurred vision, headache) occurred an average of two to three months after patients commenced therapy (range, five days to two years). From the available information, all but three cases of IH resolved within a few months after retinoid use was discontinued. There are no follow-up data. In six reports, patients were concurrently taking a tetracycline, a class of agents previously associated with IH.

DISCUSSION

Postmarketing surveillance systems suffer from underreporting, incomplete information, and lack of follow-up. These systems, however, provide information as to a temporal relationship, a pattern of presentation, relatedness to the use of the drug, and resolution of symptoms after withdrawal of the drug.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Source</th>
<th>Age</th>
<th>Gender</th>
<th>Concurrent medications</th>
<th>Dose of retinoid</th>
<th>Time from usage to onset of IH</th>
<th>Dechallenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acitretin</td>
<td>WHO</td>
<td>UNK</td>
<td>UNK</td>
<td>None</td>
<td>50 mg/d</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>FDA</td>
<td>40</td>
<td>F</td>
<td>None</td>
<td>50 mg/d</td>
<td>515 d</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>FDA</td>
<td>30</td>
<td>M</td>
<td>None</td>
<td>50 mg/d</td>
<td>Unknown</td>
<td>+</td>
</tr>
<tr>
<td>Tretinoin</td>
<td>FDA</td>
<td>24</td>
<td>M</td>
<td>Zidovudine</td>
<td>45 mg/m²/d</td>
<td>53 d</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>FDA</td>
<td>29</td>
<td>F</td>
<td>Trazodone</td>
<td>45 mg/m²/d</td>
<td>45 d</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>WHO</td>
<td>19</td>
<td>F</td>
<td>Minocycline*</td>
<td>45 mg/m²/d</td>
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<tr>
<td></td>
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<td>UNK</td>
<td>F</td>
<td>Minocycline*</td>
<td>45 mg/m²/d</td>
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<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>FDA</td>
<td>25</td>
<td>F</td>
<td>Tetracycline*</td>
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<td>+</td>
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<tr>
<td></td>
<td>FDA</td>
<td>30</td>
<td>F</td>
<td>Tetracycline*</td>
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<td>82 d</td>
<td>Unknown</td>
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<tr>
<td></td>
<td>FDA</td>
<td>31</td>
<td>F</td>
<td>Oral contraceptive</td>
<td>45 mg/m²/d</td>
<td>730 d</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>WHO</td>
<td>14</td>
<td>UNK</td>
<td>Tetracycline*</td>
<td>45 mg/m²/d</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>FDA</td>
<td>14</td>
<td>F</td>
<td>Sulfamethoxazole</td>
<td>45 mg/m²/d</td>
<td>Unknown</td>
<td>Unknown</td>
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<tr>
<td></td>
<td>FDA</td>
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<td>+</td>
</tr>
<tr>
<td></td>
<td>FDA</td>
<td>36</td>
<td>F</td>
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<td>0.75–1 mg/kg/d</td>
<td>5 d</td>
<td>+</td>
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<tr>
<td></td>
<td>WHO</td>
<td>44</td>
<td>F</td>
<td>Furosemide</td>
<td>0.75–1 mg/kg/d</td>
<td>90 d</td>
<td>Unknown</td>
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<tr>
<td></td>
<td>FDA</td>
<td>11</td>
<td>M</td>
<td>None</td>
<td>0.75–1 mg/kg/d</td>
<td>Same day</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>NR</td>
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<td>F</td>
<td>None</td>
<td>0.75–1 mg/kg/d</td>
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<td>+</td>
</tr>
<tr>
<td></td>
<td>Lit</td>
<td>67</td>
<td>F</td>
<td>Floctafenine</td>
<td>0.50–1 mg/kg/d</td>
<td>90 d</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Lit</td>
<td>75</td>
<td>F</td>
<td>Minocycline*</td>
<td>1.0 mg/kg/d</td>
<td>180 d</td>
<td>+</td>
</tr>
</tbody>
</table>

* Drugs reported to cause IH
UNK, unknown; +, positive dechallenge; −, negative dechallenge; NR, National Registry; WHO, World Health Organization; FDA, Food and Drug Administration; Lit, Medical journal literature.
TABLE 2. World Health Organization Causality Assessment of Suspected Adverse Drug Reactions

<table>
<thead>
<tr>
<th>Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certain</td>
<td>A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge)</td>
</tr>
<tr>
<td>Probable/likely</td>
<td>A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.</td>
</tr>
<tr>
<td>Possible</td>
<td>A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.</td>
</tr>
<tr>
<td>Unlikely</td>
<td>A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration that makes a causal relationship improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations.</td>
</tr>
<tr>
<td>Conditional/unclassified</td>
<td>A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data are essential for a proper assessment or the additional data are undergoing examination.</td>
</tr>
<tr>
<td>Nonassessible/unclassifiable</td>
<td>A report suggesting an adverse reaction that cannot be judged because information is insufficient or contradictory, and that cannot be supplemented or verified.</td>
</tr>
</tbody>
</table>

...and dechallenge and rechallenge data that may suggest possible, probable, or certain causation of an adverse drug event (7).

Based on our review, the temporal relationship of tretinoin, acitretin, and etretinate to symptoms and the overall pattern of IH in patients receiving these retinoids is similar to that described for isotretinoin and ATRA in previous published reports (2–6,8). The positive dechallenge data allow inference of a "probable" causal relationship of IH for these three agents, according to WHO criteria (Table 2). A "certain" causal relationship cannot be inferred because there is a paucity of dechallenge data. An independent causal relationship for these three retinoids must also be inferred with caution, because six of the patients were also using tetracycline or minocycline, agents previously causally implicated in IH (9,10).

For patients receiving retinoids, we suggest the following management guidelines: 1) prompt ophthalmologic consultation to rule out papilledema in patients using retinoid therapy in whom otherwise unexplained headaches or blurred vision develops; 2) periodic ophthalmologic consultation to rule out papilledema even in asymptomatic patients using retinoid therapy for six months or more because IH can develop without symptoms; and 3) avoidance of concomitant use of tetracyclines or vitamin A because they may potentiate the development of IH (11,12).

Acknowledgment

The authors are indebted to the national centers mentioned in this study that contributed data. The opinions and conclusions, however, are not necessarily those either of the various centers or of the WHO.

REFERENCES

Third Cranial Nerve Palsy From Midbrain Neurocysticercosis: Repeated Exacerbation on Tapering Corticosteroids

Ji Soo Kim, MD, Seon-Mi Jeong, BSc, So Young Moon, MD, and Seong-Ho Park, MD

Abstract: Third cranial nerve palsy is rare in neurocysticercosis and is usually caused by supratentorial or subarachnoid lesions with accompanying hydrocephalus or meningitis. We report a patient who presented with third cranial nerve palsy caused by neurocysticercosis involving the midbrain. The patient showed repeated exacerbation of symptoms on tapering corticosteroids. The experience with this patient indicates that tapering of corticosteroids should be performed very slowly in such cases.


The clinical manifestations of neurocysticercosis (NCC) are varied and depend on the topography, number, and size of the lesions, as well as the status of the host's immune response to the parasite (1). Common neuro-ophthalmological signs include papilledema, pupillary abnormalities, and nystagmus (2). Third cranial nerve palsy in NCC is rare (3,4), and is usually associated with supratentorial or subarachnoid lesions with accompanying hydrocephalus or meningitis (2,3). Only a small number of reports have described third cranial nerve palsy in patients with NCC involving the midbrain (5-7). We report such a case in which the third cranial nerve palsy recurred or became aggravated repeatedly upon tapering corticosteroids.

CASE REPORT

A 59-year-old man had diplopia and drooping of the lid OS. One day prior he had experienced blurred vision and an aching headache. He had no history of diabetes or hypertension.

Four days after symptom onset, examination showed ptosis OS. He had anisocoria, with the pupil OS 1.5 mm larger than the pupil OD. Pupillary response to light was impaired OS. Extraocular movements were normal OD. Abduction was normal OS, but adduction, supraduction, and infraduction were reduced to approximately one-third of the normal range (Fig. 1). Fourth cranial nerve function was considered normal OS because intorsion of the left eye was preserved on attempted downward gaze. The remainder of the examination was unrevealing.

Magnetic resonance imaging (MRI) of the brain revealed nodular lesions in the midbrain tegmentum and occipital pole, which were surrounded by ring enhancement and edema (Fig. 2). The results of testing undertaken to screen for malignancies, including tumor markers, ultrasonography of the abdomen, and computed tomography of the chest, were normal. Enzyme-linked immunosorbent assay for anticysticercal antibody in serum was negative. However, an examination of the cerebrospinal fluid showed a highly positive enzyme-linked immunosorbent assay for cysticercus of 0.41 (normal range <0.18), 8/mm3 of white blood cells, and 96 mg/dL of protein.

The patient was treated with praziquantel 50 mg/kg per day for 15 days and intravenous methylprednisolone, 1 g per day for six days. He experienced resolution of the headache and ptosis within five days. The adduction OS also improved to approximately two-thirds the normal range and infraduction to half the normal range. However, the impaired supraduction OS remained unchanged.

The intravenous methylprednisolone was changed into oral prednisolone 60 mg per day, which was tapered to 20 mg per day over the following 30 days. However, during the ensuing two months, the reduced ductions of other extraocular movements remained unchanged despite maintenance of
the prednisolone at 40 mg per day. Follow-up MRI, four months after the initial MRI, showed that the size of the lesion had decreased, but that a substantial amount of surrounding edema persisted (Fig. 3).

The patient received an another course of intravenous methyprednisolone (1 g/day) for five days, and the supraduction OU improved to one-quarter the normal range, while adduction and infraduction OS improved to approximately two-thirds and one-half the normal range, respectively.

He was placed on oral prednisolone 40 mg/d, which was tapered to 15 mg per day over the following two
months. Three days after tapering the prednisone to 15 mg per day, he revisited the clinic with worsening of ocular ductions OS. Examination showed no supraduction, infraduction, or adduction OS. He was treated with intravenous dexamethasone 16 mg per day for seven days and albendazole 1200 mg per day for 14 days. The intravenous dexamethasone was changed to prednisolone 40 mg per day and tapered by 5 mg every two weeks. The extraocular movements continued to improve. However, when the prednisolone reached 20 mg per day, the ptosis OS redeveloped, and on treating with intravenous dexamethasone 16 mg per day for four days, the ptosis disappeared. The dexamethasone was then replaced with prednisolone 35 mg per day. The prednisolone was tapered by 5 mg each month. Fifteen months after symptom onset, with prednisone 10 mg every other day, he displayed supraduction of one-half the normal range OU, infraduction OS up to two-thirds the normal range, and normal adduction OS. The pupil measured 3 mm OD and 4 mm OS with normal reaction to light OU.

The prednisolone was discontinued two months later without recurrence during the next two years.

DISCUSSION

Our patient met the diagnostic criteria of definite NCC, as proposed by Del Brutto et al (1). NCC, the most common helminthic infection of the central nervous system, is caused by the encysted larval stage of the tapeworm *Taenia solium* (1). The protean clinical manifestations of NCC are being increasingly recognized in industrialized countries.

Neuro-ophthalmological signs are usually caused by associated meningitis or hydrocephalus, and the recognition of these findings may provide a clue to the presence of serious neurologic disease (2). Hydrocephalus, found in 25% of NCC, is often accompanied by sixth cranial nerve palsy or optic neuropathy secondary to long-standing papilledema (2).

Third cranial nerve palsy, relatively rare in NCC, usually occurs because of brainstem compression by a supratentorial lesion or to meningitis with secondary hydrocephalus. Isolated third cranial nerve palsy from a midbrain parenchymal lesion has rarely been reported and is known to have a very high mortality (5–7). In our patient, the third
cranial nerve palsy worsened repeatedly on tapering corticosteroids. The initial impairment was confined to the OS and suggested the involvement of the left third cranial nerve fascicle. However, supraduction deficits of both eyes observed during the next examination indicated that the lesion extended into the opposite third cranial nerve nucleus or fascicle. The lesion might also have involved the supra-nuclear structures subserving upward gaze (8), but the lack of an improvement in supraduction with the doll’s eye maneuver in both eyes makes this possibility less likely.

The treatment of NCC remains a subject of debate. Most NCC patients have been treated with surgery, anti-helminthic drugs (albendazole or praziquantel), or corticosteroids. Corticosteroids have been used to reduce peri-lesional edema after surgical treatment or during anti-helminthic medical treatment (9,10). In our patient, whenever prednisolone was tapered to 15 to 20 mg per day, symptoms recurred or were aggravated, and resolved or improved promptly on increasing the prednisolone dose. We were able to avoid recurrence by tapering corticosteroids very slowly. Lui et al (11) and Corral et al (12) have also described a significant relationship between the rate of tapering of corticosteroids and symptom recurrence.

Although physicians are reluctant to use corticosteroids for extended periods because of their unacceptable side effects, these agents may be effective in patients with massive inflammation and surrounding edema. Our experience in this case also indicates that tapering of corticosteroids should be performed very slowly and carefully in NCC patients, especially when the lesions involve critical structures such as the brainstem.

REFERENCES
Elevated Intracranial Pressure Associated With Idiopathic Retinal Vasculitis, Aneurysms, and Neuroretinitis Syndrome

Matthew D. Hammond, MD, Thomas P. Ward, MD, Barrett Katz, MD, and Prem S. Subramanian, MD, PhD

Abstract: The idiopathic retinal vasculitis, aneurysms, and neuroretinitis (IRVAN) syndrome typically occurs in young patients and may produce multiple retinal macroaneurysms, neuroretinitis, and peripheral capillary nonperfusion. Optic disc edema has been described, but elevated intracranial pressure has not been previously documented. We report a case of a 12-year-old girl who presented with bilateral disc swelling and peripapillary hemorrhage. Brain magnetic resonance imaging (MRI) was normal, but lumbar puncture yielded an opening pressure of 360 mm H2O with normal constituents. Fluorescein angiography delineated saccular aneurysms of the retinal arteriolar vasculature, and IRVAN syndrome was diagnosed. MR venography disclosed poor filling of both transverse venous sinuses. Acetazolamide treatment of 14 months did not alter the fundus findings. IRVAN syndrome may present initially with optic nerve swelling and elevated intracranial pressure with subsequent development of the characteristic retinal vascular abnormalities.

(J Neuro-Ophthalmol 2004;24: 221-224)

A rare syndrome consisting of multiple retinal macroaneurysms, neuro-retinitis, and peripheral retinal capillary nonperfusion is known as the idiopathic retinal vasculitis, aneurysms, and neuroretinitis (IRVAN) syndrome (1–3). The vascular lesions are pathognomonic but uncertain cause. We report a case of IRVAN syndrome that had prominent disc edema, increased intracranial pressure as measured by lumbar puncture opening pressure, and dural venous sinus abnormalities. This is the first case to document elevated intracranial pressure.

CASE REPORT

A 12-year-old girl experienced intermittent blurred vision OU. Ophthalmologic examination disclosed a visual acuity of 20/20 OU, normal pupillary reactions, and indistinct optic disc margins OU. Three months later, optic nerve edema was apparent, associated with dilated parapapillary vessels and retinal hemorrhages in the posterior pole OU. Brain magnetic resonance imaging (MRI) and computed tomography (CT) scans were normal. Lumbar puncture yielded an opening pressure of 360 mm H2O with normal fluid constituents. The patient had no predisposing characteristics for idiopathic intracranial hypertension such as obesity, chronic obstructive pulmonary disease, or pregnancy, nor did she use contraceptive pills, tetracycline, or corticosteroids. Therapy was started with oral acetazolamide, 250 mg twice daily.

Examination one month later showed no change in visual function. Fluorescein angiography delineated saccular aneurysms of the retinal arteriolar vasculature. IRVAN syndrome was diagnosed and the patient was referred to our neuro-ophthalmology service for further evaluation of the persisting disc edema.

Our initial examination disclosed a normal blood pressure, visual acuities of 20/20 OU, normal color vision by Ishihara plate testing, and normal pupillary reactions. Ocular motility was full, and the patient was orthophoric at distance and near. The anterior segment examination was unremarkable. Ophthalmologic examination revealed mild anterior vitreous cells (small, pigmented, and immobile) without haze OU. Both optic nerves were moderately elevated with peripapillary edema (Figs. 1A and B). There were saccular aneurysmal dilatations present in the peripapillary retinal vasculature. IRVAN syndrome was diagnosed and the patient was referred to our neuro-ophthalmology service for further evaluation of the persisting disc edema.

Our initial examination disclosed a normal blood pressure, visual acuities of 20/20 OU, normal color vision by Ishihara plate testing, and normal pupillary reactions. Ocular motility was full, and the patient was orthophoric at distance and near. The anterior segment examination was unremarkable. Ophthalmologic examination revealed mild anterior vitreous cells (small, pigmented, and immobile) without haze OU. Both optic nerves were moderately elevated with peripapillary edema (Figs. 1A and B). There were saccular aneurysmal dilatations present in the peripapillary retinal vasculature OU. The maculae were flat with some mottling. There were aneurysmal dilatations at arteriolar bifurcations and prominent venous beading. Multiple intraretinal hemorrhages and a few nerve fiber layer hemorrhages were present in the temporal retinas OU (Figs. 1C and D). Choroidal neovascularization and retinal exudates and hemorrhages were present in the inferior periphery OU. The intraretinal hemorrhages appeared slightly increased compared with photographs taken one month earlier.
FIG. 1. Ophthalmoscopic findings of IRVAN syndrome. A: Optic disc edema, lipid deposition, and aneurysms OD. B: Optic disc edema, lipid, and hemorrhage OS. C: Retinal neovascularization OD (corresponds to Fig. 2A). D: Intraretinal hemorrhage, vascular sheathing, and vascular attenuation OD.

Additional evaluation with fluorescein angiography revealed vascular leakage around the optic nerves, vascular enhancement, saccular dilations, and peripheral retinal ischemia OU (Fig. 2). These dilatations were more obvious on the fluorescein angiographic study than by indirect ophthalmoscopy. Automated perimetry once again showed an enlarged blind spot OU, unchanged from studies one month earlier.

Lumbar puncture showed an opening pressure of 270 mm H₂O with normal fluid constituents. Complete blood count, Lyme antibody titer, anti-ds deoxyribonucleic acid, antinuclear antibodies, Sjögren-specific antibody A, Sjögren-specific antibody B, and anti-Smith antibodies, C3, C4, thyroid-stimulating hormone, RPR, and Bartonella titer were all negative.

The patient continued to deny headache or new visual changes. Her acetazolamide dose was increased to 1500 mg per day. Eight weeks later, disc edema appeared to be worsening. Magnetic resonance renography revealed that both transverse sinuses had incomplete filling (Fig. 3). However, the presence of an intramural thrombus could not be determined conclusively.

Serial examinations over the next several months showed no reproducible changes in visual function. Visual acuity remained 20/20 OU, and visual field testing by automated perimetry showed enlarged blind spots and a variable mean deviation over time, as evidenced by visual fields obtained six months and 14 months after presentation (Fig. 4). Disc edema was stable, and fluorescein angiography showed continued peripheral retinal ischemia with posterior pole aneurysmal vascular dilatations.

DISCUSSION

Our patient had the ocular manifestations of a syndrome first described by Kincaid and Schatz (1), now named the IRVAN syndrome (3). To date, only 20 cases of this syndrome have been reported (1–10), with 10 in a multicenter collaborative report (3). The most common ocular findings are the characteristic aneurysmal dilatations of the retinal and optic nerve head arterioles. Although these aneurysmal dilatations generally leak on fluorescein angiography, they do not have a predisposition to form subretinal, retinal, or vitreous hemorrhages (6,7). Peripapillary subreti-
Elevated Intracranial Pressure

FIG. 2. Fluorescein angiography. A: Retinal neovascularization and dye leakage nasal to optic nerve OD. B: Aneurysms and intraretinal microvascular abnormalities in the posterior pole OD. C, D: Peripheral retinal ischemia with capillary obliteration OD.

Vitritis has been reported in several cases and was present in our case. No specific pathogenic mechanism has been identified, although an inflammatory process, possibly autoimmune-mediated, has been postulated (4,8). It has been suggested that an inflammatory component may contribute to arteriolar wall weakening, which could lead to aneurysmal dilatation (8).

Treatment of IRVAN syndrome is problematic. Local and systemic corticosteroids have been shown to have little to no effect on disease progression (3,5,7,10), but analysis of their effect is confounded by other interventions. Panretinal photocoagulation of the ischemic retina has been associated with subsequent aneurysmal resolution (3,5,10). Capillary nonperfusion may be the most important factor in predicting vision loss (3), but data remain limited (6). Visual loss is usually secondary to complications of retinal neovascularization and may be severe despite aggressive therapeutic retinal photocoagulation or pars plana vitrectomy.

FIG. 3. Magnetic resonance venogram demonstrates incomplete filling of the transverse sinuses (arrows), the right greater than the left.
The case that we present illustrates a new aspect of the IRVAN syndrome: increased intracranial pressure. Elevated intracranial pressure has not been previously assessed in association with IRVAN syndrome, even though disc edema and prominent disc leakage on fluorescein angiography have been common findings in such patients. Two patients have been reported to have had normal cerebrospinal fluid contents but opening pressure was not described (3). Our patient’s disc edema failed to respond to acetazolamide therapy up to 2000 mg per day (with patient compliance noted through symptoms of tingling in the extremities and dysgeusia for carbonated beverages). In our case, intracranial venous obstruction appeared to be present, but we could not determine if this finding was primary or secondary to the elevated intracranial pressure (11–13). Although a recent study suggests a significantly higher incidence of MRV transverse sinus abnormalities in idiopathic intracranial hypertension patients (14), MRV may falsely indicate absent transverse sinus filling (15).

It is possible that the association between IRVAN syndrome and elevated intracranial pressure has gone unrecognized in previous reports, because opening pressures may not have been recorded. We therefore recommend that IRVAN patients with disc edema have measurement of their intracranial pressure in addition to assessment of their intracranial venous sinuses.

REFERENCES

Inferior Oblique Paresis, Mydriasis, and Accommodative Palsy as Temporary Complications of Sinus Surgery

Hiiseyin Bayramlar, MD, Murat Cem Miman, MD, and Soner Demirel, MD

Abstract: A 15-year-old boy had temporary hypertropia, supraduction deficit, ipsilateral mydriasis, and accommodative palsy after bilateral endoscopic ethmoidectomy, bilateral partial inferior turbinectomy, septoplasty, and Caldwell-Luc procedures for chronic sinusitis. Postoperative imaging did not disclose any intra-orbital abnormalities. The patient was treated with oral prednisolone 70 mg/day on a tapering schedule. Within two months, the ophthalmic abnormalities had resolved. This is the second report to describe such findings, which are attributed to damage of the inferior division of the third cranial nerve secondary to manipulation of adjacent ethmoid tissues.

The surgical drainage and removal of paranasal sinus tissue are common in the management of chronic sinusitis (1-3). The surgical approaches may be external or transnasal endoscopic, with both having the potential for orbital complications such as extraocular muscle injury or entrapment, enophthalmos, anisocoria, and even blindness (1-6).

We report a patient with postoperative temporary mydriasis, accommodation palsy, and inferior oblique paresis after sinus surgery. We believe this to be only the second case of such complications (5).

CASE REPORT

A 15-year-old boy reported chronic purulent rhinorrhea and nasal obstruction that was diagnosed as chronic sinusitis and nasal polyps. One year earlier, he had undergone bilateral endoscopic ethmoidectomy, bilateral partial inferior turbinectomy, septoplasty, and bilateral Caldwell-Luc procedures.

Because of the persistent symptoms, he underwent bilateral medial maxillectomy with revisions of the Caldwell-Luc procedures and excision of the recurrent polyps in the nasal cavities. On the left side, medial maxillectomy was performed successfully through external and transnasal endoscopic approaches. On the right side, it was difficult to find the ostium of the maxilla at the medial wall of the sinus just below the orbit because it was hypoplastic and obscured by intramaxillary fibrosis secondary to the previous surgery. Nevertheless, after removal of the nasal polyps in the right nasal cavity, natural ostium enlargement and inferior meatal antrostomy were performed successfully.

On awakening from anesthesia, the patient was noted to have anisocoria, and he reported blurred vision OD and double vision. On ophthalmologic examination, there was no periorcular ecchymosis or edema. Uncorrected visual acuity at distance was 20/30 OD (pinhole 10/10) and 20/20 OS. Visual acuity at near was 20/100 OD and 20/20 OS. The right pupil measured 7 mm; the left measured 3.5 mm in dim light. The right pupil did not constrict to direct light or a near target; the left constricted normally. The patient had an eight-prism diopter exotropia and a five-prism diopter left hypertropia in primary position and in left gaze. Supraduction OD was moderately reduced in elevation-induction (Fig. 1). Forced ductions were not performed.

Immediate computed tomography of the orbits and paranasal sinuses disclosed no abnormalities in the orbit; the medial and inferior walls were intact (Fig. 2). Magnetic resonance imaging of the orbit revealed no evidence of fluid accumulation or compression damage to the optic nerve or other intraorbital structures.

Postoperative mydriasis, accommodative palsy, and inferior oblique paresis OD caused by traumatic partial palsy of the inferior division of the right third cranial nerve were diagnosed. Oral prednisolone 70 mg daily was started to reduce postoperative edema.

On the seventh postoperative day, the diplopia was still present on left superior gaze. Near visual acuity OD had improved to 20/40. The right pupil had decreased to 4 mm in dim illumination. The patient was discharged on a tapering schedule of oral prednisolone (10 mg per week).

At four weeks after surgery, diplopia was present only in far left superior gaze. Near acuity had improved to 20/30 OD. The pupils were normal. At eight weeks after surgery, all abnormalities had resolved.
DISCUSSION

The anatomic proximity of the orbit to the adjacent sinuses exposes the orbital contents to trauma in sinus surgery. Despite this fact, relatively few ophthalmic complications have been reported (1-6). Freedman and Kern (7) reported only four minor orbital hemorrhages without visual loss in a series of 1000 consecutive intranasal ethmoidectomies. Stankiewicz (8) encountered six cases of orbital hemorrhages in a series of 90 endoscopic ethmoidectomies; in only one case did visual loss occur, and it was temporary. Maniglia et al (9) reported four cases of blindness after intranasal ethmoid sinus surgery; three cases resulted from severe orbital hemorrhages and one resulted from an orbital abscess. Griffiths and Smith (10) described two unilateral blindness cases, one from orbital cellulitis and the other from orbital hemorrhage. Other reported orbital complications are infraorbital nerve hypesthesia, diplopia caused by the injury of an extraocular muscle, enophthalmos, and permanent blindness from orbital hemorrhage, optic nerve transection, or impaction of bone against the optic chiasm during removal of a sphenoid osteoma (1-6,11-14).

Postoperative anisocoria is a rare consequence of endoscopic sinus surgery, which may result from injury to the parasympathetic fibers of the third cranial nerve. In our case, the patient had mydriasis, accommodative paresis, and inferior oblique paresis. To our knowledge, this is only the second case with such complications (5). Kosko et al (5) reported a patient with unilateral partial third nerve palsy.

FIG. 1. Our patient’s ocular motility on the first postoperative day. Note the right mydriasis, right exotropia, and left hypertropia in primary position, and reduced supraduction-in-adduction OD.

FIG. 2. Coronal computed tomography on the first postoperative day shows intact medial and inferior walls of the right orbit with a relatively hypoplastic right maxillary sinus. The other findings are a left medial maxillectomy, a right inferior meatal antrostomy, and blood and accumulated secretion at the floor of the nasal cavities.
Temporary Inferior Oblique Paresis

after bilateral sinus surgery. The authors stated that diplopia and anisocoria resolved two months after the surgery. They suggested that this complication most likely resulted from postoperative edema.

The anisocoria in our patient was also probably caused by perineural edema because of the disturbance of the inferior wall of the right maxillary sinus caused by intramaxillary manipulation during the revision of the Caldwell-Luc procedure or the surgical manipulation around the lamina papyracea while searching for the natural maxillary ostium. Postoperative imaging did not demonstrate any orbital or intracranial abnormalities. In such circumstances, as in our case, the patient can be reassured that the deficits are transient and that complete recovery may be anticipated within months. Postoperative anisocoria after sinus surgery may also result from spread of the local anesthetic agent, as in the case of Stewart et al (4). In that case, however, the anisocoria lasted only three to four hours.

REFERENCES

Effect of Age on the Pupillomotor Field

Ruediger Schmid, MD, FEBO, Per Ceurremans, Holger Luedtke, Barbara J. Wilhelm, MD, and Helmut M. Wilhelm, MD

Abstract: To differentiate physiologic variation from visual field loss with pupillomotor perimetry, the effect of age on the normal pupillomotor field must be known. Given the absence of reported data, the authors aimed to analyze the effect of age on the pupillomotor field as measured with light stimuli of different properties.

Subjects consisted of 23 healthy volunteers aged 20 to 28 years ("younger subjects") and 20 healthy volunteers aged 50 to 67 years ("older subjects"). Within a field of 20°, a sequence of 25 focal light stimuli was performed repeatedly on a monitor. The pupil light reflex (PLR) was recorded to stimuli of different diameter and luminance under mesopic conditions. The mean amplitude of the PLR was calculated for each stimulus location and condition.

Increasing stimulus luminance or size caused a larger PLR amplitude and a steeper decline of the PLR amplitude from the center to the periphery of the pupillomotor field. The older subjects had reduced mean PLR amplitude with a less pronounced decrease of PLR amplitude toward the field periphery. For the peripheral locations, the largest PLR amplitude was found in the temporal superior quadrants. There was considerable intra-individual test-retest variation in PLR amplitudes in younger and older subjects.

The PLR is markedly reduced in older compared with younger subjects. Older subjects have a relatively less pronounced central peak of sensitivity. There are intra-individual test-retest asymmetries in sensitivity within the normal pupillomotor field at any age. These findings must be considered in interpreting the results of pupillomotor perimetry.

Conventional perimetry is limited by the subjectivity of patient response, by poor fixation, and, in some cases, by poor understanding of the task. Pupillomotor perimetry is an objective method of investigating the visual field (1-3) that makes use of the pupil light reflex (PLR). It requires less patient attention, does not show any learning effect, and can indicate psychogenic visual field loss.

In pupillomotor perimetry, a small light stimulus is presented at several discrete locations in the visual field. The amplitude of the pupil's contraction to this stimulus is measured by means of infrared video-based pupillography. The mean amplitudes at the different stimulus locations result in the patient's pupillomotor field. In areas of visual field loss, the PLR is reduced compared with the PLR elicited within field areas of normal visual function. To judge the pupillomotor field of a patient, the profile in retinal sensitivity for the PLR in normal eyes must be known. Further, knowledge of the dependency of the pupillomotor field profile on age is crucial to differentiate physiological depressions of PLR sensitivity from field loss.

To our knowledge, the impact of age on the pupillomotor field has not been reported. We therefore investigated younger and older healthy subjects by pupillomotor perimetry with different kinds of light stimuli. The aim of the study was to determine the impact of age on the pupillomotor field and the influence of stimulus properties on the field profile in each age group.

METHODS

Subjects

We included 23 subjects aged 19 to 28 years (classified as "young") and 20 subjects aged from 50 to 67 years ("old"). There were 14 women and 9 men among the younger subjects, and 12 women and 8 men among the older subjects. All were healthy volunteers from whom informed consent had been obtained. The study followed the tenets of the Declaration of Helsinki. All subjects underwent a test of visual acuity, slit lamp and fundus examination, applanation tonometry, and swinging flashlight test. Normal results in all tests were required to enter the study. Bilateral mild lens opacities were allowed in the older group. Astigmatism was allowed up to ±5 diopters spherical...
Effect of Age on the Pupillomotor Field


equivalent. Corrected visual acuity was 20/20 or better for the younger and 20/25 or better for the older subjects.

Pupillography

Infrared video-based pupillography was performed with a device described in detail elsewhere (1). Light stimuli were generated on a computer screen at a distance of 30 cm from the subject’s eye. The luminance across the screen varied by approximately 3%. Before running the test, the monitor had to be switched on for 30 minutes and the subjects had then to adapt to the steady background luminance for 10 minutes. Within a visual field of 20°, a fixed sequence of 25 stimuli was performed four times to cope with intra-individual variation. Stimulus eccentricity was at 0, 5, 11, and 20° (Fig. 1). The stimulus was varied systematically between diameters of 2, 3, and 4° and luminance between 26 cd/m² and 54 cd/m² with a monitor background luminance of 1 cd/m². The stimulus interval was 2.4 seconds, with stimulus duration of 0.2 seconds. Total testing time was 4 minutes for each kind of stimulus. Only one eye was tested per subject. An infrared-sensitive camera linked to a frame grabber card recorded the direct PLR with a spatial resolution of 0.05 mm.

After artefact rejection, the contraction amplitude of the PLR was calculated from each recorded pupil trace. For artefact rejection, a smoothing of the raw data trace was performed and aberrant data were discarded. A pupil response had to occur between 200 and 500 ms after stimulus onset. The slope of the pupil tracing before onset of the light stimulus had to be less than 1 mm/s. During the light stimulus, the maximum difference between a single value and the mean of the pupil tracing had to be less than 0.3 mm and the slope during the stimulus had to be between 0.7 and 0.9 mm/second. Another restriction was applied to the whole PLR, requiring the standard deviation of the original curve (without outliers) and the smoothed curve to be less than 0.12 mm. To detect the minimum, five neighboring values were required to have a typical shape. The empirical values of these restrictions assured high-quality in determination of the PLR. No criterion was applied for the extent of the pupil response to avoid a distorted data distribution. When a discontinuity of the pupil trace (for example, blinking artefact) occurred during pupil contraction or stimulus presentation, this measurement was discarded.

Statistical Analysis

The position of the light stimulus in the visual field was defined by the eccentricity and by the angle ("phi") between the x-axis and a straight line connecting fixation mark and stimulus location. We could evaluate 93% of all stimulus responses. For evaluation, the OD results were transformed so that all eyes could be considered as the OS. A commercial software package (JMP 3.2.5; SAS Institute Inc, Cary, NC) was used for the statistics. A linear model was calculated with the contraction amplitude as response variable (ANOVA). The following factors were tested: age group, stimulus luminance, stimulus diameter, and, as random effect, the subject, nested within the age group. As co-variables, we included eccentricity and pupil resting size. The trigonometric functions of phi, sine phi, and cosine phi were used for the model as pairwise interaction terms eccentricity/sine phi and eccentricity/cosine phi, because phi, sine phi, and cosine phi are not steady functions at 0° (center of the visual field). Other pairwise interactions of the model were luminance/diameter, eccentricity/eccentricity, luminance/eccentricity, diameter/eccentricity, age group/eccentricity, age group/luminance, age group/diameter. Our model results in a continuous profile of the central visual field.

RESULTS

With increasing stimulus luminance and size, there was a larger pupil response across the pupillomotor field with a steeper decline of the PLR from the center to the periphery. Increasing stimulus size and luminance had a synergistic effect on raising the PLR amplitude. The extent of decline of the PLR amplitude from the center to the periphery of the field varied according to the angle phi. Older subjects had an overall reduced mean PLR amplitude. Increasing stimulus luminance or size resulted in a significantly larger increase of the mean PLR amplitude among the younger than the older subjects. The overall decline of PLR amplitudes from the center to the periphery was more pronounced for the young group (Table 1).
TABLE 1. Analysis of variance of pupillary light reflex amplitudes in younger and older healthy subjects

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum of squares</th>
<th>Mean square</th>
<th>Degrees of freedom</th>
<th>F ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group</td>
<td>11.4</td>
<td>11.4</td>
<td>1</td>
<td>10.22</td>
<td>0.0026</td>
</tr>
<tr>
<td>Stimulus size</td>
<td>51.2</td>
<td>25.6</td>
<td>2</td>
<td>1,239</td>
<td>0.0000</td>
</tr>
<tr>
<td>Stimulus luminance</td>
<td>48.1</td>
<td>48.1</td>
<td>1</td>
<td>2,328</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stimulus size*stimulus luminance</td>
<td>6.39</td>
<td>3.19</td>
<td>2</td>
<td>154.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Eccentricity</td>
<td>30.2</td>
<td>30.2</td>
<td>1</td>
<td>1,465</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Eccentricity squared</td>
<td>12.1</td>
<td>12.1</td>
<td>1</td>
<td>585.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Eccentricity*sine phi</td>
<td>11.2</td>
<td>11.2</td>
<td>1</td>
<td>544.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Eccentricity*cosine phi</td>
<td>28.7</td>
<td>28.7</td>
<td>1</td>
<td>1,389</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stimulus size*eccentricity</td>
<td>3.47</td>
<td>1.73</td>
<td>2</td>
<td>84.01</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stimulus luminance*eccentricity</td>
<td>4.12</td>
<td>4.12</td>
<td>1</td>
<td>199.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age group*stimulus size</td>
<td>2.19</td>
<td>1.09</td>
<td>2</td>
<td>53.10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age group*stimulus luminance</td>
<td>2.66</td>
<td>2.66</td>
<td>1</td>
<td>129.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age group*eccentricity</td>
<td>0.28</td>
<td>0.28</td>
<td>1</td>
<td>14.01</td>
<td>0.0002</td>
</tr>
<tr>
<td>Pupil resting size</td>
<td>0.88</td>
<td>0.89</td>
<td>1</td>
<td>39.05</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Subject (age group)</td>
<td>403</td>
<td>9.83</td>
<td>41</td>
<td>475.5</td>
<td>0.0000</td>
</tr>
</tbody>
</table>

* marks interaction of factors. The random effect "subject" is nested within the effect "age group," indicated by parentheses.

The raw data mean values and standard deviations for different eccentricities of the field are shown in Table 2. As an example, cross sections of the pupillomotor field at different angles for a stimulus diameter of 3° are shown for both age groups in Figure 2. For both age groups, the temporal pupillomotor field was more sensitive than the nasal field. The superior field was more sensitive than the inferior field. Based on the model, the amplitudes of the PLR across the pupillomotor field had a maximum at an angle of 148° (within the temporal superior quadrant). A three-dimensional plot of the modeled pupillomotor field is shown as an example in Figure 3.

Intra-individual variation was considerable. The single PLR amplitudes of one younger and one older subject are shown in Figure 4.

DISCUSSION

Stimulus Properties

In this study, the higher stimulus intensities better revealed the differences in sensitivity of the pupillomotor field, despite the inevitable increase in local retinal light scatter. However, the highest stimulus intensity used here (54 cd/m²) still was relatively dim. With a stimulus luminance of 26 cd/m² and a stimulus diameter of 3°, the PLR was close to the noise level for most peripheral stimulus locations. For the 2° stimulus, this was even true for some peripheral locations when a luminance of 54 cd/m² was applied.

Stimulus intensity increases with both size and luminance. For the pupillary system, larger receptive fields of the retinal ganglion cells and more extensive spatial sum-

TABLE 2. Mean pupillary light reflex amplitudes in young and old subjects at four eccentricities and for different combinations of stimulus size and luminance

<table>
<thead>
<tr>
<th>Size</th>
<th>Lum</th>
<th>Young</th>
<th>Old</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0°</td>
<td>5°</td>
<td>10°</td>
</tr>
<tr>
<td></td>
<td>Ampl</td>
<td>SD</td>
<td>Ampl</td>
</tr>
<tr>
<td>2°</td>
<td>0.35</td>
<td>0.16</td>
<td>0.22</td>
</tr>
<tr>
<td>54</td>
<td>0.50</td>
<td>0.22</td>
<td>0.39</td>
</tr>
<tr>
<td>3°</td>
<td>0.46</td>
<td>0.22</td>
<td>0.36</td>
</tr>
<tr>
<td>54</td>
<td>0.68</td>
<td>0.21</td>
<td>0.54</td>
</tr>
<tr>
<td>4°</td>
<td>0.55</td>
<td>0.18</td>
<td>0.43</td>
</tr>
<tr>
<td>54</td>
<td>0.81</td>
<td>0.31</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Lum, luminance; Ampl, amplitude.

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FIG. 2. The cross-sections of the pupillomotor field with a stimulus diameter of 3°. Mean PLR amplitudes ± SD (raw data) are shown for each stimulus location at a certain cross-section for the young and for the old group. The x-axis runs from the inferior field toward the superior field. A: The field profile at the four different angles ("phi") indicates a stimulus luminance of 26 cd/m². B: The field profile indicates a stimulus luminance of 54 cd/m².
Age Dependency of the Pupillomotor Field

The age of the subject had a clear impact on the pupillomotor field. For the older subjects, the amplitudes of the PLR across the pupillomotor field were globally reduced. The question arises whether this is caused by reduced responsiveness of the pupillomotor system with age, neuronal cell loss, increased media opacities, or decreased pupil size. The known decline of pupil size with age (5), which was found in our study population, will reduce retinal illumination to some extent. The difference in mean pupil resting size between both groups of subjects will reduce the retinal light flux for the old subjects. Because the PLR amplitude is proportional to the logarithm of the retinal light flux in a suprathreshold range, the PLR will be reduced. However, a smaller pupil will increase retinal sensitivity to a certain extent because of adaptation. Hence, it is difficult to weigh both effects on the PLR. In the present experiment, a small relationship was found between pupil resting size and contraction amplitude, but it is not possible to separate this statistically from the age effect already discussed.

Iris mechanics of the smaller pupil (6) did not have a substantial impact on the pupil's contraction here because the mechanical limit generally was not reached. A decrease in efficiency of the focal light entering the eye by cataract or vitreous clouding was unlikely to have caused a reduction of the PLR in the older subjects, as their visual acuity still was at least 20/25. It is well-established that mild media opacities generally do not reduce the PLR. With the swinging flashlight test, they may even increase the PLR in the affected eye. However, reduced neuronal sensitivity may be the principal mechanism behind the present findings. A loss of neuronal population has been described at most levels in the aged human visual system (7). Most reports indicate that axon density of the optic nerve decreases significantly with age (8,9).

Comparison to Age-Related Findings in Psychophysics and Electrophysiology

A decreased retinal sensitivity in older subjects has been shown for the normal central visual field by different methods of perimetry (10–15). An age-related decrease in differential light sensitivity, as well as in flicker sensitivity for higher frequencies, have been seen mainly in the superior parts of the field (11–13,16).

In our study, the decrease of sensitivity from the center to the periphery was less pronounced in the older subjects. One could attribute this to light scatter because of cataract or vitreous clouding (17). If so, the more peripheral stimuli might have been relatively more effective because of some scattered light reaching the fovea. Yet these differences were subtle. For the visual field, most studies have reported a steeper decline of differential light sensitivity toward the periphery with age (13,14,16). This corresponds to a more accelerated loss of peripheral photoreceptors and ganglion cells compared with central cones in aging (18,19).

In the multifocal electroretinogram (mERG), an age-related loss of amplitude and an increase in implicit time has occurred without major changes in the topography of implicit times (20). In pattern ERG, consistently lower amplitudes in older subjects have been demonstrated (21,22). These could not be explained by differences in retinal image quality but were attributed to age-related neurophysi-
Effect of Age on the Pupillomotor Field


FIG. 4. A cross-section of the pupillomotor field at an angle of 157.5°. It shows the single PLR amplitudes for one younger subject and for one older subject with a stimulus luminance of 54 cd/m² and a stimulus diameter of 3°. The substantial intra-individual test-retest variation in PLR amplitudes is apparent.

ological changes in the retina (21). In full-field electroretinogram, decreasing cone and rod b-wave amplitudes have been found with age, whereas an increase in implicit time is disputed (23,24). Age-related increases in VEP latency seem to depend on the properties of the stimulus. Postretinal mechanisms have been postulated as an explanation for these phenomena (21). With pupillomotor perimetry, the entire visual system is investigated (2,25,26). The neuronal mechanisms of the PLR might be different from those tested by psychophysics or electrophysiology.

Characteristics of the Pupillomotor and Visual Field Profile

There are no reported major inter-eye differences in the retinal sensitivity for the PLR in the same individual (27). Therefore, we investigated the pupillomotor field OD or OS by arbitrarily transforming the results into a field OS. As expected, there was an increase of the mean PLR with increasing stimulus intensity. For both groups of subjects and for all stimulus properties, the asymmetries in sensitivity for the normal pupillomotor field were subtle and showed a similar general profile. There was a peak of sensitivity in the center of the field. More peripherally, the greatest pupillomotor sensitivity was found in the superior temporal field and the lowest in the inferior nasal field, consistent with previous findings (1,3). These results are only partly in accord with asymmetries found in the normal perceptive visual field. A higher sensitivity of the inferior hemifield compared with the superior field has been reported for computer perimetry (10,13–16). The nasal-temporal asymmetry is controversial; most conventional perimetric or psychophysical studies have shown a higher sensitivity for the temporal hemifield (14,15,28). Greater sensitivity of the temporal hemifield is expected because of the higher density of photoreceptors and ganglion cells reported for the nasal retina (29–31).

The retinal ganglion cells involved in the pupil light reflex may be at least partly different from those integrated within the visual pathway (2,4,32). Thus, pupil perimetry seems to be a valuable and differential complement to visual field testing. The normal asymmetries of the pupillomotor field, although statistically significant, are very subtle compared with clinical findings of a pupillomotor field defect (2,3,32). Nevertheless, these asymmetries have to be considered when investigating a patient’s pupillomotor field.

Acknowledgment

The authors thank Professor Steven E. Smith, London, England, for valuable comments on the manuscript.

REFERENCES


Optic Nerve Enhancement in Hypotensive Ischemic Optic Neuropathy

Michael S. Vaphiades, DO

FIG. 1. Axial (A) and coronal (B) T1 postcontrast fat-suppressed orbital MRIs performed eight weeks after coronary artery bypass surgery at the time blindness was first identified. The scans show enhancement of both optic nerves.

Abstract: A 57-year-old woman who had hypotension and cardiac arrest during coronary artery bypass grafting developed hypotensive ischemic optic neuropathy with no light perception vision OU. Bilateral mid-orbital optic nerve enhancement was found on magnetic resonance imaging (MRI) eight weeks after surgery. Re-examination 16 weeks after surgery showed no light perception vision, dilated unreactive pupils, and pale optic discs. Bilateral optic nerve enhancement persisted on MRI. Optic nerve enhancement has been reported commonly in radiation-induced ischemic optic neuropathy, occasionally in arteritic ischemic optic neuropathy, and rarely in nonarteritic ischemic optic neuropathy. It has never been reported in hypotensive ischemic optic neuropathy.


A 57-year-old woman with a 34-year history of diabetes mellitus underwent coronary artery bypass grafting. During the procedure, hypotension developed, she had a cardiac arrest, and she was placed on a ventilator for several weeks. She was unconscious except for a brief period of time during the first week on the ventilator, when the patient reported that she could see normally. After eight weeks on the ventilator, when the patient regained consciousness, she reported being blind OU. She was examined by the staff ophthalmologist, who noted no light perception vision OU without response to the optokinetic drum or mirror test. The pupils were fixed and dilated at 6 mm OU. The intraocular pressures were normal and there was very mild optic nerve pallor without edema OU. The retina appeared normal.

Magnetic resonance imaging (MRI) showed mid-orbital optic nerve enhancement bilaterally (Fig. 1). Complete blood count, metabolic panel, antinuclear antibody, and angiotensin-converting enzyme were normal.

On re-examination 16 weeks after surgery, she was alert with a normal mood and affect. She affirmed that her vision had been normal before the surgery. Visual acuity remained no light perception OU and the pupils were fixed and dilated at 6 mm OU. Fundus examination disclosed markedly pale optic discs. Repeat MRI showed persistent optic nerve enhancement OU (Fig. 2). Intravenous high-dose methylprednisolone, 1 g per day for three days, did not improve vision. Her examination was unchanged at 20 weeks after surgery.

The visual loss in this patient resulted from posterior ischemic optic neuropathy (1-4) presumably related to hypotension. The unusual feature is the presence of optic nerve enhancement on MRI and its persistence 16 weeks...
FIG. 2. Axial precontrast (A) and postcontrast (B1, B2) and coronal precontrast (C) and postcontrast (D) T1 fat-suppressed orbital MRIs performed 16 weeks after coronary bypass surgery. They show persistent enhancement of both optic nerves. (B1 and B2, representing different axial levels, are both shown to best visualize each optic nerve.)

after the inducing event. There have been no reported cases of optic nerve enhancement in patients with hypotensive ischemic optic neuropathy. It has been described frequently in posterior ischemic optic neuropathy (PION) after intracranial radiation therapy (5). Lee et al (6) have reported it in three patients who had arteritic AION (AAION). The scans for their cases were performed within three weeks of the visual loss. Rizzo et al (7) reported, but did not display, optic nerve MRI enhancement in two (6%) of 32 patients with non-arteritic anterior ischemic optic neuropathy (NAION). The scans were performed within 20 days of visual loss. By contrast, 30 (97%) of 31 patients with optic neuritis in that study displayed enhancement of the optic nerve. The authors pointed out that optic nerve enhancement is a useful way to distinguish optic neuritis from NAION.

Enhancement reflects marked compromise of the blood–brain barrier, a phenomenon that apparently occurs rarely in NAION, may occur in AAION, and often occurs in PION after intracranial irradiation. It is reported here for the first time in hypotensive ION. In this latter condition, the breach in the blood–brain barrier may evidently persist for at least four months, as this case exemplifies.

REFERENCES

Superior Oblique Myokymia Caused by Vascular Compression

Masato Hashimoto, MD, Kenji Ohtsuka, MD, Yasuo Suzuki, MD, Yoshihiro Minamida, MD, and Kiyohiro Houkin, MD

Abstract: A 49-year-old man had left superior oblique myokymia for eight years. Magnetic resonance images with enhanced spoiled gradient recalled acquisition in the steady state (SPGR) and flow imaging using steady acquisition (FIESTA) disclosed a branch of the superior cerebellar artery lying on the root exit zone of the left trochlear nerve.
A 49-year-old man presented with an intermittent "fluttering" sensation OS lasting for several seconds per episode and occurring repeatedly for eight years. Slit-lamp examination showed intermittent intorsional microtremor OS, diagnosed as left superior oblique myokymia. Conventional magnetic resonance imaging of his brain showed no abnormalities. Medical treatments such as carbamazepine and baclofen provided only short-term relief. His symptoms gradually worsened, disabling him from his job as a truck driver.

To evaluate the brain stem in more detail, we used special magnetic resonance imaging sequences using enhanced spoiled gradient recalled acquisition in the steady state (SPGR) and flow imaging using steady acquisition (FIESTA). These sequences yield high-resolution images of very small structures surrounded by cerebrospinal fluid and very small vessels (1). Thin-slice (0.4 mm) sections showed the proximal cisternal segment of the left trochlear nerve at its root exit zone with a branch of the superior cerebellar artery lying on top of it (Fig. 1).

The patient elected to have a neurosurgical exploration of his left trochlear nerve. The root exit zone of the left trochlear nerve was exposed via a retrosigmoid approach. On the dorsal surface of the brain stem, a dorsal branch of the superior cerebellar artery was found to be compressing the trochlear nerve (Fig. 2A). The arterial branch was pushed aside (Fig. 2B) and small pads of Teflon were placed between the nerve and vessels (Fig. 2C).

When the patient awakened after surgery, his superior oblique myokymia was gone and has not recurred during a one-year follow-up. Immediately after surgery, the patient had a mild left trochlear nerve palsy that resolved completely in three months.

Superior oblique myokymia, as termed by Hoyt and Keane (2) in 1970, is an acquired abnormality of superior oblique muscle innervation causing episodic torsional oscillation of an eye. In 1983, Bringewald (3) postulated that it resulted from vascular compression of the trochlear nerve. However, there has been only one reported case of compression of the trochlear nerve by vessels (4,5). Samii et al (4) and Scharwey and Samii (5) described a patient who had superior oblique myokymia for 17 years. The interposition of a Teflon pad between the trochlear nerve and a compressing artery and vein at the nerve’s exit from the midbrain led to a remission lasting for a follow-up of 22 months. Their patient also experienced temporary (five-month) ipsilateral trochlear nerve palsy. The surgical photograph of that case is similar to ours.

Our patient differs in two ways from the previously reported case (4,5). First, we were able to identify by visualization at surgery that a branch of the superior cerebellar artery was the vessel compressing the trochlear nerve. Second, we were able to show the corresponding imaging abnormalities.

Pathophysiologically, vascular compression syndromes such as hemifacial spasm or trigeminal neuralgia are hypothesized to develop because the junctional area between central and peripheral myelin is particularly vulnerable to continued pulsatile pressure. This pressure is believed to result in focal demyelination and in a short-circuiting of efferent nerve impulses. Fraher (6) observed
histopathologically that the transitional zone between central and peripheral myelin in the trochlear nerve lies at its root exit zone. In our patient, an artery compressed the trochlear nerve at this transitional zone.

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PHOTO ESSAY

Bilateral Orbital Metastases from a Neuroendocrine Tumor

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Abstract: When neuroendocrine tumors metastasize to the orbit, they usually do so as solitary lesions, sometimes involving an extraocular muscle. A 70-year-old woman with a known neuroendocrine tumor had bilateral painful proptosis, orbital soft tissue swelling, and ophthalmoplegia. Imaging showed masses within all the extraocular muscles. Orbital biopsy disclosed metastatic neuroendocrine tumor cells within the connective tissue.

(A) 70-year-old diabetic woman presented with a two-week history of diplopia, increasingly prominent eyes, and bilateral periorbital pain. Visual acuity was 20/30 OU with normal color vision. The eyelids and conjunctiva were injected and edematous. There was bilateral proptosis. Eye movements were limited in all directions. Orbital computed tomography showed enlargement of all extraocular muscles bilaterally, particularly the medial and inferior recti and the left superior oblique (Figs. 1A and B). On precontrast orbital magnetic resonance imaging, the enlarged muscles had intermediate signal on T1-weighted images with foci of higher signal. After contrast, multiple ovoid areas within the extraocular muscles enhanced less than the surrounding tissue (Figs. 1C through E).

Six months previously, the patient had presented with abdominal pain. Liver biopsy had shown deposits of a
neuro-endocrine tumor but no primary tumor could be identified. Two months before onset of the orbital symptoms, $[^{111}\text{In}]$ octreotide and $[^{123}\text{I}]$ meta-iodobenzylguanidine (mIBG) scans (Fig. 2) had shown uptake in the abdomen and in both orbits.

Full-thickness biopsy of the belly of the right medial rectus muscle showed only interstitial edema and nonspecific inflammation. Adjacent orbital connective tissue showed cuboidal cells whose cytoplasm stained strongly with chromogranin (Fig. 3) and more weakly with synaptophysin, a pattern identical to that found in the earlier liver biopsy.

Orbital metastases from neuroendocrine tumors are rare, accounting for no more than 5% of orbital metastatic disease, and usually arising from gastrointestinal primary tumors whereas uveal metastases are associated with a broncho-pulmonary source (1). Orbital disease may be the initial manifestation of the systemic disease or become evident up to 20 years after diagnosis of the primary tumor (2,3). Usually the orbital metastasis consists of a unilateral solitary lesion, often involving an extraocular muscle, and resulting in proptosis, limitation of eye movements, and optic nerve compression (4).
A presentation with metastases arising in both lateral recti has been reported (5). Acute orbital inflammation is rare but may result from a solitary deposit (6). Disease arising simultaneously within all the extra-ocular muscles of both orbits and presenting as bilateral orbital inflammatory disease, as our case demonstrated, has not been reported previously. The imaging findings in our case were unusual in showing heterogeneous signal on T1-weighted sequences; previous reports have noted isointense signal on T1-weighted sequences. (7,8)

$[^{111}\text{In}]$ octreotide and $[^{123}\text{I}]$ mIBG scans identify loci of neuroendocrine tumors, including orbital metastases, but they are not specific for neoplastic lesions (7,9). Orbital uptake of $[^{111}\text{In}]$ octreotide occurs in active dysthyroid eye disease and to some extent in normal orbits (10). Physiological orbital uptake of $[^{123}\text{I}]$ mIBG does not occur.

Another surprising feature of this case is that orbital biopsy disclosed tumor cells in the connective tissue but not in the medial rectus muscle, despite the striking intramuscular abnormalities on imaging.

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THE THIRD HOYT LECTURE

William Fletcher Hoyt, MD, professor emeritus of Ophthalmology, Neurology, and Neurosurgery, University of California, San Francisco, was born and raised in Berkeley, California. He took his undergraduate education at the University of California, Berkeley, and his medical education at the University of California, San Francisco (UCSF). After a year’s study at the Wilmer Institute, Johns Hopkins University, under the mentorship of Frank B. Walsh, MD, he returned to UCSF in 1958 to found the neuro-ophthalmology service. During a 36-year academic career—all of it at UCSF—he authored 266 journal articles, co-authored (with Frank B. Walsh, MD) the biblical third edition of Clinical Neuro-ophthalmology, and trained 71 neuro-ophthalmology fellows. In 1983, he received the title of Honorary Doctor of Medicine from the Karolinska Institute. He is widely acknowledged as one of the titans of twentieth century neuro-ophthalmology. In recognition of his contributions, the North American Neuro-Ophthalmology Society (NANOS), in conjunction with the American Academy of Ophthalmology, in 2001 initiated the Hoyt Lecture to be delivered each year at the Annual Meeting of the American Academy of Ophthalmology.

Friendly Fire: Neurogenic Visual Loss From Radiation Therapy

Simmons Lessell, MD

Abstract: The author’s experience and review of the medical literature suggest that radiation-induced neurogenic visual loss presents on average 18 months after treatment and usually after cumulative doses of radiation that exceed 50 Gy or single doses to the visual apparatus of greater than 10 Gy. Visual loss may result from lesions of the disc, retrobulbar segment of the optic nerve, optic chiasm, or retrogeniculate pathways. Magnetic resonance imaging, the best means of demonstrating radiation injury to the visual pathway, may show abnormalities before the loss of vision. The second eye may show clinical manifestations of optic neuropathy many months after the diagnosis in the first involved eye. Spontaneous improvement in visual function may rarely occur. Treatment has been disappointing, but if visual dysfunction is detected early, hyperbaric oxygen might be beneficial. The risk of neurogenic visual loss must be factored into the decision to irradiate the brain.


The speed at which medical innovations are currently disseminated may seem unparalleled, but in the mid-1890s physicians were adopting new technologies with surprising alacrity. The application of ionizing radiation is a case in point. Within months of Roentgen’s 1895 discovery of x-rays, they were being used for diagnosis, and within 12 years for the treatment of brain tumors (1). In the modern era, ophthalmologists and other physicians responsible for the management of patients with brain and orbital tumors often use ionizing radiation as primary or adjunctive therapy. Unfortunately, the proximity of these tumors to the visual apparatus makes it inevitable, at least in a very small percentage of recipients, that undesirable ocular and neurologic side effects of therapeutic radiation will occur. This presentation reviews a subset of these complications, namely those that involve the visual system. The term “friendly fire,” applied to the inadvertent transmission of Creutzfeldt-Jakob disease in tissue grafts, seems appropriate in this context (2).

PATHOPHYSIOLOGY OF RADIATION NEUROTOXICITY

The twenty-first century radiation oncologist can select from several sources of radiation and multiple methods of delivery, all of which can be rather precisely focused (3). Regardless of the technique, the goal of radiation treatment remains the same—to maximize the dose delivered to the lesion while minimizing the dose to neighboring tissues. However, even with perfect planning and execution, the protection of normal tissue adjacent to the target cannot be assured. One explanation for this has recently been adduced (4). When cultured human skin fibroblasts are bombarded with alpha particles in quantities so low that only 1% of the cells are traversed by a particle, damage signals are transmitted to the adjacent bystander cells via gap junctions. The bystander effect has been documented by others, and nitric oxide may play a role in the process (5–7).

Nearly all the important neuro-ophthalmic complications of radiation therapy occur in a form called “late delayed radiation neurotoxicity,” a predominantly white mat-
vascular endothelium. Disruption of the blood-brain barrier is time-dependent and dose-dependent. The pathologic response in endothelial cells is documented in the optic nerves and shows loss of endothelial cells. A dose-related depletion of endothelial cells was recognized in the optic nerves. A dose-related loss of endothelial cells was recognized in the optic nerves of patients who had received proton radiation for choroidal melanomas as compared with patients with choroidal melanomas who had not been radiated.

Proton magnetic resonance spectroscopic analysis in living patients with radiation necrosis of the brain supports the conclusion that the primary effect is not on glial cells. The early changes are incompatible with demyelination or glial cell injury. Severe lesions are associated with elevated levels of lactate, supporting a primary role for ischemia.

Whatever may be the exact cellular pathogenesis, the result is "3-H tissue": hypovascular, hypocellular, and hypoxic. The hypoxia differs from that in most other injuries in that the oxygen gradient between the normal and radiated tissue is gradual, a situation that inhibits spontaneous repair. The end-stage pathology of radiation optic neuropathy is characterized by narrowed and occluded blood vessels, loss of axis cylinders and myelin, and the presence of fibrin exudates.
SAFE AND UNSAFE RADIATION DOSES

Radiation damage to the anterior visual pathway is not ordinarily encountered unless the total cumulative dosage of fractionated radiation exceeds 50 Gy. When radiation neuropathy has occurred after treatment with low cumulative dosages, the toxic effects of the radiation in some cases were probably potentiated by the concurrent administration of chemotherapeutic drugs (18). With stereotactic radiosurgery, patients may be treated with high doses of radiation at a single session (19,20). Generally, single doses to the anterior visual pathway of 8 Gy are safe. In one large series, patients receiving as much as 12 Gy to a short segment of the optic nerve were protected unless they had received previous or concurrent external beam radiation (21). Patients receiving cancer chemotherapy, and those with Cushing syndrome, pituitary tumors (especially growth hormone-producing tumors), or diabetes can have radiation neuropathy after receiving doses lower than those usually considered dangerous. Previous radiation may also potentiate the toxic effects of chemotherapy when the drugs are administered intra-arterially (22). The size of the radiation fractions is also an important variable: 1.9 Gy or less is considered safe (23,24). Other important variables include the interval between fractions, total treatment time, and the volume of irradiated tissue.

CLINICAL FEATURES OF VISUAL PATHWAY RADIATION TOXICITY

Visual symptoms usually do not develop until approximately 18 months after the completion of radiation therapy, but the latency range is wide (25–27). There is some relation between the dose of radiation and the latency to the onset of symptoms, with the latency being shorter with higher doses. Pain is exceptional (28). The onset of visual symptoms may be acute and is apt to be marked by progressive loss of vision in one or both eyes. In my experience with bilateral visual loss associated with radiation, vision is lost first in one eye. The second eye typically becomes symptomatic as vision is fading in the first eye. Loss of vision can be severe, to the point of total or functional blindness.

Radiation-induced lesions in the anterior visual pathway typically cannot be demonstrated on computerized tomographic (CT) scans (29). Magnetic resonance imaging (MRI) with gadolinium enhancement is the preferred diagnostic method. Damaged neural tissue shows enhancement and sometimes swelling (29,30). The enhancement fades within three months of symptom onset as atrophy supervenes.

When the radiation has been directed to the eye or orbit, the optic disc may be the focus of damage (radiation papillopathy), in which case opthalmoscopic abnormalities will be obvious from the outset (31). The optic disc is edematous and often accompanied by subretinal fluid, peripapillary hard exudates, and cotton-wool spots. Fluorescein angiography shows nonperfusion of the superficial disc vasculature. The disc remains swollen for weeks to months and then atrophies. Brown et al (31) reported radiation injury in eight cases of choroidal melanoma, two paranasal sinus carcinomas, one retinoblastoma, one choroidal metastatic tumor, one lacrimal sac tumor, and one frontal astrocytoma. The mean interval from the completion of radiation to the onset of visual impairment was 12.6 months (range, 3–22 months) after 60Co plaque and 19.3 months (range, 5–36 months) after external beam radiation. The latency to visual loss ranged from two to four years in another study (32). In the study of Brown et al (31), patients radiated from a 60Co plaque had typically received high doses of radiation (a mean of 12.5 Gy), except for one diabetic patient. Among their patients who had received external beam total doses of 55 Gy, papillopathy occurred after as little as 36 Gy. Gragoudas et al (32) reported their experience with a cohort of patients who received proton radiation for uveal melanomas. Patients who received 30 cobalt Gray equivalent (CGE) or less to the optic disc did not have radiation papillopathy. The risk of papillopathy increased with higher doses; at 70 CGE, nearly all patients had papillopathy.

With the techniques currently used (and that are being continuously improved), the complication rate is very low and the cost-to-benefit ratio is favorable. From an as-yet-unpublished study in which I participated at our institution, I have gained insight into the prevalence of optic neuropathy after radiation treatment by the sophisticated techniques now in use. Thirty-six consecutive patients with locally advanced paranasal and nasal cavity malignancies were treated with hyperfractionated-accelerated radiation therapy (four MV photons and 160 MeV protons), with the optic nerves and chiasms receiving a daily dose of 20 CGE and a total cumulative dosage of 56 CGE. Neuro-ophthalmic follow-up averaged 33.3 months (range, 12.4–108.5 months). Although one patient had ophthalmoscopic evidence of bilateral mild optic disc pallor during follow-up, no defect in acuity, color vision, or visual field could be identified in that patient or in any other patients.

In the next section, I describe case histories of patients who represent examples of radiation toxicity to the visual pathway.

MRI Abnormalities Before Clinical Manifestations

A 71-year-old woman (Case 1) had binocular diplopia consequent to a left sixth cranial nerve palsy. A tumor involving the left cavernous sinus, clivus, and sphenoid sinus was demonstrated on MRI scan. Biopsy showed that the lesion was an atypical meningioma and she received external beam radiation to a total dose of 55 Gy. One year after the completion of radiation, routine MRI scan
showed enhancement of the optic chiasm (Fig. 1). However, she had normal visual acuity, color vision, static and kinetic visual fields, pupils, and fundi. No abnormalities were found when the visual tests were repeated two months later. Three weeks after that last examination, she noticed decreased vision OD. Best-corrected visual acuities had declined to 20/40 OD and 20/30 OS. The OD had dyschromatopsia and there were bilateral nerve fiber bundle visual field defects. Both optic discs were slightly pale. Treatment with high intravenous doses of methylprednisolone and hyperbaric oxygen (HBO) was instituted within 11 days of the onset of symptoms but vision relentlessly declined, eventually in bilateral blindness.

A 74-year-old woman (Case 2) with polymyalgia rheumatica and hypertension had a head CT scan because of an episode of syncope. A mass demonstrated in the sphenoid sinus proved to be an inverted papilloma. The lesion was treated with radiation to a total dose of 54 Gy in 30 1.8 Gy fractions over 44 days. The average and maximum doses were 31.7 Gy and 57.6 Gy to the right optic nerve, 32.1 Gy and 57.1 Gy to the left optic nerve, and 42.3 Gy and 49.9 Gy to the optic chiasm. One year later, she noticed blurred vision OD, especially in the superior and temporal portions of the visual field. There were no other symptoms. The optic discs appeared normal at that time but right optic atrophy later developed. Examination two months after the onset of visual symptoms showed that visual acuity was 20/25 OU with normal Ishihara plate color vision. Bilateral nuclear cataracts appeared sufficiently dense to account for the reduced acuities. An incomplete, relative, upper altitudinal visual field defect was seen OD; the visual field OS was full. A relative afferent pupil defect was not demonstrable. The right optic disc was pale but the left was normal. There were no clinical symptoms or laboratory signs of temporal arteritis. An MRI performed one week later showed enhancement of the intracranial segments of both optic nerves without evidence of tumor (Fig. 2). Two weeks after the MRI study, she noticed “waves of liquid” OS. Visual acuities were unchanged, but she now had marked dyschromatopsia OD. The OS retained normal color vision. There was a complete, absolute, superior visual field defect OD and a superior Bjerrum scotoma OS to the 14e white stimulus on the Goldmann perimeter. Fundus appearance was unchanged, as was the MRI scan.

Kihlstrom and Karlsson (34) indicate that clinically undetected radionecrosis may sometimes be revealed by MRI studies, but these authors were almost certainly referring to lesions outside of the visual pathways. In light of evidence that there is early disruption of the blood–brain barrier in radiation injury, it is not surprising that MRI signs may be present before the development of clinical symptoms and signs. The existence of such cases might have therapeutic implications (see below).

Normal MRI Soon Before Onset of Clinical Manifestations

A 37-year-old man (Case 3) had diplopia and pain OS. There was a left Horner syndrome and a partial left third cranial nerve palsy. Neuroimaging studies showed a mass involving the sella, the preoptic cistern, and both sides of the cavernous sinuses that proved to be a nonchondroid chordoma. After subtotal resection, he was treated with external beam radiation. The estimated dose to the chiasm was 60 CGE. Six months later, he was free of diplopia and there were no signs of radiation injury on enhanced MRI. However, within a month the visual acuity OS began to fail. Examination one month later showed that while the OD was normal in all respects, the OS acuity was 20/50, and there was dyschromatopsia, a dense superior altitudinal visual field defect, and a pale optic nerve. There was enhancement of the intracranial segment of the left optic nerve on MRI. Despite high doses of oral dexamethasone, he became blind OS. By that time, there was a temporal visual field defect OD and bilateral optic disc pallor. Despite HBO therapy, visual acuity declined to 20/40 OD and dyschromatopsia developed. The patient was anticoagulated but there was no further change in visual function.

Cases of visual loss developing within weeks of a normal MRI lesions force us to acknowledge that a normal MRI scan does not exclude impending radiation optic neuropathy. MRI may actually underestimate the extent of radiation-induced brain lesions. At autopsy in one case (35),
FIG. 2. Case 2. MRI signal abnormalities precede clinical manifestations of left radiation optic neuropathy. Unenhanced (left) and enhanced (right) coronal T1-weighted MRI scans performed on a 71-year-old woman who had received 54-Gy external beam radiation for a sphenoid sinus inverted papilloma one year earlier. They show enhancement of both optic nerves (arrows). At the time of this scan, the patient had clinical manifestations of a right optic neuropathy. Two months later, manifestations of a left optic neuropathy developed. A repeat MRI scan at that time was unchanged.

histopathologic evidence of radiation injury exceeded the boundaries of the lesion on MRI by as much as 46%.

Long Interval Between Consecutive Involvement of the Two Optic Nerves

A 70-year-old man (Case 4) had pain in and below the left orbit and in the left pre-auricular region. CT scanning showed a tumor in the left maxillary, ethmoid, and sphenoid sinuses that proved to be an invasive squamous cell carcinoma. He was treated with external beam radiation to a total dose of 66.7 Gy. Eighteen months later, he noticed that he could not see well in the upper field OD and hallucinated “bursting bubbles” in that area. Two weeks later, the visual acuity OD was 20/200, and there was dyschromatopsia, a dense superior altitudinal visual field defect, a relative afferent pupil defect, and a pale right optic nerve. The visual field OS was completely normal (Fig. 3). He refused an MRI scan. CT scanning showed no evidence of tumor and the right eye became blind. Seven months later, he presented with a superior altitudinal visual field defect OS (Fig. 3), dyschromatopsia, and a pale left optic nerve. An MRI scan showed enhancement in both optic nerves. Within two weeks, visual acuity had declined to 6/200 OS. Despite HBO treatment and the administration of high doses of oral prednisone, he became blind OU. In my experience, it is distinctly unusual for a patient to have such a long hiatus (seven months) before the second eye becomes symptomatic.

Spontaneous Visual Improvement

A malignant melanoma was resected from the temple of a 71-year-old man (Case 5). When left parotid and cervical node metastases were detected one year later, he was treated with parotidectomy, radical neck dissection, and interferon. He received 50 Gy to the left parotid gland, followed by an electron boost totaling an additional 10 Gy. Nine months later, painless loss of vision developed OD, accompanied by visual hallucinations. The right optic disc was edematous and MRI showed enhancement of the right intraorbital optic nerve. Despite treatment with high doses of oral prednisone, the right eye developed NLP vision within two weeks. Two months later, vision had declined from 20/20 to 20/70 OS, despite daily 100-mg doses of oral prednisone. MRI disclosed enhancement of the optic chiasm and both optic nerves but no evidence of metastases; cerebrospinal fluid examination was normal. Several weeks later, the right eye remained NLP and acuity OS was 20/70. There was a new visual field defect OS (Fig. 4) and dyschromatopsia. The right optic disc was atrophic and the retinal vessels were narrowed. The left fundus was unremarkable. He had to resort to large-print books. Subsequent to discontinuation of the prednisone, he began to appreciate some return of vision OS. Re-examination six months later showed a visual acuity of 20/40 OS, an expanded visual

FIG. 3. Case 4. A long latency between development of clinical manifestations of radiation optic neuropathy in the two eyes. Serial Goldmann perimetry OS shows new nerve fiber bundle visual field loss seven months after radiation optic neuropathy had developed OD.

FIG. 4. Case 5. Spontaneous improvement in visual field after radiation optic neuropathy. Serial Goldmann perimetry OS in a patient who had undergone radiation to the left parotid gland for metastatic melanoma. The initial visual field (left) was performed 11 months after radiation; the follow-up field, which shows expansion, was performed six months later.
field (Fig. 4), and normal color vision OS. He could now read conventional-sized print.

Despite literature suggesting that spontaneous improvement in vision in patients with late delayed radiation injury of the visual pathways is unknown (27), cases have been reported. Brown et al (31) mention three patients with radiation papillopathy who enjoyed improvement. In one case, visual acuity improved spontaneously from finger counting to 20/50 within eight months. In the two other cases, the improvement in acuity is not quantitated. The rate of spontaneous improvement in cases of radiation papillopathy may actually be higher than the literature would suggest when the irradiated lesion is intraocular, given that non-neurogenic visual loss from growth of the primary lesion, retinal detachment, or radiation-induced cataract could obscure spontaneous improvement.

**Retrogeniculate Blindness**

Four years after a 55-year-old man (Case 6) had undergone resection of a renal cell carcinoma, visual hallucinations developed and he realized that his peripheral vision was restricted (36). Visual acuities were 20/20 OU, but there was a partial right homonymous quadrantanopia. MRI scans showed a hemorrhagic lesion in the left occipital lobe. The resected brain lesion was a metastasis. He was treated with external beam whole-brain radiation of 30 Gy with a 15-Gy boost to the region of resection. He also received two cycles of interleukin-2. He was free of eye or neurologic symptoms until 18 months after the completion of radiation when he realized that his vision was decreasing OU. Examination showed that he could only see hand movements OU. His pupils reacted normally to light and fundus examination was unremarkable. T2-weighted MRI showed hyperintensity in both cerebral hemispheres (Fig. 5). He was treated with high doses of oral dexamethasone but his vision never returned.

This previously reported case (36) serves as a reminder that vision may be impaired when the retrogeniculate visual pathways are irradiated. This case appears to be the only published example of radiation-induced retrogeniculate blindness, but radiation necrosis can cause homonymous hemianopias (37). Radiation predisposes patients to cerebral hemorrhages from telangiectases (38) and to cerebral infarctions secondary to premature or accelerated atherosclerosis (39).

**TREATMENT**

Attempts to treat delayed radiation injury of the visual pathways have generally failed to reverse or even halt the loss of vision. A tabulation of virtually all reported cases of delayed radionecrosis of the optic nerves and chiasm shows this rather dramatically (40). With a few exceptions (41), patients have been unsuccessfully treated with large intravenous doses of corticosteroids. Because radiation injury is not an inflammatory disorder, it is difficult to invoke the anti-inflammatory effects of corticosteroids. The role of corticosteroids in reducing vasogenic edema has been cited as a rationale for its use. Swelling of the chiasm and optic nerves are MRI features of radiation injury, but it is not clear that vasogenic edema contributes to tissue injury in this disorder. Because radiation injury may be initiated by free radicals, treatment with very high doses of prednisone, known to have antioxidant properties, could theoretically be justified.

Heparin and warfarin have their advocates (42,43) who postulate that anticoagulation might promote blood flow to irradiated tissues. There are additional theoretical benefits of heparin, given that it suppresses certain injurious tissue mediators. There have been reports of treatment success, but not in cases of radiation injury to the visual pathway. Of note, one study (44) described a patient in whom bilateral radiation optic neuropathy developed while being treated with an anticoagulant.

HBO therapy seems to offer more promise than any of these other forms of treatment (45,46). It can increase the...
partial pressure of oxygen in tissue up to a limit of 3.0 atm in single-place chambers (47). Up to 6.0 atm can be achieved in multiple-place chambers. HBO changes the oxygen gradient and stimulates revascularization of the capillary bed (48). Common, relatively minor side effects include barotrauma (45) and lenticular myopia (49). The latter may persist for months. Rare side effects include seizures and pulmonary toxicity (50).

Borrnatt et al (27) reported their experience with HBO therapy in four patients with delayed radiation injury of the anterior visual pathways. Their patients were treated with three days of intravenous methylprednisolone and 30- to 90-minute “dives” in which they breathed 100% oxygen at 2.4 atm. One patient, treated 16 days after diagnosis, improved from no light perception to light perception in one eye. A temporal hemianopia in the other eye cleared within seven months. A second patient treated three weeks after onset of visual loss had improvement in visual field, color sense, and visual acuity. Visual acuity improved from 9/200 to 20/40 OD and from 3/200 to 20/40 OS. The third patient, treated with HBO two months after diagnosis, and the fourth patient, treated six weeks after diagnosis, sustained no benefit.

In their review of published cases, Borrnatt et al (27) compared visual outcomes among three groups of patients: those receiving no treatment, those receiving HBO therapy at 2.0 atm, and those receiving HBO therapy with 2.4 or greater atmospheres. The visual outcomes shown in Table 1 suggest that HBO is effective at higher atmospheres.

Reden et al (51) used corticosteroids and HBO to treat 13 patients with delayed anterior visual pathway radiation injury. No patient responded to this treatment. Borrnatt et al (27) suggest that the failure in these cases might have resulted from a delay in instituting HBO therapy. If, as these authors suggest, HBO is effective only if given soon after the patient has symptoms, efforts should be made to detect anterior visual pathway radiation injury as early as possible. Guy and Scharz (52) advise that HBO treatment be initiated within three days of the onset of visual symptoms. As noted, some patients may have MRI signs of radiation injury that antedate the loss of vision. If a patient has had radiation to lesions near the optic nerves or chiasm, one could consider obtaining frequent enhanced MRIs during the period of highest risk—10 to 20 months after the radiation therapy has been completed. Because the two eyes are often involved serially, similar testing should be started after one eye has developed radiation neuropathy to detect the earliest evidence of radiation neuropathy on the other side. If the MRI scans show the signs of radiation optic neuropathy, HBO treatment could be given prophylactically.

Electrophysiological testing might also help in the early detection of radiation damage to the visual pathway. Radiated animals show reduced signal amplitude and a delay in neural conduction (53). In patients with anterior visual pathway radionecrosis, the visual evoked potential (VEP) may be abnormal months before the loss of vision (54). Kellner et al (55) evaluated the VEP in patients with normal vision who were radiated for uveal melanomas. Five patients had radiation papillopathy, all of whom also had abnormal VEP latency. There were also several cases in which the VEP was normal when visual function and the fundus examination were still normal. These findings suggest that serial testing of VEPs during the high-risk period in appropriate patients might provide early evidence of an optic neuropathy and allow optimal application of HBO therapy.

**CONCLUSION**

A small proportion of patients irradiated for tumors in proximity to the optic nerves, chiasm, and retrogeniculate visual pathways will have potentially devastating visual complications. Until ionizing radiation can be delivered without damaging the adjacent normal tissue, physicians must scrupulously factor this risk into all decisions involving the use of therapeutic radiation. They must also be vigilant to the signs of radiation injury and be receptive to such diagnostic and therapeutic measures as become available to detect, prevent, or reverse radiation neurotoxicity.

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Recent Advances in Radiation Oncology

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Abstract: The field of radiation oncology has experienced dramatic progress in recent years. Advances in areas of tumor delineation, treatment planning, delivery, and verification allow modern radiotherapy to deliver high doses with great accuracy, less patient morbidity, and in a highly individualized manner. A good understanding of what can be achieved with modern radiotherapy is important in ensuring an effective multidisciplinary approach to the management of cancer and other benign, yet rapidly proliferating, lesions.

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The past 10 years in radiation oncology have been exciting and full of advances. The large body of high-level evidence supporting the use of radiotherapy as an integral component of cancer care continues to grow. As technology progresses, radiation oncology has evolved into a highly sophisticated and technically demanding specialty.

Radiotherapy involves the use of high-energy radiation, primarily photons in the form of x-rays, to kill proliferating cells in cancers or benign tumors. In addition to photons, other subatomic particles such as electrons, protons, and neutrons can be used. Because most radiotherapy is accomplished using linear accelerators that generate and deliver high-energy x-rays, this article will focus primarily on photon-based radiotherapy.

Radiation causes damage to cells by interfering with the cell's ability to grow and reproduce. Cells that are growing and multiplying are especially sensitive to the effects of radiation. Neoplastic cells reproduce more frequently than normal cells, so they are more susceptible to damage from radiation. Normal cells can also be affected by radiation, but they are better able to recover from radiation damage. The damage to normal cells and the process of repair after radiation treatments underlie the side effects of radiation. These side effects are related to the dose of radiation and the volume of normal tissue that receives radiation. The difference between the responses of neoplastic and normal tissue is critical to radiation's therapeutic ratio. Recent advances have been aimed at amplifying this difference.

As tumors are often immediately adjacent to critical normal structures, the challenge in radiation delivery is primarily a geometric one. One advantage of radiation is that some tissues can be treated to a modest dose and some to a high dose within the same field arrangements. The greater the number of tumor cells, the greater the dose required to destroy them. This has been the rationale for the shrinking-field techniques and the current dose-sculpting techniques of intensity-modulated radiotherapy (IMRT).

Radiation can also be delivered by many different schedules or "fractionation" schemes, ranging from a single treatment to more than 40 treatments delivered daily over a period of weeks. The radiobiologic benefit of fractionated treatment is that it allows normal tissue to repair and therefore tolerate a higher total dose of treatment. The decision between using a single fraction versus multiple fractions is based on the type of disease, its geometry relative to normal tissues, and the radiation oncologist's experience.

Modern imaging techniques, extending beyond computed tomography (CT) to magnetic resonance imaging (MRI) and positron emission tomography, allow better delineation of targets and adjacent critical normal structures. The incorporation of information from these modalities is crucial to the future of radiation oncology.

CORNERSTONES TO MODERN RADIATION THERAPY

Dose Calculations

Modern high-speed computers have, together with CT imaging, improved the accuracy of radiation dose calculations. Previous estimates of doses were based on one measured point dose and simple rules calculated by hand or on a calculator. Modern dose calculation algorithms calculate dose with vastly improved accuracy using complex algorithms (1) such as Monte Carlo simulation, an algorithm that simulates the interactions of billions of photons with the patient during a treatment.
Three-Dimensional Computed Tomography-Based Virtual Simulation

CT guidance in defining solid tumor targets and surrounding critical normal tissue structures has allowed radiation therapy to evolve from two-dimensional (2-D) to three-dimensional (3-D) treatment methods. In the past, when 2-D conventional x-ray simulators and planar radiography were used to image the treatment portals, bony and surface landmarks were frequently the only markers the radiation oncologist had to establish the external beam path and field to encompass the target. Radiation therapy beam direction choices were restricted to the anterior-posterior or lateral planes, where one could easily recognize and reproduce bony anatomy position for treatments.

In virtual CT simulation, a complete CT image data set of the relevant region is used to contour target volumes and normal tissue structures. Contours and CT slices are reformatted into 3-D representations, or volumes, which can be visualized from any angle. The CT data used for target volume generation are much more precise than the inferred target volumes used in the 2-D era.

In 1978, Reinstein et al (2) and McShan et al (3) took the first steps toward clinically usable 3-D radiation treatment planning with the development of the beam's eye-view display. The beam's eye-view display provides the radiation oncologist a view from the perspective of the head of the treatment machine, looking down the rays of the divergent beam. This display allows a view of the anatomy similar to that of a 2-D simulator radiograph. However, the 3-D volumes can also be projected onto the beam's eye-view display, giving the radiation oncologist a look at how the treatment beam relates to the tumor volume and the critical normal structures. Previously unusable nonstandard beam angles, such as superior-inferior oblique or vertex projections, can now be planned, projected, and visualized. Figure 1 shows several images from a virtual simulation, including a 3-D volume rendering of a pituitary adenoma patient, a sagittal reconstruction image, a vertex field projection without any target or normal tissue structures (as would have been seen on a 2-D simulator), and the same vertex field projection with the target and critical structures visible.

Multi-leaf Collimators

To shape radiation fields, early linear accelerators used primary collimators in the x-axis and y-axis to create the smallest necessary rectangular field. Lead alloy, custom-shaped blocks were then placed on mounts in the head of the machine to further refine the shape of the fields. The physical process of creating the blocks and changing them for each patient and for each field involved substantial time and effort. Manufacturers have now developed multi-leaf collimators (MLCs), in which the solid tungsten collimators are split into multiple, individual leaves that can slide against one another and be set individually to create the shape of any of the external blocks used previously.

Figure 2 is a view into the head of an MLC of a linear accelerator, its leaves in position to treat a particular target. Each leaf position is computer-controlled and does not require human intervention, allowing a greater throughput of patients undergoing radiotherapy. Automated MLCs are an essential component of the implementation of IMRT.
Intensity-Modulated Radiation Therapy

In IMRT, a technique that has risen to the forefront of radiotherapy during the past decade, the intensity of the radiation varies across the treatment field (hence “intensity-modulated”), in contrast to the homogeneous fields previously used (4-8).

Conventional 3-D planning computer systems use trial and error to develop a treatment plan. A medical physicist or dosimetrist creates a plan with specific beam geometries and shapes, after which dosages are calculated and evaluated. Each plan is then modified iteratively until an acceptable plan is reached.

By contrast, IMRT uses an “inverse planning” algorithm. With inverse planning, the goals of the treatment plan (desired dosages to targets and dose limits for critical normal structures) are specified beforehand and the algorithm determines the photon intensity pattern necessary to achieve these goals. Whereas previous treatment fields used homogenous fields (the same photon intensity throughout the entire field), the “intensity-modulated” fields in IMRT use heterogeneous or variable photon intensities within the same field. The technique used in the delivery of these intensity patterns varies by treatment system.

The two most common IMRT delivery methods currently in use are: (1) the static, segmental field “step-and-shoot” MLC technique (9); and (2) the dynamic, “sliding window” MLC technique (10). Figure 3 demonstrates one example of a static, segmental field technique and the beamlet fluence pattern that can be achieved. Other radiation delivery techniques are described in the next section.

Inverse planning and IMRT allow for the conformation of the radiation dose around critical structures (optic chiasm, optic nerves, parotid glands), a capability not previously possible with conventional 3-D planning and delivery systems. This conformation has allowed additional dose escalation to the target and increased sparing of normal tissue. Clinicians now can devote more effort toward reducing the side effects of radiotherapy.

An example of an IMRT case is shown in Figure 4, a head and neck IMRT parotid-sparing plan. In patients with head and neck tumors, several normal tissue structures can be delineated, each with its own specific tolerance dose. Sparing the parotid gland, long been recognized as a critical structure (11), has resulted in improved salivary flow rates and avoidance of long-term xerostomia (12). IMRT is now being applied to almost all clinical sites currently treated by radiation oncologists.

RADIATION DELIVERY TECHNIQUES AND SYSTEMS

Radiation delivery techniques and systems are moving toward the ultimate goal of delivering a maximal dose to the target volume and a minimal dose to the surrounding normal tissue. Three components are necessary to achieve this goal: (1) rapid dose fall-off outside the target volume; (2) conformality of the prescribed dose to the target volume; and (3) impeccable repositioning accuracy. Each of the techniques and systems described excels in the three components to varying degrees, but with different costs in terms of time and complexity of treatment.
Stereotactic Radiosurgery and Stereotactic Radiotherapy

When the total radiation dose is delivered in a single session, the technique is termed “stereotactic radiosurgery” (SRS). The term “radiosurgery” is actually a misnomer because no surgical procedure occurs. The name comes from the fact that its creator, Lars Leksell of the Karolinska Institute in Sweden, was a neurosurgeon. “Stereotactic” refers to the precise 3-D positioning of the patient and targeting of the lesion.

In the setting of intracranial lesions, positioning accuracy is obtained by attaching a stereotactic head ring to the patient’s skull with surgical pins. Because the skull surrounds the brain, rigid immobilization of the skull translates into rigid immobilization of its contents. SRS allows for the delivery of a biologically high radiation dose in an effort to maximize local control of malignant tumors or to achieve obliteration of benign lesions such as arteriovenous malformations (AVMs).

When the total dose is delivered in more than one fraction, it is known as fractionated stereotactic radiotherapy (SRT). Immobilization devices less invasive than those used in SRS are used for SRT, such as the rigidly immobilized bite block. Fractionated SRT permits a high degree of conformality to neoplastic lesions with minimum acute and long-term toxicities. However, because of the delivery systems described, the volume of nontarget tissue that receives a significant dose is strongly dependent on the size of the target and the conformality of dose to the target. Although the use of multiple isocenters can increase conformality, conformality is achieved at the expense of dose homogeneity (more “hot” and/or “cold” spots) within the target. This inhomogeneity within the target (which may affect tumor control rates) and surrounding normal tissue contrasts with the homogeneity that can be obtained with IMRT, which does not typically use stereotactic immobilization.

GammaKnife

First developed by Leksell for SRS in 1968, the GammaKnife system (Elekta AB, Stockholm, Sweden) concentrates radiation from 201 intersecting beams arising from Cobalt-60 sources mounted within a hemispherical assembly. Typical treatment plans are developed in a forward planning method, and these plans are limited in conformality as the beams are all circular. To treat a complex lesion, multiple isocenters, or dose “spheres,” are treated to encompass the lesion. Lesion localization is accomplished with a stereotactic localization frame bolted to the patient’s skull.

Arc-based linear accelerator radiotherapy has also been developed. At the University of Michigan, a technique using segmental, conformal stereotactic radiotherapy using standard MLCs set at various positions along the arc gives comparable conformality to GammaKnife SRS while improving on homogeneity (13).

GammaKnife and linear accelerator-based SRS may be used to treat intracranial lesions of less than 10 mL, such as metastatic lesions, meningiomas, AVMs, acoustic neuromas, pituitary tumors, and skull base tumors. The size of lesions treated is limited because as a lesion becomes larger, the inhomogeneity of the treatment increases (undesirable in terms of tumor control), and the dose fall-off is less steep (undesirable in terms of side effects).

CyberKnife

An image-guided robotic stereotactic system called the CyberKnife (Accuray, Sunnyvale, CA) combines a linear accelerator tube, real-time image guidance, and an industrial robot that has six-axis range of motion (14). The robotic maneuverability is significantly better than that of a conventional linear accelerator, allowing for the implementation of a wider range of treatment plans than any other system. Real-time orthogonal x-ray fluoroscopy tubes determine the patient’s position relative to the desired reference position, allowing the robotic arm to make any necessary adjustments, essentially “tracking” the target. No invasive stereotactic head frame is necessary for this system, as it uses the skeletal structures as a reference frame. The CyberKnife, as seen in Figure 5, can be used to treat the same lesions as the GammaKnife or linear accelerator-based systems.

The CyberKnife plans are generated either with forward 3-D conformal planning or with inverse planning. Although this system is not considered IMRT, it produces comparably conformal plans. For an unusual geometric target such as a helically shaped tumor wrapped around the spine, the CyberKnife may produce better conformity than IMRT. However, the treatment times are much longer because the robotic arm needs to move to each beam angle.

Extracranial Stereotactic Radiation Therapy

The extracranial application of stereotactic principles, or “extracranial stereotactic radiotherapy” (ESR), involves the delivery of highly conformal radiation treatment to sites outside the skull, using the principles of stereotaxy for target localization. The recent evolution in tumor imaging, 3-D treatment planning, gated radiotherapy, and tumor tracking have made it physically possible to deliver highly conformal dose distributions to body targets in the lung, pancreas, liver, and spine.

The CyberKnife can be used for ESR. For tumor tracking outside the skull, markers visible to the x-ray imagers can be implanted adjacent to the tumor or directly in it. External surrogate markers visible to an infrared camera can also be placed for additional tracking information. If a patient is breathing, the treatments can be “gated,” or only turned on when the markers are in the desired treatment.
FIG. 5. CyberKnife system. A: A 6-MV linear accelerator is mounted on a six-axis robotic arm. Underneath the treatment table are the real-time x-ray imaging panels. The x-ray tubes are mounted in the ceiling above the patient. The infrared external marker tracking device is mounted in the ceiling above the patient. B: Isocentric GammaKnife or linear accelerator-based radiosurgery treatment. C: Nonisocentric CyberKnife treatment.
The TomoTherapy system. A: An in-line linear accelerator with a temporally modulated MLC is mounted on a gantry along with other components. It will perform megavoltage CT and diagnostic CT. B: The equipment rotates continually as the patient is translated slowly through the beam. The resultant motion of the treatment fan beam is a spiral with respect to the patient.

TomoTherapy

Another system capable of delivering IMRT is TomoTherapy (TomoTherapy, Inc., Madison, WI). In place of MLCs, a narrow fan collimator and beam rotate isocentrically around the patient. As this rotation occurs, one-dimensional intensity modulation is created and continually modified by shooting vanes of attenuating lead into the aperture at right angles to the direction of the slit. Additionally, the treatment table moves continuously through the field as the modulated beam rotates, thus creating a spiral beam pattern as seen in Figure 6. In addition to the IMRT delivery, the same radiation beam can be used to image the patient for near real-time CT patient information. Treatment can then be altered to account for any target motion caused by bodily functions such as breathing. With TomoTherapy, treatment plans are created with an inverse planning algorithm. The TomoTherapy treatment system can be used for most intracranial and extracranial lesions currently treated by linear accelerators.

FUTURE DIRECTIONS

With the ability to deliver ever more conformal plans, eliminating patient motion will become especially critical. Tumor-tracking and real-time imaging methods are still in development and further work is needed to realize their full potential. Techniques such as active breathing control can fix the patient at a point within the breathing cycle, avoiding the positional influence of the diaphragm (15).

Geometric anatomic information can now be fused with functional anatomic information to allow new targets to be established for radiotherapy. Imaging modalities such as functional magnetic resonance imaging and spectroscopy, positron emission tomography, and molecular imaging techniques are likely to reveal the extent of disease much better than CT or MRI, and may even be able to predict the response of target and normal tissues to radiation during treatment. With the addition of these modalities, a new era of "image-guided" therapies will emerge.

Another recent technical advance in radiation oncology is proton beam-based therapy. Proton beams have a much more favorable beam dose profile (the "Bragg peak") when compared with photons. Most of the proton dose is deposited at a depth related to its energy and without the exit dose seen with photons, as shown in Figure 7. Proton beams can create a more conformal treatment compared with photons, but photon-based IMRT has been able to accomplish most of these objectives without the significant expense of a proton treatment facility. In the future, by combining "intensity-modulation" technology with proton therapy (IMPT), it may be possible to exceed the capabilities of all current systems. But because proton facilities require extremely large and costly cyclotrons (more than $100 million compared with less than $10 million for photon IMRT systems), only a few centers have been able to

![Proton versus Photon dose profiles. Protons have dose deposition at a set depth ("Bragg peak"). During proton treatments, a spread-out Bragg peak (SOBP) pattern is generated by summing decreasing proton energies and their individual proton Bragg peaks to create a treatment range (plateau region). As compared with the photon dose profile, the SOBP dose profile has a much lower entrance dose and no exit dose.](image)
use them. Proton beam therapy will only come into wide clinical use when its costs are reduced dramatically.

Another priority will be to develop a better understanding about normal tissue tolerances to partial organ irradiation. Clinicians will then be better able to weigh the trade-offs between dose to target and dose to normal tissue. The resources to analyze the vast amounts of data generated during each treatment are only now beginning to be mobilized for the above priority.

Critical assessment will be needed to prove the benefit of technologies such as IMRT, which are more time-consuming and costly than conventional methods. If, as expected, these new technologies increase tumor control and reduce side effects, large benefits are in store for our patients.

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REFERENCES

Thomas R. Hedges, Jr: Witness to the Birth of Modern Neuro-Ophthalmology

Nicholas J. Volpe, MD and Laura J. Balcer, MD, MSCE

As the first fellow in neuro-ophthalmology under Frank B. Walsh, MD, at the Wilmer Institute in Baltimore, Maryland, Thomas R. Hedges, Jr, MD, was present at the dawn of neuro-ophthalmology as a subspecialty. Through his relationships with many of the field's greatest figures, he has gained unique insights and personal perspectives on the development of the field. The author of 90 original manuscripts, he is the co-founder of the International Neuro-Ophthalmology Society (INOS) and a charter member of the Frank B. Walsh Society. Now Professor Emeritus of Ophthalmology at the University of Pennsylvania School of Medicine and Emeritus Chief of the Ophthalmology Section at Pennsylvania Hospital in Philadelphia, he has been a mentor to countless students, residents, fellows, and faculty at Penn. This interview took place at his home on January 28, 2003.

NJV: Where did it all start?

TRH: I was born in Cleveland, Ohio in 1923, and I grew up in Sandusky, Ohio. I lived my whole younger life there with the exception of summers with my uncle on his dairy farm in Kent, Ohio. We had horses to pull the wagon into town when we took the grain to be sold. Every morning we fed the cows at 5 AM and every evening we drove them back from the pasture to the barn for milking.

NJV: How did you become interested in ophthalmology?
TRH: My father’s career as an optometrist probably had a great deal to do with it. He graduated from the Optometry School at Ohio State University in Columbus, a school that is still among the best of the American optometry schools. He studied under Charles Sheard, MA, PhD, ScD, who wrote the standard text of the time on physiological optics entitled Selected Writings in Visual and Ophthalmic Optics.

NJV: What about your undergraduate life?

TRH: I was on the championship swim team at Ohio State and qualified for the Olympics as part of a medley relay team. But that was 1939, and the 1940 Olympics were to be held in Tokyo. The events of World War II led to the cancellation of those games.

By this time, most of my friends were in the service. When I went to enlist, a navy lieutenant recruiter said, “I see here you are accepted at medical school. We need you for that. Get out of here and get on with it. We’ll need you more when you get to be a doctor.” I knew that I wanted to go to medical school, so that was it.

NJV: Why did you go to Cornell for medical school?

TRH: I had been accepted at the medical schools of Harvard and Cornell. I visited Harvard first, but I was put off by my student guide who was less than enthusiastic. When I asked about the anatomy course, he replied, “Why would you care about that? It’s so basic we try to avoid it.”

After I saw Cornell and New York Hospital, I just fell in love with the place and the people. I thought the faculty was impressive in the basic sciences and clinical medicine. Physiology and anatomy were taught by Professors Eugene F. DuBois (Physiology), George Papanicolaou (Anatomy and Histology), and Vincent du Vigneaud (Biochemistry). John McLean, MD, in ophthalmology and Harold Wolff, MD, in neurology stand out since they played such an important role in my future.

When I entered Cornell Medical School in January 1944, I was assigned to a room on the fifth floor of the old Nurses’ Residence, which was made into a dormitory for men. We lived in little cubicles that were no bigger than closets. The guy next door to me was quiet, unassuming, and very serious. His name was Ed Norton (later to become chair of ophthalmology at the Bascom Palmer Eye Institute, Miami).

World War II was well underway at this time so we were all in uniform. Ed and I were midshipmen in the Navy V-12. One of our memories was marching around the hospital once or twice a week. We agreed that we had fought the “Battle of 68th and York,” (referring to the address of Cornell Medical School and New York Hospital).

During this time, I saw a lot of Ed Norton. I was drawn to him by his consuming interest in medicine and his wonderful personality. Through our exposure to Harold Wolff, Ed and I realized that we had a great interest in neurology. In 1945, Wolff had written the first textbook on headache, called Headache and Other Head Pain. This book had a great influence on both of us. In that year, I found another book in the Cornell library that influenced me. It was Neuro-Ophthalmology by Donald J. Lyle, MD, of the University of Cincinnati. I showed it to Norton.

My wife Ann and I were married in 1946. I told her about my interest in Lyle’s book. She found it at a medical bookstore and gave it to me as a Christmas present.

Norton and I attended lectures given by another neurologist, Louis Houseman, MD. We told him that we
thought neuroanatomy was poorly taught. He said we ought to build a brain, and he promised to show us how. So Norton and I each built a brain out of clay and wire on a wood cut-out frame. We spent about 100 hours on that project. That model meant so much to me that I carried it with me wherever I went. The thing finally fell apart in the heat of the attic in the first house we had in New Jersey.

NJV: What were your earliest formal exposures to ophthalmology?

TRH: The lectures of McTean at Cornell. They made ophthalmology an engrossing and challenging subject. After the first lecture, I remember walking up to him and telling him of my interest in his material. He later offered me a residency in ophthalmology.

NJV: But you didn't accept the offer...

TRH: Because it came during my rotating internship at St. Luke's Hospital in Cleveland, where I had become fascinated with neurology. I had met Jack Nichols, MD, a neurologist at Western Reserve University. Nichols often made rounds late at night, and somehow I'd find a way to go on those rounds. He arranged for me to do a fellowship in neurology at the Cleveland Clinic.

FIG. 3. As a Navy Midshipman, 1944.

The neurology-psychiatry section at the Cleveland Clinic was run by Louis Karnosh, MD, a true intellectual with an interest in everything from bookbinding to making paper to wood cut illustrations. Most importantly, he wrote a book that dealt with psychiatry almost as an art form, called *Engrammes of Psychiatry*.

I also met Otto Glaser, MD, who had written the first textbook of neurophysiology. I told him that I wanted to learn more neuroanatomy. He said, “Fine, we will spend evenings doing an orange stick dissection of the fixed brain.” We concentrated on the visual pathways and the venous sinuses because Glaser had told me that the venous sinuses have a lot to do with brain swelling.

I had realized that I was not cut out for psychiatry or neurosurgery, so I was in a quandary between ophthalmology and neurology in that spring of 1949.

NJV: How did you resolve the quandary?

TRH: I went back to Cornell to see if I could obtain a residency position in ophthalmology from McLean. He said that he had two ophthalmology residents—Ed Norton and Paul Wetzig—and didn't have room for anyone else. But he said that Walsh was interested in taking on a young man with a background in neurology. He asked if I knew how to do visual fields. I had done finger waving, but I hadn't actually done formal fields. He gave me Walsh's phone number and said he would recommend me.

I left the office and went to the first phone I could find and called Walsh. He was interested in my background and asked me if I could get to Baltimore. I went down on the train the next day and he accepted me as his first fellow.

NJV: What was it like to work with Walsh?

TRH: It changed my whole life. He was a tall, good-looking man, completely personable, with the kindly manner and the grace of a true gentleman. He was straight in...
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FIG. 5. Frank B. Walsh, MD in 1949, when Hedges became his first fellow.

bearing and quick in step. He had been one of the first chief residents at Wilmer in 1933, and had started early in gathering material for the first volume of his book. By the time I joined him, he was on the staff at Wilmer and in part-time private practice with Charles M. Iliff, MD. He was about 54 years old, but in no way did I think of him as an “older” man. His scientific curiosity and verve were the peak of anything I had encountered in any of my professors. He had a remarkable single-mindedness.

His offices were at 12 West Reed Street, near the Washington Monument in Baltimore, an older building suitable for his practice of general ophthalmology and neuro-ophthalmology. He wanted me to work with him there and at his Wilmer clinic. We spent afternoons at the Wilmer and evenings in his office writing. Our association was a model, I think, for the fellowships which were beginning to shape the future of neuro-ophthalmology.

NJV: Were you examining patients with Walsh in his office—cataracts and all?

TRH: Yes, and I will never forget a woman with headaches who came to be examined by the “great Dr. Walsh.” I didn’t find anything wrong and told Walsh. In his very stately way, he said “Madam, everything appears to be all right.” As he began to usher the patient by the elbow to the door, she turned to him and protested, “But doctor, I came in because I cannot read. I think I need reading glasses.” “Oh,” he replied. He picked up the prescription pad, wrote down the number +2.50, handed it to her, and told her that that would do the trick. He disliked refractions and had very little patience with routine eye exams.

NJV: How did Walsh get you started in research?

TRH: He sent me to the brilliant Jonas Friedenwald, MD, PhD, who ran the Ophthalmic Pathology Laboratory at Wilmer. We read slides together twice a week. I told him that I was interested in the optic nerve. The lab had many specimens of posterior segments of the eye obtained at autopsy with clinical records that went back to the time of the great neurosurgeon Harvey Cushing, MD.

Friedenwald walked over to a green file cabinet and said, “Here are the 300 to 400 files of optic nerve sheath hemorrhage that I have collected all these years. Go through them and see what you can find out.”

Walsh had suggested that a good project would be to find out how many hemorrhages and papilledema they had. In the end, we restricted our research to aneurysm patients. In 1951, Walsh and I wrote the paper that became the Jackson Lecture that year (1).

Looking back on it now, I only wish I had had a copy machine to save the clinical data, which included notes from Cushing and Walter Dandy, MD (then professor of neurosurgery at Johns Hopkins University). I had gone back through Cushing’s and Dandy’s records, including Cushing’s drawings of all the operative findings. I had them all in front of me with details of each patient’s course. The most fascinating patients were those who had had ruptured aneurysms.

NJV: Which patients had had optic nerve sheath hemorrhages?

TRH: All the patients had optic nerve sheath hemorrhage, many due to birth injury, accidents, or trauma. The most interesting case was one of a tetralogy of Fallot in a 38-year-old woman who had received a fatal injection of Diodrast and had died of acute massive increase in intracranial pressure. At autopsy she had only petechial hemorrhages in the brain and no intracranial subarachnoid hemorrhage. There were, however, massive subhyaloid hemorrhages in the eyes, large optic nerve sheaths, and many orbital hemorrhages.

Up until then, it was always thought that the hemorrhages might have gone through the optic canal. We concluded that the origin of these subhyaloid and vitreous hemorrhages—Terson syndrome—was a massive increase in intracranial and venous pressure. To try to prove that the sheath space in the optic canal was such a minute microscopic opening, and that blood could never go through there, I went to the morgue one Sunday afternoon and
injected India ink under high pressure into the subarachnoid space of a cadaver. I could not get it to go through.

One day, late in my fellowship year, I got a call from the technician at the Hopkins morgue. A young girl who had been rehearsing her senior high school year play had dropped dead. I was allowed to do the dissection from the chiasm to the posterior segment of the eye. I found hemorrhages in the chiasm, third cranial nerve intracranially, orbit, optic nerve sheath, and vitreous, again illustrating the explanation for Terson syndrome. These pathologic findings had their origin in the sudden rise of intracranial pressure with a concomitant increase in venous pressure transmitted to the orbit.

NJV: What had laid the groundwork for neuroophthalmology as a subspecialty?
TRH: There were two major advances. First, there were the early textbooks by Lyle in 1945, followed in the same year by Cogan's *Neurology of the Ocular Muscles*. In 1946, Kestenbaum published *Clinical Methods of the Neuro-ophthalmology Examination*, and, most important, there was Walsh's *Clinical Neuro-Ophthalmology*, which came out in 1947. Walsh's text was as complete as could be at that time. He had written 1,500 pages followed by as in-depth an index as anyone had compiled to date. He said that the index was the most important part of the book—any book. Luckily he had an assistant who made it so accurate and complete that the volume was completely usable by the clinician.

The second and the most important development was the fact that teaching centers were setting up neuroophthalmology fellowships.

NJV: How did you transition into an ophthalmology residency?
TRH: One day during my time with Walsh in the spring of 1950, he said to me, "Doctor, you are going to go see Dr. Alan Woods (then the chair of Ophthalmology at Wilmer) for a residency interview today." That evening, I came back from interviewing for residency with Dr. Woods. It had not gone well. Later that evening, as Walsh and I were working on the second edition of the book, he suddenly looked up at me and said, "And how did things go with Dr. Woods?" Seeing the hard expression on my face, he said, "I figured." He knew that I had failed the "Woods course."

Walsh picked up the telephone and called Francis H. Adler, MD, professor and chair of Ophthalmology at the University of Pennsylvania. I remember his saying "I have a young man who needs a residency in ophthalmology. Would you look at him?" I went up to Philadelphia where I had the interview with Harold G. Scheie, MD, because Adler had gone back to the Marine Biological Laboratory in Woods Hole, Massachusetts to finish writing his book on ocular physiology. Adler and Scheie offered me a residency to start in ophthalmology in July 1950.

NJV: What do you recall of your ophthalmology residency?
TRH: Scheie, who ran the residency, was a great clinician but a hard taskmaster. One of my fellow residents called him "The Sabre." He ran that residency as he must have run his group in the army. Morning rounds started at 7:30 AM—not 7:31 or 7:29, but 7:30—and if you were late, God forbid. One morning, I presented a headache patient to him. He made no comments, walked over to the patient, pulled the hair back and exposed herpes vesicles, and said, "Herpes zoster, Doctor. If you open your eyes and look, you may eventually be a clinician!"

NJV: What events followed your residency?
TRH: In 1952, the Korean conflict was on everybody's mind. I felt I should volunteer. I was assigned to William Beaumont Hospital in El Paso, Texas—the only ophthalmologist at a hospital that took care of the huge Army base at Fort Bliss, the White Sands Missile Proving Grounds, Biggs Air Force Base, and the air base at Alamagordo. I had a 60-bed eye unit in the hospital. I saw general ophthalmology patients and patients with MS and strokes.

NJV: What happened when your military service was over in 1954?

TRH: Adler asked me to come back to Penn. William C. Frayer, MD, and I covered Scheie’s office and various clinics associated with Penn, which included the University Hospital, the old Philadelphia General Hospital, the Veterans Hospital, and the Children’s Hospital of Philadelphia. During this time, I befriended Francis C. Grant, MD, who was professor and chief of Neurosurgery at Penn. He suggested that I work on meningiomas. Eventually, Grant and I wrote a paper on tuberculum sellae meningiomas. (2)

NJV: What was your time at Wills Eye Hospital like?

TRH: Irving H. Leopold, MD, ophthalmologist-in-chief at Wills, and a professor of ophthalmology at Penn, asked me to come to Wills in 1959 to work in his office and do neuro-ophthalmology with Nathan M. Schlezinger, MD, professor of Neurology at Jefferson Medical College and chief of neuro-ophthalmology at Wills. I also helped the residents with retinal detachments, corneal transplants, and things I had never done in my life. Two or three years later, a position opened up at Pennsylvania Hospital. I was very eager to become part of that historic hospital.

NJV: What were your most important interests and activities at Pennsylvania Hospital?

TRH: During my time at Wills, I had started to develop an interest in the ophthalmic manifestations of increased intracranial pressure. I told this to Lewis Coriell, MD, PhD, who had founded the South Jersey Medical Research Institute, now the Coriell Institute for Research. He did much of his research on Rhesus monkeys and suggested that if I came over to his lab, I could use his monkeys for my research.

I had worked on intracranial pressure for about three years when Thomas Langfitt, MD, chief of Neurosurgery at Pennsylvania Hospital, and Jim Weinstein and Neal Kassell, who were Penn medical students, and I transferred the monkeys to Pennsylvania Hospital, where we continued to develop our techniques. We simulated brain tumors using balloons inserted into the intracranial vault. Kassell designed a screwbolt that fit in the head through which we could continuously measure intracranial pressure. We carried out that work together for almost 10 years. A fairly large series of papers came out of that research, including one on the importance of hydrostatic or vascular mechanisms in the production of the ocular signs, especially papilledema, with acute increase of intracranial pressure (3). We believed that in the pathogenesis of papilledema, elevation of venous pressure played an important role in the ocular signs, especially with acute increases in intracranial pressure. I do not think that axoplasmic stasis alone can explain these ocular signs.

NJV: Was it around this time that neurologists began to enter the field of neuro-ophthalmology?

TRH: Yes, in the early 1960s. Walsh had said, “They [neurologists] cannot do refractions. You cannot evaluate a patient with vision loss unless you can do a refraction.” Of course, even he did not like refraction! By then, however, William F. Hoyt, MD (then Chief of Neuro-Ophthalmology at the University of California, San Francisco) had started his fellowship program. Robert B. Daroff, MD, a neurologist, came as a fellow to Hoyt in 1957. Bob was so bright that he paved the way for bringing neurologists into neuro-ophthalmology.

NJV: You ran the neuro-ophthalmology course at the American Academy of Ophthalmology Annual Meeting for a number of years. How did that start?

FIG. 7. With Alfred Huber, MD (center) and David Knox, MD (right) in 1986 (INOS Meeting, Hakone, Japan).
The First International
Neuro-Ophthalmologic Meeting

La Napoule, France
April 12-16, 1976

TRH: There had been no courses in neuro-ophthalmology at that meeting until Walsh started one in 1960. Our course grew out of a meeting in a small room at the Palmer House in Chicago in 1962 that included Walsh, Lyle, Smith, John W. Henderson, MD (Ann Arbor, MI), and me. Walsh ran the course in the beginning. Henderson took it over for about five years and then I took it over. I ran it for about 20 years, and it gradually grew into a three-day course.

NJV: You were also instrumental in founding the International Neuro-Ophthalmology Society (INOS). Tell us about that...

TRH: In 1975, I was at a meeting in Dallas of the American Academy of Ophthalmology. In the breakfast line, I ran into an old friend, Alfred Huber, MD, professor of ophthalmology at the University of Zurich, and a leader in European ophthalmology. He had written an authoritative book entitled *Eye Symptoms in Brain Tumors*.
Huber and I were determined to start an international society. My wife Ann reminded me that the University of Pennsylvania was a trustee for the fourteenth century Chateau de La Napoule, near Cannes. After a hundred phone calls, it became the site for our first meeting. In 1976, 58 people gathered from all over the world (Fig. 8A and B). Walsh was the honorary chair.

The meeting was a great success. I remember that the EMI ("Emmy") scan, now known as the CT scan, was the promising new diagnostic tool. All were impressed that the Beatles and English Music Incorporated (EMI) had donated money to help develop the technology.

INOS really took off at the second meeting, held in Warrington, Virginia at the Airlie House in 1978. David G. Cogan, MD, and Melvin G. Alper (Chevy Chase, MD) arranged that meeting, to which over 100 people came. INOS has met every other year for the past 26 years. The number of attendees has doubled to about 200.

NJV: Walsh died in 1978. What events do you remember from that time?

TRH: We were attending the second INOS meeting in 1978. Walsh got into my car in Baltimore and I saw that he didn’t look well. At the meeting, Hoyt’s first fellow,
Richard L. Sogg, MD (Palo Alto, CA), a concert pianist, was playing the piano after dinner. Walsh said it was worth coming to the meeting just to hear Dick play the piano. But his breathing was not good, so the next day Richard C. Lindenbergh, MD (formerly professor of neuropathology at Johns Hopkins University), got him into the car and took him back to Baltimore. Later that day, Lindenbergh called to say that Walsh had oat cell carcinoma of the lung. On the way back to Philadelphia, I stopped at the hospital to see him. He said he was sorry to have missed part of the meeting.

He died six months later. I saw him in the hospital just before that. His last words to me, now in a weak voice, were “Tom, you will be glad to know that Miller (Neil R. Miller, MD, Baltimore, MD) has agreed to write the next edition of the book.”

NJV: What legacy do you want to leave to neuro-ophthalmology?

TRH: I am most proud of the fact that I was part of the beginning of modern neuro-ophthalmology, and of the fact that my son Tom went into neuro-ophthalmology. From the beginning of my career, I have taken great pleasure in teaching students, residents, and fellows who have come to work with me. Hopefully, this effort, along with my clinical research in the field, has contributed to the development of neuro-ophthalmology over the years.

I am proud of the fact that, together with Huber, I founded INOS, which has done much to bring neuro-ophthalmologists internationally closer together. I am especially grateful to have been a part of the highly talented and thoughtful University of Pennsylvania neuro-ophthalmology group. I am fortunate to have had my many mentors, students, and, most of all, my wonderful wife Ann to support me through both the good and the difficult times.

REFERENCES

Book Reviews

Section Editor: Barrett Katz, MD, MBA

**Handbook of Neuro-Ophthalmology and Orbital Disease: Diagnosis and Treatment, Second Edition**


**Scope:** Limited to 160 pocket size (12.5 x 20 cm) pages, this textbook provides a concise, highly clinically oriented discussion of 17 topics in neuro-ophthalmology by Robert Tomsak and five topics on orbital disease by Mark Levine. Some of the chapters address symptoms or signs (diplopia, headache, ptosis). Others address diagnostic entities (anterior ischemic optic neuropathy, optic neuritis, optic glioma, ocular myasthenia, and orbital fractures). Two chapters deal with treatments (nystagmus and oscillopsia, and botulinum toxin). There are many tables dealing with diagnostic classifications and treatment options, black and white photographs of faces and fundi, visual fields, pathological specimens, and various diagrams. Although the publisher's Web site states that “case reports throughout illustrate approaches to treatment,” there are only four in the neuro-ophthalmology chapters and none in the orbital chapters. The reprinted preface to the first edition states that the book “is aimed at physicians at the resident level and up.”

**Strengths:** The book’s greatest strength is its compact size, a true “hand book” that easily can be carried in a pocket. The clinical approach includes various “pearls,” such as a list of prism prescribing tips adapted from The Fine Art of Prescribing Glasses Without Making a Spectacle of Yourself by Müller and Rubin, and a pragmatic approach to the treatment of headaches. The chapters have a consistent format. The text reads fluently and tables are used effectively to avoid incorporating lists in the main text. Each chapter has a suitable list of references for further study.

**Weaknesses:** Its size limits how deeply this book can explore neuro-ophthalmic and orbital diseases. There is no discussion of chiasmal disease, except in the context of gliomas, or post-chiasmal visual loss. There is no mention of gaze palsies or dorsal midbrain syndrome. Occasionally there are unsatisfactory statements such as “special attention should be given to the visual field examination” or “emphasis on visual field testing is mandatory” without any further explanation. The use of Octopus rather than Humphrey visual fields and reference to “seldom-used tests such as the Lancaster red-green test,” without any mention of the value of Hess charts or the Lees screen, fail to reflect the reality of clinical practice. The introductory paragraph of the chapter on optic neuritis makes it clear that the author wishes to include within that entity inflammatory optic neuropathies not due to demyelinating disease, yet the rest of the chapter only deals with the management of acute demyelinating optic neuropathy. The need to investigate atypical optic neuritis is not made clear.

**Recommended Audience:** General ophthalmologists and neurologists who need a quick guide to the management of neuro-ophthalmic and orbital disease will benefit most from this book.

**Critical Appraisal:** This book achieves a great deal in a small amount of space. It manages to cover most of the common neuro-ophthalmic and orbital diseases that an ophthalmologist will encounter, although the failure to cover post-chiasmal visual loss will disappoint neurologists. The text is easy to read and absorb, emanating an aura of simplicity. But the book does no more than scratch the surface of neuro-ophthalmology.

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**Neuro-Ophthalmology: The Requisites in Ophthalmology**


**Scope:** This is an introductory text on clinical neuro-ophthalmology aiming for a place between briefer board review outlines and a comprehensive reference book. It is part of a “Requisites” series, with volumes for other ophthalmic subspecialties. The book’s size and writing style suggest that it is designed to be read in its entirety rather than being used piecemeal for specific topics.

The book’s 256 pages are broadly divided into four parts: history, the sensory visual system, the visual motor system, and miscellaneous topics. The two larger middle sections each begin with a chapter on examination techniques. These skills (for example, measuring strabismus with a single Maddox rod) are presented with enough detail that a beginner would be able to accomplish the task without additional training.

The remaining chapters, each about 20 pages in length, have a uniform organization: an outline, the presented material, a recapitulation of the major teaching points, and suggested readings. Each chapter covers an anatomical grouping, such as “Optic Nerve Disorders.” Typically, they start with a review of the relevant anatomy and then go through a selection of common diseases. The more important conditions have sections that discuss evaluation and management but may not include sufficient detail to be used as an exclusive source.

Strengths: This book makes outstanding use of illustrations, often using several techniques to show different sides of a topic. For example, internuclear ophthalmoplegia is illustrated with 1) a sagittal diagram of the eye movement circuits in the brainstem; 2) a pseudo-three dimensional drawing of the connections between the cranial nerve nuclei, the medial longitudinal fasciculus, and the eyes in right and left gaze; 3) a set of clinical photos showing eye movements; and 4) an axial magnetic resonance image showing the lesion. The authors also make good use of tables and boxes to emphasize teaching points and to provide more extensive differential diagnoses than could be included in the text. It is clear that the illustrations were a major design consideration and not an afterthought to the written material.

Weaknesses: The more neurologic topics such as headache are not as rigorously discussed using the same format of anatomy through treatment. Similarly, nystagmus is treated descriptively without the same level of specific examination techniques, evaluation and treatment options, or even illustrations.

Recommended Audience: Residents and general ophthalmologists and neurologists would benefit from this book.

Critical Appraisal: In addition to being an excellent introduction to the field, its size, organization, and illustrations make it useful for a brief review when one is faced with a neuro-ophthalmic patient in office practice.

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The Headaches, Second Edition

Scope: This 1,000-page, 7-pound book represents the "state of the art" in the field of headache. The three editors of this multi-authored text are the academic cognoscenti of the international headache world. The 140 contributors read like a "Who's Who" of the headache community in Europe and North America, and include a number of our own NANOS members.

Contents: The book is divided into seven sections, including "Basic Science Aspects of the Headaches," "Secondary Headaches," "Cranial Neuralgias," "Headache and Facial Pain Associated with Disorders of the Skull and Cervical Spine," and "Special Problems in Headaches and their Management." There are 132 chapters that comprehensively cover nearly all aspects of headache. The text is organized and written in a manner reminiscent of the current Walsh and Hoyt textbook. While the prose is copious, there is also an appropriate supplement of graphs, tables, and pictures.

The Basic Science section is comprised of 15 chapters covering peripheral and central pain transmission, central sensitization, serotonin receptors, channelopathies and their purported relationship to migraine, and cortical spreading depression. The section on migraine consists of 40 chapters and 300 pages, and includes another discussion of the pathophysiology of migraine. The chapter on acute and preventive therapy of migraine nicely summarizes dozens of studies of various drugs, though it falls short on treatment recommendations.

Strengths: This text is the most comprehensive and scientifically based single source for information about headache. The chapters concerning pathophysiology, pain mechanisms, biochemistry, genetics, and anatomy are comprehensive and well presented. The text is well written and edited, despite having numerous authors. The book is organized, very well referenced, and contains a comprehensive index.

Weaknesses: Several medications that are gaining widespread use in headache treatment in the United States, such as topiramate and botulinum toxin, are not mentioned. While the common headaches such as migraine, cluster, and tension type headaches are extremely well covered, there is inadequate information on some of the less common headache disorders, such as hemimigraine continua and "short-lasting unilateral neuralgiform headache with conjunctival injection and tearing" (SUNCT).

Considering the significant number of headache and facial pain problems that stem from the eye and its structures, there is only rudimentary coverage of ocular issues. For example, there is little more than a mention of Horner syndrome in association with headache. While the topic of painful ophthalmoplegia is covered well, including a nice table on differential diagnosis, there are less than two pages given to this topic. For the physician looking for treatment recommendations and guidance, this is not the appropriate source.

Recommended Audience: This text is recommended for those with a major interest in headache disorders, specifically headache specialists. It is also would be an appropriate addition to any comprehensive medical library, or as a resource in a neurology departmental library. It is not a book appropriate for medical students, ophthalmology residents, or those with only a passing interest in headache.

Critical Appraisal: This is an excellent and comprehensive reference book on headache that contains excellent discussions about pathophysiology and a slightly dated but otherwise comprehensive review of headache therapy. It
rightfully belongs on the shelf of the headache specialist, and in each serious reference library.

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**Imaging Cerebrovascular Disease**


**Scope:** This is a timely and complete comprehensive review of established and developing neuroimaging techniques. It is assembled by 38 contributing authors (17 radiologists, 16 neurologists, and 5 neurosurgeons) and contains approximately 400 illustrations. It is formulated for clinicians managing patients with cerebrovascular disease.

**Contents:** There are five major sections. “Imaging Cerebrovascular Anatomy” and “Imaging Cerebrovascular Physiology” discuss the currently available methods of neuroimaging with emphasis on their technical aspects and specific role in cerebrovascular disease. “Imaging Ischemic Cerebrovascular Disease” and “Imaging Hemorrhagic Cerebrovascular Disease” approach the same material from a more clinical perspective. “Recent Developments” provides a view of newer techniques—particularly interventional methods for stenotic vessels—and technologies for addressing aneurysms and arteriovenous malformations.

**Strengths:** The book’s greatest strength is its practical value for neuroradiologists and clinicians. The technical information is necessarily detailed for neuroradiologists, yet still comprehensible to clinicians. The clinical content will be valuable to neuroradiologists. There is uniformity of approach between chapters that is unusual in books with many authors, including a realistic explanation of the limitations of each method of neuroimaging, such as the misclassification of severity of carotid stenosis by ultrasound. There is emphasis throughout the book on possible new therapies and their optimal methods of assessment of patients with acute stroke. For example, there is a useful algorithm based on time since onset of symptoms and signs for possible thrombolysis. The quality of illustrations is high.

**Weaknesses:** Some readers may dislike the repetition between the first and second sections, which cover similar material from both the radiological and clinical perspectives. There is no mention of computed tomography angiography in the diagnosis of cerebral venous sinus occlusion. Important issues in clinical management, particularly whether magnetic resonance angiography can replace catheter angiography for detection of intracranial aneurysm in symptomatic patients, are not addressed as directly as some readers might wish.

**Recommended Audience:** This book is highly recommended for any clinician involved in the management of patients with acute or chronic cerebrovascular disease. It is particularly useful for those confused by the plethora of imaging techniques available and who feel insufficiently informed when discussing cases with their neuroradiological colleagues. Neuro-ophthalmologists would benefit by having a copy readily available.

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**Greenfield’s Neuropathology, Seventh Edition**


**Scope:** Since its first edition in 1958, this book has been the gold standard and foremost encyclopedic source of everything and anything the thoughtful clinician/scientist would want to know about pathology of the central nervous system. The current seventh edition continues in this extraordinary tradition. It is a two-volume set, with over 1,000 pages in each volume. A series of over 50 outstanding experts from around the world have contributed to this new edition. The texts are not meant to be read cover to cover; rather, they offer a compendium of the histopathology of normal and abnormal central nervous system tissue.

Readers expect a new edition to maintain the standards that made previous editions such classics. They will not be disappointed. This edition continues the highest standard of scholarly presentation marked by comprehensiveness, elegance of illustration, and aesthetics of design. The style is wonderfully compelling; the individual entities are easily found for reference, the index is complete, and the references are up to date.
The first volume includes formal presentations on the central neuron itself, structure and function of glia, the cellular basis of pathology of the central nervous system, and chapters on raised intracranial pressure, hypoxia, vascular disease, malformations, and nutritional metabolic and neurodegenerative disorders. There is a wonderful section on neonatal neuropathology. Also included in volume one are chapters on mitochondrial disorders, neuro-toxicology, trauma, and epilepsy. There is a cogent chapter on ophthalmic neuropathology, and others on lysosomal diseases, presentations of a disordered hypothalamus or pituitary gland, an overview of regional neuropathology of the spinal cord and vertebral column, and summaries of epilepsy and trauma. The second volume presents a different analysis of neuropathology, one organized about etiologically identifiable events. These include chapters on viral disease, parasitic disease, bacterial disease, aging and dementia, prion disease, and disorders of movement and neurodegeneration. There are also presentations on the neuropathology of psychiatric disorders, disorders of muscle and nerve, and tumors of the central and peripheral nervous system.

There is a useful table of abbreviations employed, a complete bibliography to each chapter, and a reasonable and detailed index.

Strengths: The book’s strengths are its aesthetic appeal: the wonderful illustrations—both photographic and schematic—the elegance of the prose, and the completeness of topics. The illustrations are of exceptional quality. The book is a pleasure to hold and look through. Though intimidating, if taken in small bites it is wonderfully palatable.

Weaknesses: The weakest chapter is the one on ophthalmic neuropathology. Indeed, some of the included fundus photographs are of borderline value and quality.

Recommended Audience: It is often said, if rarely true, that “this is one book that all should be familiar with.” *Greenfield’s Neuropathology* is just such a text. Like a telephone book, you do not need to know every line that is in it, but you need to know where it is, and how to use it. Everyone with an interest in the central nervous system will find something of value in this book.

Critical Appraisal: This is an outstanding presentation by gifted authors of the pathology of the central nervous system. It is elegantly presented and organized, superbly illustrated, impeccably referenced. The definitive work in the field, it is a living testament to Sir Francis Bacon’s comment that the liquor of knowledge would soon vanish were it not conserved in books.

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The Prevention of Stroke

Scope: The Prevention of Stroke is a short, well-written, concise, and nicely organized text that provides an accurate and current review of major stroke topics.

Contents: The text is organized into three general categories of stroke: those at risk for stroke, approaches to stroke prevention, and the control of risk factors and recurrent stroke. The first section on risk for stroke offers a concise review of stroke epidemiology, with useful chapters on non-modifiable risks and non-traditional modifiable risks (including physical inactivity, alcohol use, inflammation, infection, homocystine, oral contraceptives, and estrogen replacement therapy). The chapter on genetics and stroke contains a nice glossary of terms and a user-friendly set of tables that are complete and practical.

There are five chapters on some social and political issues of stroke prevention. These include community and mass screening strategies; quality improvement methodology; and local, state, and national opportunities to educate the public about stroke prevention through both governmental and nonprofit organizations. Although this section is devoted to stroke, important parallels may be drawn for most any other disease.

The last section contains the more traditional chapters addressing how best to control specific risk factors such as hypertension, and lifestyle interventions. The appropriate use of medical and surgical techniques to prevent stroke are also reviewed. New endovascular approaches to treatment of stroke, aneurysm, and arteriovenous malformation are discussed in both practical and current applications.

Strengths: The organization and completeness of the monograph are its great strength. The innovative and complete helicopter view of the area is refreshing. For example, an entire chapter is devoted to controversies about asymptomatic intracranial aneurysms—a difficult area for all clinicians. As a concise text, this book offers the advantage of being readable from cover to cover.

Weaknesses: The only drawbacks to this text are those related to its compact size. With only 266 pages, the text tempts the reader who would like more detail. Fortunately, the references are adequate to direct the interested student to further sources for more depth.

Recommended Audience: Any clinician that regularly sees patients with stroke and wishes to have a broader background in the understanding of stroke risk and general approaches toward reducing those risks would benefit from reading this book.
Critical Appraisal: Those that have some interest in the administrative world of stroke, either at their hospital, in their managed care settings, or in the local, regional, or national public policy arena would find this an excellent introduction.

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Neurology and Neurosurgery: Basic Principles

Scope: This is a single-author, comprehensive neurology textbook. The book intends to be a reference source for all physicians involved in neurological matters.

Contents: This is basically a neurology text. Topics are organized in seventeen different chapters in a very traditional format. The first eight chapters deal with pertinent basic science, from a short history of neurology and neurosurgery, to embryology, neuroanatomy, neurophysiology, neuropathology, the neurologic exam, neurodiagnostic tests, and neurogenetics. The remainder of the book deals with specific clinical conditions of the nervous system. Chapters 9 to 17 deal with specific clinical conditions.

Strengths: Many of the topics are introduced to the reader with a rather interesting historical comment. The clinical aspects of each topic are well discussed. It is clear that the author is a consummate clinician with a keen interest in teaching the importance of clinical neurology. The illustrations are pertinent and well annotated. Although the book clearly represents the personal knowledge and experience of the author, it presents classic neurological concepts that are an important asset for anyone dedicated to this field of medicine.

Weaknesses: The reader will find that each of the first eight chapters discusses the topic broadly and does not get into enough detail. This is especially true for the neurophysiology, neuropathology, and neurogenetics chapters, as well as for the section dealing with current neuroradiological tests. The text is not presented in a dynamic, reader-friendly format, but in a dull, rather monotonous one that makes it unattractive for young readers, particularly medical students and residents. Treatment and management discussions, on the other hand, are rather outdated. For example, multiple sclerosis treatment lacks discussion on the pharmacotherapies. Although claimed within the book's title, this is not a neurosurgery textbook. Neuro-ophthalmology topics are essentially absent.

Recommended Audience: Resident and students are the intended audience, but because of the monotonous format of this book, I doubt they will find it attractive.

Critical Appraisal: This is a basic neurology text authored by an accomplished clinician whose main goal is to remind the reader of the importance of classic clinical concepts. It is well-organized and clearly written, and the figures and illustrations are pertinent. But the dull and at times redundant format, as well as the lack of updated data, may disappoint the reader.

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Opsoclonus-Myoclonus Syndrome During Pregnancy

To the Editor:

Opsoclonus-myoclonus syndrome (OMS) is a rare condition characterized by opsoclonus with oscillopsia, generalized myoclonus, ataxia (mainly in the legs), and occasionally learning and behavioral disorders. Nearly 50% of children with OMS have neuroblastoma. In adults, the most common causes are idiopathic, with less common causes being encephalitis, drug intoxication, and paraneoplastic disorders (1). We have encountered two cases that developed during pregnancy.

Case 1

A 33-year-old woman developed progressive dizziness, nausea, and gait difficulty in the ninth month of pregnancy. She had rapid, irregular, and oscillatory eye movements, and myoclonic jerks of the neck and limbs. She was unable to sit or stand because of truncal ataxia. Routine laboratory studies of blood and urine were normal. Serological tests for infectious pathogens were unremarkable; tumor markers and serum antibody to Ri antigen were not detectable. The cerebrospinal fluid contained 9/mm³ lymphocytes, 60 mg/dl protein, and 53 mg/dl glucose. Brain magnetic resonance imaging showed no abnormalities. On the decision of the obstetrician, she delivered a healthy child by cesarean section. Thereafter, she was treated with oral prednisolone (60 mg per day), which was gradually tapered over two months. At the three-month follow-up, she had minimal residual opsoclonus and mild dizziness.

Case 2

A 34-year-old woman developed nausea, vomiting, oscillopsia, dizziness, and unsteady gait in the fifth month of pregnancy. She showed opsoclonus and nonrhythmic myoclonic jerks involving the neck and upper extremities, mild dystonia on knee-heel testing, and truncal ataxia. She was unable to stand without assistance. Routine laboratory studies, CSF studies, and brain MRI were normal. Serum antibody to Ri antigen, syphilitic serology, and autoantibody screen were negative. As her neurologic symptoms did not improve within the following three weeks, she was treated with intravenous prednisolone 60 mg per day. After the treatment, the myoclonus gradually disappeared, but the opsoclonus and severe dizziness remained almost unchanged for two weeks. In the sixth month of pregnancy, she suffered a spontaneous miscarriage. Thereafter, the clinical symptoms improved markedly. One month after the termination of pregnancy, she was walking steadily with some residual dizziness and mild ocular flutter.

The relationship between OMS and pregnancy is unclear. Interestingly, chorea gravidarum, another movement disorder of uncertain etiology, occurs only in pregnancy. At Tokyo Metropolitan Neurological Hospital, eight patients have been diagnosed with clinically definite OMS in the past ten years. Considering the fact that this rare disorder occurred during pregnancy in 25% of our cases, we wonder if there is a susceptibility factor in pregnancy. Goto et al (2) previously reported a 35-year-old woman who developed vomiting, dizziness, and gait instability in the seventh month of pregnancy. Her examination resembled that of our patients. She was treated with clonazepam and oral prednisolone 60 mg per day and gradually improved within the following several months. She delivered a healthy child. Six months after the onset of OMS, she had recovered completely.

In our two cases and that of Goto et al (2), the neurologic symptoms were entirely similar to those of OMS unrelated to pregnancy. The conditions of the fetuses were good, except in the case that miscarried. In all three cases, the OMS occurred in the middle to late stages of pregnancy. Whether the symptoms improved because the pregnancy ended or because of corticosteroid therapy remains unclear. However, the OMS gradually improved after spontaneous miscarriage in our Case 2. Taken together, these results raise the possibility that pregnancy influences the appearance of OMS.

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REFERENCES

Projector Light Visual Fields

To the Editor:

The article entitled "Laser Pointer Visual Field Screening" by Lee et al (1) fails to mention the historical...
legacy of the use of projector light visual fields in neuro-ophthalmology. During my fellowship year with J. Lawton Smith, MD (Miami, FL) in 1979, Dr. Smith routinely used the projector light technique for doing central visual fields. Indeed, in his little book titled *The Optic Nerve* (2), he describes the technique and shows a photograph of how to do the test, as well as where to order a projector light. On Neuro-Ophthalmology Tape #57, “Visual Fields–2” (3), he goes into more detail about how to use this method of visual field testing.

Dr. Smith learned the technique from David G. Cogan, MD, during his neuro-ophthalmology fellowship year in Boston in 1958, and used it in his clinical practice for the next 36 years until his retirement. Dr. Smith told me that he had tried a laser pointer, but liked the original incandescent projector light better because it was less expensive and it was easier to vary the light intensity by partially masking the light with a finger.

Having used the projector light method of qualitatively testing visual fields on many occasions, I can personally vouch for its utility and versatility. Also, I vividly remember watching Dr. Smith test a supine bedridden patient. Dr. Smith lay on the floor next to the bed and used the hospital room ceiling as the “tangent screen!”

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REFERENCES
Thirtieth Annual Meeting of The North American Neuro-Ophthalmology Society, Orlando, Florida, March 27 to April 1, 2004

From March 27 to April 1, 2004, more than 300 neuro-ophthalmologists from 28 countries gathered in Orlando, Florida, to teach, tease, and torment one another with cases and state-of-the-art lectures at the thirtieth Annual Meeting of the North American Neuro-Ophthalmology Society (NANOS). Then they took time out to sunbathe, bike, and boogie.

The meeting began on Sunday with a one-day Frank B. Walsh Session, masterfully coordinated by Pamela S. Chavis, MD (Richmond, VA), and keenly mentored by neuroradiologist Anne Osborne, MD (Salt Lake City, UT) and neuropathologist Nitya R. Ghatak, MD (Richmond, VA). The mentors had put extra effort into providing enrichment PowerPoint material with each case. There were 23 mystifying platform presentations that quieted even the most intrepid quizmeisters. As usual, the answers arrived by handout at the end of the day. The proceedings were issued on CD-ROM to attendees and are available to others at NANOS headquarters.

Monday was occupied with a symposium on neurologic infectious disease, with invited guest speaker Joseph R. Berger, MD (Lexington, KY), who delivered splendid lectures on progressive multifocal leukoencephalopathy and neurologic complications of HIV infection. There were also lectures on tuberculosis, syphilis, Lyme, and Bartonella; on fungi, on infectious (more likely autoimmune) choroidopathies, and on prion diseases. In the early afternoon, Preston C. Calvert, MD (Alexandria, VA) coordinated an examination skills transfer class, and Laura J. Balcer, MD (Philadelphia, PA) presented a biostatistics laboratory. In the later afternoon, there were eight platform free papers, including one on the controversial topic of visual restitution training in those with hemianopia delivered by Susanne Trauzettel-Klosinski, MD (Tubingen, Germany), the sponsored foreign guest of NANOS.

Tuesday included 24 platform presentations, and Wednesday began with an ocular motility symposium featuring Joseph L. Demer, MD, PhD (Los Angeles, CA) on functional anatomy of the extraocular muscle pulleys; Michael C. Brodsky, MD (Little Rock, AR) on the phylogeny of dissociated vertical divergence, oblique muscle overaction, and congenital strabismus; R. John Leigh, MD (Cleveland, OH) on current concepts in supranuclear eye movement control; Mark J. Morrow, MD (Hattiesburg, MS) on treatment of ocular oscillations; and Agnes M. Wong, MD (Toronto, ON) on Listing’s Law. In the late afternoon, 80 posters were on display to a lively crowd.

Thursday morning, the final half-day, was devoted to neurosurgical innovations and complications. Gregory S. Kosmorsky, DO (Highland Heights, OH) reviewed concepts of hydrocephalus; Mark Luciano, MD, PhD (Cleveland, OH), an invited lecturer and neurosurgeon from the Cleveland Clinic, gave two fine presentations on cerebrospinal fluid diversion procedures; Robert C. Sergott, MD (Philadelphia, PA) focused on visual complications of surgical procedures; Kimberly Peele Cockerham, MD (Palo Alto, CA) reviewed advances in orbital surgery; and Alejandro Berenstein, MD (New York, NY), an invited lecturer and renowned interventional neuroradiologist, discussed current approaches in intracranial endovascular procedures.

At the traditional Wednesday night banquet, the following awards were announced: the Thomas and Susan Carlow Young Investigator Award went to John B. Kerrison, MD, Wilmer Institute (Baltimore, MD), for his presentation entitled "Candidate Gene Analysis in X-linked Congenital Nystagmus (NYS1)," the Fellow Award went to Guy Jirawuthiworavong, MD, MA, Jules Stein Eye Institute (Los Angeles, CA), for his presentation entitled "Frequency of Antiretinal Antibodies in Normal Human
FIG. 2. John B. Kerrison, MD (Baltimore, MD), winner of the Thomas and Susan Carlow Young Investigator Award, with Dr. Agnes Wong and Kathleen B. Digre, MD (Salt Lake City, UT).

FIG. 3. Guy Jirawuthiworavong, MD, MA (Los Angeles, CA), winner of the Fellow Award, flanked by Leah Levi, MD (La Jolla, CA) (left) and Dr. Digre.

FIG. 4. H. Stanley Thompson, MD (Iowa City, IA), winner of a Distinguished Service Award, with Dr. Digre.

Serum”; the Resident Physician Award went to Gregory F. Wu, MD, PhD, University of Pennsylvania (Philadelphia, PA), for his presentation entitled “Visual Function and Disease Phenotype in Multiple Sclerosis;” the Medical Student Award went Paula Wynn, Columbia University, for her presentation entitled “A Quantitative Approach to Identifying Non-Organic Contributions to Field Defects Using the Multifocal Visual Evoked Potential (mfVEP).”

Presented for the first time this year, the Frank B. Walsh Award went to Margaret M. Wong, MD (Toronto, ON), for her presentation on “Frozen Eyes and Muscle Cramps.”

The Distinguished Service Awards went to H. Stanley Thompson, MD (Iowa City, IA), James A. Sharpe, MD (Toronto, ON), and Jonathan D. Wirtschafter, MD (Minneapolis, MN). Simmons Lessell, MD (Boston, MA) was acknowledged for giving the third Hoyt Lecture on “The Neuro-Ophthalmic Complications of Radiation” at the 2003 Annual Meeting of the American Academy of Ophthalmology. The lecture has been published in this issue of the Journal of Neuro-Ophthalmology.
Outgoing NANOS President Kathleen B. Digre, MD (Salt Lake City, UT) received a plaque for her dedication to NANOS during her two-year term. She will be succeeded by Larry Frohman, MD (Newark, NJ). The following new board members were announced: Deborah L. Friedman, MD (Rochester, NY), President Elect; Nancy J. Newman, MD (Atlanta, GA), Vice President; Leah Levi, MD (San Diego, CA), Secretary; and Michael C. Bruck, MD (Little Rock, AR), board member. Outgoing board members are Steven A. Newman, MD (Charlottesville, VA), Vice President; Laura J. Balcer, MD (Philadelphia, PA), Secretary; Andrew G. Lee, MD (Iowa City, IA), board member; and Neil R. Miller, MD (Baltimore, MD), board member.

Jonathan D. Trobe, MD
Ann Arbor, Michigan
FIG. 8. Susan Pepin, MD, (Hanover, NH), Andrew G. Lee, MD (Iowa City, IA), and Steven A. Newman, MD (Charlottesville, VA).

FIG. 9. Joseph F. Rizzo, III, MD (Boston, MA) (left) explains his poster findings to Michael L. Rosenberg (Edison, NJ), Steve R. Hamilton (Seattle, WA), and Marc H. Levy, MD (Sarasota, FL).
FIG. 10. E. Ulysses Dorothea (Houston, TX), Jade S. Schiffman, MD (Houston, TX), and Rosa A. Tang, MD (Houston, TX).

FIG. 11. Ralph A. Sawyer, MD (North Potomac, MD) and Robert M. McFadzean, MD (Glasgow, Scotland).
FIG. 12. Line dancing at NANOS 2004 night out.
Upcoming Meetings

September 21–23, 2004
The 27th Annual Japanese Neuroscience Meeting
Osaka International Convention Center (Grand CUBE Osaka), Japan
http://www.congre.co.jp/neuro2004/
Contact: neuro2004@congre.co.jp

September 24–27, 2004
European Association for Vision and Research (EVER)
Vilamoura, Portugal
Contact: ever@skynet.be

October 3–6, 2004
129th Annual Meeting of the American Neurological Association
Toronto, Ontario
http://www.aneuroa.org/
Contact: Julieratzloff@llmsi.com

October 15–17, 2004
Joint Meeting of the Asian Neuro-Ophthalmology Society (ASNOS) and Japanese Neuro-Ophthalmology Society (JNOS)
Nagoya, Japan
http://www.shinkeiganka.com/asnos.html
Contact: (fax) 81-42-778-9417

October 16–21, 2004
Congress of Neurological Surgeons 54th Annual Meeting
San Francisco, California
Contact: info@ICNS.org

October 23–26, 2004
Joint Meeting of the American Academy of Ophthalmology (AAO) and the European Society of Ophthalmology (SOE)
New Orleans, Louisiana
http://www.aao.org/annual_meeting/
Contact: meetings@aao.org

October 23–27, 2004
34th Annual Meeting of the Society for Neuroscience
San Diego, California
http://web.sfhn.org/
Contact: info@sfhn.org

February 2–4, 2005
International Stroke Conference
New Orleans, Louisiana
http://strokeconference.americanheart.org/portal/strokeconference/sc/
Contact: strokeconference@heart.org

February 12–17, 2005
Copper Mountain Resort
Copper Mountain, Colorado
http://www.nanosweb.org/meetings/
Contact: (860) 586-7507

March 3–6, 2005
American Society of Neuroimaging 28th Annual Meeting
Orlando, Florida
http://asnweb.org/meeting/meeting2005.shtml
Contact: asm@llmsi.com

March 9–13, 2005
American Association of Pediatric Ophthalmology & Strabismus Annual Meeting
Orlando, Florida
http://www.aapos.org/annualmeeting05.htm
Contact: aapos@aao.org

March 18–21, 2005
XXV Congress of the Pan American Association of Ophthalmology
Santiago, Chile
http://www.paaos.org/congress.htm
Contact: info@paaos.org

April 9–16, 2005
57th Annual Meeting of the American Academy of Neurology (AAN)
Miami, Florida
http://am.aan.com/
Contact: memberservices@aan.com

April 16–21, 2005
American Association of Neurological Surgeons Annual Meeting
New Orleans, Louisiana
http://www.aans.org/annual/
Contact: 847.378.0500, info@aans.org
May 1–5, 2005
The Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting
Fort Lauderdale, Florida
http://www.arvo.org/Meetings/meetgrid.asp
Contact: (240) 221–2900, arvo@arvo.org

May 21–27, 2005
43rd Annual Meeting of the American Society of Neuroradiology (ASNR)
Toronto, Ontario
http://www.asnr.org/
Contact: (630) 574-0220

May 25–28, 2005
14th European Stroke Conference
Bologna, Italy
http://www.eurostroke.org
Contact: Hennerici@eurostroke.org

June 18–22, 2005
15th Meeting of the European Neurological Society
Vienna, Austria
http://www.ensinfo.com
Contact: gerard.said@bct.ap-hop-paris.fr

June 19–22, 2005
7th Meeting of the European Neuro-Ophthalmological Society (EUROS)
Moscow, Russia
Contact: conf@msi.ru

June 14–18, 2005
Canadian Congress of Neurological Sciences Annual Meeting
Ottawa, Ontario
http://www.ecns.org/ecns_information/events.html
Contact: web@ecns.org

June 23–25, 2005
47th Annual Scientific Meeting of the American Headache Society
Philadelphia, Pennsylvania
http://www.ahsnet.org/calendar
Contact: ahshq@talley.com

June 25–28, 2005
8th European Congress of Neuropathology
Amsterdam, The Netherlands
http://www.euro-cns.org/congresseur.php
Contact: a.vanschendel@amc.uva.nl

September 17–20, 2005
9th Congress of the European Federation of Neurological Societies
Athens, Greece
http://www.efns.org/efns2005
Contact: efns05@kenes.com

September 25–29, 2005
Joint Meeting of the 15th Congress of the European Society of Ophthalmology and the 103rd Annual Meeting of the German Society of Ophthalmology
Berlin, Germany
http://www.soeye2005.org
Contact: soe2005@porstmann-kongresse.de

November 5–11, 2005
XVIII World Congress of Neurology
Sydney, Australia
http://www.wcn2005.com
Contact: wcn2005@icmsaust.com.au

November 29–December 2, 2005
16th International Neuro-ophthalmology Society Meeting
Odaiba, Tokyo, Japan
http://www.secretariat.ne.jp/inos2006/
Contact: inos@secretariat.ne.jp