jects. These findings constitute new evidence in support of the view that the transport of vitamin A in retinitis pigmentosa is unimpaired, but do not rule out the possibility that the mechanism of release of retinol from retinol-binding protein may be abnormal.

The well-known tendency of the retinol concentration in blood to increase with age probably reflects a gradual diet-related increase in the storage of retinyl esters in the liver that commonly continues throughout life, but can be greatly accelerated by vitamin supplementation. It seems likely that the presence of a high concentration of retinyl esters in the liver might increase production and release of retinol-binding protein into the circulation. There was some indication that the retinol concentration in blood increased with age (Table 1) in the retinitis pigmentosa patients in this study as well as in the normal subjects previously examined. Although the retinitis pigmentosa patients and the normal subjects were not precisely matched by age, statistical analysis reveals no significant difference between the groups with respect to the concentration of retinol in the circulation. It would appear that some uncontrolled factor of age, diet, or methodology may have accounted for the reduced concentrations of retinol in blood that have been reported in retinitis pigmentosa.

Excellent technical assistance was provided by Mrs. Martha H. Rollins and advice concerning statistical analysis of the data was obtained from Ms. Barbara Campbell.

From the Department of Ophthalmology, University of Washington School of Medicine, Seattle. This study was supported by United States Public Health Service Research Grant No. EY 00343 and Training Grant No. EY 00050 from the National Eye Institute. Submitted for publication April 29, 1974. Reprint requests: Dr. S. Futterman, Department of Ophthalmology, University of Washington School of Medicine, Seattle. Wash 98195.

Key words: retinol, retinol-binding protein, retinitis pigmentosa, vitamin A, retina, carotene.

REFERENCES


A possible cause of decreased vision in cryptococcal meningitis. CARL KUPFER AND EDNA MCCRANE.

The optic nerves, chiasm, optic tracts, and lateral geniculate nuclei of six patients having fatal cryptococcal meningitis were examined histopathologically using the Smith-Quigley stain for myelin and periodic acid-Shiff stain for cryptococcal organisms. A correlation was made between the invasion of visual pathways by the cryptococcal organism, the presence or absence of papilledema, and the preservation or loss of visual acuity. In three patients with papilledema and loss of visual acuity, multiple cryptococcal abscesses were present in the optic
nerve and tracts. In three patients with papilledema but normal visual acuity, minimal or no involvement of the visual pathways by cryptococcus was noted despite widespread evidence elsewhere in the brain and meninges. It appears that loss of visual acuity in cryptococcal meningitis may represent direct invasion of the visual pathways by the organism.

Although cryptococcal meningitis can be treated successfully in over 50 per cent of cases, approximately 20 per cent of patients surviving are left with severe visual disability. Even though the decrease in visual acuity often occurs in conjunction with papilledema and a significantly elevated cerebrospinal fluid pressure, it has been suggested that the loss in vision is not related to the papilledema or increased intraventricular pressure, but possibly to the direct invasion of the visual pathways by cryptococcal organisms. The purpose of this report is to determine whether this explanation can be substantiated by relating the presence or absence of a visual acuity deficit in patients having cryptococcal meningitis and papilledema to the invasion of visual pathways by the organisms.

Methods. Autopsy reports of patients having a diagnosis of cryptococcal meningitis were reviewed. Six cases in which papilledema was present, visual acuity had been recorded and the optic nerves, optic chiasm, optic tracts, and/or lateral geniculate nuclei were available for examination. The clinical data is summarized in Table I. The optic nerves, chiasm, optic tracts, and lateral geniculate nuclei were fixed in 10 per cent neutral formalin and processed in paraffin. Cross-sections of the optic nerves and chiasm, and coronal sections of the optic tracts and lateral geniculate nuclei were sectioned at 12 \( \mu \) thickness and stained with Luxol fast blue and periodic acid-Schiff in combination.
Fig. 3. A, minimal involvement of right optic tract by cryptococcal organisms in Case 4.
B, small foci (at arrows) of cryptococcal organisms in lamina 5 of the right lateral geniculate
nucleus in Case 5. C, no invasion of this optic tract by cryptococcal organisms despite massive
involvement of adjacent brain tissue (see arrows).

The determination of the presence of cryptococcal organisms in these visual pathways were made
by an observer (EMcC) who was unaware of the clinical findings.

Results. Table II summarizes the findings in the six cases with respect to papilledema, visual
acuity, and invasion of the visual pathways by cryptococcal organisms. There is a correlation be-
tween decreased visual acuity and cryptococcal invasion of the visual pathways as well as a corre-
lation between preservation of visual acuity in the presence of papilledema but little or no invasion
by cryptococcal of the visual pathways. There is no apparent relationship between the level of
visual acuity and use of intrathecal therapy or other systemic diagnosis. Fig. 1 demonstrates in-
vasion of optic tracts by cryptoccocus in Case 1. Fig. 2 demonstrates multiple foci of cryptococcal
organisms in the optic tracts in Case 2. In sharp contrast, there was little involvement of one optic
tract in Case 4 (Fig. 3, A), slight involvement of lamina 5 in one lateral geniculate nucleus in
Case 5 (Fig. 3, B), and no involvement of the visual tracts by cryptoccocus in Case 6 despite
massive involvement of the meninges and other portions of the central nervous system (Fig. 3, C).

Discussion. These findings are significant because patients with cryptococcal meningitis who
sustain a sudden loss of vision may be considered candidates for, and may undergo, a subtemporal
decompression if the surgeon believes that the decreased visual acuity is secondary to increased
intracranial pressure. However, if the loss of vision represents a direct invasion of the visual pathways
by cryptoccocus, this extensive neurosurgical procedure in a seriously ill patient is unjustified.

What remains to be determined is why the cryptoccocus spreads directly to the visual pathways in some patients and not in others, despite extensive meningitis and encephalitis. Such
a study is now underway.

Summary. From a retrospective examination of both the clinical and autopsy records of six pa-
tients with a diagnosis of cryptococcal meningitis,
Table I

<table>
<thead>
<tr>
<th>Case</th>
<th>Age, color, sex</th>
<th>Papilledema (diopters)</th>
<th>Visual acuity</th>
<th>Intrathecal amphotericin</th>
<th>Other diagnosis</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>35 WM</td>
<td>1</td>
<td>20/400 OU</td>
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<td>Hodgkin's disease</td>
</tr>
<tr>
<td>2</td>
<td>2 WF</td>
<td>1</td>
<td>NLP</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>21 WF</td>
<td>1</td>
<td>1-2</td>
<td>Yes</td>
<td>Periarteritis nodosa</td>
</tr>
<tr>
<td>4</td>
<td>65 WM</td>
<td>1-2</td>
<td>20/20 OU</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>24 WM</td>
<td>1-2</td>
<td>20/20 OU</td>
<td>Yes</td>
<td>Hodgkin's disease</td>
</tr>
<tr>
<td>6</td>
<td>32 WM</td>
<td>1-2</td>
<td>20/20 OU</td>
<td>Yes</td>
<td>Hodgkin's disease</td>
</tr>
</tbody>
</table>

Table II

<table>
<thead>
<tr>
<th>Case</th>
<th>Papilledema</th>
<th>Decreased visual acuity</th>
<th>Cryptococcus in visual pathways</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>Yes</td>
<td>Marked</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>Yes</td>
<td>Marked</td>
</tr>
<tr>
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<td>+</td>
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</tr>
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<td>+</td>
<td>No</td>
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</tr>
<tr>
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<td>+</td>
<td>No</td>
<td>Slight</td>
</tr>
<tr>
<td>6</td>
<td>+</td>
<td>No</td>
<td>None</td>
</tr>
</tbody>
</table>

decreased visual acuity appears to be related to direct invasion of the visual pathways by the cryptococcal organisms rather than to increased intracranial pressure and attendant papilledema.

The authors wish to acknowledge the advice of Dr. John Bennett in the preparation of this paper.


Key words: cryptococcal meningitis, visual acuity, increased intracranial pressure.

REFERENCES


Kinetics of corneal epithelial regeneration and epidermal growth factor. PATRICK C. HO, WILKES H. DAVIS, JAMES H. ELLIOTT, AND STANLEY COHEN.

Purified epidermal growth factor (EGF), isolated from mice submaxillary glands, was used to study regeneration of rabbit corneal epithelium. The progressive decrease in area of standardized 7 mm. central corneal epithelial wounds was determined by serial standardized photography. The projected fluorescein-stained area was measured by planimetry. It has been found that EGF in the concentrations studied (0.05 mg. per milliliter; 0.5 mg. per milliliter; and 2.0 mg. per milliliter) when given topically four times daily, increased the corneal epithelial healing rate compared to saline controls. A 40-fold variation of EGF concentrations failed to effect a statistically significant change in corneal epithelial healing rate. No sign of toxicity was detected clinically and histologically with topical application of EGF on rabbit corneas with intact epithelium and on corneas denuded of epithelium.

Ulcers and erosions of the corneal epithelium are a major cause of ocular morbidity and visual loss. Delayed corneal re-epithelialization may be associated with or follow microbial infections, alkali burns, penetrating keratoplasties, radiation keratoconjunctivitis, toxic keratoconjunctivitis, dry eyes, and the recurrent corneal erosion syndrome. Prolonged ulceration or erosion of the cornea eventually results in thinning or melting of the corneal stroma. Current conventional therapeutic alternatives for long-standing corneal ulcers or erosions are not uniformly successful and thus far no single therapeutic modality has been demonstrated to have uniform efficacy in the promotion of corneal epithelial repair.

Recently, epidermal growth factor (EGF), first isolated by Cohen from mice submaxillary glands, has been shown to enhance the healing of experimental corneal epithelial wounds. The present studies report our findings on the ocular toxicity of EGF and quantitate the kinetics of corneal epithelial regeneration in rabbits following topical application of highly purified and characterized EGF.

Material and method. Epidermal growth factor. EGF was isolated from the submaxillary glands of adult male mice and purified by the new procedure of Savage and Cohen involving a two-step column fractionation. It is a white powder soluble in water. EGF solutions of three concentrations (0.05 mg. per milliliter, 0.5 mg. per milliliter, and 2.0 mg. per milliliter) were prepared by dissolving EGF

*EGF was kindly supplied by Dr. S. Cohen at Vanderbilt University School of Medicine.