INTRODUCTION
Thrombosis of the cavernous sinus is one of the most dramatic of neuro-ophthalmic conditions. Within a short period, a swollen orbit, limited ocular motility and impaired vision develop, and life is threatened. Rapid diagnosis and therapeutic action are required. Morbidity is high, and outcome cannot be certain. Therefore, this striking syndrome, first pathologically recognized by Duncan in 1821 and later clinically defined by Bright in 1831 and especially the eye findings by Knapp in 1868 (Clifford-Jones et al., 1982), is very pertinent to all physicians engaged in the care of patients who present with acute complaints of periorcular pain, orbital congestion and double vision. The following review includes the anatomy, pathology, presentation, differential diagnosis, diagnostic approaches and management of cavernous sinus thrombosis, and is obtained from selected references and especially from the literature of the past decade.

ANATOMY
In 1732, to describe the anatomic space adjacent to the sella turcica, Winslow coined the term, cavernous sinus. Containing a varied array of blood vessels and nerves, Dwight Parkinson has referred to this space as a veritable anatomic jewel box. Shaped like an envelope, the cavernous sinus lies between the dura on the medial edge of the middle cranial fossa and the peristeum of the sella turcica. It extends over 2.0-2.5 cm from the superior orbital fissure to the petrous apex and is about 1.0 cm in width. Often thought to consist entirely of a trabeculated venous canal, microscopic dissection and anatomic casts in recent years have suggested that a portion of the cavernous sinus is composed of a network of extradural veins that surround the internal carotid artery. As a result, dissection within this parasellar space is possible, especially in its posterior aspect. Nonetheless, Harris and Rhoton (1976) have identified three main venous spaces within the cavernous sinus, one medially, anteroinferiorly and posteroinferiorly. The cavernous sinus receives venous flow from many regions which explains its susceptibility to infection. It receives venous flow from the face by way of connections through the superior orbital vein with the facial vein and from the pterygoid plexus. Anteriorly, it also receives the sphenopalatine and superficial middle cerebral veins. Posteriorly, the superior petrosal and inferior petrosal sinuses are connected to the cavernous sinus. The paired cavernous sinuses are interconnected by small anterior and posterior intercavernous channels. Pulsations of the internal carotid artery may aid in expelling blood from the cavernous sinus. Flow through the cavernous sinus, however, is multi-directional and depends mainly on pressure gradients in neighboring sinuses, but tends to be posterior into the petrous sinuses.

The lateral wall of the cavernous sinus is composed of both superficial and deep layers of the dura (Umansky and Nathan, 1982). The superficial layer is formed by the dura mater on the medial side of the middle cranial fossa. The deep layer is formed by the sheaths of the oculomotor, trochlear, ophthalmic and maxillary nerves. These layers are easily separated from one another. The sympathetic nerves course about the wall of the internal carotid artery and may leave it as it emerges from the foramen lacerum. These nerves briefly pass with the sixth nerve in the posterior cavernous sinus before jumping to the ophthalmic nerve with which they enter the orbit. The sixth nerve runs entirely within the cavernous sinus lateral to the carotid artery and often is divided into several filaments. Posteriorly, the forward reflection of the cavum trigeminale extends into the lateral wall of the sinus.

PATHOLOGY
Aseptic thrombosis of the cavernous sinus occurs with trauma, tumor invasion, aneurysmal expansion, dehydration, emaciation and hypercoagulable states. Septic thrombosis is much more common and occurs according to Shaw (1952) from the spread of infection through various routes: 1.) from the face via the angular and ophthalmic veins; 2.) from the middle ear via the superior petros sinus; 3.) from the teeth, maxillary sinus and cervical vertebrae via the pterygoid plexuses which empties into the inferior ophthalmic vein; 4.) from the sphenoid sinus by direct extension or draining emissary veins; 5.) by extension from an infected internal jugular vein, lateral sinus or petrosal sinus; or 6.) from the plexus of veins surrounding the internal carotid artery. Often there is a latency of 5-6 days between the initial infection and the subsequent signs of cavernous sinus thrombosis. The extension of an infection into the cavernous sinus is explained by several mechanisms: 1.) a continuous, infected clot bridges the initial infected site to the cavernous sinus; 2.) a septic embolus lodges in the cavernous sinus; or 3.) bacterial toxins induce endothelial changes and thrombosis of the cavernous sinus which subsequently becomes infected. Complications include thrombosis of the veins which drain into the cavernous sinus resulting in increased intracranial pressure or venous infarction, septicemia, brain abscess, subdural empyema, pituitary insufficiency, orbital abscess and pulmonary embolism. If the carotid artery becomes inflamed, it may thrombose, form an embolus or fistula or seed a mycotic aneurysm in distal branches of the middle
cerebral artery. In 1952 Shaw reported lung infection in 17 of 50 cases which he thought were invariably a result of septic emboli. Pulmonary emboli probably are derived from a thrombus that has extended from the cavernous sinus into the inferior petrous sinus and its draining jugular vein. Abscesses of the orbit were also found by Shaw in 9 of 50 patients. In this report, infection originated in 61% from furuncles of the nose and face, 15% from the paranasal sinuses, 8% from the middle ear, 9% from dental infections (usually from the maxillary area) and 9% from miscellaneous sources. The high incidence of furuncle infection of the face or "muzzle area" is reflected in the isolation of 70% Staphylococcus aureus and 22% streptococcal organisms in this series. Staphylococcus aureus is also a common pathogen in acute sphenoidal sinusitis, a predisposing condition to thrombosis of the cavernous sinus (Lew et al., 1983). Anerobic streptococcal infections are less commonly encountered in cavernous sinus thrombosis, but important pathogens to consider when selecting antibiotics. In patients with a history of chronic sinusitis that exceeds one month, often with preceding antibiotic coverage, anerobes, coagulase-negative staphylococci, gram negative organisms and fungi, particularly species of Aspergillus (Sekar et al., 1980), should be considered. The frequency of primary middle ear infections appears to be less than that noted earlier in this century.

PRESENTATION

In patients with cavernous sinus thrombosis, fever is almost invariably present (DiNubile, 1988). Headache occurs in half of the patients and is much more common in those patients with facial infections. Typically, both the headache or periorbital pain worsen over time. Paresthesias or pain over the face, in the distribution of the first and second trigeminal divisions, may occur. A very early ocular sign is swelling of the eyelids and chemosis. This is followed by proptosis and swelling of the face. Ophthalmoplegia is often present soon after and results from orbital congestion, infection of oculomotor muscles (Welsh, 1987) or inactivation of oculomotor nerves. The sixth cranial nerve is commonly the first cranial nerve affected because of its course directly through the cavernous sinus. involvement of the third, fourth and first two divisions of the cranial nerve soon follows and usually indicates more extensive disease because these nerves are more protected in their course in the lateral wall of the cavernous sinus. With involvement of the oculomotor nerve the pupil is dilated and fixed to light unless the sympathetic plexus about the carotid artery is disrupted in which event the pupil remains fixed but in a mid-position. Rarely, patients with a sixth nerve paresis and a post-ganglionic Horner's syndrome have been described who have selective lesions in the posterior cavernous sinus or distal portion of the petrous part of the carotid canal (Parkinson and Mitchell, 1979). In those patients who are not obtunded, loss of sensation of the cornea and forehead and the cheek and palate in the respective first and second branches of the trigeminal nerve may be demonstrated. Although initially alert, obtundation and lapses into a delirium develop in a majority of patients. In those patients with an impaired sensorium, only a depressed corneal reflex may be found. Vision is blurred for near if the parasympathetic fibers of the third cranial nerve for accommodation are involved. Vision is also limited by arterial insufficiency, venous stasis with engorged retinal veins, retinal hemorrhages, papilledema and keratitis from loss of corneal sensation. Fibber and Sogg (1978) have provided evidence that elevated intracranial pressure and increased resistance to flow from high intraorbital pressure may contribute to ischemic changes in the optic nerve. Not infrequently the media is clouded, and visualization of the fundus is impeded. These ocular signs generally progress either acutely or subacutely, and occasionally chronically. Not infrequently, spread through an intercavernous sinus to the opposite cavernous sinus occurs over several days and is marked by contralateral chemosis, edema of the eyelids and lateral rectus paresis. In persistent cases, the failure of involvement of the opposite cavernous sinus should give pause toward the correctness of the diagnosis. Signs of a thrombotic facial or mastoid vein, although infrequent, or infected furuncle should also be sought. Invasion of the meninges is indicated by a stiff neck, generalized headache and altered mental status. Venous infarcts or carotid arterial emboli are heralded by focal neurologic signs.

Variation in the rapidity of the symptom complex has been commented upon by a number of observers. The more acute forms of cavernous sinus thrombosis appear to occur in patients with facial infections. This may be due to the virulence of staphylococcal or streptococcal organisms. More subacute or chronic evolution tends to develop in patients with paranasal sinus, middle ear or dental infections.

DIAGNOSIS

Clinical Features

In 1926 Eagleton suggested six, often-quoted, points as guides to the diagnosis of cavernous sinus thrombosis: 1) a known site of infection, 2) septicemia, 3) early signs of venous congestion such as full retinal veins, 4) ocular nerve, ophthalmic or maxillary nerve deficits, 5) abscess or phlebitis contiguous to the cavernous sinus and 6) signs of an intracranial infection (e.g. headache, stiff neck, obtundation). Whereas not all of these points must be present to initiate expectant management, they should be sought.

The differential diagnosis of cavernous sinus thrombosis includes a variety of acute and subacute infections of the orbit. Orbital vein thrombosis is occasionally a complication of a hypercoagulable state or embolization of a fistulous internal carotid artery. This painful orbital swelling differs from a cavernous sinus thrombosis with its dramatic suddenness. The conjunctival and orbital swelling and ophthalmoplegia of orbital cellulitis makes distinction from cavernous sinus thrombosis difficult. Tenderness to retropulsion of the globe and spread of infection from an adjacent ethmoidal sinus is common in orbital cellulitis (Haynes and Cramblett, 1967; Goodwin, 1985). Pseudotumor of the orbit and the superior orbital fissure syndrome of Tolosal-Hunt both present with painful ophthalmoplegias that are similarly difficult to separate from the early stages of a cavernous sinus thrombosis. Possible distinction between the entities is made by the pat-
Aspergillus infection should be considered in patients with sinusitis, pseudotumors, or orbital cellulitis. Aneurysms of the orbit and cavernous sinus are known to cause thrombosis of the cavernous sinus or the internal carotid artery. Lateral expansion of the sinus is usually associated with the presence of diabetes mellitus, roentgenographic signs of ethmoidal infection and a blackish eschar in the nose or over the face. As previously mentioned, aneurysm causes a painful acute ophthalmoplegia with expansion of the cavernous carotid artery. This appearance of fever, bilateral orbital edema, ophthalmoparesis and subsequent altered mental status as factors giving consideration to thrombosis of the cavernous sinus or the internal carotid artery. Lateral expansion of the cavernous carotid artery in the form of an aneurysm causes a painful acute ophthalmoplegia with partial facial anesthesia due to compression of the cranial nerves in the lateral wall of the cavernous sinus. This condition usually differs from cavernous sinus thrombosis in the absence of orbital swelling, antecedent infection and fever. Its diagnosis is readily confirmed by modern imaging studies of the cavernous sinus region. Recognition of the painful ophthalmoplegia of an acute or subacute carotid-cavernous sinus fistula is assisted by the presence of prominently tortuous, arterialized conjunctival vessels and auscultation of a bruit over the eye. Subperiosteal mucocoeles cause an indolent pain, low-grade orbital swelling and ophthalmoplegia that may mimic a chronic cavernous sinus thrombosis. Fine serial sections of the sinuses adjacent to the orbit and cavernous sinus with modern imagers are currently able to identify these lesions. Trichinellosis is now rare, but Barr (1966) has reported the sudden appearance of fever, bilateral orbital edema, ophthalmoplegia and subsequent altered mental status as factors giving consideration to thrombosis of the cavernous sinus. Diffuse myalgia, lack of chemosis and eosinophilia are the usual indications for trichinosis that lead to further serologic study or muscle biopsy.

Neuroradiology

CT may show signs of orbital involvement similar to orbital cellulitis, i.e., scleral thickening, swollen ocular muscles and retrobulbar densities. It may also show a dilated superior orbital vein, orbital abscess or cortical vein infarct, but it rarely shows a thrombus in the cavernous sinus. Thin transverse and coronal sections through the orbits and parasellar region with bone windows are indicated in all patients suspected of a cavernous sinus process. Dynamic or slow infusion of a large volume of contrast accompanied by coronal sections may reveal impaired filling of the involved cavernous sinus. Magnetic resonance scanning is perhaps now the procedure of choice to show altered flow or a thrombus in the cavernous sinus as well as most of the soft tissue abnormalities disclosed by CT scanning (Savino et al., 1986). With the availability of these non-invasive studies, cerebral angiography, orbital or jugular venography are no longer needed to confirm the diagnosis of cavernous sinus thrombosis.

MANAGEMENT

In 1936 Grove reported more than 400 cases of cavernous sinus thrombosis; the mortality approximated 100%. The high mortality rate prompted Eagleton to suggest ligation of the internal carotid artery, evisceration of the orbit and drainage of the cavernous sinus through a sphenoidal fistula. The availability of antibiotics has significantly changed the approach to this most dramatic neuro-ophthalmic condition. First, widespread use of oral antibiotics for infections about the face, in the sinuses and the ear has greatly reduced the incidence of cavernous sinus thrombosis. Secondly, the mortality of cavernous sinus thrombosis is much diminished. Shaw in 1952 reported recovery in 52 of 60 patients, and Yarington in 1977 confirmed that the mortality had fallen to 12-14%. DiNubile (1988) contends that mortality remains closer to 30%. Morbidity, however, remains a very serious concern. Ophthalmic or neurologic deficits are found in over half of the survivors (DiNubile, 1988). Shaw (1952) reported cranial nerve deficits to persist in 40%. In addition, blindness occurred in 5 of 60 patients and another 4 of 60 patients had limited vision. Considerations for further lowering the mortality and morbidity rates should focus on rapidity of diagnosis and institution of treatment, selection of antibiotics, use of corticosteroids and decision for anti-coagulant and thrombolytic therapy.

Yarington (1977) has argued that because the morbidity of cavernous sinus thrombosis is so high, intravenous antibiotics should be begun immediately in all individuals suspected of having cavernous sinus thrombosis. No delay in treatment should be permitted for confirmatory studies. After blood cultures have been drawn, the institution of intravenous antibiotics is perfectly reasonable. CT scanning with bone windows, a dynamic CT scan or MR study and a spinal fluid analysis should follow soon after in order to confirm or reconsider the diagnosis. The choice of the antibiotic depends on the availability of a Gram stain of infected material, but in general should include coverage against a penicillinase-resistant organism, such as nafcillin, and a third-generation cephalosporin, such as
ceftazidime. If the source of infection is from the teeth, ear or sinus, metronidazole or chloramphenicol should be given for protection against anaerobic pathogens. In patients with a methicillin-resistant staphylococcal infection or serious penicillin allergy, vancomycin in combination with either sulfamethoxazole and trimethoprim or metronidazole may be used. Broad spectrum, intravenous antibiotics often leads to clinical improvement within several days, but overall recovery is generally slow. There is no proven benefit to corticosteroids in patients with cavernous sinus thrombosis, but their recently shown efficacy in reducing the morbidity of bacterial meningitis in children would argue in favor of their use (Lebel et al., 1988). If there is any reason to suspect involvement of the pituitary gland, replacement corticosteroid therapy is also advisable. The benefit of anticoagulants remains unproven and is controversial. One argument often advanced in their favor is that impeding thrombosis improves the access of antibiotics to the infection. In 1988, Levine and associates reviewed their experience in seven patients and the literature pertaining to cavernous sinus thrombosis since the advent of the antibiotic era. They concluded that morbidity was reduced when anticoagulation was used early in the course of this disease, but was of no benefit in reducing mortality or morbidity in a well-established thrombosis of the cavernous sinus. Pertinently, there were few complications of heparinization. Southwick (1988) has also suggested that anticoagulation prior to involvement of the opposite cavernous sinus may reduce mortality and morbidity. Unless the disease is far advanced, a heparin dosage to bring the partial thromboplastin time to 1.5 to 2.0 of the control is recommended until the patient is stable. This practice is consistent with the current treatment for cerebral venous thrombosis (Southwick et al., 1988). Thrombolytic agents such as fibrinolysin and streptokinase have been used successfully, but in a limited number of patients (Harvey, 1974); future use of these or similar enzymatic agents should be anticipated. Persistent abscess formation in the brain, pituitary, orbit or offending sinus, despite adequate antibiotic coverage may require surgical drainage.

SELECTED REFERENCES