paraesophageal hiatal hernia usually had obstructive symptoms (Table 1). While symptoms were mild in about half the cases of sliding type, they were severe in more than 75 percent of the paraesophageal type and 50 percent of the patients required operation.

Operative repair of paraesophageal hiatal hernia is recommended at its earliest stage whether symptoms exist or not.

Summary

Two cases of paraesophageal hiatal hernia were complicated by gastric volvulus. A distinct symptom complex occurs with obstruction and is associated with diagnostic radiographic criteria.

Of two hundred and seventy-four admissions to Cedars of Lebanon Hospital for hiatal hernia during a five-year period, thirteen were for paraesophageal hiatal hernia. Nine of the patients had symptoms and four required surgical repair.

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Primary Amebic Meningoencephalitis In California

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PRIMARY AMEBIC MENINGOENCEPHALITIS, to be distinguished from infections caused by Entamoeba histolytica, is a newly recognized disease entity. The infrequently encountered causative organism is usually a ubiquitous, free living, soil ameba of the Naegleriidae family (species Naegleria). The first cases were reported in 1965 from Australia[1] and since then, to our knowledge, 54 cases have been documented. In the United States, the disease has been detected in Florida,[2,3] Texas,[4] Virginia[5,6,7,8] and Georgia.[9] Elsewhere, this diagnosis has been made in Australia,[1,10] Czechoslovakia,[11,12] Britain,[13] Ireland,[13] New Zealand[14] and Africa.[15] This account will document the first reported occurrence of primary amebic meningoencephalitis in California and will describe its clinical, epidemiological and pathological characteristics. Furthermore, the entity will be reviewed to acquaint others with this rapidly fatal disease in order that it will be promptly recognized and early vigorous attempts at appropriate therapy undertaken. In addition, as new cases are recognized, measures should be instituted to prevent further outbreaks.

Report of a Case

A 16-year-old caucasian girl was admitted to Harbor General Hospital on April 29, 1971, with

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complaint of headache and nuchal rigidity of one day's duration. Five days before admission, on a week-end day, she swam in a remote desert valley hot spring near San Bernardino, California (in the southern Sierra Nevada mountains). The night before swimming, the patient had become intoxicated with alcohol and vomited. She returned home and was well until four days later, when she awoke with severe frontal headache. Nuchal rigidity ensued along with photophobia, mild sore throat, fever, chills, sweats, mild arthralgias, myalgias and nausea. She had not noted earache or change in taste or smell.

Her past history revealed excellent health and she denied head trauma. While swimming, she was accompanied by several friends, none of whom had similar symptoms.

On physical examination, body temperature was 40° C (104° F), pulse 98 rate and respirations 24 per min, and blood pressure 140/80 mm of mercury. She was alert, well developed and well nourished. The neck was decidedly rigid and Brudzinski's sign was evoked. The right tympanic membrane was minimally injected but was otherwise not unusual; the left tympanic membrane was normal. The nasal mucosa appeared normal. No abnormality was noted on examination of the heart, lungs and abdomen. There were no skin lesions or adenopathy. Funduscopic examination showed no abnormality. There was mild conjunctival injection. Neurological examination was significant in that there were no lateralizing signs, cranial nerve abnormalities or pathological reflexes.

Laboratory data on admission showed hematocrit of 39 percent, leukocytes 12,600 per cu mm with 80 percent polymorphonuclear leukocytes, 2 percent band forms, 15 percent monocytes and 3 percent lymphocytes. With the exception of trace proteinuria, the urinalysis, platelet count, prothrombin time, partial thromboplastin time, fibrinogen, serum electrolytes, blood urea nitrogen, calcium, bilirubin, SGOT, LDH, alkaline phosphatase, total protein and albumin were all normal. A mono-spot test was negative, and skull and chest roentgenograms were interpreted as normal. On lumbar puncture the opening pressure of 280 mm of water. The fluid, which was slightly cloudy, contained 310 leukocytes per cu mm (68 percent polymorphonuclear, 32 percent lymphocytes) erythrocytes 90 per cu mm, protein 72 mg per 100 ml, glucose 70 mg per 100 ml (blood glucose of 156 mg two hours earlier) and a negative Gram stain for bacteria. A wet mount examination of the spinal fluid was not performed.

A presumed diagnosis of viral meningoencephalitis was tendered and the patient was kept under observation. Six hours later she became obtund. Eight hours after admission she was comatose, with decerebrate posturing. A repeat lumbar puncture at that time showed pressure of 550 mm of water. Gradual removal of fluid lowered the pressure to 230 mm. The fluid was purulent and contained 3,330 leukocytes per cu mm (78 percent polymorphonuclear and 22 percent lymphocytes), 250 erythrocytes per cu mm, protein of 290 mg and glucose of 82 mg per 100 ml. Blood glucose was 259 mg per 100 ml (the patient was receiving 5 percent dextrose intravenous infusion). Gram and acid-fast stains failed to demonstrate any organisms. Because of rapidly progressive purulent meningitis, ampicillin 2 grams intravenously every four hours was started. There was no significant improvement over the next 48 hours. The temperature increased to 40.6° C (105° F) and leukocytes rose to 20,400 per cu mm of peripheral blood. Sixty hours after admission the patient had papilledema, extensor plantar reflexes and periods of apnea. Despite respiratory support and dexamethasone and mannitol infusions to decrease cerebral edema, she became hypothermic and cardiac arrest occurred. She could not be resuscitated and died four days after admission. Cultures of the cerebrospinal fluid from the two lumbar punctures and blood cultures were negative for any bacterial growth. Viral cultures of the cerebrospinal fluid, nasal and rectal swabs were also negative.

Autopsy Findings

The brain weighed 1,360 grams and there was herniation of the cerebellar tonsils. The leptomeninges, most prominently at the base, were thickened, edematous and opacified. The olfactory bulbs were similarly edematous and the left one was also necrotic (Figure 1). A superficial, hemorrhagic, necrotizing process involved the frontal, parietal and temporal lobes and cerebellum. A small round area of hemorrhage involved the left caudate nucleus.

Microscopically, hemorrhagic, necrotizing, purulent meningitis with some lymphocytes was seen, predominantly in the pons and cerebellum.

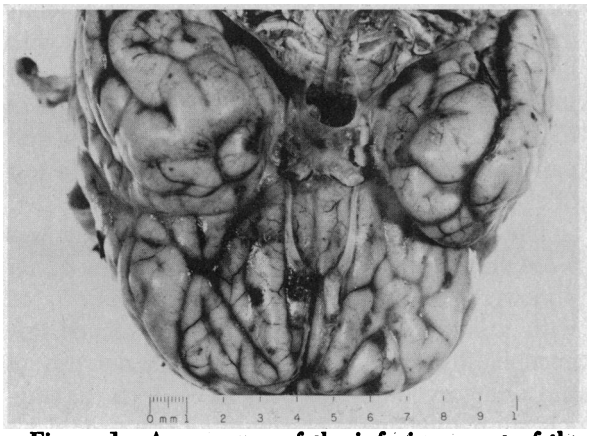

Figure 1—Appearance of the inferior aspect of the anterior portion of the brain, showing necrotic left olfactory bulb and focal superficial cortical hemorrhages.

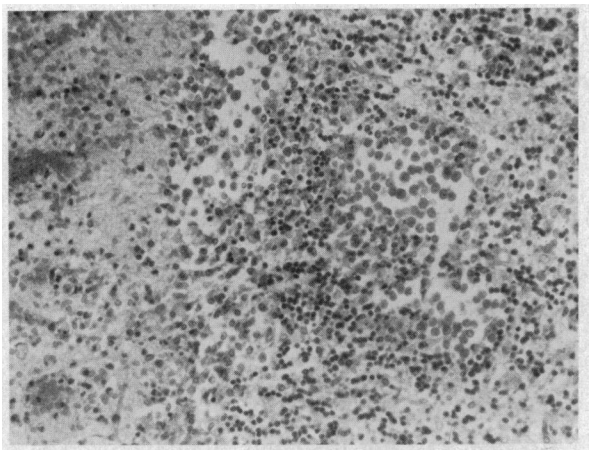

Figure 2.—Cerebellum showing clusters of amebae, virtually without inflammatory response. (Hematoxylin and eosin X550)

Extending in the Virchow-Robin spaces, it affected the superficial portions of the underlying brain. Typically, deeper in the brain, clusters of organisms were located in perivascular spaces, remarkably without an inflammatory response in the immediate vicinity (Figure 2). However, microabscesses were scattered throughout the cerebral cortex, some containing clumps of amebae. A few organisms could be seen in the inflamed meninges. With hematoxylin and eosin stain, the ameba were magenta, round, approximately 10 to 12 microns in diameter, and contained a dark, centrally located karyosome surrounded by a thin, clear halo (Figure 3). Some bi-nucleated and tri-nucleated forms were identified. Although other stains, including periodic acid-Schiff, iron hematoxylin, Best's carmine, Masson trichrome,

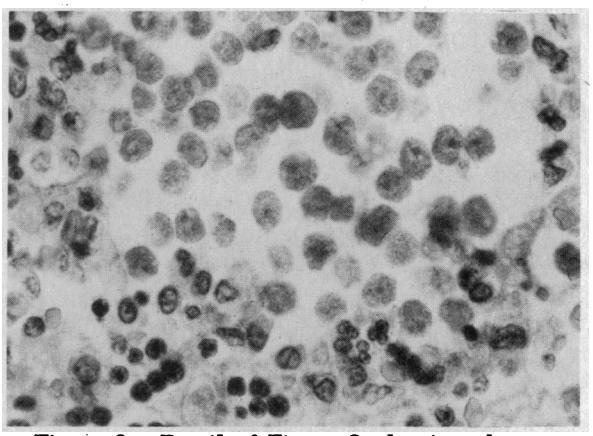

Figure 3.—Detail of Figure 2, showing characteristic morphologic features of the ameba. Note the dark, central karyosome, perinuclear halo and coarse, clumped cytoplasm. (Hematoxylin and eosin X1200)

Gram's, silver methename, phosphotungstic acid hematoxylin and Giemsa, were utilized, none proved superior to hematoxylin and eosin for identification and characterization of the organism.

The left olfactory bulb and tract, which contained rare organisms, were virtually destroyed by hemorrhagic necrosis and acute inflammation. The right olfactory bulb and tract were minimally affected. Many small blood vessels in proximity to the inflammation were thrombosed.

The lungs weighed 900 grams together and were edematous. A few small foci of early bronchopneumonia were evident. The kidneys were grossly unremarkable but microscopically showed pronounced hydropic change of the proximal convoluted tubules and cells lining Bowman's capsule. Of anatomic curiosity only was the finding of a well defined muscularis mucosa of the bladder. On detailed examination, amebae were not found in any tissue but the brain.

A suspension of refrigerated brain tissue was injected intracerebrally into mice but in two weeks produced no pathologic changes. Similarly, tissue cultures, utilizing monkey kidney, Hela and Wi 38 cells, failed to demonstrate the amebae. Using methods described by Culbertson et al[25] and Carter,[19] ameba, not well speciated, were cultured from samples of water from the hot springs pool in which the patient swam.

Discussion

The case reported here is similar to cases described by other observers. Classically, primary

amebic meningoencephalitis is an overwhelming, rapidly fatal meningoencephalitis that affects a previously healthy child or young adult with a history of recent swimming in fresh-water lakes, brackish water or pools of diverted river water. Of particular interest is a recent report from New Zealand[14] of an outbreak associated with bathing in a mineral spring. This is epidemiologically similar to the case herein reported. In both situations, water of 100° F originated in deep subterranean springs. In our case vegetation around the mineral pool was sparse, but the water had abundant moss and algae on the rock enclosing it. Week-end activities at this desert spring are described as crowded with young men and women bathing nude. Increased environmental CO_2 and bacteria facilitate the excystment and survival of Naegleria gruberi.[25] As a result, crowded conditions at the mineral pool may have enhanced the density of pathogens during the time our patient swam. Why others were not similarly afflicted with the disease remains unclear.

Epidemiologic observations of this disorder unassociated with swimming should be emphasized. Primary amebic meningoencephalitis has occurred in a patient with advanced alcoholic liver disease who had dental extractions.[4] An intriguing report of three cases occurring in children playing in a warm, muddy puddle was recently reported in England.[16] Furthermore, the isolation of Hartmanella species from normal throats has been noted.[17]

The history of swimming in a remote desert hot springs was, unfortunately, unavailable until the day of our patient's death. Nevertheless, the syndrome of primary amebic meningoencephalitis was considered in the differential diagnosis, but was discounted when the typical history of swimming was not obtained. Few cases have been diagnosed antemortem.[16,18] Most have occurred in an area of endemicity or in a setting of other documented cases.[11,18] The diagnosis is invariably confirmed by the finding of motile trophozoites in the cerebrospinal fluid wet mount. Unfortunately, this procedure is not routinely employed in the evaluation of spinal fluid; because of the epidemiologic observations detailed above, it should be a routine examination in any case of meningitis. In this case, retrospective examination of a Gram stain of the cerebrospinal fluid revealed a few identifiable organisms. Culture methods are available to grow free-living amebae in both tissue cultures[20] and on plain agar with live organisms.[19] Recently an agglutination test for Acathameba has been described,[21] in addition to a complement fixation test.[23] Even so, the spinal fluid wet mount remains the diagnostic test of choice.

The pathological findings in the present case were in keeping with those reported by other observers:[6,10] purulent meningitis is associated with a superficial necrotizing and hemorrhagic encephalitis. Basilar meningitis with necrosis of the olfactory bulbs and tracts confirm the suggested pathogenesis of migration of organisms through the nasal mucosa to the olfactory apparatus. While cerebral edema is a usual accompaniment of the inflammation, herniation of the cerebellar tonsils has not, to our knowledge, been emphasized.

Trophozoites in tissue sections have a characteristic appearance. Hematoxylin and eosin stain gives the best results for identification of the organisms, although, as pointed out by many investigators,[8] differentiation of the amebae from gitter cells may be difficult. An awareness of their morphological features and characteristic perivascular distribution, usually without accompanying inflammation, should make histological diagnosis apparent.

The spinal fluid findings in the present case were comparable with those reported by other observers,[10,8,18] but it should be emphasized that the spinal fluid appears more purulent than the cell count might indicate. This may well be a reflection of the number of amebae present. Erythrocytes are invariably present in small to moderate numbers and may correlate with the degree of necrosis and inflammation as can be seen from the pathological specimens. Similarly, hypoglycorrhachia is a feature and may be profound in advanced cases.[18] This would add another entity to the large list of disorders causing low spinal fluid glucose.

Of the patients reported in the literature, only four survived. Acanthamoeba astronyxis was isolated from a child who played in "mud holes and pools of fresh water." This organism was cultured from spinal fluid and the child survived although treated only with ampicillin.[5] Two cases were reported in a mini-epidemic referred to above[16] in which three children played in a mud puddle. After the death of one patient, the two remaining

children, who had been similarly exposed, were observed; when meningitis was noted, they were treated with amphotericin B. Amebae were isolated from only one of the two patients who survived. It is debatable whether these represent formes frustes of the disease, as suggested by Symmers,[18] or successful therapy. While motile cells were observed on a few occasions in spinal fluid examinations in the case reported by Grundy and Blowers,[15] the clinical manifestations, chronicity and lack of definite evidence of amebae make a diagnosis of primary amebic meningoencephalitis uncertain. However, because it may well represent a variant of this disorder and because of its apparent response to chloroquine, this case should be noted as one of possible response to therapy.

Susceptibility testing *in vitro* has yielded variable results, probably reflecting difficulty in method. It appears that most organisms are sensitive to amphotericin B,[23,24] and on the basis of a few clinical trials some amelioration of the disease was noted.[23] In cases recognized early, intraventricular and intravenous amphotericin B therapy is suggested.[18] Treatment with metronidazole, chloroquine (with the exception noted above[15]) and emetine has been disappointing. Of interest is the report that suggests *in vitro* antagonism between amphotericin B and steroids.[14] Since most patients are treated with steroids to decrease intracerebral edema, perhaps other measures should be employed instead.

It is apparent that free-living ameba are ubiquitous. Previous cases of amebic meningoencephalitis have occurred in endemic regions (Virginia, Florida, Czechoslovakia, Australia, New Zealand). The case reported here emphasizes that this disease does not necessarily have a localized distribution and that it should be considered in the differential diagnosis of unexplained meningoencephalitis. Furthermore, the organisms should be sought in examination of the cerebrospinal fluid.

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