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Cerebral cryptococcosis in Malaysia

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SYNOPSIS Cryptococcal infection of the brain as encountered in a tropical country is reviewed. The meningitic form is not uncommon and there has been, in the last decade, an apparent, if not real, rise in incidence in Malaysia as in Singapore. Only exceptionally was there overt evidence of immunological deficiency. Hydrocephalus was present in about three-quarters of the patients with meningitis and shunts were employed readily. The presence of multiple small intracerebral cysts could be suspected clinically but treatment for this complication was ineffective. The antifungal agent used most frequently was 5-fluorocytosine. Resistance to this drug developed in about one patient in four. There is a need for further epidemiological studies and for a continuing search for new antifungal agents.

Stoddard and Cutler (1916) described the clinical and pathological features of cerebral cryptococcosis and blastomycosis. The case reports that followed were, most often, from the United States (Mosberg and Arnold, 1950) and, later, Australia (Cox and Tolhurst, 1946). Pallis (1949) described the symptoms, signs and, postmortem findings in a Chinese sailor who died in Singapore with cryptococcal meningitis. Four years later, a similar case was reported in peninsular Malaya (Institute of Medical Research, Kuala Lumpur, 1953). In neighbouring Thailand, there is increasing awareness of the existence of cryptococcal meningitis (Vejjajiva, 1973). The disease is recognized in India (Ichaporia *et al.*, 1970) and has been reported from tropical areas of east and west Africa (McGill *et al.*, 1969; Mpairwe and Patel, 1970; Collomb *et al.*, 1973; Osuntokun, 1973). In Venezuela, the *per capita* incidence is estimated to be higher than in the United States (Angulo-Ortega *et al.*, 1961).

Amphotericin-B has been used to treat cryptococcal meningitis since 1957 (Appelbaum and Shtokalko, 1957). Until the introduction of 5-fluorocytosine, 10 years later, it was the only effective drug. The management by a shunt of associated hydrocephalus was mentioned in 1961 (Elkins and Fonseca, 1961).

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This communication concerns cryptococcal meningitis and granuloma as they have been observed in a tropical country in South-east Asia.

METHODS

From 1964 until February 1975, 30 persons with cryptococcal infection of the brain were admitted to the neurology or neurosurgery service at the General Hospital, Kuala Lumpur. The annual incidence increased steadily so that, during the last year of the survey, there were seven patients (representing 0.4% of admissions to the neurosurgical wards). The duration of hospitalization ranged from one to 27 weeks (mean nine weeks). The cryptococcal infection presented in 27 instances as meningitis and in three as granuloma. One man was found to have a granuloma two years after the first signs of meningitis.

Most often, the diagnosis was made by examination of lumbar or ventricular cerebrospinal fluid stained with India ink. This was performed in a standard and consistent manner by a single experienced pathology technician. In four cases, the organism was first seen after biopsy of a granuloma, in one, at postmortem examination of the brain, and, in one, after culture of cerebrospinal fluid performed at another hospital. The shape and metachromasia of the cryptococcal polysaccharide capsule were well demonstrated in histological preparations stained with toluidine blue. Twenty patients were submitted to cerebral angiography and, in 14, the ventricular system was displayed directly either

through pneumoencephalography or through positive contrast ventriculography.

Shunts (either ventriculoatrial or ventriculoperitoneal) were inserted into 15 patients with symptomatic hydrocephalus. Three drugs were employed: 5-fluorocytosine alone was used in 17 patients, amphotericin-B in three, and miconazole (an imidazole derivative under investigation as an antimycotic agent) in two. The usual policy was to administer 5-fluorocytosine until three successive samples of cerebrospinal fluid showed no cryptococcus. In two cases, a combination of 5-fluorocytosine and amphotericin-B was used and in three, 5-fluorocytosine was started when amphotericin was not tolerated. Twice miconazole was prescribed after 5-fluorocytosine had not proved efficacious. One patient received no antifungal agent. Many received a short course of steroid therapy. Postmortem examination of the brain was performed in six instances.

RESULTS

Of the 30 patients, 17 were male and 13 were female. The ages ranged from 6 to 56 years with a median of 23 years. The racial representation was proportional to that for all admissions. Twenty were Chinese, six Malay, three Indian, and one Orang Asli (aboriginal). Nine patients were students and the occupations included grass-cutter, engine cleaner, carpenter, hawker, cigar factory worker, clerk, businessman, and salesman. Most jobs involved outdoor work but no other common factor was evident. Two patients were on long-term steroid therapy and none suffered from reticuloendothelial neoplasia. A survey of hospitals in other parts of the country uncovered another 25 cases of cryptococcal meningitis in the same period of time. All parts of east and west Malaysia were represented.

The duration of symptoms before admission was between two weeks and one year. Headache was described except where there was no reliable history and papilloedema was present in all but three of those with meningitis. The temperature was normal or slightly elevated. Meningismus was usual but not invariable. Sixth nerve palsy was present in about one half the cases (12/27). Slightly less common were ataxia of gait (8/27) and confusion. One patient had a third nerve palsy. Tremor in two and seizures (with or without focal characteristics) in three were observed before admission. These latter two symptoms sometimes occurred later in the course of the disease. A primary spinal form of cryptococcosis was not encountered but two persons complained repeatedly, during treatment, of sciatic pain. One of these underwent a myelogram which showed abnormalities consisten with arachnoiditis.

TABLE 1

INITIAL CSF IN MENINGITIS

	Lumbar CSF ($n=18$)	*Ventricular CSF* ($n=7$)
Protein (g/l)	0.82(0.23–2.40)	0.34(0.08–0.96)
Glucose (mmol/l)	2.0(0.3–4.2)	3.5(0.3–5.3)
White cells/mm^3	161(0–520)	30(0–90)

Table 1 gives mean values and ranges for routine biochemical and cytological examination of the cerebrospinal fluid (before shunting procedure) in cases of meningitis. The majority of the cells were always lymphocytes. In two of the 20 samples of lumbar cerebrospinal fluid and two of the seven samples of ventricular fluid the biochemical values were normal. In two of these four samples (one lumbar and one ventricular) the number of cells was within normal limits. In all but three cases of meningitis, the diagnosis was made by staining the cerebrospinal fluid with India ink. In some instances before 1968, cryptococci were not seen in the initial specimen of cerebrospinal fluid but were identified subsequently. However, since then, if the first sample of cerebrospinal fluid submitted to this laboratory has been negative for cryptococci, all other specimens have also been negative. The yield from ventricular fluid has not been higher than that from lumbar fluid. The India ink test was negative in all four patients with cryptococcal granuloma despite the fact that two of the lesions were within the temporal horn. In only one of these four patients did organisms appear postoperatively in the lumbar cerebrospinal fluid. Pulmonary lesions were demonstrated in about one-third (10/27) of the chest radiographs. Slightly less than one half the skull radiographs (12/26) showed evidence of increased intracranial pressure either in the form of splitting of the sutures or of erosion of the sella turcica.

TABLE 2

PATIENTS WITH SYMPTOMATIC DISSEMINATED CEREBRAL INVASION

Basis for diagnosis	*Symptoms*			*Hydrocephalus*	*Treatment*	*Outcome*
	Seizures	*Tremor*	*Confusion*			
Necropsy	−	+	+	−	Miconazole	Death
	+	−	+	+	Shunt, 5-FC*	Death
	+	−	+	−	Nil	Death
	+	−	+	+	Amphotericin-B	Death
Clinical	?	+	+	?	5-FC	Death
	+	−	+	+	Shunt, 5-FC	Death
	+	−	+	+	Shunt, 5-FC	Residual dementia and seizures
	+	−	+	+	Shunt, 5-FC	Residual dementia
	−	+	−	+	Shunt, 5-FC	Residual ataxia and tremors

+ : present. ?: lack of information. − : absent. 5-FC*: 5-fluorocytosine.

TABLE 3

PATIENTS WITH GRANULOMA

Symptoms	*Site*	*Pathology*	*Lumbar CSF stained with India ink*		*Outcome*
			Preop.	*Postop.*	
Headache, no papilloedema, right 3rd nerve palsy, left hemiplegia	R temporal horn	Cystic lesion, granulomatous walls	−	+	Death
Headache, vomiting, no papilloedema, left 3rd nerve palsy, right hemiparesis	L temporal horn	Cystic lesion, granulomatous walls	−	+	Recovery
Headache, vomiting, papilloedema, left hyperreflexia	R frontal lobe	Numerous organisms, little tissue reaction	?	−	Recovery
Meningitis 2 yr previously, subsequent hydrocephalus, papilloedema, seizures, left 3rd nerve palsy, left hemiparesis	R temporal lobe	Firm granulomatous mass	−	−	Residual seizures and hemiparesis

+ : positive. − : negative. ?: test not done.

Of the 27 patients with meningitis, 17 were shown to have hydrocephalus and six to have normal ventricular size. Three died before any contrast studies were performed, and in one, none were thought necessary. Neither aqueduct stenosis nor complete obstruction of the fourth ventricular outlets was encountered; where pneumoencephalography or ventriculography were done, hydrocephalus was consistently of the communicating type. The mental status often improved dramatically after insertion of a shunt. When cerebrospinal fluid containing cryptococcus was shunted into the blood, no resultant ill-effects were observed. Elevated intracranial pressure in the absence of hydrocephalus was documented in five cases.

In Table 2 is summarized some of the information regarding nine patients who had symptoms compatible with disseminated cerebral invasion. Minimum criteria for diagnosis on clinical grounds were tremor or marked confusion associated with seizures. Postmortem examination, when performed, showed multiple round intracerebral lesions usually measuring less than 3 mm in diameter and eliciting little reaction from the surrounding brain. This polycystic disease was maximal in the corpus striatum and involved to a lesser degree the thalamus and at least a portion of the cerebral cortex. Lesions in the brain stem and cerebellum were, when present, detected only with microscopic examination. Necropsy in two other patients who had neither tremor nor seizures revealed a few small cysts distributed much less densely and extensively. Usually, the presence of multiple small intracerebral cysts was suspected

TABLE 4

EFFECT OF TREATMENT ON PROTEIN AND GLUCOSE IN LUMBAR CSF

	With shunt (5 patients)	*Without shunt (4 patients)*
Protein (g/l)		
Initially	0.60	1.38
Subsequently	3.42	0.61
Glucose (mmol/l)		
Initially	2.3	0.9
Subsequently	1.7	2.4*

* Statistically significant difference from pretreatment value ($P < 0.05$).

when a patient with cryptococcal meningitis remained confused even after adequate management of such hydrocephalus as was present. Seizures may sometimes have been a complication of ventricular cannulation for diagnostic or therapeutic purposes but usually they were taken to indicate cortical invasion. Tremor of the upper limbs was the least common but most specific of the three signs. Ataxia of gait, a more common sign in cryptococcal meningitis, is most reasonably attributed to hydrocephalus.

Four patients (Table 3), two of whom have been reported previously (Selby and Lopes, 1973) had cerebral granulomata. In three, there was no previous history suggestive of meningitis. The fourth had been diagnosed to have meningitis two years earlier but the organism had not been demonstrated despite several lumbar punctures. The presentation in all four cases was that of a mass lesion and the diagnosis was made only after histological examination of a surgical specimen. The India ink test, so reliable in cases of meningitis, was negative preoperatively in the three patients submitted to lumbar puncture. The treatment was surgical excision followed by 5-fluorocytosine, and there were three survivors.

Retrospective analysis of a series in which several antifungal agents were used and in which factors other than choice of drug influenced the morbidity and mortality does not constitute an ideal drug trial. However, an attempt was made to assess the efficacy of 5-fluorocytosine. For this purpose, cases were selected in which 5-fluorocytosine was the sole drug and the dosage was 200 mg per kg body weight and where hydrocephalus, if present, was appropriately treated. These criteria were satisfied in 11 patients. Eight showed progressive clinical improvement and eradication of cryptococci from the cerebrospinal fluid. The median time for cryptococci to disappear from the cerebrospinal fluid was three weeks. In one instance, cryptococci were detected after 21 weeks of treatment but not thereafter. The other three patients never improved satisfactorily and cryptococci were still demonstrable in the cerebrospinal fluid after three months of treatment. Two of them died and a third responded subsequently to miconazole. The number of patients treated with amphotericin-B is too small to allow any conclusions to be drawn (only two received a full course of treatment).

Table 4 shows values of biochemical tests on

TABLE 5

ANALYSIS OF MORTALITY

Age (yr)	*Sex*	*Months from onset to death*	*Necropsy performed*	*Direct cerebral involvement*	*Hydrocephalus*	*Intracranial event leading to death*
24	M	1	+	MSIC	–	DCI
19	M	4	+	MSIC	Tr	DCI
6	M	2	+	MSIC	–	DCI
48	F	2	+	MSIC	+	DCI
56	M	?	–	MSIC	?	DCI
36	M	6	–	–	+	Hydrocephalus
40	M	1	–	–	+	Hydrocephalus
21	M	3	+	Occ.	+	Hydrocephalus
38	F	2	–	–	?	Hydrocephalus (presumed)
23	M	8	–	MSIC	+	DCI and/or hydrocephalus
52	F	6	+	Occ.	+	Shunt revision
46	M	5	–	Gran.	–	Resection of granuloma
21	M	2	–	?	?	Refused treatment

+ : present. MSIC: multiple small intracerebral cysts. – : absent. Occ.: occasional intracerebral cyst.
?: lack of information. Gran.: granuloma. Tr: treated. DCI: disseminated cerebral invasion.

samples of lumbar cerebrospinal fluid taken from the same patients before and after initiation of treatment. The latter samples were taken between nine and 14 weeks after the starting of drug therapy (usually but not always with 5-fluorocytosine). In the absence of a shunt, the values moved closer to normal; in the presence of a shunt they became more aberrant. No correlation was observed between the cerebrospinal fluid biochemistry and the detection of cryptococci in the cerebrospinal fluid nor between the biochemistry and the ultimate fate of the patient. It has been stated elsewhere that hypoglycorrhachia worsens the prognosis (Atkinson, 1969; Diamond and Bennett, 1974).

Of the entire series of 30 patients, 13 died, so that the overall mortality rate was 43%. This is comparable with that in other series (Sarosi *et al.*, 1969; Edwards *et al.*, 1970; Tay *et al.*, 1972; Diamond and Bennett, 1974). Of the 17 survivors, nine were well and eight had a moderate to severe neurological deficit (decreased visual acuity in four, dementia in two, ataxia in one, and hemiparesis in one).

An analysis of the 13 deaths (with six necropsies) is shown in Table 5. The terminal event was often respiratory. Aspiration and bronchopneumonia were common and cryptococcal infection of the lungs may occasionally have been a contributing factor. Nevertheless, an effort was made in each instance to cite one neurological complication as crucial. Multiple small intracerebral cysts were seen in four necropsies and there was strong clinical evidence that they caused the death of one other patient. Three patients died in a manner consistent with intracranial hypertension and one can say in retrospect that there was hydrocephalus of unrecognized severity. A fourth died after repeated revisions failed to establish a functioning shunt and the ventricular size increased progressively. Two patients died shortly after surgery. One patient refused treatment and died outside the hospital. In another, no decision regarding the mode of death was made. In summary the two major causes of morbidity and mortality in cryptococcal meningitis are disseminated cerebral invasion and hydrocephalus.

DISCUSSION

Cryptococcal infection of the central nervous system has been reported, at least sporadically, from many parts of the world. Precise epidemiological data are not available but what is known suggests a higher incidence in tropical than in temperate zones. A ratio of five new cases per year to a population of 10 million is slightly less than that derived from statistics (102 cases from 1950–66) for New York City (Littman and Jinks, 1968). However, the proportion of cases unreported was undoubtedly much higher in Malaysia. The ratio of patients with cerebral cryptococcosis to those with other neurological or neurosurgical problems is high compared with that in Europe or North America. In Malaysia and in Singapore (Tay *et al.*, 1972) there has been a steady rise in the annual number of cases identified. The most likely cause for this phenomenon is a greater awareness on the part of medical practitioners. Since the introduction of BCG in the 1960s, the incidence of tuberculous meningitis has declined precipitously to less than that of cryptococcal meningitis. The latter is now to be considered whenever there is increased intracranial pressure with a paucity of localizing signs. It is almost as common as chronic subdural haematoma and much more so than pseudotumor cerebri.

Clinical infection depends upon the dosage and type of organism and upon the adequacy of host defences. The usual pathogenic cryptococcus is strain A and this was identified here in the few cases where typing was performed. The status of the immune system in cryptococcal infection is a subject of current interest (Diamond and Bennett, 1973a; Diamond *et al.*, 1974). An attempt has been made to assay cell-mediated immunity by culturing lymphocytes with heat-killed cryptococcus and measuring their ability to incorporate thymidine. Lymphocytic function in patients with cryptococcal meningitis was found to be inferior to that in persons with a positive skin test for pathogenic cryptococcus but no clinical sign of infection. Of a series in New York City, 39% were associated with diseases such as diabetes mellitus, cirrhosis, lymphoma, and leukaemia where impairment of cell-mediated immunity is recognized (Littman and Jinks, 1968). In this series from Malaysia, such predisposing illnesses were exceptional. Many of the patients were young and most of them were previously healthy. All three major

racial groups (Malay, Chinese, Indian) were susceptible. Intracranial tuberculoma, on the other hand, tends in Malaysia to occur in the Indian sector of the population (Selby, 1973). The absence of any evidence for an excessively virulent organism, the affliction of young previously healthy persons of all races and the presence of a tropical climate suitable for the proliferation of cryptococcus lead to the conclusion that most of these cases of cerebral cryptococcosis occurred because of exposure to a large dose of the fungus. Lacking any information about the incidence of asymptomatic infection, one can pass little comment on the possibility that the patients admitted with overt cryptococcal infection represent a small proportion of those exposed to the same dose and that they suffer from a specific immunological defect. Pigeon droppings are commonly incriminated as a source of infection but there may be other reservoirs (Littman and Jinks, 1968). In a study from Thailand, cryptococci could often be cultured from soil contaminated with pigeon droppings but not from soil in the vicinity of the temples of Bangkok (Taylor and Duangmani, 1968).

Cryptococcal infection of the central nervous system results in meningitis or granulomata (either single or multiple). Granulomata have been found in the brain (Selby and Lopes, 1973), spinal cord, and cauda equina (Carton and Mount, 1951; Ley *et al.*, 1951; Ramamurthai and Anguli, 1954), skull (Reeves, 1967), and spinal column (Epstein, 1969). Meningitis is usually intracranial but occasionally spinal (Davidson, 1968). Chronic infection, high cerebrospinal fluid protein, and frequent lumbar punctures may be conducive to spinal arachnoiditis. Persistent and spontaneous sciatic pain has rarely been documented but it is possible that milder forms are not reported. Sciatica occurred twice in this series and, both times, resolved without definitive treatment. The two common complications of meningitis are disseminated cerebral invasion and communicating hydrocephalus. The cerebral cortex and striatum are found, inexplicably, to be susceptible to invasion. One can postulate that lenticulostriate vessels passing through the anterior perforated area provide a trellis for perivascular spread. Endarteritis, common in tuberculous and syphilitic meningitis, is relatively insignificant in cryptococcal meningitis. Cranial nerve involvement is limited to the optic and abducens nerves, which are vulnerable to increased intracranial pressure.

Early diagnosis, availability of good antifungal agents, and surgical treatment of complications are important in the management of cryptococcal meningitis. The high incidence of papilloedema in this series suggests that many of the patients were seen late in the course of the disease. We attribute this to social and economic conditions. Perhaps the paucity of early cases accounts for the high rate of success with India ink examination of the cerebrospinal fluid. Contrary to the experience of others (Edwards *et al.*, 1970; Gonyea, 1973), we have found large volumes of cerebrospinal fluid, use of ventricular or cisternal fluid, and repeated examination all to be unnecessary for diagnostic purposes. One failing of the India ink test is a relative insensitivity in the presence of cryptococcal granuloma.

5-fluorocytosine penetrates the blood brain barrier well, is free of significant toxicity, and is comparable with amphotericin in its efficacy against cryptococcus (Utz, 1972). Three drawbacks are its cost, the development of resistance in 25% of cases (Block *et al.*, 1973), and its inability to act quickly enough to be effective against fulminating infection. Our preference, now, is to begin drug treatment of cryptococcal meningitis with 5-fluorocytosine alone. As long as the clinical course remains satisfactory, no other antifungal agent is used. Others (*Medical Letter*, 1972) have recommended that 5-fluorocytosine be reserved for those patients who fail to respond to amphotericin-B in doses which are tolerated. A third approach to be considered, particularly in the presence of severe infection, would be to use 5-fluorocytosine plus amphotericin-B. Synergism in the actions of 5-fluorocytosine and amphotericin-B on some cultures of cryptococcus has been demonstrated *in vitro* (Shadomy *et al.*, 1975). The experience of others in intraventricular administration of amphotericin-B *via* a subcutaneous reservoir is not encouraging (Diamond and Bennett, 1973b).

Disseminated intracerebral invasion should be considered when there is unexplained confusion, seizures, or tremor. It may or may not be

associated with increased intracranial pressure and its treatment remains unsatisfactory. The pathological features (displacement of brain tissue with little adjacent reaction or vascularity) render it conceivable that no antifungal agent will effect satisfactory resolution. Hydrocephalus may be present when the patient is first seen or may develop subsequently. When dealing with a known case of cryptococcal meningitis, one can use pneumoencephalography as safely as ventriculography, since communication between the ventricles and the subarachnoid space is the rule. Isotope cisternography has been recommended (Wilhelm *et al.*, 1973) and computerized axial tomography would be ideal if available. Where there is symptomatic hydrocephalus, we believe that shunting is preferable to cerebrospinal fluid drainage, frequent lumbar punctures, or expectant treatment. After a shunt has been performed, the cerebrospinal fluid biochemistry is not useful to follow progress. Intracranial pressure monitoring might be helpful in the management of the occasional situation where there is increased intracranial pressure but no hydrocephalus.

Cryptococcal granuloma, more often than not, arises without previous evidence of meningitis (Selby and Lopes, 1973). Diagnosis may be difficult, as there may not be large numbers of cryptococci in the cerebrospinal fluid. Treatment consists of surgical excision combined with the administration of 5-fluorocytosine.

Cryptococcal meningitis in Malaysia warrants further investigation, especially from epidemiological, microbiological, and pharmacological points of view. Too little is known about the reservoir of infection. The frequency of asymptomatic infection could be assessed by serological and skin testing. Increased availability of medical care should lead to earlier diagnosis. Finally, there is still no ideal anticryptococcal drug.

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REFERENCES

Angulo-Ortega, A., Rodriguez, C., and Galindo, G. G. (1961). Criptococosis en Venezuela. *Myopathologia et Mycologia Applicata*, **15**, 367–388.

Appelbaum, E. and Shtokalko, S. (1957). Cryptococcal meningitis arrested with Amphotericin-B. *Annals of Internal Medicine*, **47**, 346–351.

Atkinson, J. A. (1969). The cerebrospinal fluid glucose concentration. Steady state and kinetic studies in patient with cryptococcal meningitis. *American Review of Respiratory Disease*, **99**, 59–66.

Block, E. R., Jennings, A. E., and Bennett, J. E. (1973). 5-fluorocytosine resistance in *Cryptococcus neoformans*. *Antimicrobial Agents and Chemotherapy*, **3**, 649–656.

Carton, C. A., and Mount, L. A. (1951). Neurosurgical aspects of cryptococcosis. *Journal of Neurosurgery*, **8**, 143–156.

Collomb, H., Dumas, M., and Girard, P. L. (1973). Neurological disorders in Senegal. In *Tropical Neurology*. Edited by J. D. Spillane, Oxford University Press, pp. 133–142.

Cox, L. B., and Tolhurst, J. C. (1946). *Human Torulosis. A clinical, pathological, and microbiological study*. Melbourne University Press.

Davidson, S. (1968). Cryptococcal spinal arachnoiditis. *Journal of Neurology, Neurosurgery, and Psychiatry*, **31**, 76–80.

Diamond, R. D., and Bennett, J. E. (1973a). Disseminated cryptococcosis in man: decreased lymphocyte transformation in response to cryptococcus neoformans. *Journal of Infectious Diseases*, **127**, 694–697.

Diamond, R. D., and Bennett, J. E. (1973b). A subcutaneous reservoir for intrathecal therapy of fungal meningitis. *New England Journal of Medicine*, **288**, 186–188.

Diamond, R. D., and Bennett, J. E. (1974). Prognostic factors in cryptococcal meningitis. *Annals of Internal Medicine*, **80**, 176–181.

Diamond, R. D., May, J. E., Kane, M. A., Frank, M. M., and Bennett, J. E. (1974). The role of the classical and alternate complement pathways in host defenses against *cryptococcus neoformans* infection. *Journal of Immunology*, **112**, 2260–2270.

Edwards, V. E., Sutherland, J. M., and Tyrer, J. H. (1970). Cryptococcosis of the central nervous system. *Journal of Neurology, Neurosurgery, and Psychiatry*, **33**, 415–425.

Elkins, E. W., and Fonseca, J. E. (1961). Ventriculovenous anastomosis in obstructive and acquired hydrocephalus. *Journal of Neurosurgery*, **18**, 139–144.

Epstein, B. S. (1969). *The Spine*, pp. 384–385. Lea and Feibiger: Philadelphia.

Gonyea, E. F. (1973). Cisternal puncture and cryptococcal meningitis. *Archives of Neurology*, **28**, 200–201.

Ichaporia, R. N., Grant, K. B., and Waria, R. S. (1970). Cryptococcal meningitis. *Journal of the Indian Medical Association*, **54**, 425–427.

Institute of Medical Research, Kuala Lumpur (1953). *Annual Report*, p. 20.

Ley, A., Jacas, R., and Oliveras, C. (1951). Torula granuloma of the cervical spinal cord. *Journal of Neurosurgery*, **8**, 327–335.

Littman, M. L., and Jinks, E. W. (1968). Cryptococcosis: current status. *American Journal of Medicine*, **45**, 922–932.

McGill, P. E., Sequeira, A., Jindari, A., Nguli, E. T., Forrester, A. T. A., and Fulton, W. F. H. (1969). 5-fluorocytosine in the treatment of cryptococcal meningitis. *East African Medical Journal*, **46**, 663–668.

Medical Letter. (1972), **14**, 29–30.

Mosberg, W. H., and Arnold, J. G. (1950). Torulosis of the central nervous system: review of the literature and report of five cases. *Annals of Internal Medicine*, **32**, 1153–1183.

Mpairwe, Y., and Patel, K. M. (1970). Cryptococcal meningitis in Mulago Hospital, Kampala. *East African Medical Journal*, **47**, 445–447.

Osuntokun, B. O. (1973). Neurological disorders in Nigeria. In *Tropical Neurology*, pp. 161–190. Edited by J. D. Spillane, Oxford University Press; London.

Pallis, C. (1949). Cryptococcal meningitis. *Proceedings of the Alumni Association*, vol. 2, pp. 452–457. King Edward VII College of Medicine: Singapore.

Ramamurthai, B., and Anguli, V. C. (1954). Intramedullary cryptococcal granuloma of the spinal cord. *Journal of Neurosurgery*, **11**, 622–624.

Reeves, D. L. (1967). Cryptococcal (torula) granuloma of the skull. *Journal of Neurosurgery*, **27**, 70–72.

Sarosi, G. A., Parker, J. D., and Doto, I. L. (1969). Amphotericin-B in cryptococcal meningitis. *Annals of Internal Medicine*, **71**, 1079–1087.

Selby, R. C. (1973). Neurological disorders in Malaysia. In *Tropical Neurology*, pp. 229–320. Edited by J. D. Spillane. Oxford University Press.

Selby, R. C., and Lopes, W. M. (1973). Torulomas (cryptococcal granulomata) of the central nervous system. *Journal of Neurosurgery*, **38**, 40–46.

Shadomy, S., Wagner, G., Espinel-Ingroff, A., and Davis, B. A. (1975). *In vitro* studies with combinations of 5-fluorocytosine and Amphotericin-B. *Antimicrobial Agents and Chemotherapy*, **8**, 117–121.

Stoddard, J. L., and Cutler, E. C. (1916). Torula infection in man. *Studies from the Rockefeller Institute for Medical Research*, Monograph 6.

Tay, C. H., Chew, W. L. S., and Lim, L. C. Y. (1972). Cryptococcal meningitis: its apparent increased incidence in the far east. *Brain*, **95**, 825–832.

Taylor, R. L., and Duangmani, C. (1968). Occurrence of *Cryptococcus neoformans* in Thailand. *American Journal of Epidemiology*, **87**, 318–322.

Utz, J. P. (1972). Flucytosine. *New England Journal of Medicine*, **286**, 777–778.

Vejjajiva, A. (1973). Neurology in Thailand. In *Tropical Neurology*. Edited by J. D. Spillane, Oxford University Press, pp. 335–354.

Wilhelm, J. P., Siegel, B. A., and James, A. E. (1973). Brain scanning and cisternography in cryptococcosis. *Radiology*, **109**, 121–124.