

Contribution Of Plasmodium Falciparum And Other Infections To
Acute Central Nervous System Disease At The University Teaching
Hospital Of Lusaka.

By

Charles Chomba Masase;

B.Sc. HB, MBChB

**A Dissertation Submitted In Partial Fulfillment Of The Requirements For The
Masters Of Medicine Degree (Internal Medicine) Of The University Of Zambia.**

University Of Zambia

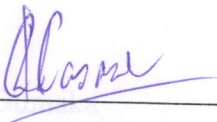
School Of Medicine

June 1999

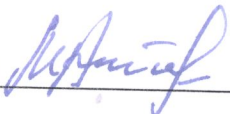
M. MED.
MEDIC
1999
01

DECLARATION

I hereby declare that the work presented in this dissertation has not been presented either wholly or in part for any other degree and is not currently submitted for any degree.

Signed 
(Candidate)

Signed ~~XXXXXXXXXX~~ DR MWABA PETER
(Supervisor)

Signed  Prof. M. ATAZZHANOV
(Co-supervisor)

DEDICATION

Chiti

Musonda

Chomba-Bumaka

You gave me the reasons to persevere

ACKNOWLEDGEMENTS

Translating my thoughts to what is contained herein was not without frustration. There came a time when I felt like a novice walking a tight rope in a storm. Quitting seemed an inevitable step and I will always remember the following for their words of encouragement and I quote:

Professor Atadzhanov; “Charles some people have had to re-write their dissertations more than seven times.”

Dr A. Mwinga; “You sit down and write something that you and your children will read to appreciate in future.”

Dr F. Kasolo; “I had to re-write literally everything for your colleague.”

I wish to register my special acknowledgements to the following for their priceless contributions:

Profesor J.O.M Pobee for introducing me to the world of research.

Dr P.Mwaba, my contemporary and friend, for being an inspiration to me and many other upcoming scholars of medicine.

My special thank you will go to Dr P. Nyendwa for being there for me when the “relentless storm” hit hardest.

CONTENTS

	<u>Page</u>
Declaration.....	i
Dedication.....	ii
Acknowledgements.....	iii
Contents.....	iv
List of figures and tables.....	v
List of abbreviations.....	vii
Abstract.....	iix
Chapter one: Introduction	
1.1 Background information and literature review.....	1
1.2 Justification for the study.....	36
1.3 Objectives.....	38
1.4 Ethical consideration.....	38
Chapter two: Methodology	
Materials and Methods.....	39
Chapter three:	
Results.....	41
Clinical features.....	41
Lab results.....	44
Chapter four:	
Discussion.....	47

LIST OF FIGURES AND TABLES.

Figure 1: Annual (1996-2000) UTH admissions; malaria, cerebral malaria, meningitis and all ailments.....	4
Figure 2: Annual(1996-2000) UTH mortalities per 100 admissions;malaria, cerebral malaria, and meningitis.....	5
Figure 3: UTH malaria positivity on blood films (1991-1998).....	5
Figure 4: Annual (1994-97) commonly isolated pathogens from CSF.....	14
Table 1: UTH annual (1996-2000) admissions, discharges and deaths; malaria, cerebral malaria, meningitis and all ailments.....	4
Table 2: Commonly isolated pathogens from CSF; UTH.	14
Table 3: Results; sex distribution.....	41
Table 4: Results; presenting symptoms.....	42
Table 5: Results: Presenting signs.....	43
Table 6: Results: P.falciparum on blood films.....	44
Table 7: Results: CSF glucose.....	45
Table 8: Results: CSF proteins.....	45
Table 9 Results: CSF NA+.....	46

LIST OF ABBREVIATIONS

- i) AIDS- Acquired immuno-deficiency syndrome
- ii) AM- Aseptic meningitis
- iii) AME- acute meningo-encephalitis
- iv) CM- Cerebral malaria
- v) CMV -Cytomegalo virus
- vi) C.neoformans -Cryptococcus neoformans
- vii) CSF- Cerebrospinal fluid
- viii) CSO- Central statistical office
- ix) EBV- Ebstein-barr virus
- x) HAM –Human T lymphotropic virus I-associated myelopathy
- xii) H.influenzae- Haemophilus influenzae
- xiii) HIV- Human Immuno-deficiency virus
- xiv) HSV- Herpes simplex virus
- xv) IL- Interleukin
- xvi) JICA -Japanese Co-operation Agency
- xvii) ME- Meningoencephalitis
- xviii) MRNA-messenger Ribonucleic acid
- xix) M.tuberculosis- Mycobacterium tuberculosis
- xx) N.meningitides- Neisseria meningitides
- xxi) PCR- Polymerase chain reaction
- xxii) RBC- Red blood cell
- xxiii) RNA -Ribonucleic acid

- xxiv) RPR -Rapid protein reagenin
- xxv) T.gondii -Toxoplasma gondii
- xxvi) TNF -Tissue necrosis factor
- xxvii) T.pallidum -Treponema pallidum
- xxviii) UTH -University Teaching Hospital at Lusaka, Zambia.
- xxix) VZV -Varicella Zoster Virus
- xxx) WBC -White Blood Cell
- xxxi) WHO -World Health Organisation

ABSTRACT

Three hundred patients presenting with acute central nervous system (CNS) disease were enrolled in this one-year study from June 1997 to June 1998. This was a longitudinal prospective study looking at the contribution of *Plasmodium falciparum* and other infections to acute central nervous system disease. It also looked at the clinical and laboratory features of patients presenting with acute CNS disease.

The clinical features were vast though most of the patients had a headache (84%), fever (70%) and confusion (40%). The other symptoms included convulsions (17%), weight loss (31%), diarrhoea (40%) while 34% of the patients had given a history of vomiting. The major signs were fever (87%), wasting (64%), meningeal signs (62%), lymphadenopathy (50%), papilloedema (19%), anaemia (54%) and 44% had non-specific macular popular dermatosis.

The study has demonstrated that *Plasmodium falciparum* is an important cause of acute CNS diseases as 20% of the patients in this study had positive malaria parasite slides. The contribution of other infections were mainly bacteria and it has been shown that *Cryptococcal neoformans* (6.7%), *Streptococcus pneumoniae* (3.3%), *Neisseria meningitides* (2.7%), *Haemophilus influenzae* (0.7%), other bacteria (6.7%) are important causes of acute central nervous system disease. This study population, which had a 1:1 male to female ratio, had a high HIV seroprevalence rate of 75%. The biochemical results did not appear to be helpful except in situations where patients had hypoglycaemia. The RPR results were positive in only 3.3% of the study population. No acid alcohol bacilli were seen or isolated.

The study has demonstrated that *Plasmodium falciparum* and other infections are an important cause of acute CNS diseases and should therefore always be considered in the management of affected individuals. The range of bacteria pathogens has increased with HIV related infections being common though there was limitation on the range of viral infections.

CHAPTER ONE

1.1 BACKGROUND INFORMATION AND REVIEW OF LITERATURE

Diseases of the central nervous system (CNS) are not only limited to cerebral malaria (CM) and to bizarre manifestations of viral, bacterial and parasitic infections, but also reflects the expression of many non-infectious diseases in a particular environment where malnutrition, trauma, perinatal injury, cerebrovascular and degenerative diseases tend to show patterns of nineteenth century Western proportions. These are among the many factors that must be taken into consideration when assessing patients and comparing epidemiological surveys.

INFECTIONS

The variety of infectious agents, which can damage the nervous system, is vast and their clinical manifestations are protean. In addition to the general predisposing factors, which include poverty, ignorance, deprivation and inadequate education, is the prevalence and persistence of insect and other vectors which thrive in humid climates and which survive throughout the seasons. A few of these infections are discussed in this dissertation.

Malaria

Worldwide, there are over 300 million new cases of clinical malaria every year. Malaria is more prevalent in countries with poor social economic development. Malaria kills over 1 million people every year world wide, mostly children under 5 years and pregnant women. The drugs used to treat and prevent malaria are losing their efficacy as the malaria parasite builds up resistance to them. Mosquitoes on the other hand,

have also become resistant to insecticides used against them. This demands an urgent need for new efficacious drugs and insecticides to be made available in areas of high endemicity. (WHO Background document on the Introduction of Medicines for Malaria Venture 1999). Protection of children and pregnant mothers is easy with insecticide treated nets. WHO recommends the use of Pyrethrum derived insecticides to treat these nets before use (WHO facts sheet no 94 on malaria October 1998). It has been shown that Africa's GDP would be up to \$100 million greater if malaria had been eliminated (WHO Backgrounder No 1 for the G8 discussions. July 2000).

Malaria is endemic throughout Zambia. The predominant parasite is *Plasmodium falciparum* in 95% of the patients seen, and this is the one causing severe disease. Malaria accounts for close to 40% of all under 5 deaths in the country. For adults, malaria is the most common reason for health centre visits. For both adults and children malarial related anaemia has a substantial impact, impairing school and work performance, increasing the overall malaria related morbidity and mortality. Malaria has been documented as a contributing cause of approximately 20% of all pregnancy-related deaths in Zambia and is strongly associated with low birth weight babies and peri-natal mortality. The precise contribution of CM remains undocumented. Within the Zambian health care reform process, an analysis of relative disease burden was undertaken using *disability-adjusted life- years (DALYs)*, a method that allows for a combined measure for both morbidity and mortality. The emotional, social and economic impact of malaria on the individual and the household cannot be overemphasised. Repeated malaria infections, anaemia and high death rates cause untold suffering to millions each year.

Public sector records show rising trends in malaria morbidity and mortality, from

Africa and South America; the eradication of measles should greatly diminish the incidence of SSPE. There are conflicting reports on its pathogenesis and management (Ng T H K, et al. 1991; 1967). Several authors have reported the use of intraventricular interferon or the combined use of interferon plus isoprinosin (Gascon, et al. 1992).

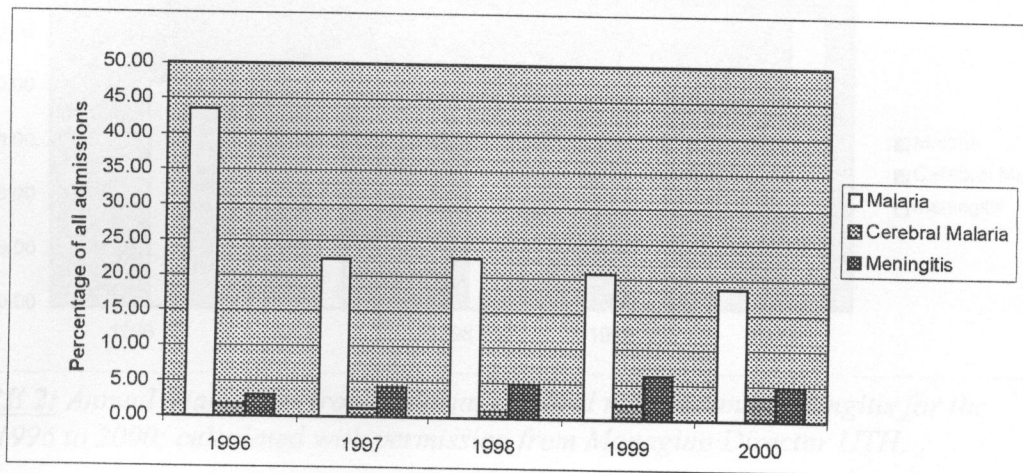


FIGURE 1. Annual admissions for malaria, cerebral malaria and meningitis as percentages of all admissions to the UTH medical emergency ward (1996-2000), with permission from, Managing Director.

Table 1. Admissions for malaria, cerebral malaria and meningitis compared to all admissions to the UTH adult medical emergency wards (1996 - 2000).

Year	Malaria			Cerebral Malaria			Meningitis			Total Admission
	Admission	Discharge	Death	Admission	Discharge	Death	Admission	Discharge	Death	
1996	10734	9927	807	8	2	6	1119	652	467	36354
1997	6055	5410	645	319	236	83	1164	652	512	27034
1998	6339	5563	776	282	191	91	1365	772	593	27995
1999	5951	5135	816	606	431	175	1791	1012	779	28786
2000	4683	3982	701	840	613	227	1221	561	660	25010

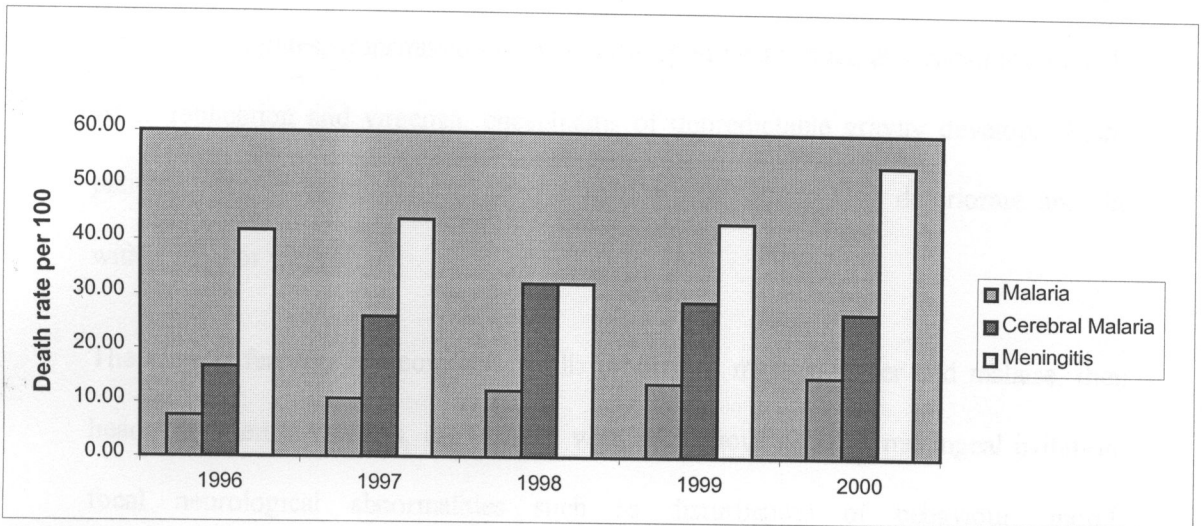


FIGURE 2: Annual death rates from malaria, cerebral malaria and meningitis for the period 1996 to 2000; calculated with permission from Managing Director UTH.

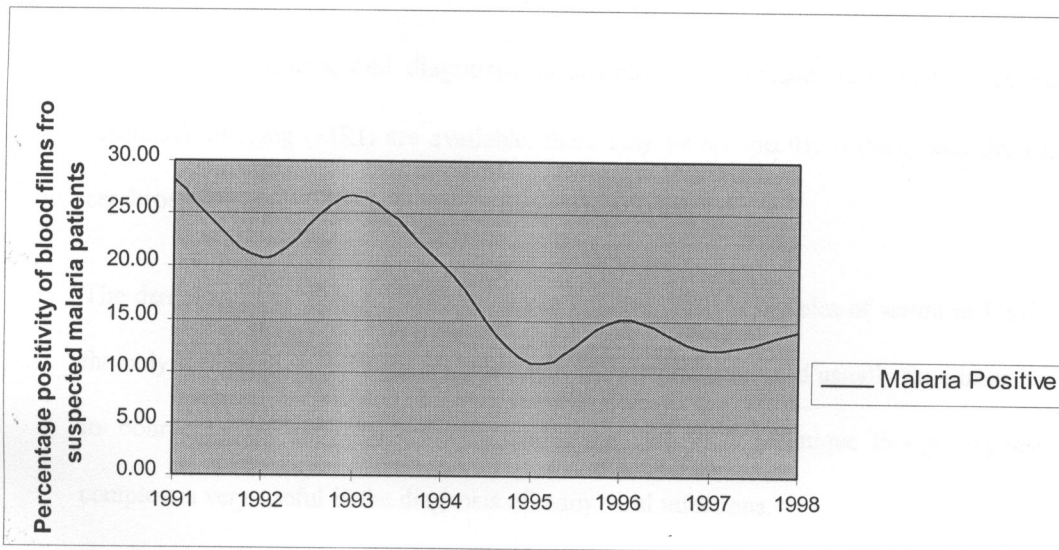


Figure 3: Malaria positivity on blood films from adult patients with suspected malaria during the period 1991 to 1998, calculated with permission from UTH Managing Director.

Acute viral encephalitis: Due to direct invasion of the brain parenchyma and is indistinguishable clinically from the postinfectious encephalitides where perivenous demyelination is probably triggered by allergic or immune reactions caused by a latent viral infection. Globally, viruses are by far the most common cause of encephalitis. The

arboviruses cause epidemic encephalitides in many parts of the world. The majority are perpetuated by zoonoses, often inconspicuous infections obtained from birds and smaller vertebrates; transmission is by an arthropod vector such as a mosquito or tick. After replication and viraemia, encephalitis of unpredictable gravity develops. Many patients recover spontaneously after a mild attack; others may deteriorate and die within days or weeks.

The clinical features are common to all: prodromal myalgia, fever and malaise, then headache, mental changes, drowsiness, with or without signs of meningeal irritation; focal neurological abnormalities such as disturbances of behaviour, mood, disorientation, deterioration of speech, level of consciousness, fits (focal or generalized), raised intracranial pressure and a deepening coma.

Even when sophisticated diagnostic neuroimaging techniques such as (CT) or magnetic resonance imaging (MRI) are available, there may be no specific features and the EEG and cerebrospinal fluid (CSF) may not be diagnostically helpful.

The demonstration of sequential changes in antibody titre in samples of serum or CSF may be the only means of establishing the true agent in sporadic cases and usually the illness has taken its course by the time the agent is confirmed. The PCR technique though expensive and complex is very useful in the diagnosis of many viral infections.

Eastern equine encephalitis: Mainly on the Atlantic and Gulf coasts of America and tends to occur in summer and autumn and the mortality may be as high as 70%; (Schoub et al. 1992) Western equine encephalitis, which despite its name occurs throughout the USA and eastern South America, tends to be less severe.

Japanese encephalitis: This is a mosquito-borne arboviral infection, which still claims many lives in South-East Asia. The virus is antigenically related to the flaviviruses of St Louis encephalitis and Murray Valley encephalitis and to the West Nile virus. The illness is usually severe, and fatal in about 25% of cases, with neuropsychiatric sequelae in a further 30%. It mainly affects the young, but a shift now to the elderly may be due to early immunization. CT and MRI show thalamic involvement. An inactivated Japanese encephalitis virus vaccine is now available and its use should reduce the incidence in due course (Steiner, et al. 1989). Sporadic and epidemic attacks of encephalitis continue to be reported from different parts of the world and often the reasons for these fluctuations remain obscure. For example, Rift Valley fever has recently been recorded in Egypt after an absence of over 12 years. In 1993, patients began to complain of a febrile illness with headaches, retro-orbital pain, nausea, vomiting and loss of vision with or without features of a generalized encephalitis (Freier, et al. 1993).

In this pattern of illness a reasonably firm clinical diagnosis can be made because of the frequent finding of macular and paramacular retinal lesions, often with haemorrhage and oedema, occurring at a time when there has been an abnormally high number of abortions in cattle and buffalo, but the true reason(s) for the recurrence remain cryptic.

Poliomyelitis: New infections are now uncommon and it is realistic to anticipate worldwide eradication by the end of the millenium. In 1992, 15 445 cases of paralytic poliomyelitis were reported, compared with 32 419 in 1988. Thus China (about 20% of the world population) conducted two national vaccination days in December of 1993, targeting all children below 4 years, the largest public health event in history. No indigenous wild poliovirus cases were reported in the USA, (Thongchareon et al 1989)

England or Wales (Arthur et al. 1993). Vaccine-associated paralytic poliomyelitis is the prominent form of the disease not only in Western countries, but also in the developing world. In those vaccine-related cases reported in the USA there were three high-risk groups: infants receiving the first oral polio vaccine dose, unvaccinated or inadequately vaccinated adults who are in contact with recipients of oral polio vaccine, and immunocompromised individuals. Wild poliovirus causing disease is still a problem in small pockets of individuals in Western Europe who for religious reasons refuse vaccination, as exemplified by the 1992 outbreak in Holland. While apparent outbreaks are still reported worldwide (Hull, et al 2001; 2000) it is imperative to separate paralytic poliomyelitis from other causes of paralysis in infancy.

Dengue: The haemorrhagic variety, still causes considerable morbidity and fatality in South-East Asia, and yellow fever similarly in Africa and South America.

Lassa fever: An acute haemorrhagic febrile illness occurring in West Africa. It carries a fatality of up to 20%. It is caused by an arenavirus spread by a rodent (*Mastomys natalensis*) and causes a wide spectrum of clinical disease, from asymptomatic or trivial malaise to fatal illness, and is often associated with neurological manifestations during the acute disease or in early convalescence. Delirium, convulsions and coma occur in critically ill patients; deafness may occur towards the end of an acute illness and is believed to be the result of cochlear nerve damage. A recent paper (Sutter et al 1991) emphasizes the importance of metabolic encephalopathy, severe tremor, self-limiting encephalitis, late ataxia and subacute or chronic neuropsychiatric sequelae.

Rabies virus: Rabies remains endemic throughout the world (Otten, et al. 1992) except for the UK, Australasia, the Caribbean and Scandinavia. In Indonesia about 700 000 people are treated for exposure to the virus each year and worldwide more than one

million receive rabies vaccine annually. No patient has survived the established disease. Whereas vaccines derived from cell cultures are now much safer and more effective than animal-derived preparations (Solbrig, et al. 1991), sadly the vast majority of human exposure to rabies occurs in developing countries most of which cannot afford cell culture vaccines. The majority will have access only to vaccines derived from animal neural tissue, which unfortunately may result in a disabling immune response. Reports of such neurological complications range from 1:1200 (Warrell, et al. 1988) to 1:120 (Petricciani et al, 1993). Consequently many people in developing countries who are bitten and potentially exposed to rabies will deliberately avoid vaccination, fully aware of the possible hazards.

Attempts to control the animal reservoir of rabies have not been successful and even in developed countries wildlife reservoirs affecting racoons and foxes still persist. The need for low-cost safe rabies vaccines equally acceptable in the developed and developing world remains a technological challenge.

Human immunodeficiency virus: infection is causing major morbidity and mortality in Africa and there is a similar trend in South-East Asia. The vast spectrum of neurological complications, (Nicholson, et al. 1990) including opportunistic infections, tumours, neurological manifestations attributed to HIV from muscle disease through peripheral nerve, myelopathy, radiculopathy, meningitis and encephalopathy and other complications, cannot be adequately covered in a short review. Since the early months of 1981, when five young homosexuals in the Los Angeles area developed *Pneumocystis carinii* pneumonia, the gradual awareness of this syndrome and its complications in acquired immune deficiency states, the emergence of associated problems such as drug resistant pulmonary tuberculosis and multiple infections such as

tubercle and toxoplasmosis, have presented challenging diagnostic problems and dilemmas to physicians throughout the world, the successful management of each crisis only delaying the inevitable fatal outcome.

At the UTH before the advent of HIV/AIDS cryptococcosis was considered rare but it is now routinely tested for in all CSF samples sent for microscopy and culture and its laboratory incidence together with other common bacterial pathogens are illustrated in figure 4. Other opportunistic infections that have been documented in other centres to present with acute meningoencephalopathies such as human herpes viruses, HIV itself, toxoplasmosis, syphilis and tuberculosis are not routinely sought probably due to prohibitive costs and/or expected low yields in some infections and to date there is no surveillance data for the same. However, from nearby Tanzania there was a report of a 35-year old man who was treated for malaria for a one-week history of headache to later die at home. At autopsy the diagnosis of fulminant toxoplasma encephalitis was made by haematoxylin eosin and immuno histochemical stain with P30 anti-body for toxoplasma antigen (Ng'walali et al; 2001). In South Africa a survey (Silber et al;1999) of 60 migrant labourers from Southern African countries presenting to hospital there with suspected meningitis produced the following results: sixty six percent were positive for HIV, 9 had tuberculous meningitis, 7 cryptococcal meningitis, 9 aseptic meningitis, 2 neurosyphilis and 20 normal lumbar punctures. All patients with tuberculous , cryptococcal and viral aseptic meningitis were HIV seropositive.

Human lymphotropic virus-1: A recent discovery concerns the related human T lymphotropic virus (HTLV)-1 which may be responsible for certain patterns of chronic myelopathy seen in the tropics, separating this group of illnesses from the tropical paraparesis and ataxic neuropathic group. HTLV-1-associated myelopathy was first described in the Caribbean (Swaddiwuthipong et al 1988) and Japan, and is also found in many parts of Africa (Lang et al. 1999). Previously described under many guises,

including tropical paraparesis and ataxic neuropathy, (Krebs et al. 2000) its relation to adult T-cell leukaemia and clinical progress is now well established (Simpson et al. 1996).

HTLV-1-associated myelopathy/tropical spastic paraplegia (HAM/TSP) is a condition, which appears in the fifth decade as a slowly progressive spastic paraparesis. There is usually sphincter involvement with some sensory changes. HTLV-I specific uveitis can present acutely or subacutely with vitreous opacities, mild iritis and retinal vasculitis (Gessain, et al. 1985).

There may be some mild pleocytosis with raised IgG and positive oligoclonal bands on a CSF study. HTLV-I specific cytotoxic T lymphocytes were isolated in the CSF of HAM/TSP patients (Roman et al. 1988). The transmission of HTLV-I virus is reported to be through infected T lymphocytes (this can occur sexually), through blood transfusions, or vertically from mother to infant through milk (Montgomery et al. 1993).

HAM/TSP has been reported not only in the tropics but also in immigrants in Europe and the USA (Yamaguchi, et al. 1994) and needs to be differentiated from multiple sclerosis, (Mochizuki et al. 1992) subacute combined degeneration, syphilis and Behçet's disease. The neuroimaging of patients with TSP/HAM shows normal myelography and periventricular low density with ventricular enlargement on brain CT; MRI shows high-intensity signals in the periventricular and subcortical white matter. Features of spinal cord atrophy have been described (Jacobson, et al. 1992). HTLV-II is a close relative of HTLV-I, structurally similar but molecularly distinct, and has been associated with chronic spastic paraparesis and high titres of HTLV-II antibodies in the serum and CSF.

Clearly the full spectrum of human illnesses due to this family of retroviruses is yet to be determined. All human retroviruses studied to date have been lymphotropic; whether they will all prove to cause disease of the nervous system remains to be elucidated. From the clinical point of view, presentations may be multiple; toxoplasmosis, lymphoma, progressive leucoencephalopathy and HIV encephalopathy may all overlap in the same individual.

Thus multiple focal brain lesions may be due to the simultaneous development of lymphoma, toxoplasma abscesses or tuberculosis. Opportunistic infections, including parasites, fungi, bacteria as well as viruses, may cause diagnostic difficulties of unparalleled complexity.

Rickettsiae

This group of illnesses, (Hino et al. 1989) which usually present as an acute meningoencephalitis, are transmitted to man by the bites of ticks or mites and occur throughout the world except in Antarctica. Mediterranean spotted fever (*Rickettsia conorii*) in Africa, Asia and the Mediterranean basin, (Cruickshank et al. 1989) scrub typhus (*R. tsutsugamushi*) in Asia and the Pacific, typhus (*R. prowazekii*) and Q fever (*Coxiella burnetii*) are ubiquitous. Whereas the incubation period and clinical features vary between organisms, all patients manifest high fever, rash and headache, with meningoencephalitis developing during the second week of the illness (Poser et al. 1990) Non-focal neurological features include: headache, neck stiffness and photophobia, confusion, impairment of consciousness and fits. When present, the distinctive eschar at the site of the bite may suggest the diagnosis. CSF examination is rarely helpful and treatment should be started on clinical suspicion. The response to tetracycline or chloramphenicol is usually gratifying.

Bacterial Infections

Bacterial meningitis in infants, children and adults remains a serious cause of morbidity and mortality (Alcindor et al. 1992). Early recognition followed by prompt, appropriate and effective antibiotics is not available in many parts of the world. As vaccination is not yet comprehensively effective and not generally available this heavy burden of preventable and treatable disease will continue for the predictable future. With the exception of the neonatal period, *Haemophilus influenzae*, *Neisseria meningitidis* and *Streptococcus pneumoniae* still account for about 70% of all cases; neonatal meningitis may be caused by almost any organism and the most frequently encountered pathogens are Gram-negative bacilli, particularly *Escherichia coli* and other enteric bacilli, *Pseudomonas* and group B streptococci (Shaked et al. 1991). In the elderly, Gram-negative bacilli and *Listeria spp.* should be considered. Confirmatory CSF examination should not delay treatment. In the search for an early appropriate antibiotic in a high-incidence part of Africa, long-acting chloramphenicol injections were found to be as effective as four times a day ampicillin for 8 days.

In the year 1997 about 5381 CSF specimens were examined and cultured for bacterial and cryptococcal meningitis at UTH. Approximately 11% of specimens (586) yielded species of which 48% (220) were *Cryptococcus*, *Streptococcus pneumoniae* 19% (111), *Salmonella* 10% (61), *Neisseria meningitidis* 8% (50) other *Streptococcus species* 2% (14), *Haemophilus influenzae* 2% (13) *Klebsiella* 2% (10), *Staphylococcus aureus* 2% (10), *Escherichia coli* 1% and anaerobic species 1%. This trend has continued over the years as highlighted in the table2 and figure 4.

Table 2. Commonly isolated pathogens and the total number of CSF specimens examined at UTH during the period 1994-97.

year	S pneumoniae	C neoformans	N meningitidis	H influenzae	All Specimens
1994	217	189	176	39	4311
1995	205	231	85	17	4289
1996	25	66	18	0	1085
1997	111	228	50	10	5381

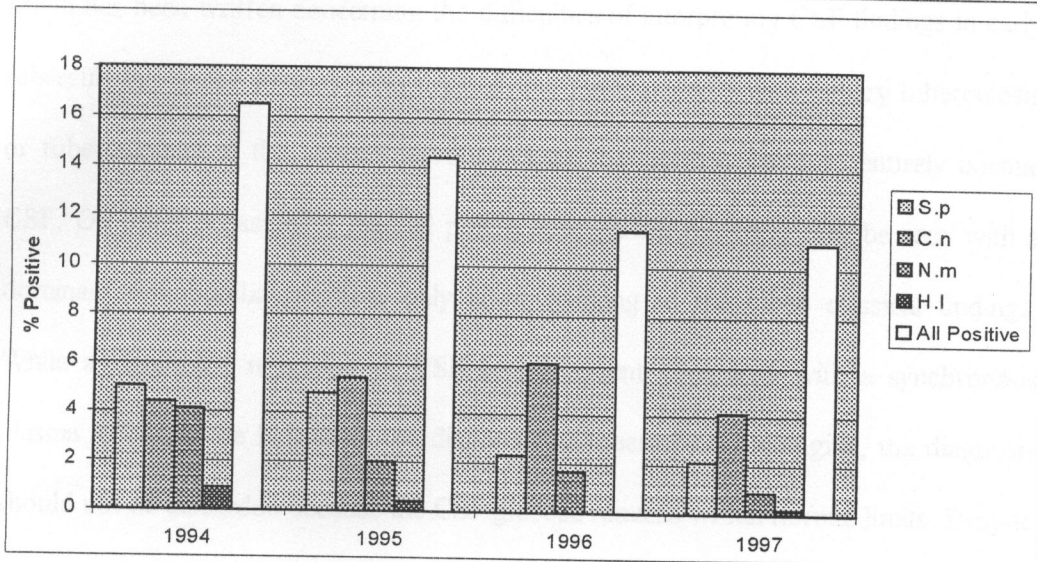


Figure 4: Annual percentage positivity of common pathogens isolated from the CSF of patients with suspected meningo-encephalitis: S.p-Streptococcus pneumoniae, C.n-Cryptococcus neoformans, N.m-Neisseria meningitidis, H.i-Haemophilus influenzae. With permission from the Managing Director -UTH.

Tuberculosis (see also under Human Immuno-deficiency Virus above) Involvement of the nervous system remains common, and despite the now worldwide availability of effective antituberculous therapy the classical syndromes, spinal cord compression from tuberculous osteitis, tuberculous meningitis, and intracranial tuberculomas—continue to cause significant morbidity and mortality (Raoult et al. 1986 ; 1990). As far as tuberculous osteitis is concerned it is important to appreciate that this may occur at any

spinal level and is not restricted to the dorsal vertebrae; whereas in the early stages of the granulomatous process involving adjacent vertebrae and the intervening disc the cord is usually compressed anteriorly, this is not invariably so. There may be one or more posterior compressive lesions arising from tuberculous osteitis in the laminae and pedicles, and epidural tuberculomas can easily be confused with epidural tumours and other focal pathologies.

Much has been written concerning the difficulties of interpreting CSF findings in early tuberculous disease. It should be stressed that some patients with miliary tuberculosis or tuberculomas of the central nervous system may initially have an entirely normal CSF. On other occasions a marked polymorphonuclear response may be seen with a dominant eosinophilic reaction, only later changing to the more classical findings. While a significant reduction of CSF sugar content compared with a synchronous plasma level may be helpful in the diagnosis of tuberculous meningitis, the diagnosis should not be discarded because the CSF glucose remains within normal limits. Despite access to the most sophisticated diagnostic facilities it is still often necessary to embark upon antituberculous therapy on the grounds of clinical suspicion without confirmatory diagnostic support. It may be hazardous to wait until serial investigation confirms or refutes the diagnosis. Perhaps the use of polymerase chain reaction techniques will answer some of the questions (Berkley et al. 2001). The technique is more specific than CSF enzyme linked immunosorbent assay (ELISA) but false positives, in addition to the complexity of the technique, make it impractical for worldwide use.

Intracranial tuberculoma, single or multiple, remains the most common cause of a space-occupying lesion in many parts of the world. CT facilities are now more widespread and the most common finding is a hypodense lesion on an unenhanced scan

with a ring or disc-like enhancement with contrast and surrounding hypodensity. Where tuberculosis is common, physicians frequently promptly embark on a course of antituberculous therapy without histological verification. After 3 months of treatment a repeat brain scan will show clearing of the lesion. While there are regional differences in the optimal combination of antituberculous drugs, chemotherapy is usually given for 6–12 months, depending upon the severity of the disease and response to treatment; corticosteroids are not given routinely, but dexamethasone in high doses during the acute phase of raised pressure may be helpful in reducing cerebral oedema. Obstructive hydrocephalus may develop at any stage of the illness, sometimes acutely; it is the most likely explanation for sudden neurological deterioration and should be treated promptly by surgical drainage.

Leprosy remains by far the most common cause of chronic mononeuritis multiplex in the world (Lewis et al. 2001; 2000). The World Health Organization currently estimates that there are 5.5 million patients with leprosy worldwide, a fall of about 50% since the 1980s. Nevertheless, despite much publicity and public health measures, the disease is frequently overlooked or misdiagnosed, often neglected and still generally feared. Thus the extent of the illness in a community may be difficult to estimate, but all reasonable attempts to do so indicate that, despite the availability of effective treatments, prevalence throughout the world is essentially unaltered. It remains true (Peltola et al. 2001) that: ‘leprosy should be considered whenever confronted by a chronic and symptomless skin rash that does not correspond with a common dermatosis or which does not respond to standard treatment for similar lesions. Leprosy should be considered in all cases of transient, recurrent or persistent numbness of paraesthesiae especially when this is localized to a more or less well-

defined area of skin. Hypopigmentation, with impaired sensitivity to light touch and pinprick, and particularly focal impairment or absence of sweating, should strongly suggest the diagnosis and a careful search should be made for thickening of peripheral nerves. Most commonly palpable are the great auricular nerves in the neck, the ulnar nerve just above the medial epicondyle, the median nerve at the wrist, the lateral popliteal nerve below the head of the fibula and the sural nerve on the dorsum of the foot. Early thickening may be difficult to clinch. Trained paramedical staff often become expert in detecting and confirming the presence of leprosy in suspects. Even those with advanced disease, severe neuropathy, deformity and incapacity may be helped by skilled reconstructive surgery.

Brucellosis occurs in many tropical and subtropical areas and the nervous system may be affected in up to 5% of patients in a variety of ways (Ross et al. 1991). It can cause an acute meningoencephalitis with papilloedema, convulsions and coma. Spinal presentation is with spastic or flaccid paraparesis due to cord compression or myeloradiculopathy, and central involvement with hemiparesis and ataxia. Diagnosis depends on blood or CSF culture of brucella, or more commonly on ELISA of the blood and CSF (Adeghola et al. 1999). Treatment with rifampicin, tetracycline and streptomycin should be for 3 months in those presenting with the subacute or chronic forms.

Spirochaetes.

Neurosyphilis is again on the march and is increasingly occurring in the wake of HIV infection. The old clinical adage remains true, 'to know all the manifestations of syphilis is to know the whole of medicine', but even here there are new twists to perplex even experienced physicians. When a young and apparently otherwise healthy male presents with acute onset of unilateral neural deafness, who would immediately suspect secondary syphilis? Other frequently occurring spirochaetal infections affecting the nervous system include borreliosis or relapsing fever (*Borrelia recurrentis*, louse borne; *B. duttonii*, tick borne), usually presenting as a febrile meningoencephalitis. Leptospirosis may affect any part of the nervous system, including an acute neuropathy (Zumla et al. 1999). Lyme disease (*B. burgdorferi*) is spread to man by infected ticks. While there is a very extensive literature (WHO 1999) on its diverse neurological and systemic manifestations, now recognized as the leading vector-borne disease in the USA, this malady occurs mainly in temperate climates. The neural manifestations span from meningitis, encephalitis, focal cranial neuropathies, radiculitis neuropathy, encephalopathy and post-borreliosis syndromes.

Trypanosomiasis.

African trypanosomiasis produces progressive central nervous system damage which if untreated results in death. Involvement occurs within a few weeks in the case of *Trypanosoma rhodesiense*, but usually takes much longer in the case of *T. gambiense*, months or even years. Leptomeningitis with distended ventricles, demyelination and perivascular cuffing develops and trypanosomes aggregate in the choroid plexus with an eosinophilic CSF reaction. In experimental studies trypanosomes shelter in the ependymal cells. It is also suggested

that after clearing the parasite from outside the central nervous system with chemotherapy there may be an immune-mediated reaction against the intracellular parasite from outside the central nervous system and this may explain the encephalopathy noted with melarsoprol use and its prevention with steroids. Early clinical symptoms are those of an encephalopathy, with lassitude, sleepiness, walking difficulty, ataxia, tremor, dysarthria and back and neck stiffness; headaches and papilloedema may also occur. The CSF is usually under pressure, with high protein and pleocytosis and the appearance of a modified plasma cell containing a large eosinophilic inclusion of IgG (morular or Mott cells). Therapy for African trypanosomiasis has been transformed by the introduction of eflornithine, (Turner , 1973) which is best given intravenously and has been shown to be effective in late stages of the disease when the CNS is involved, which is not the case with pentamidine and suramin. The problems of early diagnosis and introduction of cheap, safe and effective therapy before irreversible cerebral damage occurs are immense; meanwhile the prognosis for established sleeping sickness must remain grim.

American trypanosomiasis (Chagas' disease) remains a major cause of morbidity and mortality in developing countries; the myocardium is usually heavily parasitized, frequently associated with complicated cardiac arrhythmias and presenting clinically with syncope. American trypanosomiasis caused by *T. cruzi* can involve the nervous system in the acute stage with trypanosomes in the CSF (Finkel et al. 1992). In its chronic stage enlargement of hollow organs is the diagnostic hallmark. Myositis and neuritis due to demyelination and axonal degeneration with remyelination and regeneration have been described (Medana et al. 2001). Recent reports of the occurrence of acute Chagas' disease in patients with the acquired immune deficiency

syndrome (AIDS) are usually due to reactivation of chronic or dormant infection. Fatal meningoencephalitis in patients with AIDS, as well as other causes of depressed immunity, are well recognized (Garg 2000).

Amoebiasis.

Amoebic cerebral abscesses, although uncommon, have been recognized since 1849 (Muphy et al. 2001) and, providing the possibility of *Entamoeba histolytica* is considered early, the response to can be impressive a 5-nitroimidazole compound. *E. Histolytica* can cause single or multiple cerebral abscesses, which are noted on CT and may be clinically silent. Granulomatous amoebic meningoencephalitis commonly occurs in immunocompromised and debilitated individuals, including patients with AIDS. The disease has a subacute course and is generally fatal (Tuner 1997).

Amoebic serology is usually positive with immunofluorescence, cellulose acetate precipitation and countercurrent immunoelectrophoresis. Brain biopsy occasionally shows *E. histolytica* trophozoites. Oral or intravenous metronidazole should be started and followed by diloxanide furoate to eliminate colonic cysts; the latter may not be successful. Surgical excision of cerebral granulomas has been reported, but the general condition of the patient should be taken into consideration carrying out invasive procedures. Most patients die despite treatment, but survival following early treatment with metronidazole supplemented with rifampicin and tetracycline has been described.

Naegleria fowleri can cause amoebic meningoencephalitis in both tropical and temperate climates. The organism prospers in moist soil and cases have been reported in children who have been swimming or playing in stagnant water. It is presumed that amoebae cross the nasal epithelium and extend to the brain through the olfactory nerves (Lockwood et al. 1994). The

neurological complications of meningoencephalitis may be subacute or acute. Amoebae can be isolated from the CSF, with neutrophilia and low glucose content. The changes may not be florid in patients with a subacute course due to *acanthamoeba*. The organisms can be identified if kept at room temperature. Treatment should start immediately with intravenous amphotericin B for 10 days; miconazole, rifampicin and tetracycline may enhance the effect of amphotericin B.

Helminths

Cysticercosis.

The larva of the pork tapeworm is the most common parasite to invade the central nervous system and the manifestations of neurocysticercosis may be seen worldwide. *Taenia solium* will be mainly considered in this section. Systemic infection with other adult or larval cestodes such as the dwarf tapeworm (*Hymenolepis nana*) or the beef tapeworm (*T. saginata*) are now rarely encountered. Presumably improvements in sanitation and meat inspection since the 1960s have been largely responsible. However, other cestodes such as the fish tapeworm (*Diphyllobothrium*) should not be completely forgotten because of increased consumption of sashimi and sushi from raw salmon (De Silva et al. 1988). It is believed that the fish tapeworm infects about 10% of people living in Scandinavia (Chimelli et al. 1997). There, megaloblastic anaemia and its associated neurological complications may occur as a long-term consequence of infection because the adult tapeworm competes with the host for dietary vitamin B₁₂.

The larval form of *T. solium* is probably the most common cause of cystic lesions in the brain worldwide. The cysticercus, a fluid-filled bladder containing the invaginated head or scolex of the larval form, may infect all parts of the central nervous system, including the subarachnoid spaces and cisterns and, rarely, the sella turcica. Hydrocephalus is common and chronic meningitis with a lymphocytic or occasionally eosinophilic pleocytosis may be found when cysts are present in the subarachnoid

space or ventricles in close proximity to the meninges (Milord et al. 1992). CT and MRI have greatly facilitated diagnosis.

The cystic lesions may be seen to contain more dense nodules, corresponding to the scolex; calcifications where cysts have died and cysts on nodules may enhance with contrast material as the cysticerci degenerate. However, there may be no radiological evidence of parasitic lesions and a negative scan does not eliminate the diagnosis if other clinical evidence is persuasive.

A less common pattern is the racemose (bunch of grapes) cluster of cysts within the cisterns (Spina-Franca et al. 1978). The proliferating form consists of multiple interconnecting bladders of different sizes, but lacks scolices. These tend to occur in parts of the nervous system where the parasite is not closely confined by host tissue; the bladders may become large and extend into the spinal column. Careful examination may be required to reveal the degenerating scolex. It may be that racemose cysticerci are aberrant cysticerci of *T. solium* or other cestodes such as *T. multiceps* or *T. serialis* (the latter two are canine tapeworms of which the larval forms infect sheep and rabbits). Coenuri contain multiple scolices and may bud off daughter bladders; this condition is rare. To confirm the diagnosis of racemose cysticercosis requires pathological examination of the cystic lesion. When plain radiographs of soft tissues fail to reveal calcified lesions a number of available serological tests have been described. A recently introduced enzyme linked immunoelectrotransfer blot assay is sensitive and specific. Cisternal, parenchymal and intraventricular cysticerci may occur in the same patient, causing local disturbances—of which the most common is focal epilepsy. Larger cysts may produce mass effects: hydrocephalus commonly occurs and

inflammation of blood vessels adjacent to cysts may cause brain thrombosis and infarction. Cysticercosis involving the basilar cisterns carries a poor prognosis.

Treatment of racemose and cisternal cysticercosis is difficult (Woodhouse et al. 1993) and there are few satisfactory controlled trials to guide management. Anticysticercal drugs, corticosteroids, shunting procedures and surgical removal or decompression of cysts have been recommended. Praziquantel, an isoquinolone, and albendazole and imidazole have been used extensively in the treatment of parenchymal disease. Serial scans indicate that cysticerci are frequently eliminated or at least markedly reduced in numbers; the drugs are less effective for the cisternal and racemose manifestation. It is still not known whether albendazole is superior to praziquantel and in refractory cases both drugs are used. Praziquantel has been associated with a more adverse reaction that may be due to the host's inflammatory reaction to dying parasites, and headache, nausea and frequent seizures are common. Corticosteroids may ameliorate some of these effects and are usually prescribed, but there are few controlled trials to support this strategy.

Those with hydrocephalus due to cisternal disease and arachnoiditis will require shunting if there are symptoms and if serial scans indicate deterioration; some have recommended that a ventricular shunt should be considered in all patients with hydrocephalus before medical therapy is attempted (Rosenberg et al. 1992). If racemose and cisternal cysts are focally impairing the egress of CSF, surgical removal is sometimes recommended, but such procedures may be difficult and at times hazardous.

Ischaemic cerebrovascular disease is an underrecognized and relatively common complication (Morehead 1849). Inflammatory occlusion of the arteries at the base of

Onchocerciasis.

River blindness, endemic in large areas of Africa and Central America and caused by the filarial worm (*Onchocerca volvulus*), is transmitted by an insect vector. This breeds in fast-flowing rivers. Adult worms can survive in humans for many years, intermittently releasing microfilariae into the skin. More calamitous is migration into the anterior and posterior segments of the eye causing irreversible blindness, making onchocerciasis the most common cause of blindness in the world. The parasite occurs in both rain forests and savanna, where it is more likely to invade the eye. The anterior segment disease (Salokannel 1987), sclerosing keratitis and uveitis, is usually evident but the extent of posterior segment damage is more difficult to ascertain. In rain forest areas blindness is more likely to be due to posterior segment involvement with choreoretinitis and optic nerve lesions. The introduction of the antiparasitic agent ivermectin for the insect vector (*Simulium spp.*) was promising; spraying rivers with larvicide is very expensive and vector reinvasion after the discontinuation of spraying has occurred. Mass treatment with ivermectin (a semisynthetic macrocyclic lactone) is most encouraging. The drug is safe, well tolerated and effective in reducing microfilarial counts. A recent study concluded that annual ivermectin treatment may reduce the incidence of blindness by up to 80% in a savanna region. While most of the studies of onchocerciasis relate to blindness, a possible relationship with seizures has been suspected. Recent evidence (Del Brutto et al. 1988) from western Uganda describes an improvement in seizure activity after ivermectin treatment in a community with demonstrable microfilariasis (*O. volvulus*). It may be that further studies will indicate more widespread systemic and central nervous system involvement than is currently suspected.

Nematode infections.

While the adult form of *Gnathostoma spinigerum* has been known since the nineteenth century, when it was discovered in the stomach of a tiger in the London Zoo, the neurological manifestations of the mature parasite in man have been recognized more recently (Jung, et al. 1981). Those who prefer uncooked fish, shrimps and frogs in the tropics may acquire the larval third stage and present with a curious and sometimes

fatal multifocal neurological illness. During the acute stage there may be a febrile illness with headache, neck stiffness and a rash; on occasions the parasite can be extracted from a skin lesion. A painful radiculomyelopathy may then develop with intensive girdle pain, paraparesis and eosinophilia in blood and CSF (Earnest et al. 1987). This phase may subside, but if unrecognized or untreated the parasite may then migrate through the spinal cord into the brain. Death may occur because of brain stem involvement and at autopsy the live gnathostome may be seen emerging. A patient seen recently in London had spent only a few weeks in Hong Kong on business; he had developed a complete paraplegia with a wheelchair existence and a dense hemianopia as a consequence of his preference for fresh crustacea in exotic restaurants.

Angiostrongylus cantonensis (rat lungworm) similarly affects those in South-East Asia who consume poorly cooked snails, prawns and crabs. Neurological complications include meningitis, papilloedema and extraocular palsies with an eosinophilic CSF pleocytosis. Brain abscesses may occur and CT shows well-circumscribed enhancing lesions. Both these nematodes are treated with albendazole with steroid cover.

Strongyloides stercoralis, another nematode affecting the nervous system with an eosinophilic meningitis, usually occurs as part of the 'hyperinfection syndrome' with multiple cerebral infarcts, vasculitis and larval depositions (Lobato et al. 1981).

Hydatid disease.

This may present as intracranial cysts, occasionally spectacularly large with the features of space occupying lesions and obstructive hydrocephalus, or with a basal arachnoiditis due to multiple smaller lesions (Del Brutto 1992). CT and MRI may reveal the diagnostic daughter cysts. Surgical excision and shunting are usually required. When hydatid disease affects the spine, paraplegia may result and it is usually impossible to excise all the diseased bone effectively. In consequence the prognosis is poor. Albendazole reduces cyst size and, at least in the gerbil, (Shanz et al. 1992) is more effective than mebendazole and praziquantel.

Schistosomiasis.

This long-known parasite of man, the earliest case known to have occurred was 5000 years ago in an Egyptian adolescent from the predynastic period (Negess et al. 1985), continues to afflict mankind and it is believed that at present more than 250 million people worldwide are affected. Neuroschistosomiasis is uncommon but important because it responds well to appropriate treatment. Acute schistosomiasis (Katayama fever) presents as fever, cough, arthralgia, abdominal pain and urticaria; the neurological manifestations may be conspicuous headache, neck stiffness, evidence of raised intracranial pressure and fits. Involvement of the lower spinal cord and conus medullaris and/or cauda equina due to *Schistosoma mansoni* or *S. haematobium* has been well described, (Brown et al. 1982) but the diagnosis may be elusive even when suspected. Ova may be absent from stool and urine; available serological tests may be negative and eosinophilia absent (Bhatia et al. 1993). However, eosinophilia in the CSF is usually present and the CT and MRI findings may clinch the diagnosis. The interval of time between exposure and neurological presentation may be many years. It is recommended that all denizens where *S. mansoni* and *S. haematobium* prevail, and all travellers even with a remote history of recreational exposure to fresh water who present with a painful cauda equina or spinal syndrome, should commence praziquantel and corticosteroids without waiting for the results of laboratory or imaging tests (Mabey 1993). The results may be gratifying. *S. japonicum* can also affect the cerebral hemispheres, with fits and other focal neurological presentations; this is uncommon in the West.

Toxocariasis.

Toxocara canis transferred from dogs to humans through the eggs and the worm occasionally involves the central nervous system; unilateral retinal disease may occur in children; encephalitis and encephalomyelitis (Kipp, et al. 1994) have been reported in adults. Serious and persistent organic neurological and psychological deficits have been described and related to multiple brain infarcts from vasculitic lesions and eosinophilic granulomas. Myelitis with larvae in CSF and small arterial lesions may occur. Immune vasculitis should be prevented by early anthelmintic treatment, but there is a paucity of evidence of therapeutic efficacy.

Trichinosis.

This parasitic disease, which develops after ingestion of undercooked meat contaminated with larvae of *Trichinella spiralis*, occurs both in tropical and temperate climates, and there have been large outbreaks in France related to the ingestion of horse meat (Schmutzhard, et al. 1988). The acute illness, with fever, headaches, myalgia, periorbital oedema, nausea and diarrhoea with a marked blood eosinophilia, increased serum muscle enzymes and specific antibodies, is well known. Less so are the neurological manifestations, which are protean, making sporadic cases difficult to identify. Encephalopathy with a wide variety of focal deficits and numerous small hypodense CT changes in cortex and white matter has been clearly described (Punyagupta et al. 1975). The brain shows multiple small ischaemic cavities throughout the white matter and pons. Arteriolar microthrombi are present without an inflammatory infiltrate or remnants of *Trichinella* larvae. Toxaemic, allergic and larval pathogenic mechanisms have been proposed and a recent study suggests that hypereosinophilia may be implicated in the genesis of cerebral lesions. Early diagnosis and prompt treatment with anthelmintic therapy such as diffusible benzimidazole with corticosteroids is mandatory.

Paragonimiasis.

This trematode causes major neurological problems in the Far East, especially Korea.

It presents as an intracranial space-occupying lesion. *Paragonimus westermani* is transmitted to man through ingestion of crab and crayfish; the metacercariae travel to the lungs and mature. The adult can live in the lung for several years and is usually asymptomatic. It can produce pulmonary symptoms, the most characteristic of which is cough with rusty sputum (Belani et al. 1987). Neurological presentation is due to cerebral involvement as a result of the development of cysts in ectopic sites; various intracranial sites can be affected (Cataltepe et al. 1992). The diagnosis is established by demonstrating *P. westermani* eggs in sputum, feces and pleural fluid. A monoclonal antibody assay has recently been reported. Treatment with praziquantel may be successful (Taylor et al. 1989).

NUTRITIONAL AND TOXIC FACTORS

The clinical features of the major classical nutritional disorders of the central and peripheral nervous systems are well known, as is the importance of the vitamin B complex for the development and functioning of the nervous system. Thus beriberi usually due to the discarded germinal layer of polished rice presents clinically in the wet or dry form: the salient neurological features are painful polyneuropathy with tender calves and sensitive soles. Pellagra, due to a similar dietary deficiency mainly involving the nicotinic acid obtained in white maize presents clinically often in endemic spring attacks with diarrhoea, a light-sensitive erythematous rash progressing to thickening and atrophy with glossitis, diplopia, dysarthria, myelopathy and neuropathy with psychological and behavioural changes. Wernicke's encephalopathy may be acute or insidious, with vomiting, nystagmus, diplopia, confusion, ophthalmoplegia, retinal haemorrhages, polyneuropathy, and a dramatic Korsakoff's syndrome with amnesia and confabulation. However, it will be appreciated that even in communities known to be thiamine deficient from the consumption of processed rice, or in maize-eating

populations known to be vulnerable to pellagra from niacin deficiency, it is common to see the consequences of the lack of thiamine, pyridoxine and niacin and perhaps also pantothenic acid in combination necessitating appropriate blunderbuss therapy.

It will also be appreciated that there are numerous local and usually well recognized nutritional syndromes. The impact of the structural adjustment program and chronic alcohol consumption on these disorders is yet to be appreciated. The effects of HIV related malabsorption syndromes would have a greater impact on the nutritional disorders seen.

Clinically and epidemiologically it is often difficult to separate the consequences of nutritional deficiency from environmental toxins because they tend to occur in similar settings and the manifestations may be indistinguishable. The problem is further compounded by the increasing quantities of chemicals, often indiscriminately used in industry and agriculture as well as medicine. Toxic pesticides merit particular attention and many of the hazards arise from the lack of precautions and facilities for handling and storing these neurotoxic products safely.

The peripheral nervous system is commonly affected and has been frequently studied because it is easier to recognize clinically and to investigate electrodiagnostically and by nerve biopsy. While the pathophysiology may vary according to the putative toxin, distal axonal degeneration—so-called ‘dying back’ phenomenon (Cook, et al. 1992) — is the most common mechanism; initially, longer or larger nerve fibres are involved, then degeneration begins in the distal regions of the nerve fibres, progressing proximally with time. However, mechanisms are probably more complex: experimental evidence suggests that many toxic agents act at the level of the axon rather than the

cell body, (London, et al. 2000) impairing axonal transport; others may disturb anabolic mechanisms in the region of the neuronal perikaryon. Whatever the precise mechanism, clinical features are similar. Early symptoms are usually sensory with paraesthesiae, suprasensitivity, hyperalgesia and pain, followed later by peripheral weakness and wasting. Impairment of tendon reflexes occurs early and all sensory modalities may be variably affected. Some have associated myelopathic disturbances with spasticity and extensor plantar responses. Involvement of the autonomic nervous system with defective sweating and vasomotor disturbances commonly occurs.

The list of known agents is legion. Heavy metals such as arsenic, lead and thallium are often found in traditional folklore medications (Cavanagh, et al. 1979). For example, arsenical polyneuropathy (acute, or more commonly chronic) occurs very widely. Acute symptoms may include: vomiting, diarrhoea, burning discomfort in the eyes, excessive tears, photophobia, congestion and facial swelling, followed by a predominantly sensory neuropathy. Mees' lines (transverse white bands across the finger-nails) frequently occur, as does increased pigmentation of the extremities with patches of depigmentation, hyperkeratosis and descemation of palms and soles. Here the diagnosis may be confirmed, if facilities permit, by demonstrating high concentrations of arsenic in scalp hairs and nail clippings. Illicit liquor, crude abortifacients and well water deliberately contaminated by an enemy have all been reported (Spencer, et al. 1979). It will also be recalled that certain ocean fish and marine crustacea, such as the pomfret, plaice, halua and hilsa, may contain relatively high concentrations of arsenic. Another source of arsenical poisoning is said to be contaminated opium. The mechanism is thought to be direct reaction of arsenical compounds with the sulphhydryl group of proteins; electrophysiologically the signs of

distal axonal degeneration and nerve biopsies show loss of myelinated fibres and degeneration of myelin into rows of myelin ovoids;(Senayake, et al. 1991) segmental demyelination and inflammatory changes do not occur. In the acute stages dimercaprol and/or penicillamine must be given early; when there is a delay, response may be poor.

Lead may to cause a peripheral neuropathy in adults and an encephalopathy in children. Lead neuropathy tends to be predominantly motor, more evident in the upper limbs where the extensors of the wrists and fingers are affected early and asymmetrically, tending to affect the dominant hand (Senayake, et al. 1972). Proximal involvement is slow and occurs later, and sensory disturbances are minimal or absent. Associated abdominal colic and the characteristic anaemia with punctate basophilia, when present, may suggest the diagnosis. Potential sources include reconditioning of car batteries and burning lead-containing batteries for cooking, illicit liquor distillation by means of lead pipes or radiators, and contaminated water.

Thallium may be a constituent of rodenticides. The acute painful neuropathy may be associated with gastrointestinal symptoms, non-specific signs, but the occurrence of alopecia within 3 weeks should suggest the diagnosis (Le Quesne, et al. 1977).

Potassium ferrocyanide, given orally is the present treatment of choice.

Of the many conventional medications that may provoke peripheral neuropathy brief mention will be made of those drugs widely used in the treatment of tropical bacterial and parasitic infections. Peripheral neuropathy, particularly in those genetically disposed to slow acetylation of isoniazid for the treatment of tuberculosis, is well known, as is the similar hazard of ethionamide, from sulphonamides widely used in bacillary dysentery and urinary tract infections; similarly the optic neuritis related to ethambutol. Chloroquine, a standard antimalarial agent, may produce a neuromyopathy

after prolonged use, with muscle fibres showing vacuolation and peripheral nerves showing involvement of terminal axons with Schwann cell defects (Windebank, et al. 1984). Clioquinol, previously widely used in the symptomatic treatment of diarrhoea and intestinal amoebiasis is now known to be the causative agent of subacute myelo-optic neuropathy; (Cavanagh, et al. 1974) unfortunately clioquinol continues to be prescribed in certain countries and the complication is still sporadically encountered. The aromatic diamidines used in the treatment of leishmaniasis and trypanosomiasis have been associated with an odd, uncommon focal disturbance of sensory function of the trigeminal nerve.

Industrial chemicals of known potential neurotoxicity rarely cause hazards in developed societies; it is where appropriate safety measures and conditions are not practised that outbreaks continue to occur. Well known is trio-ortho-creasyl phosphate; commonly used as an industrial solvent, it has been the culprit in many reported outbreaks (Loftus, et al. 1963). Accidental contamination of food, particularly edible oils, may produce not only classical peripheral mixed neuropathy, but also signs of cord involvement. Unfortunately, the damage is permanent and there is no curative or generally available protective agent. In unprotected environments, carbon disulphide and acrylamide may produce similar hazards. Insecticides widely dispensed in tropical countries are a common cause. The most common culprit is the group of organophosphorous insecticides; the defect is believed to be mainly at the postsynaptic border of the neuromuscular junction. Clinically the onset may be acute or delayed.

Particularly well documented in recent years are the toxic effects of the root crop cassava, a major crop sustaining millions of people in Africa (Nakae, et al. 1973).

Flour made from cassava roots may contain a high concentration of linamarin, a cyanogenic glycoside, resulting in chronic cyanide intoxication and clinically 'tropical ataxic neuropathy'. The clinical features in addition to painful neuropathy and ataxia may include blurred vision and impaired hearing of cochlear type; occasionally upper motor neurone lesions are seen. This pattern of illness is usually slowly progressive.

Konzo is a clinically distinct pattern of tropical myelopathy because of its abrupt onset and dominant upper motor neurone pattern of involvement (Vora, et al. 1962). A recent study in rural Zaire (Roman, et al. 1985) was able to determine the cyanergine content of the locally used cassava flour and blood cyanide concentrations in cases and controls. This detailed study indicated that not only was there a significant sustained high blood cyanide concentration, but also that the deficient sulphur intake impaired the conversion of cyanide to thiocyanate. Even though the immediate causes are poverty and shortage of food, a relatively minor change in traditional cooking habits could prevent much disability.

Lathyrism and cycad poisoning are two other well-known examples of neurotoxic plant poisons affecting the central nervous system. Lathyrism, endemic in parts of India, Bangladesh and Ethiopia, is caused by excessive consumption of peas of the lathyrus family (chickling peas). It presents as a slowly progressive spastic paraparesis: neuropathological studies have shown selective atrophy of the pyramidal, spinocerebellar and dorsal columns of the spinal cord. The neurotoxin is an amino acid, -N-oxalylamino-L-alanine, which is thought to act by excessive and prolonged exhaustion stimulation, a so-called excitatory amino acid. Once damage has occurred there is no effective treatment. In a similar manner excessive consumption of the seed of the false-sago palm, either as a foodstuff or as a medicinal component may have an

excitatory neurotoxic effect and may be one of the constellation of factors responsible for the occurrence of amyotrophic lateral sclerosis and parkinsonism, dementia complex in the Pacific Mariana Islands (Howlett, et al. 1992).

Rarer plant toxins include that of *Gloriosa superba* (glory lily): (Tylleskar, et al. 1992) accidental ingestion may cause alopecia, aplastic anaemia and polyneuropathy due to colchicine which impairs exoplasmic transport in peripheral nerves and also damages skeletal muscle. Podophyllin (from the dried rhizome and root of the mandrake) also has neurotoxic properties. A recent report from Hong Kong (Spencer, et al. 1987) described encephalopathy and sensory-motor polyneuropathy and autonomic changes after ingestion of a broth containing herbal guyjiu. Another poisonous shrub of the buckthorn family (*Karwinskia humboldtiana*), which grows freely in Mexico and Texas, may cause a progressive polyneuropathy, terminating in respiratory and bulbar paralysis (Angunawela, et al. 1971).

All these essentially irreversible and disabling toxic disturbances of the central autonomic and peripheral nervous systems are preventable and presumably will continue to be observed and reported in the developing world until nutritional, economic and educational disparities are resolved.

EPILEPSY

This is a major neurological disorder in the tropics and particularly Zambia and has important medical and social implications (Senayake, et al. 1992). Attempts to determine accurately the magnitude of the problem have encountered considerable difficulties, including differences in definition and methods of case detection. It is

therefore difficult to determine what significance should be attributed to the reported relatively low prevalence in certain parts of the country and the fact that other regions have a very high prevalence, sometimes as much as ten times the average for industrialized countries. It would appear that rural prevalence is lower than in urban areas, partial seizures more common than primary generalized ones and mortality rates for epilepsy appear to be higher in tropical countries generally in comparison to those in industrialized areas. Known aetiological factors present a bewildering spectrum (Senayake, et al. 1991). Cysticercosis accounts for about half the cases of epilepsy of late onset in several countries. Other parasitic infections known to cause epilepsy include: schistosomiasis, paragonimiasis, sparganosis, hydatid disease, toxoplasmosis, trypanosomiasis, cerebral malaria and cerebral amoebiasis. Tuberculous, pyogenic, viral and fungal infections can also cause epilepsy as a late sequel as well as being a feature of the acute illness. Poor antenatal and perinatal care resulting in perinatal brain damage probably contributes to a higher prevalence. Despite these problems there have been impressive attempts to sharpen the epidemiological profile of epilepsy. Thus a recent survey (Rwiza, et al. 1992) of a rural Tanzanian population showed a prevalence of 11.4 per thousand in a population of 18183. It was possible to study 203 of these in detail: 32.5% had partial seizures, 85.2% tonic-clonic ones and 8.4% had unclassifiable fits; 95% initially sought aid from outside the immediate family, a traditional healer, a priest and 80% had consulted traditional healers. Fewer than 20% of the patients were receiving regular anticonvulsants. The authors stress the importance of improving patient attitudes, and in particular, acceptance of anticonvulsant therapy. No such data exists for the Zambian set up and therefore there is need to define the spectrum or contribution of this disorder to the disease burden.

1.2 JUSTIFICATION FOR THE STUDY

The contribution of Falciparum malaria and other infections to acute neurological disorders seen at the University Teaching Hospital remains unknown though clinical observations are that these disorders are on the increase. The limitations in diagnostic facilities coupled with the high morbidity and mortality associated with these disorders needs to be defined and studied so that interventional strategies could be worked out. The impact of HIV and newer infections on the neurological disorders seen at UTH needs to be defined.

Empirical treatment is commonly employed for most C.N.S infections presenting as acute neurological disorders the world over. This is due to limited access to nervous tissues for direct biopsies, prohibitive costs of other more reliable and informative tests, if available, and the need to commence “treatment” promptly to minimise residual neurological damage. It is noteworthy of the fact that attempts to isolate viruses, mycobacterium and toxoplasma from C.S.F are often disappointing in individual patients but less so in cohorts.

At UTH too empirical treatment is the cornerstone in the management of patients presenting with acute neurological disorders but this is restricted to malaria, bacterial infections, Cryptococcus and rarely mycobacteria. Viruses, toxoplasma and other opportunistic infections related to HIV/AIDS are not commonly adequately considered in the management of such patients and this could be one of the reasons behind the increasing number of deaths from “cerebral malaria and meningitis”. It is against this background that a study to look at the contribution of Falciparum malaria and other infections to acute central nervous system disorders was undertaken.

1.3 OBJECTIVES

To determine the frequency of Falciparum malaria and other infections in patients presenting with acute central nervous system disorders at the University Teaching Hospital.

Specific Objectives:

- 1 To determine the contribution of Falciparum malaria to patients presenting with acute central nervous system disorders.
- 2 To determine the contribution of infections other than Falciparum malaria to patients presenting with acute central nervous system disorders.
- 3 To determine the clinical features associated with patients presenting with acute central nervous system disorders.
- 4 To determine the laboratory features of patients presenting with acute central nervous system disorders.

1.4 ETHICAL CONSIDERATIONS

This study was presented to and approved by the Research and Ethical Committee at UNZA as an integral part of the broader study on the impact of HIV on neurological disorders in Zambia. All the tests done were considered as essential and ideally routine in trying to make the most likely diagnosis for each individual patient. Obtaining informed consent from all the patients was obviously impossible due to the nature of the clinical illness.

All the test results likely to cause embarrassment, disappointment or social and mental disturbance or discomfort to the patients and/or their relatives were withheld and only revealed to them upon request and after counselling.

CHAPTER TWO:

2.1 MATERIALS and METHODS

This was a one-year longitudinal prospective study aimed at determining the contribution *Falciparum malaria* to patients presenting with acute central nervous system disorders. The study was conducted between June 1997 and June 1998. Three hundred patients were recruited for the study.

a) Recruitment Site:

The medical emergencies admission ward at UTH was used. This ward receives patients from the adult filter clinic at UTH and the latter receives from public and private satellite clinics and hospitals around and sometimes outside Lusaka. Some patients come directly from home.

b) Method of Patient Selection:

Patients coming to the admission ward with the presumptive diagnosis of cerebral malaria, meningitis, encephalitis and/or meningoencephalitis, or acute central nervous system disorder were considered for enrolment. Recruitment to the study was dependent on the physical presence of the author in the admission ward and upon fulfilment of the inclusion criteria here given

c) Inclusion Criteria:

- i. Adults aged 16 years and above
- ii. Appropriate initial working diagnosis as explained in b) above.
- iii. History of acute onset central nervous system symptoms less than two weeks.
- iv. No prior therapy received before admission to UTH
- v. Consent by relatives to have all investigations performed as per study protocol

d) Exclusion Criteria:

- i. Less than 16 years old.
- ii. History of taking antimicrobials or brufen before admission to the hospital.
- iii. History of recent head injury prior to onset of central nervous system disorder.
- iv. Pregnancy.

e) Samples collected

The following samples were collected and immediately rushed to the laboratory for prompt and appropriate tests and storage.

- i. Two thick blood films on slides for malaria parasites.
- ii. C.S.F. studies for bacteria, Mycobacterium, Cryptococcus, HSV 1 and 2 and biochemistry
- iii. Random blood sugar
- iv. Blood for urea and electrolytes, Liver function tests, anonymous unlinked HIV, RPR

f) Study Samples Size:

A total of 300 patients were recruited to the study.

2.2 DATA ANALYSIS.

This was done with the help of Epi Info 6; version 6.04b-January 1997.

CHAPTER THREE

RESULTS

A total of 300 patients were recruited for the study and all of them had complete results. All the laboratory specimens were processed within 24 hours except in situations where special tests were required and a feedback on these results was given to the attending clinicians at the earliest possible time.

3.1 DEMOGRAPHIC DETAILS.

a. Age:

Age range: 16 to 72 years

Mean age: 28 years

Std deviation: 10.7

b. Table 3: Sex.

Sex	Frequency	Percent
Female	155	51.6
Male	145	48.4
Total	300	100.0%

The age range of the study population was 16 to 72 years and mean was 28 years. Females were 51.6% (155) and males 48.4% (145) with a female to male ratio of about 1:1.

3.2 CLINICAL FEATURES

The clinical features were recorded from either the patients or the history was obtained from the next of kin or whoever had brought the patient to the hospital. Getting full relevant details was often difficult. Tables 2 and 3 list some of the common symptoms and signs.

**Table 4 : Presenting symptoms
of 300 cases of Patients presenting with
Acute CNS disorders**

Sign	Total Number (%)
Fever	260 (87)
Wasting	190 (64)
Meningeal Signs	185 (62)
Anaemia	161 (54)
Oral Candida	90 (30)
Rash	130 (44)
Lymphadenopathy	150(50)
Motor Weakness	30 (10)
Malnutrition	82 (28)
Scar of Herpes Zoster	45 (15)
Papilloedema	60 (19)
Confusion	30 (10)
Cranial Nerve Palsy	40(14)

Table 5 : Presenting signs of 300 cases of Patients presenting with Acute CNS disorders

Symptom	Total Number (%)
Headache	250 (84)
Fever	210 (70)
Confusion	120 (40)
Forgetfulness	60 (20)
Slowness	110 (37)
Weight loss	92 (31)
Vomiting	100 (34)
Social Withdrawal	36 (12)
No history available	30 (10)
Diarrhoea	120 (40)
Fits	50 (17)
Paralysis	15(5)
Others	20(7)

3.3 LABORATORY FEATURES

1. BLOOD RESULTS

a) *P. falciparum*:

For each of the patients two blood slides were prepared and submitted to the laboratory at the same time. Three slides done about eight hours apart are recommended in an individual

Table 6: *P. falciparum* on blood films.

MP SLIDE	FREQUENCY	PERCENT
NEGATIVE	240	80%
POSITIVE	60	20%
TOTAL	300	100.0%

patient (Le Quesne et al 1977) but this was not feasible for the study as patients were recruited from a transit ward. A patient was considered positive if one or both the slides were positive.

Out of the 300 patients 60 (20%) were positive and 240 (80%) negative.

b) HIV test results

Of the 300 patients studied, 225 patients (75%) had been exposed to the HIV infection and only 25 % were negative.

c) RPR results

Of the 300 patients studied, 10 (3.3%) had positive results for RPR though none had spirochetes seen on microscopy of the CSF.

d) Random blood sugar

Of the 300 patients studied, 75 (23%) had lower sugar than normal but 1 patient had higher sugars than normal.

e) Urea and electrolytes

Of the 300 patients studied, only 5 (1.7%) had abnormal urea and electrolytes.

The abnormal results were those from chronic renal failure.

f) Liver function tests

Only 10 patients (3.3%) had abnormal liver function tests.

2. CSF RESULTS

a) Biochemistry

300 reports were obtained for biochemistry of CSF, i.e. glucose, Na⁺ and total proteins.

Table 7: CSF Glucose (normal 2.2-3.9 mmol/l).

CSF GLUCOSE	FREQUENCY	PERCENT
ABNORMAL	30	10%
NORMAL	270	90%
TOTAL	300	100.0%

For glucose 30 (10%) of the results were abnormal while 270 (90%) were normal

Table 8: CSF protein (normal 0.2-0.5 g/l).

CSF PROTEIN	FREQUENCY	PERCENT
RAISED	180	60%
NORMAL	120	40%
TOTAL	300	100%

For proteins 180 (60%) of the results were abnormal while 120 (40%) were normal

Table 9: CSF Na+ (normal 137-145 mmol/l).

CSF Na+	FREQUENCY	PERCENT
ABNORMAL	36	12%
NORMAL	264	88%
TOTAL	300	100.0%

Cerebral spinal fluid sodium was abnormal in 36 (12%) of the study population

b) Microscopy and culture

Table 9: CSF WBC

Cerebral spinal fluid WBC was raised in 135 (45%) of the study population.

CSF WBC	FREQUENCY	PERCENT
RAISED	135	45%
NORMAL	165	55%
TOTAL	300	100.0%

Other microscopy and culture results were as follows: The results reported were those that had both microscopy and culture positive.

C neoformans 20 = 6.7%

S pneumoniae 10=3.3%

N meningitides 8 =2.7%

H influenzae 2= 0.7%

Other bacteria 20 =6.7%

Of all the 300 samples sent for analysis, only 60(20%) patients had pathogens isolated as tabulated above.

CHAPTER FOUR

DISCUSSION

This study was conducted at the University Teaching Hospital to find out the contribution of *Plasmodium falciparum* and other infections to acute CNS disease. During this study, the following has been established:

The age range of patients in this study was 16 to 72 years and the mean of 28 with a sex ratio of 1:1 and this was a reflection of the general adult population in Zambia. The mean age of 28 years suggested that the population in the study was mostly in the reproductive age group, which is expected to be prone to sexually transmitted diseases including HIV.

The clinical picture of the patients in this study was vast with the majority of the patients presenting with a headache and fever, 84% and 70 % respectively. This does seem to suggest that the majority of the patients in this study had an infectious cause of the CNS disorder seen at the UTH. A good number of patients presented with either recent or immediate past diseases that may indicate retroviral disease, such as wasting and oral candidiasis. It was also evident from the physical examination that most of these patients had stigma of retroviral disease as was evidenced by the presence of wasting (87%), fevers (64%) and old herpes zoster scars. The other symptoms were mixed with some patients presenting with convulsions and only a small number had cranial nerve palsies. Apart from anaemia, some patients had meningeal signs though only 20% of this cohort had pathogens isolated from the cerebrospinal fluid.

Falciparum malaria in this group of patients contributed to about 20% of the patients presenting with acute CNS disorders and therefore it is important that any patient presenting with such disorders should have malaria excluded. Of the patients who had positive slide for *P falciparum* (15%) had sterile CSF making the diagnosis of CM almost certain. However, it is not uncommon to find *P falciparum* in the blood of some unaffected individuals living in

malaria endemic areas. The prevalence of HIV in patients who were positive for malaria did not in any way differ from the other patients and this raises the issue of whether HIV infection worsens the outcome in patients with CM.

The CSF glucose results were abnormal in only 10% of all the samples sent for studies, while protein abnormality was observed in 60% of the patients. The CSF protein content was more than the electrolyte abnormality seen, as only 12 % were abnormal. The pattern of abnormality seen was more predictable in the group that had pyogenic meningitis and was non-specific for most of the other conditions including CM. The CSF cell count was elevated in 45% of the patients. The pathogens cultured seemed to suggest that Cryptococcal neoformans has become the commonly isolated pathogen followed by Streptococcus pneumonia. The range of bacteria grown on culture has also changed, as even organisms that traditionally do not cause meningitis in adults, such as E.Coli, were isolated from the CSF. This pattern quite clearly points to the impact of the HIV epidemic on disease pattern and one has to be careful when diagnosing causes of neurological disorder in our environment.

The HIV sero-prevalence rate in this cohort was 75% and this was much higher than in the general population and may seem to suggest that many patients getting admitted to our hospital have HIV related diseases. It is important therefore that the problem of patients presenting with neurological disorder should be tackled in the general context of HIV. This high prevalence of HIV has cost implications on the health sector and should be addressed.

Hypoglycaemia in this group was 23% but most patients had received glucose prior to admission and the prevalence may thus be higher than was seen in this study. This may also explain the observation on the CSF glucose that was only abnormal in 10%.

Of all the patients seen, only 3.3% had tested positive to the RPR though none had spirochetes seen on CSF. It should be noted that the RPR may be falsely be positive in patients who have malaria. Only 1.7% had abnormal urea and electrolytes while liver abnormality was seen in 3.3% of all our patients.

This study has highlighted that there is a striking contrast between our situation and that prevailing in the western countries where major advances in the treatment of all common diseases including HIV infection and its associated opportunistic complications have led to significantly improved survival and reduced morbidity rates for the population (Van der Horst 1997). Patients in resource rich western countries have at their disposal a large armamentaria of diagnostic and therapeutic agents of proven efficacy, which have improved the quality of life, and longevity of their HIV-affected populations. The unavailability of resources to treat African patients with HIV disease and its infectious and non-infectious complications despite the proven scientific efficacy of anti-infectives and anti-retroviral drugs, raises several major ethical issues. The right of all human beings to enjoy living standards conducive to good health is enshrined in Article 25 of the United Nations Universal Declaration of Human Rights, established just over 50 years ago. This states that “everyone has the right to a standard of living adequate for the health and well-being of themselves and of their family, including food, clothing, housing, and medical care and necessary social services, and the right to security in the event of unemployment, sickness, disability, widowhood, old age, or other lack of livelihood in circumstances beyond their control (United Nations 1948).

In 1978, the World Health Organization and the United Nations Children's Fund sponsored an International Conference on Primary Health Care at Alma-Ata in the former Soviet Union (WHO 1978). At that conference a statement, the ‘Alma-Ata Declaration’, was formulated and opened with the reaffirmation that health is a fundamental human right and that the attainment of the highest possible level of health is an important worldwide social goal. The Alma-Ata Declaration states that the gross inequality in the health of people, particularly between the developed and developing countries is politically, socially and economically unacceptable and it calls for a new international economic order to address this inequality. Following this Declaration, the

World Health Organization set the goal of achieving “Health for All by the Year 2000”, an objective that has failed.

The processes by which Health for All could be achieved are listed in the Ottawa Charter which was formulated at the First International Conference on Health Promotion, held in Ottawa in 1986 (Anon 1996). This outlines five principals for the delivery of health promotion programs: 1) establishing public health policies; 2) creating supportive environments; 3) strengthening community action; 4) developing personal skills and 5) reorganising health services. In 1996, the United Nations embarked on a “Special Debt Relief for Africa” initiative with the World Bank and the International Monetary Fund (Jubilee 2000). The Jubilee 2000 initiative, which calls for a cancellation of debts owed by the poorer nations to the wealthier ones as a millennial gesture, is generating wide support but its critics argue that wealth freed by such a cancellation might not reach those in greatest need. The overwhelming tragedy is that the poor peoples of the world are unable to help themselves. In Zambia, with an income of one US dollar or less per day, the poorest quarter of the human population cannot afford even the most basic requisites for healthy living, let alone diagnostic and therapeutic agents. Governments in the developing world are limited in their ability to provide basic health care, partly as a result of their requirement to pay interest on loans from the wealthy nations. In Zambia, for example, for every dollar spent on health care, four dollars are spent on servicing international debt. It is therefore no surprise that infectious diseases for which effective treatments are available in the West, are taking their toll as a direct result of poverty consequential upon an unjust social and economic order. The failure to take advantage of medical advances and to translate them into practical solutions to alleviate human suffering world-wide should evoke searching ethical questions for medical health personnel worldwide.

Wealthy nations have a moral duty to press for the creation of a more just, equitable and healthy global society. With core support from development aid, several

influential groups, including religious organisations, charities and non-governmental organisations, within developing countries can positively contribute to the efforts at supporting the health services and improving the overall health of the people. The wealthier global community, must respond to the pressing need for more long-term support for provision of adequate health care provision in Africa rather than merely supporting sporadic and often short-lived disease control programs and specific research projects. While African governments battle with repayment multi-billion pound debts, there are signs of continued deterioration of health care delivery (Jubilee 2000).

Regrettably, the current world order does not allow for equity of health care provision and the majority of patients in sub-Saharan Africa will continue to have to face an invariably fatal outcome. As the numbers of patients with AIDS increases in Africa, there is an urgent need for uniform, appropriate and sustainable management approaches towards the overall management of AIDS patients in sub-Saharan African countries.

CHAPTER FIVE

CONCLUDING REMARKS AND RECOMMENDATIONS

This study has demonstrated that most of the patients presenting with acute neurological disease at the UTH in Lusaka have no definitive diagnosis.

The results obtained in this study strongly suggest that physicians and laboratory scientists should respond to the prevailing HIV epidemic by formulating a more inclusive management protocol for patients presenting with an acute febrile illness accompanied by altered sensorium.

Laboratory tests need to be expanded beyond the usual search for *plasmodium* in blood and commonly occurring bacteria and *C.neoformans* in CSF. HIV counseling and testing should be encouraged to enable the attending physicians address each individual patient's needs more comprehensively. There's need for surveillance studies including postmortems for opportunistic infections associated with HIV if only to improve on awareness by practitioners.

CM is always a possibility as suggested by malaria positive results of about 20% in the study and the laboratory records. Therefore inclusion of anti-malarial drugs in the initial treatment whilst awaiting laboratory results would be justified. CM is known to be fatal within 72hrs from onset, which further justifies prompt empirical treatment.

Currently the first line antibiotics in the treatment bacterial meningitis at UTH are a combination of benzathyl penicillin and chloramphenical. However, ampicilin and ceftazidime or cefotaxime have been recommended to be appropriate empiric treatment in patients with impaired cellular immunity (Sutter et al 1991).

Treatment of viral AME is usually symptomatic and the infections themselves are self-limiting (Rwiza et al 1992). However, in some centres, alpha-herpes viruses, VZV and HSV, which

have the thymidase kinase gene, are on suspicion empirically treated with acyclovir to minimise residual neurological damage (Senayake et al 1991). This is one practice that ought to be considered at UTH.

Mycobacterial, fungal and parasitic infections tend to take a more chronic course than most viral and bacterial infections but a more elaborate and comprehensive management protocol than the status quo could improve on early detection and reduce on mortalities.

One other thing this study was able to elicit is that there is need for more participation in the management of information by practitioners. Data collection at present has been delegated to ill qualified clerical staff with apparent insufficient supervision and guidance from professionals. To lamp all CNS infections under *meningitis* is not a good example in a University Teaching Hospital.

BIBLIOGRAPHY

- Adeghola R A, Usen S O, Weber M. et al. *Haemophilus Influenzae* type b meningitis in Gambia after introduction of a conjugate vaccine. *Lancet* 1999; 354:1091-1092. ✓
- Alcindor F, Valderrama R, Canaveggio M et al. Imaging of human T-lymphotrophic virus type I-associated chronic progressive myeloneuropathies. *Neuroradiology* 1992; 35:69-74 ✓
- Anon. Ottawa Charter for Health Promotion. *Can J Publ Hlth* 1986; 77: 425-430. ✓
United Nations. *The UN System-made Special Initiative for Africa*. New York: United Nations, 1996. ✓
- Angunawela R M & Fernando H A. Acute ascending polyneuropathy and dermatitis following poisoning by tubers of *Gloriosa superba*. *Ceylon Med J* 1971; 16:233-2352 ✓
- Angunawela R M & Fernando H A. Acute ascending polyneuropathy and dermatitis following poisoning by tubers of *Gloriosa superba*. *Ceylon Med J* 1971; 16:233-2352 ✓
- Arthur R R, El-Sharkawy M S, Cope S E et al. Recurrence of Rift Valley fever in Egypt. *Lancet* 1993; 342:1149-1150. ✓
- Belani A, Leptrone D & Shands J W. *Strongyloides* meningitis. *South Med J* 1987; 80:916-918. ✓
- Berkley J A, Mwangi I, Ngetsa C J et al. Diagnosis of acute bacterial meningitis in children at a district hospital sub-Saharan Africa. *Lancet* 2001; 357:1753-1757. ✓
- Bhatia B & Misra S. Recurrent Guillain-Barré syndrome following acute filariasis. *J Neurol Neurosurg Psychiatry* 1993; 56:1133-1134. ✓
- Brown W J & Voge M. *Neuropathology of Parasitic Infections*. Oxford: Oxford University Press, 1982:240. ✓
- Browne S G. Leprosy. *BMJ* 1968, 3:725-728. ✓
- Cataltepe O, Colak A, Ozcan O E et al. Intracranial hydatid cyst: experience with surgical treatment in 120 patients. *Neurochirurgia* 1992; 35:108-111. ✓

- Cavanagh J B. The 'dying back' process: a common denominator in many naturally occurring and toxic neuropathies. *Arch Pathol Lab Med* 1979; 103:659-664 ✓
- Cavanagh J B, Fuller N H, Johnson H R M & Rudge P. The effect of thallium salts with particular reference to the nervous system. *Q J Med* 1974; 43:293-319. ✓
- Chimelli L, Scaravilli F. Trypanosomiasis. *Brain Pathol* 1997 Jan; 7(1):599-611 ✓
- Cook G C. Effect of global warming on the distribution of parasitic and other infectious diseases: a review. *J R Soc Med* 1992; 85:688-691. ✓
- Cook G C. Protozoan and helminthic infections. In Lambert H P (ed.) *Infections of the Central Nervous System*. New York: Marcel Decker, 1991:264-282. ✓
- Cruickshank J K, Rudge P, Dalgleish A G et al. Tropical spastic paraparesis and human T cell lymphotropic virus type 1 in the United Kingdom. *Brain* 1989; 112:1057-1090. ✓
- Del Brutto O H & Sotelo J. Neurocysticercosis: an update. *Rev Infect Dis* 1988; 10: 1075-1087. ✓
- Del Brutto O H. Cysticercosis and cerebrovascular disease: a review. *J Neurol Neurosurg Psychiatry* 1992; 55:252-254. ✓
- De Silva H J, Goonetilleke A K E, Senaratna N et al. Skeletal muscle necrosis in severe falciparum malaria. *BMJ* 1988; 296:1039. ✓
- Earnest M P, Reller L B, Filley C M & Grek A J. Neurocysticercosis in the United States: 35 cases and a review. *Rev Infect Dis* 1987; 9:961-979. ✓
- Finkel M J & Halperin J J. Nervous system borreliosis—revisited. *Arch Neurol* 1992; 49:102-107. ✓
- Freier J E. Eastern equine encephalomyelitis. *Lancet* 1993; 342:1281-1286. ✓
- Gardner H A R, Martinez A J, Visvesvara G S et al. Granulomatous amoebic encephalitis in an AIDS patient. *Neurology* 1991; 41:1993-1995. ✓

- Garg R. K. Cerebral malaria. *J Asso Physicians India* 2000 Oct;48:1004-1013. Brewster D R, Kwitkowski D & White N J. Neurological sequelae of cerebral malaria in children. *Lancet* 1990; 336:1039-1043. ✓
- Med Hyg* 2001 Jan-Feb;64(1-2 Suppl):57-67 ✓
- Gascon G G, Crowell J, Stigsby B et al. Subacute sclerosing panencephalitis. *Neurology* 1992; 43:454-455.
- Gessain A, Barin F, Vernant J C et al. Antibodies to human T-lymphotrophic type 1 in patients with tropical spastic paraparesis. *Lancet* 1985; ii:407-409. ✓
- Hino S & Hiroshi D. Mechanisms of HTLV-1 transmission. In Roman GC, Vernant JC & Osame M (eds) *HTLV-1 and the Nervous System*. New York: Alan R Liss, 1989:495-501. ✓
- Howlett W P, Brubaker G, Mlingi N & Rosling H. A geographical cluster of konzo in Tanzania. *J Trop Geogr Neurol* 1992; 2:102-108. ✓
- Jacobson S, McFarlin D E, Robinson S et al. HTLV-1-specific cytotoxic T lymphocytes in the cerebrospinal fluid of patients with HTLV-1-associated neurological disease. *Ann Neurol* 1992; 32:651-657. ✓
- Jubille 2000. *A debt cutter's handbook*, London: Jubilee, 2000. 1996. ✓
- Jung R C, Rodriguez M A, Beaver P C, Schenthal J E & Levy R W. Racemose cysticercus in human brain: a case report. *Am J Trop Med Hyg* 1981; 30:620-624. 17100 Kipp W, Kasoro S ✓
- & Burnham G. Onchocerciasis and epilepsy in Uganda. *Lancet* 1994; 343:182-184 (letter). ✓
- Kirk I J, Fine P D, Sexton J D & Muchmore G. Rocky mountain spotted fever: a clinical review based on 48 confirmed cases 1943-1986. *Medicine* 1990; 69:35-45. 434344 ✓
- Krebs F. C, Ross H McAllister J, Wigdahl B. HIV-I-associated central nervous Sutter R W, Patriarca PA, Brogan S et al. Outbreak of paralytic poliomyelitis in Oman: evidence of widespread transmission among fully vaccinated children. *Lancet* 1991; 338:715-720.

- Lang J, Duong Q H, Nguyen V G et al Immunogenicity and safety of low-dose system dysfunction. *Adv Pharmacol* 2000; 49:315-385 ✓
- Le Quesne P M & McLeod J G. Peripheral neuropathy following a single exposure to arsenic. *J Neurol Sci* 1977; 32:437-451. ✓
- Lewis R, Nathan N, Diarra L, et al. Timely detection of meningococcal meningitis epidemics in Africa. *Lancet* 2001; 358:287-293. ✓
- Loftus L R. Peripheral neuropathy following chloroquine therapy. *Can Med Assoc J* 1963; 89:917-920. ✓
- Lobato R D, Lamsa E M, Portillo J M et al. Hydrocephalus in cerebral cysticercosis: pathogenic and therapeutic considerations. *J Neurosurg* 1981; 55:786-793. ✓
- Lockwood D N J & Pasvol G. Recent Advances in tropical Medicine. *BMJ* 1994;308:1559-1562. ✓
- Mabey D. Onchocerciasis: ivermectin and onchocercal optic nerve lesions. *Lancet* 1993; 341:153-154. ✓
- Medana I M, Chaudhri G, Chan-Ling T, Hunt N H. Central nervous system in cerebral malaria: 'Innocent bystander' or active participation in the induction of immunopathology? *Immuno Cell Biol* 2001 Apr; 79(2):101-120. ✓
- Milord F, Pepin J, Loko L, Ethier L & Mpia B. Efficacy and toxicity of eflornithine for treatment of *Trypanosoma brucei gambiense* sleeping sickness. *Lancet* 1992; 340:652-655. ✓
- Mochizuki M, Watanabe T, Yamaguchi et al. Uveitis associated with human *Ophthalmol* 1992; 114:123-129. ✓
- Montgomery R D. The epidemiology of myelopathy associated with human T-lymphotrophic virus 1. *Trans R Soc Trop Med Hyg* 1993; 87:154-159.11 ✓
- Morehead C. Notes on the pathology and treatment of diseases of the brain, as observed in the European General Hospital at Bombay. *Trans Med Phys Soc Bombay* 1849; 9:112-115 ✓

- Muphy S C; Breman J G. Gaps in the childhood malaria burden in Africa: Am J Trop R E. Hypoglycaemia is an important complication of falciparum malaria. Q J Med 1989; 71:477-483. ✓
- Nakae K, Yamamoto S, Shigematsu I & Kono R. Relation between subacute myelo-optic neuropathy (SMON) and clioquinol: a nationwide survey. Lancet 1973; 196 ✓
- Negess Y, Lanoie L O, Neafie R C et al. Loiasis: 'calabar' swellings and involvement of deep organs. Am J Trop Med Hyg 1985; 34:537-546. ✓
- Ng T H K, Chan Y W, Yu Y L et al. Encephalopathy and neuropathy following ingestion of a Chinese herbal broth containing podophyllin. J Neurol Sci 1991; 101:107-115. ✓
- Ngalali I M et al, East African Journal, Vol 28, No. 5, May 2001. ✓
- Nicholson K G. Rabies. Lancet 1990; 335:1201-1206. ✓
- Otten M W, Denning M S, Jaiteh K O et al. Epidemic poliomyelitis in the Gambia following the control of poliomyelitis as an endemic disease. 1. Descriptive findings. Am J Epidemiol 1992; 135:381-392. ✓
- Peltola H, Burden of meningitis and other severe bacterial infections of children in Africa: implications for prevention. Clin Infect Dis 2001; 32:64-75. ✓
- Peral I M, Visvesvara G S, Martinez A J et al. Naegleria and acanthamoeba infections: Review. Rev Infect Dis 1990; 12: 490-513 ✓
- Petricciani J C. Ongoing tragedy of rabies. Lancet 1993; 342:1067. ✓
- Pittella J. E.H. Neurocysticercosis. Brain Pathol 1997 Jan;7(1):681-693 ✓
- Pittella J E. Neuroschistomiasis Brain Pathol 1997 Jan;7(1):649-662. ✓
- Poser C M, Roman G C & Vernant J C. Multiple sclerosis or HTLV-1 myelitis? Neurology 1990; 40:1020-1022. ✓
- Punyagupta S, Juttijudata P & Bunnag T. Eosinophilic meningitis in Thailand. Am J Trop Med Hyg 1975; 24:921-931. ✓

- Raoult D, Zuchelli P, Weiller P J et al. Incidence, clinical observations and risk factors in the severe form of Mediterranean spotted fever among patients admitted to hospital in Marseilles 1983–1984. *J Infect* 1986; 12:111–116. ✓
- Roman G C. lymphotropic virus type 1 in Japan. *Lancet* 1994; 343:213–216. The neuroepidemiology of tropical spastic paraparesis. *Ann Neurol* 1988; 23(supplement):113–120. ✓
- Roman G C, Spencer P S & Schoenberg B S. Tropical myeloneuropathies: the hidden endemias. *Neurology* 1985; 35:1158–1170. ✓
- Rosenberg S, Chaves C J, Higuchi N M L et al. Fatal meningoencephalitis caused by reactivation of *Trypanosoma cruzi* infection in patients with AIDS. *Neurology* 1992; 42:640–642. ✓
- Ross K L, Tunkel A R & Scheld W M. Acute bacterial meningitis in children and adults. In Scheld W M, Whitley R J & Durck D T (eds) *Infections in the Central Nervous System*. New York: Raven Press, 1991:335–409. ✓
- Rwiza H T, Matuja W B P & Mteza I. The past medical profile of epilepsy patients in an African rural community. *J Trop Geogr Neurol* 1992; 2:146–150. ✓
- Salokannel J. Intrinsic factor in tapeworm anaemia. *Acta Med Scand Suppl* 1987; 517:1–51. ✓
- Schantz P M & McAley I. Current status of foodborne parasitic zoonoses in the United States. *Southeast Asian J Trop Med Public Health* 1991; 22(supplement):65–71. ✓
- Schantz P M, Moore A C, Munoz J L et al. Neurocysticercosis in an orthodox Jewish community in New York City. *N Engl J Med* 1992; 327:692–695. ✓
- Schmutzhard E, Boongird P & Vejajiva A. Eosinophilic meningitis and radiculomyelitis in Thailand caused by CNS invasion of *Gnathostoma spinigerum* and *Angiostrongylus cantonensis*. *J Neurol Neurosurg Psychiatry* 1988; 51:80–87. ✓
- Schoub B D, Johnson S & McAnerney J M. Observations of subacute sclerosing panencephalitis in South Africa. *Trans R Soc Trop Med Hyg* 1992; 86:550–551. ✓

- Senanayake N, de Silva W A S & Salgado M S L. Arsenical polyneuropathy: a clinical study. *Ceylon Med J* 1972; 17:195-203 ✓
- Senanayake N & Roman G C. Epidemiology of epilepsy in the tropics. *J Trop Geogr Neurol* 1992; 2:10-19. ✓
- Senanayake N & Roman G C. Toxic neuropathies in the tropics. *J Trop Geogr Neurol* 1991; 1:3-15. ✓
- Shaked Y. Rickettsial infections of the central nervous system: the role of prompt antimicrobial therapy. *Q J Med* 1991; 79:301-306. ✓
- Silber et al: Meningitis in a community with a prevalence of tuberculosis and HIV infection; *J Neurol Sci* 1999 January; 162(1): 20 - 6. ✓
- Simpson D M, Berger J R. Neurological manifestations of HIV infection. *Medical clinics North America*. 1996; 80 (6):1363-1394. ✓
- Solbrig M V & McCormick J B. Lassa fever: central nervous system manifestations. *J Trop Geogr Neurol* 1991; 1:23-30. ✓
- Spencer P S, Ohta M & Palmer V S. Cycad use and motor neurone disease in Kii Peninsula of Japan. *Lancet* 1987; ii:1462-1463. ✓
- Spencer P S, Sabri M I, Schaumburg H H & Moore C L. Does a defect of energy metabolism in the nerve fibre underlie axonal degeneration in polyneuropathies? *Ann Neurol* 1979; 5:501-507 ✓
- Spina-Franca A & Mattosinho-Franca L S. American trypanosomiasis (Chagas' disease). In Vinken P J & Bruyn G W (eds) *Handbook of Clinical Neurology*, vol. 35, part III. Amsterdam: Elsevier-North Holland, 1978:85-114. ✓
- Steiner I, Wirguin I, Morag A et al. Intraventricular interferon treatment for subacute sclerosing panencephalitis. *J Child Neurol* 1989; 4:20-24. ✓

Sutter R W, Patriarca PA, Brogan S et al. Outbreak of paralytic poliomyelitis in Oman: evidence of widespread transmission among fully vaccinated children. *Lancet* 1991;338:715-720 ✓

Swaddiwuthipong W, Weniger B G, Wattanasi S & Warrell M J. A high rate of neurological complications following Semple anti-rabies vaccine. *Trans R Soc Trop Med Hyg* 1988; 82:472-475. ✓

Taylor D H, Morris D L, Reffin D et al. Comparison of albendazole, mebendazole and praziquantel chemotherapy of *Echinococcus multilocularis* in a gerbil model. *Gut* 1989; 30:1401-1405. ✓

Thongchareon P. Japanese encephalitic virus encephalitis: an overview. *Southeast Asian J Trop Med Public Health* 1989; 20:559-573. ✓

Tuner G. Cerebral Malaria. *Brain Pathol* 1997 Jan ; 7(1) :569-582. 22 71 ✓ Turner L H. Leptospirosis. *BMJ* 1973; 1:537-540. ✓

Phillips

Tylleskar T, Banea M, Bikangi N, Cooke R D, Poulter N H & Rosling H. Cassava cyanogens and konzo, an upper motorneurone disease found in Africa. *Lancet* 1992; 339:208-211. ✓

Van der Horst CM, Saag MS, Cloud GA, Hamill RJ, Graybill JR, Sobel JD, Johnson PC, Tuazon CU, Kerkering T, Moskovitz BL, Powderly WG, Dismukes WE. Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. *N Eng J Med* 1997; 337(1): 15-21. ✓

United Nations. *Universal Declaration of Human Rights*. New York: United Nations, 1948.

Vora D D, Dastur D K, Braganca B M et al. Toxic polyneuritis in Bombay due to ortho-cresyl phosphate poisoning. *J Neurol Neurosurg Psychiatry* 1962; 25:234-242. ✓

Warrell D A & Warrell M J. Human rabies and its prevention: an overview. *Rev Infect Dis* 1988; 10(supplement 4):5726-5731. ✓

World Health Organization. *Declaration of Alma-Ata*. International Conference on Primary Health Care, Alma-Ata, USSR, 6-12 September 1978. Geneva: World Health Organization. 1978.

Windebank A J, McCall J T & Dyck P J. Metal neuropathy. In Dyck P J, Thomas P K, Lambert E H & Bunge R P (eds) *Peripheral Neuropathy*. Philadelphia: W B Saunders, 1984; 2133-2161.16 ✓

Woodhouse J I J. The prevalence of clinical peripheral neuropathies in human chronic Chagas disease. *J R Army Med Corps* 1993; 139:54-55. ✓

WHO. Detecting meningococcal meningitis epidemics in highly-endemic African countries. *Wkly Epidemiol Res* 2000; 75:306-309. ✓

WHO Backgrounder No 1 for the G8 discussions. July 2000 ✓

WHO facts sheet no 94 on malaria October 1998 ✓

WHO. *Global tuberculosis control 1999*. Geneva WHO, 1999. ✓

WHO Background document on the Introduction of Medicines for Malaria Venture 1999. ✓

Zumla A, Mwaba P, Rook G, Lukas S. Tuberculosis. In James D G, Zumla A (eds) *The granulomatous disorders*. Cambridge University Press, 1999:132-160. ✓

APPENDIX 1

CLINICAL FEATURES

BASIC INFORMATION ON ADULT PATIENT

GENERAL

- 0.1 Sex: (M,F) 0.2 Age:y.....m
- 0.3 Marital Status: married/widower/widow/divorced/single
- 0.4 Profession:.....
- 0.5 Residential and Postal Address.....
- 0.6 Number of Years in School: primary/secondary/university
- 0.7 Treatment prior to admission: (Y,N)
1. anti-malaria 2. antibiotics 3. others
- 0.8 Date of Admission:.....

1. COMPLAINT AT PRESENT

(a)

(b)

(c)

(d)

2. PRESENTATION AT PRESENT

- 2.1 Forgetfulness (Y,N)
- 2.2 Slowness of thought (Y,N)
- 2.3 Social withdrawal (Y,N)
- 2.4 Seizures (P,G)
- 2.5 Paralysis (Y,N)
- 2.6 Weight Loss (Y,N)
- 2.7 Malnutrition (Y,N)
- 2.8 Chronic Diarrhoea (Y,N)
- 2.9 Fever (Y,N) for weeks
- 2.10 Persistent cough (Y,N) for weeks
- 2.11 Minor muco-cutaneous manifestation (Y,N)
 - 1. Seborrheic Dermatitis
 - 2. Pruritus
 - 3. Fungal nails
 - 4. Oral ulcers
- 2.12 Herpes Zoster (Y,N) How many times.....
- 2.13 Oral Candidiasis (Y,N)

2.14 Oral Hairy Lrukoplakia (Y,N)

2.15 Chronic and disseminated Herpes simplex (Y,N)

2.16 Lymphadenopathy (Y,N)

1. Generalised 2. Cervical 3. Inguinal 4. Axillary

2.17 Kaposi Sarcoma (Y,N)

2.18 Tuberculosis (Y,N)

1. Present 2. Past 3. Relapse

4. Pulmonary 5. Extra-pulmonary

2.19 Bacterial Infections (Y,N)

1. Sepsis 2. Pneumonia 3. Meningitis 4. Others

2.20 Meningeal Signs (Y,N)

1. Headache (Y,N) 2. Photophobia (Y,N)

3. Neck Stiffness (Y,N) 4. Kernigs (Y,N)

2.21 Cranial Nerve Palsies (Y,N)

o of Cranial nerve(s):.....

2.22 Level of Consciousnes

1. Alertness 2. Confusion 3. Drowsy 4. Coma

2.23 Motor system

1. Normal (Y,N) 2. Paraplegia (Y,N)

3. Hemiplegia (Y,N) 4. Weakness (Y,N)

- 2.24 Sensory 1. Normal (Y,N) 2. Impaired

APPENDIX 2

LABORATORY RESULTS

A PATIENT STUDY NUMBER:

B DEMOGRAPHIC DETAILS

1. Age: years

2. Sex: M/F

C DURATION OF ILLNESS

D BLOOD TESTS

1. HIV antibodies Y/N

2. MP 1) Y/N

 2) Y/N

3. RPR Y/N

4. Toxoplasma antibodies Y/N

5. Urea and electrolytes

6. Liver function tests

7. Random blood sugar

E CSF TESTS

1. Biochemistry

(1.1) Na⁺ normal? Y/N If N Specify

(1.2) Glucose normal? Y/N If N Specify

(1.3) Protein normal? Y/N If N Specify

2. Microscopy

- (2.1) WBC normal? Y/N If N Specify
- (2.2) Bacteria isolated? Y/N If Y Specify
- (2.3) Cryptococcus isolated? Y/N
- (2.4) AAFB isolated? Y/N
- (2.5) T. Pallidum Y/N
- (2.6) Viral tissue cultures? Y/N if Y Specify