MULTIFOCAL CYSTICERCAL ENCEPHALITIS

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Dissertation submitted in fulfilment of the requirement

for Part III of the Degree of Master of Medicine (Neurology)

at the University of Cape Town

November 1990

To Glenn my wife

for the years of

patience and understanding

also

In memory of my parents

I, Alan J G Thomson hereby declare that the work on which this thesis is based is original (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other University.

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ACKNOWLEDGEMENTS

I wish to thank:

Dr D Philcox and the consultant staff of the Department of Neurology, Groote Schuur Hospital for the excellent learning experience of the past few years.

Professor S Benatar and the Department of Medicine, University of Cape Town for financial assistance.

Dr R Eastman for reviewing this script and his helpful suggestions.

Professor L Handler and Dr M Wright for allowing me access to the files and films of the Neuroradiology Department of Groote Schuur Hospital and for reviewing the films with me. To the secretarial staff of that Department for their help in obtaining the films.

Dr R Bowen and Dr C Sinclair-Smith for tracing the histology slides and for reviewing these with me. Dr J Kane-Berman, Chief Medical Superintendent, Groote Schuur Hospital; Dr G Lawrence, Medical Superintendent, Red Cross War Memorial Children's Hospital; and Dr P Roux, Medical Superintendent, Somerset Hospital for permission to review their hospital's records. The staff of the Medical Records departments of the above hospitals in particular that of Groote Schuur Hospital for the large amount of work so willingly done.

Ms S Lyons for secretarial help in filing of case records during the prospective drug trials and for the recalling of these patients. The paediatric departments of Frere Hospital and Cecilia Makiwane Hospital for the tracing and return of these patients.

Ms E Jordaan of the MRC Biostatistics Unit for her expertise; Ms L Heuer for preparation of the manuscript; Ms S Abrahams and Ms L Jolly of the Department of Medical Graphics, Groote Schuur Hospital for their expert assistance. Mr M Jaffer and Mr T Adonis for the original photographic work.

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ABSTRACT

Between and inclusive of the years 1975-1989 two hundred and thirty nine patients attending Groote Schuur Hospital and the Associated Teaching Hospitals of the University of Cape Town have been retrospectively identified as having neurocysticercosis. One hundred and twenty three (51.46%) were children 12 years of age or younger. Fourteen (5.86%) were adolescents between and inclusive of the ages 13 to 19 years. One hundred and two (42.68%) were adults 20 years of age or older. Two hundred and twelve (88.7%) of these patients were African almost exclusively belonging to the Xhosa speaking peoples and coming from or originating from the Eastern Cape homeland regions of the Transkei and Ciskei.

Although the clinical features of neurocysticercosis are protean these patients were divided into three clinical groups - a seizure group, a raised intracranial pressure group and an asymptomatic group. One hundred and ninety patients (79.5%) presented with seizures alone or in combination with other neurological deficit. Eighty six patients (35.9%) presented with features of raised intracranial pressure due to hydrocephalus in 32, due to focal space demanding lesions in 4 and due to multifocal cysticercal encephalitis in 50. Ten patients (4.1%) were 'asymptomatic' and were found to have neurocysticercosis following on computerised tomography (CT) scan done for investigation of head injury.

Using radiological criteria 116 patients in this series were found to have cysticercal encephalitis, 66 with focal encephalitis and 50 as noted above with multifocal encephalitis.

The vast majority of the 50 patients with multifocal encephalitis were found to be children 12 years of age or younger. There were 44 children compared to 2 adolescents and 4 adults. The adults were all younger than 30 years of age. The clinical radiological laboratory and electroencephalographic findings of these 50 patients are reviewed and discussed.

Twenty nine of these 50 patients formed part of an open therapeutic study on the use of Praziquantel (a pyrazinoisoquinoline derivative) in the treatment of cysticercosis. The other twenty one of these 50 patients had not been treated with Praziquantel and their case histories

were reviewed retrospectively.

Although matched the numbers that were followed from both the prospective (Praziquantel) group and in particular the retrospective (non-Praziquantel) group were far too small for any valid comparisons and conclusions concerning Praziquantel therapy in patients with multifocal cysticercal encephalitis.

AIMS

1. To review and record the case histories of patients with neurocysticercosis who attended the Teaching Hospitals of the University of Cape Town between and inclusive of the years 1975-1989. This was done in order to categorise.
   a. the racial distribution of these patients
   b. the districts of origin of these patients
   c. the age distribution of these patients
   d. the distribution of these patients in three major clinical groups consisting of:
      i. seizure group
      ii. a raised intra-cranial pressure group; and
      iii. an asymptomatic group
2. To identify those patients who presented with raised intra-cranial pressure or generalised encephalopathy and whose computed tomographic scans showed features of multifocal cysticercal encephalitis. this was done in order to categorise:
   a. the age distribution of these patients
   b. the sex distribution of these patients
   c. the clinical findings, the radiological findings, the laboratory findings, the serologic findings and the electroencephalographic findings in these patients.
3. To record the response to treatment in the acute encephalopathic phase of multifocal cysticercal encephalitis in patients from:
   i. a retrospective group treated with corticosteroids and anticonvulsants
   ii. a prospective group treated with corticosteroids, anticonvulsants and Praziquantel (a pyrazinoisoquinoline derivative). This was done in order to categorise:
      - the efficacy or not of corticosteroids in controlling the cerebral oedema of multifocal cysticercal encephalitis
      - the benefit or not of adding Praziquantel to the therapy of these patients
4. To record the long-term follow-up of patients with multifocal cysticercal encephalitis in both these retrospective and prospective groups in order to categorise if possible:

a. The outcome and 'natural history' of multifocal cysticercal encephalitis in the corticosteroid treated retrospective group

b. The effect, if any, on the prognosis of patients with multifocal cysticercal encephalitis treated with Praziquantel in addition to corticosteroids.

PART I

NEUROCYSTICERCOSIS

LITERATURE REVIEW OF SELECTED TOPICS

INTRODUCTION

Cysticercosis, a parasitic infestation of great importance in man, is due to the invasion of human tissue by the larvae of the tape worm Taenia solium. The disease has a worldwide distribution but is most prevalent in developing countries (Marques-Monter 1971; Mahajan 1982). In these endemic regions cysticercosis constitutes a major health problem, because of the large numbers of people infected. It is the commonest parasitic infestation of the central nervous system producing significant morbidity and mortality (Trelles and Trelles 1979; Sotelo 1988). In addition to the severe health and economic problems created by the human disease, cysticercosis of the more usual intermediate host, the domestic pig, also results in large economic losses due to wastage of the infected meat or 'measly pork' (Velasco-Suarez et al 1982; Acevedo-Hernandez 1982).

In recent years, increased awareness of the prevalence and importance of this condition has developed with the dramatic improvement in diagnosis afforded by the development of Computerised Tomographic (CT) scanning of the brain (Minguetti and Ferreira 1982, Mazer et al 1983; Rodriquez-Carbajal et al 1987). CT scanning of the brain in conjunction with improved serologic techniques has allowed better appreciation of the wide spectrum of clinical symptomatology produced by this disease (Chang et al 1988). Added impetus to the importance of early diagnosis is given by the recent advances in medical treatment of cysticercosis which may in the individual patient significantly reduce morbidity and improve prognosis (Vascoucelos et al 1987; Sotelo et al 1988). Perhaps of even greater importance would be the identification in endemic areas of populations at risk. Using appropriate serologic techniques, field trials would presumably identify the enormity of the problem and the socio-economic value of educating these communities and instilling the need to improve both sanitation and farming methods (Schenone et al 1982).

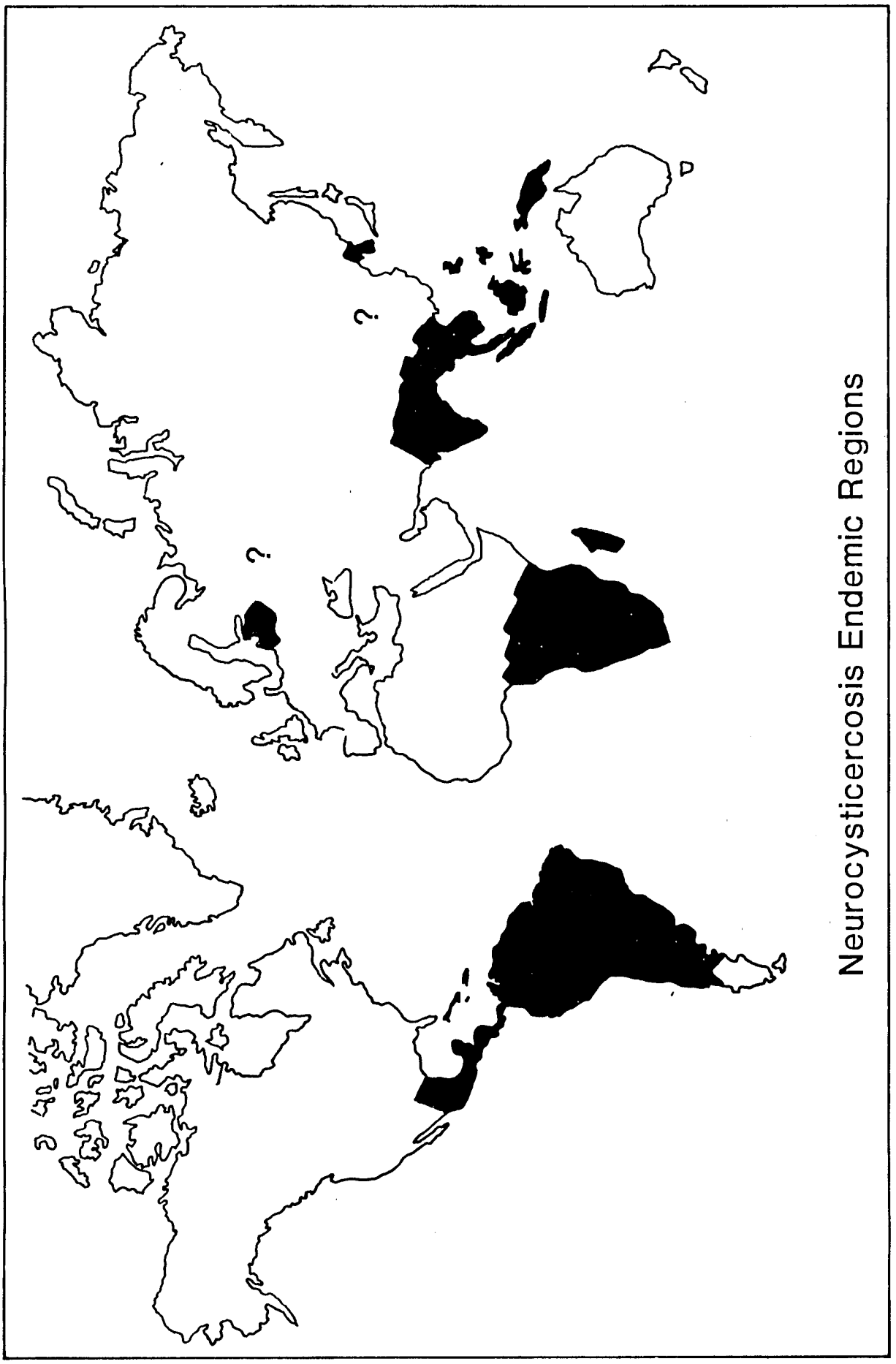


Figure 1

EPIDEMIOLOGY

The recognised endemic regions of the world are those areas where free range pig farming is practised by people who do not ensure adequate sanitation and thus effective removal of human excreta from their environment (Figure 1). Voluminous literature on the subject of cysticercosis has been published by health care professionals in the countries of Latin America (Schenone et al 1982). In particular, there are numerous publications from Mexico where the disease is extremely prevalent in certain regions (Sotelo et al 1985a; Grisolia and Wiederholdt 1982; Lombardo and Mateos 1961). Other well known endemic regions in Asia are India (Wadia et al 1988; Vinayan et al 1977; Balasubramaniam et al 1971) as well as the Far East in particular China (Trelles and Trelles 1979; Feng 1987), Korea (Chang et al 1988), Indonesia (Subianto et al 1978) and Thailand (Trelles and Trelles 1979). The endemic regions of Europe are the Slav countries of Eastern Europe such as Poland (Stepien 1962) and Rumania (Arseni and Cristesau 1972) as well as the Mediterranean countries such as Spain (Lobato et al 1981). In Africa the frequency of taeniasis and cysticercosis due to taenia solium varies widely from country to country being reported infrequently from Kenya (Nelson et al 1965) but more frequently from Zimbabwe (Gelfand and Jeffrey 1973) and South Africa (Heinz and Klintworth 1965; Powell et al 1966; Tuch and Saffer 1984; Thomson et al 1984; Van Dellen and McKeown 1988).

During the era of British rule in India cysticercosis was well recognised in soldiers returning to Great Britain after tours of duty in that country (MacArthur 1934). In more recent times with the increase in tourism and immigration the people of the more affluent countries of Western Europe and North America are at greater risk for the development of the disease (Earnest et al 1987).

AETIOLOGY - LIFE CYCLE

To understand the pathogenesis of human cysticercosis the life cycle of the cestode Taenia solium must be reviewed (Figure 2). Man is the only definitive host of this parasite and usually harbours a single adult worm in the small bowel where it may live for many years producing few if any symptoms of gastro- intestinal discomfort. In Taeniasis (infestation due to adult Taenia Solium), the tape worm, may reach lengths of 2-7 metres and

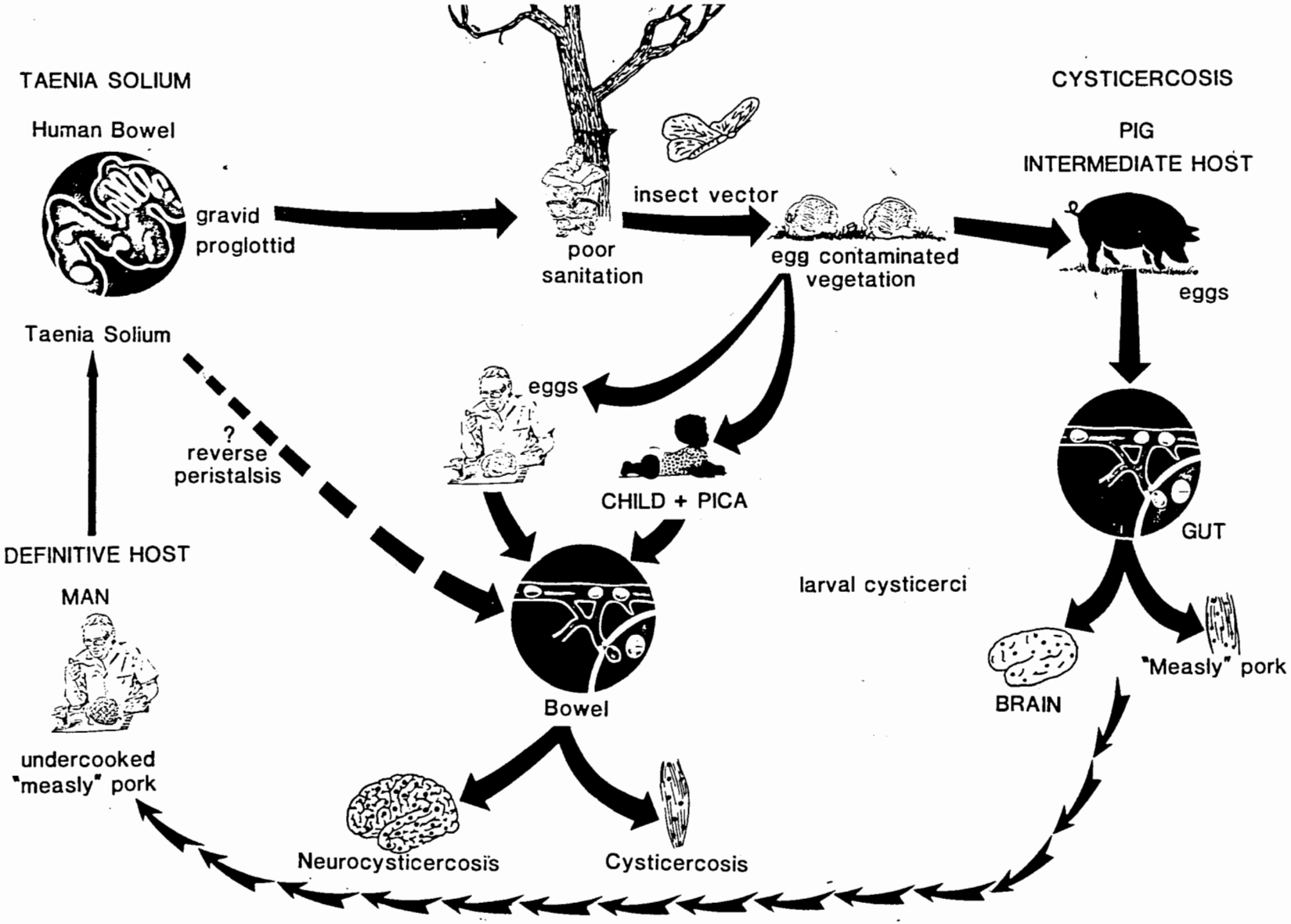


Figure 2: Life Cycle

consists of a minute head or scolex, a short non-segmented neck and a segmented body or strobilia. These segments or proglottides which may number up to one thousand, mature and enlarge as they grow distally. They are hermaphroditic and the distal sexually mature ones may contain thirty to fifty thousand fertile ova each. These distal gravid proglottides when shed are passed with the faeces either intact or ruptured (Marquez-Monter 1971; Trelles and Trelles 1979; Olive and Angulo-Rivero 1962).

The expelled ova under conditions of poor sanitation will contaminate the environmental soil and vegetation and may be spread over large areas by insect and bird vectors as well as possibly by the wind as has been demonstrated in the case of the ovine (sheep) tape worm (Gemmell and Lawson 1982). The survival of these ova even in adverse climatic conditions is ensured by their tough surrounding membrane (Laclette et al 1982).

Should the usual intermediate host, the domestic pig, ingest contaminated faeces or vegetation, porcine cysticercosis results. The outer membranes of the ova are digested by the gastric juices and the released oncospheres (embryos) penetrate the ileal wall gaining access to the vascular and lymphatic channels by which means they are distributed to the various host tissues. The small oncospheres after lodging in the distal capillaries penetrate the vascular wall and enter the adjacent tissue. The tissues most commonly involved are the muscles, subcutaneous tissues and the brain. Over a period of 9-10 weeks the oncospheres invaginate and encyst forming the 'bladder worms' or larval cysticerci (Marques-Monter 1971; Trelles and Trelles 1979). These cysticerci remain viable in the host tissues for variable periods of time surviving on occasion for many years.

If the infected meat or 'measly pork' from a slaughtered pig is then eaten by man in an undercooked state, Taeniasis results. The ingested larval cysticerci are activated by the bile and pancreatic juices in the duodenum and evagination of the scolex occurs (Canedo 1982). The evaginated scolex adheres to the mucosa of the small bowel by means of its hooklets and over some months the adult tape worm with its gravid proglottides develops. The life cycle of Taenia solium is completed.

Man can, unfortunately, also function as an intermediate host in the life cycle of Taenia solium. Human cysticercosis occurs when vegetation or water contaminated by the ova of Taenia solium is ingested. Perhaps the well-known perverted appetite (Pica) of small children leads to compulsive eating of dirt (Geophagia) and results in the heavy larval infestation found in some patients. Pica is thought to be more common in malnourished children particularly those with iron deficiency anaemia (Lukens 1984). External auto-inoculation with Taenia ova may result from anus to finger to mouth contamination in people with taeniasis. Internal auto-inoculation is also thought to possibly occur when gravid proglottides are regurgitated into the stomach by reverse peristalsis, allowing digestion of the outer membranes of the ova and activation of the embryos (Trelles and Trelles 1979; Olive and Angulo-Rivero 1962). Although (as noted in the pig), all tissues are at risk, it is the brain, muscles, and subcutaneous tissues that are the most commonly infected in human cysticercosis which may be asymptomatic or symptomatic. Obviously unless cannibalism is practised the life cycle of Taenia solium is interrupted when the human becomes the intermediate host.

PATHOGENESIS

As mentioned previously once the solid hexacanth embryos or oncospheres have transversed the gut wall they are carried by the blood stream to the various body tissues in particular the central nervous system. Even congenital neurocysticercosis has been histologically documented in a 2 month old infant (Krivoy et al 1988). Symptomatic cysticercosis can be sub-divided into 4 groups. The first group consists of larvae in the central nervous system (neurocysticercosis); the second group comprises patients with larvae in sub-cutaneous tissues, muscles and viscera (disseminated cysticercosis); the third group consists of patients with larvae in the eyes and orbits (ophthalmocysticercosis); and the fourth group who have cysticercotic larvae in more than one of the above locations (mixed cysticercosis) (Zenteno-Alanis 1982). Depending on where the oncospheres lodge in the nervous system two types of bladder worm or cysticercosis will develop (Rabiela-Cervantes et al 1982).

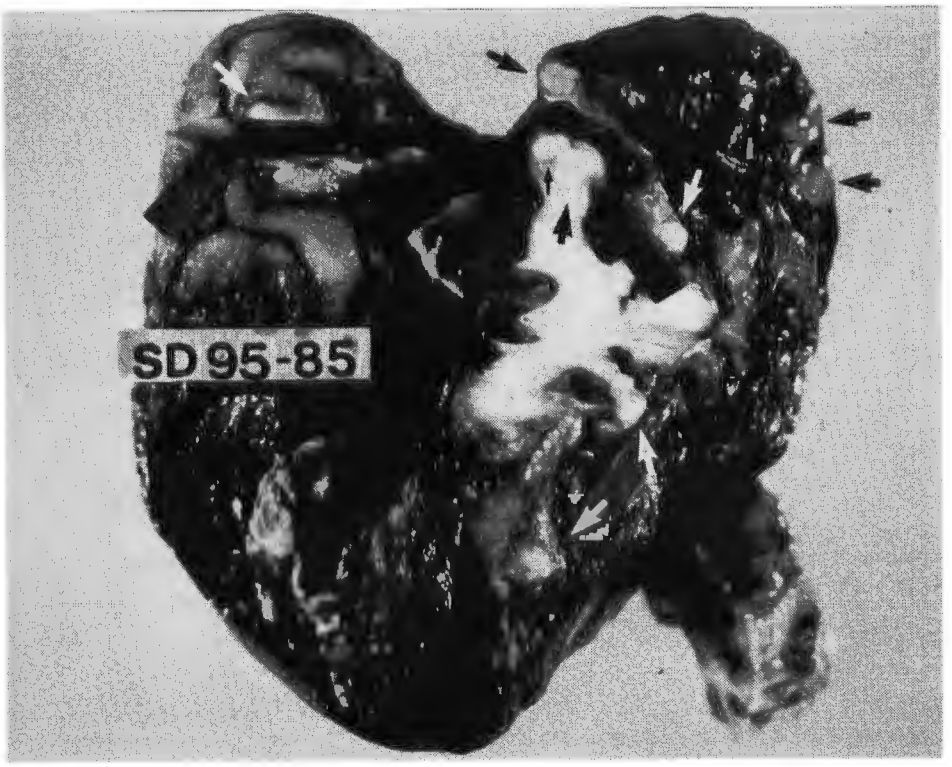


Figure 3
Surgical specimen - Hemispherectomy for intractable epilepsy following an infarct in the territory of the right middle cerebral artery. Infarcted hemisphere with subarachnoid/cortical mantle cysticercosis (white and black arrows)

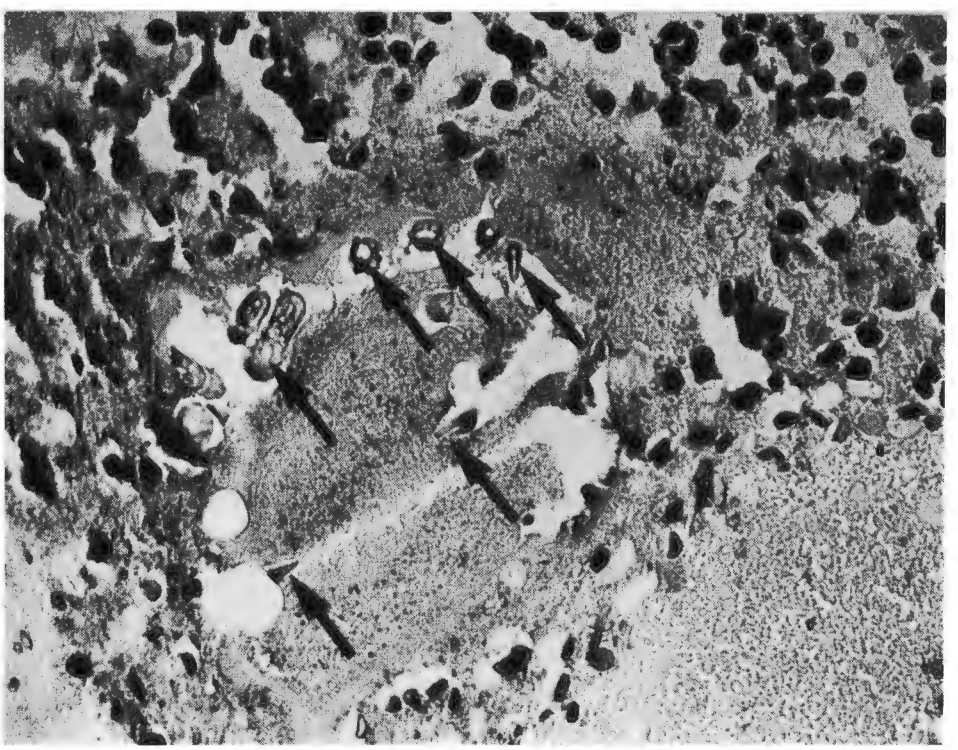


Figure 4
Microphotograph demonstrating a degenerate cyst with numerous hooklets - histology from specimen shown in Figure 3.

The first type named cysticercus cellulosae is a semi-translucent or opalescent round or oval cyst. Contained within the thin uniform cyst wall is the invaginated scolex with its suckers and hooks which if ingested, while still viable, would evaginate and develop into the adult worm. The cysts of cysticercus cellulosae are usually small and vary in size from a few millimetres to 2 centimetres and only very occasionally up to 4 cms. (Figure 3, Figure 4). Their small size appears to be the result of their location (1) in the confined subarachnoid spaces between the gyri of the cerebrum and the folio of the cerebellum (2), in the adjacent grey matter (3), in the deep end-arteriolar tissues of the internal capsule and the basal ganglia and (4) in the smaller recesses of the ventricles. These cysts, while the cyst wall is viable and intact, do not elicit an inflammatory reaction in the adjacent tissue and are usually asymptomatic irrespective of the viability of the scolex. On occasion however an exceptionally large viable cyst may produce symptoms and signs as the result of tissue compression and distortion (Berman et al 1981; Joubert and Van As 1990). However, with the death of the cyst wall it is thought that the parasite's antigens leak out and produce an inflammatory/allergic response in the adjacent tissues resulting in the production of symptoms and signs (MacArthur 1934; Marquez-Monter 1971; Trelles and Trelles 1979; Nash and Neva 1984). On the other hand some authorities believe that the enlarging cysts invoke the inflammatory reaction by immunological, chemical or mechanical means and that this inflammation produces the death and disintegration of the cysts (Rabiela-Cervantes et al 1982). Whatever the mechanism of inflammation, it seems that cysticercus cellulosae usually only become symptomatic when there is an inflammatory reaction in the surrounding tissue. The extent of this inflammatory response and the consequent clinical result depends on the location and the number of parasites in the brain.

The second type named Cysticercus Racemosae is much less common and appears to evolve from cysticercus when this parasite is not confined and can enlarge in the larger subarachnoid spaces of the basal cisterns, insula and sylvian fissure as well as in the larger ventricular spaces. These cystic lesions range in size from 4-12 cms and range in shape from a single multilobulated cyst to a complex of multiple attached bladders resembling a bunch of grapes (Figure 5). These cysts have viable parasitic capsules but do not contain

Figure 5
Surgical specimen - racemose cyst being removed from the Fourth Ventricle.

scoleces. Initially they may be free floating and may only produce symptoms of intermittent hydrocephalus due to intermittent obstruction of cerebrospinal fluid (CSF) pathways (Bickerstaff et al 1952). With time these cysts collapse and flatten becoming attached to the pia-arachnoid or ependyma producing repeated bouts of inflammation with the development of a thickened adhesive arachnoiditis and a granulomatous ependymitis. The extensive fibrosis produced by these inflammatory lesions results in either obstructive or communicating hydrocephalus as well as on occasion infarction of brain tissue due to the associated inflammatory endarteritis (Barinagarrementeria and Del Brutto 1989).

Apparent intermediate forms of cysticerci, ranging from the cellulosa to the racemose form, were also found in nervous tissue as was the co-existence of both cellulosae and racemose forms in a single brain (Rabiela-Cervantes et al 1982).

Racemose cysts may also develop from Coenurus Cerebralis the larval stage of the dog tapeworm Multiceps Multiceps. These cysts contain numerous invaginated scolices and thus can be readily distinguished from the racemose form of cysticercosis. However, when degenerative changes occur in these cysts it becomes impossible to differentiate histologically the racemose cysts of either type of parasite. If, however, under these circumstances parenchymal cysts are present in addition, the likely diagnosis is that of cysticercosis (Kuper et al 1958; Bickerstaff et al 1952).

PATHOLOGY

The symptoms and signs presented by patients with neurocysticercosis are extremely varied and there are no clinically diagnostic neurologic syndromes. These facts are easily understood when the major factors governing the neuropathological changes are understood (Marquez-Monter 1971; Trelles and Trelles 1979; Sotelo 1988).

These factors are:

1. The number of the infesting parasitic larvae which may vary from one to several hundred.

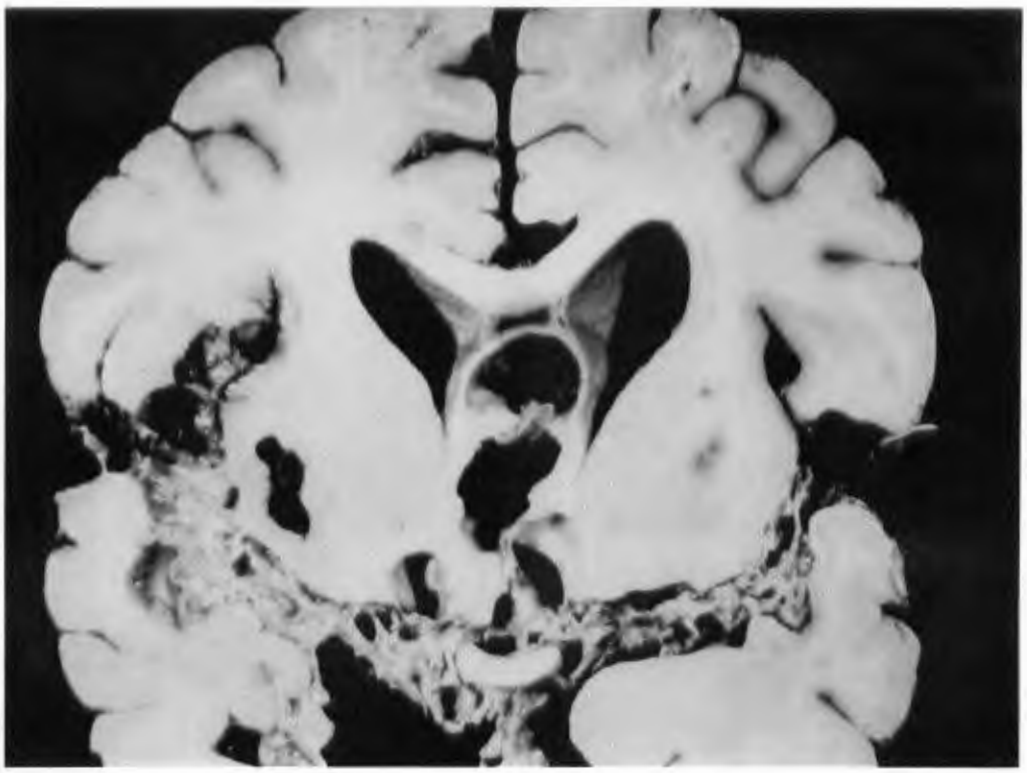


Figure 6

Autopsy specimen - Coronal section of the brain showing the presence of racemose cysts.

1. in the subarachnoid space of the basal cisterns and Sylvian fissures
2. in the Third Ventricle

2. The neuroanatomic location of the parasite which to some extent depends on the amount of blood flow to the involved tissue. This is most commonly the subarachnoid space and the adjacent brain parenchyma and less commonly the deeper parenchyma and ventricles. All of these regions in varying combinations may be involved in some patients.

3. The varying rate of evolution of the parasite or in other words the natural history of the disorder. This is largely unknown but appears to depend on the neuroanatomic location of the parasite, and the interactions at the parasitic host interface. These interactions are determined by peculiarities of the parasite as well as;

4. By the varied immune responses elicited in the host brain and meninges. These responses can range from immune tolerance to severe allergic inflammatory lesions with associated oedema and local involvement of blood vessels progressing to granuloma formation with gliosis/fibrosis and eventual calcification.

5. The possible development of complications such as hydrocephalus, cerebral infarction and cerebral shifts and pressure cones which can only add to the variability and complexity of the clinical picture.

Prior to the advent of CT scanning of the brain, the experience gained from autopsy and neurosurgical reports, although documenting the presence of parenchymal cysts, had emphasized the morbidity and mortality due to the racemose cysts in the larger subarachnoid spaces and ventricular systems (Cardenas 1962; Arana and Asenjo 1945; Bickerstaff et al 1952; Kuper et al 1958) (Figure 6). Most of the deaths due to neurocysticercosis were related to the presence of these racemose cysts and the associated inflammatory fibrosis resulting in hydrocephalus, infarction or mass lesions. The cysts of the smaller cysticercus cellulosae which were located in the narrower subarachnoid spaces and ventricular recesses as well as in the brain parenchyma were found frequently at autopsy in 'asymptomatic' adults dying from other causes. Only minor inflammatory change with minimal pericyst parenchymal compression was found in these patients with cysticercus cellulosae. The evolutionary spectrum from viable cysticercus cellulosae through focal granuloma to focal calcific lesion was occasionally found in the same patient (Rabiela-Cervantes et al 1982). The parenchymal cysts, except for occasional

Figure 7
Microphotograph - Cysticercus cellulosae with marked inflammatory infiltration of the overlying pia-arachnoid demonstrating the superficial position of the parasite in the cortical mantle.

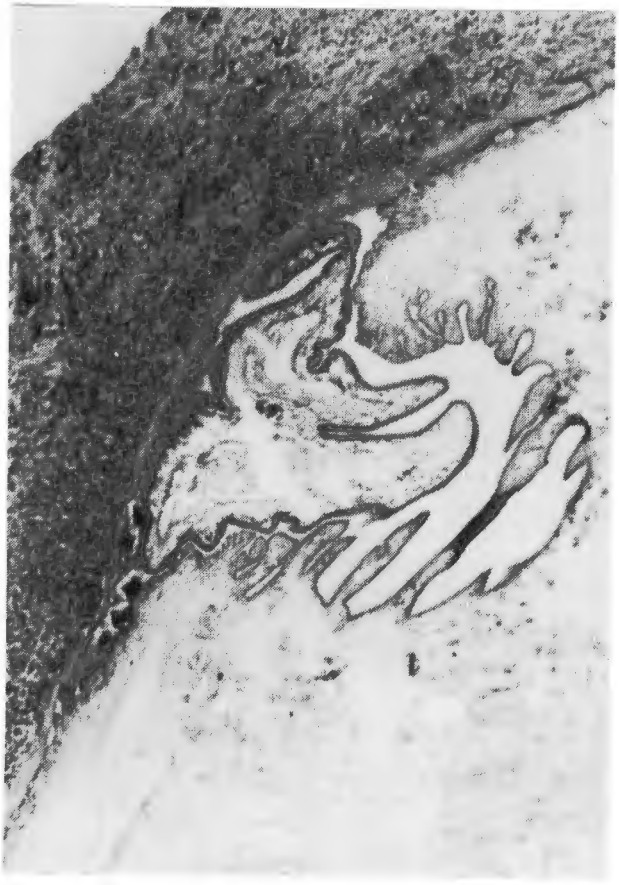


Figure 8
Microphotograph demonstrating endarteritis in cerebral tissue in the neighbourhood of a cyst

giant cysts were thought to produce no symptoms until evolution of the calcific foci with the adjacent neurons known to be potentially epileptogenic. Therefore, with the exception of this well known association of epilepsy and calcific foci seen on x-rays of soft tissues and skull, it was not until the use of CT scanning of the brain in endemic areas, that a previously seldom reported form of neurocysticercosis was recognised with increasing frequency. This is the cysticercosis cellulosae form of the parasite in the parenchyma and deep sulci of the cerebral and cerebellar hemispheres. This parenchymal form, has become established as an important form of symptomatic neurocysticercosis (Carbajal et al 1977; Handler and Mervis 1983; Minguetti and Ferreira 1983, Mazer et al 1983). Standard views and sections of the brain, as shown by CT scanning, by MR imaging and by routine autopsy demonstrate that the parasitic lesions appear to lie well within the brain substance. However it has been shown at autopsy that by careful dissection many of the cysts actually lie within the narrow subarachnoid spaces of the deeper cortical sulci and only displace or distort the adjacent grey matter. Thus although undoubted parenchymal lesions are found in the deep grey matter nuclei, in the internal capsule and in the brain stem it appears that many of the cortical grey matter lesions originate in the subarachnoid space of the sulci (Rabiela-Cervantes et al 1982; Lotz et al 1988) (Figure 7; Figure 8). The sum of these sulcal and parenchymal lesions constitutes the most common form of neurocysticercosis (Carbajal and Duran 1982; Suss et al 1986). Whatever the precise neuroanatomical location of these 'parenchymal' lesions a severe inflammatory allergic type reaction may develop around the encysted embryos. There may be significant parenchymal involvement with a host tissue reaction of lymphocytes and plasma cells infiltrating the pericyst and capsular tissue. The surrounding brain parenchyma is oedematous with perivascular mononuclear cell infiltration (Madrazo et al 1983; Rangel et al 1987).

These inflammatory oedematous lesions have aptly been labelled acute cysticercal encephalitis (Madrazo et al 1983). Acute cysticercal encephalitis may be: 1) focal either remaining asymptomatic or manifesting with seizures and/or focal neurologic deficit; or 2) multifocal and so extensive that severe diffuse cerebral oedema results with critically raised intra-cranial pressure (Rangel et al 1987). Associated meningeal reaction may be extensive enough to produce changes in the cerebrospinal fluid and qualify the inflammatory process for

classification as cysticercal meningoencephalitis.

CLASSIFICATION NEUROCYSTICERCOSIS - PATHOLOGICAL, RADIOLOGICAL, CLINICAL

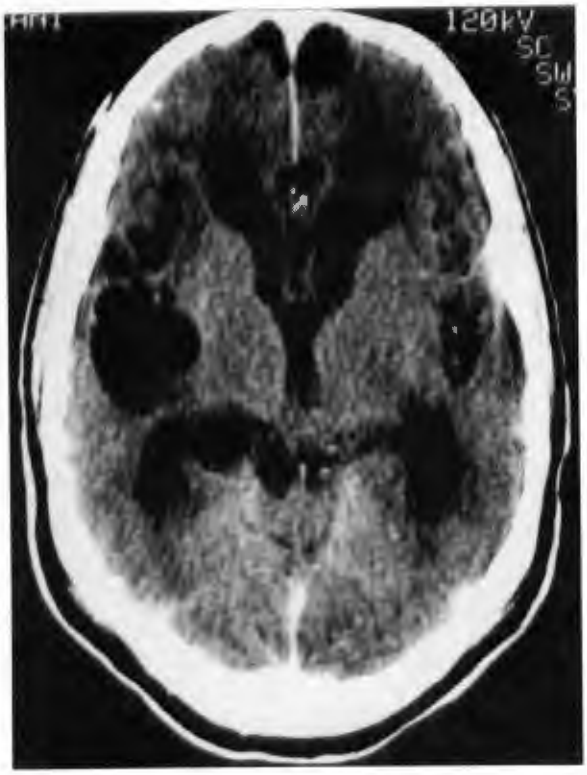
Classifications of neurocysticercosis based on clinicopathologic manifestations are, due to the protean features of the disease, not easily conceived and are thus often incomplete, overlapping or cumbersome. Four classifications will be briefly described. In 1949 Stepein and Chorobski developed from their large series the following classification (Stepein and Chorobski 1949; Stepein 1962):

Group 1: The parasitic cyst is single in most cases and produces the symptoms and signs of a space demanding lesion. 41.7% of their cases were so classified.

Group 2: The parasitic cysts are numerous and produce cerebral swelling/oedema with symptoms of psychosis, dementia or raised intracranial pressure. This form of the illness was most common in children. 25.7% of their cases were so classified.

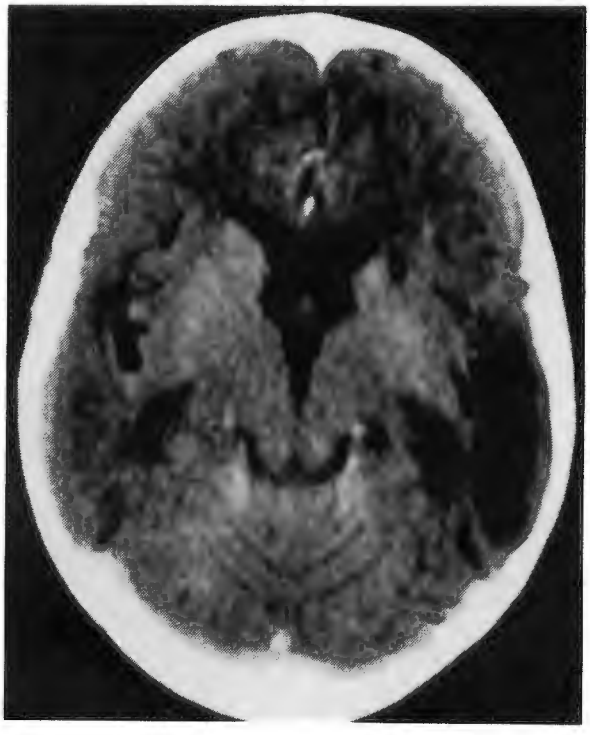
Group 3: The parasitic cysts are located mainly at the base of the brain and cause chronic basal leptomeningitis and/or ependymitis with internal hydrocephalus and symptoms of raised intracranial pressure. 32.6% of the cases were so classified.

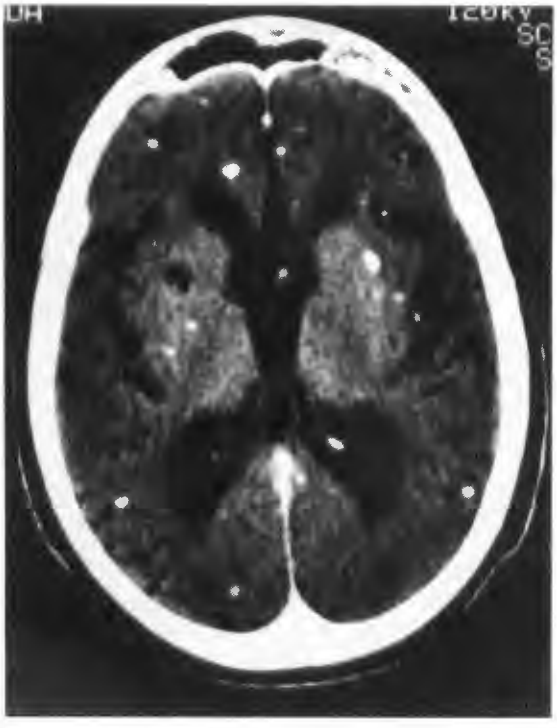
This classification derived from a group of selected symptomatic neurosurgical patients as well as from autopsy material is perhaps not encompassing enough. Of interest the incidence of the various clinical features of the disease reported in these papers is markedly different from the incidence found in earlier reports of patients in Great Britain who were mainly ex-British Indian Army soldiers (MacArthur 1934; Dixon and Hargreaves 1944). Amongst these latter patients epilepsy was by far the most common symptom while symptoms and signs of raised intra-cranial pressure and focal neurological deficits occurred much less commonly.



Radiology 1
CT scan demonstrating hydrocephalus and a mass of racemose cysts in the left Sylvian Fissure.

Radiology 2
CT scan demonstrating a large right tempero-parietal infarct and a lacune lateral to the head of the right Caudate Nucleus. Other CT scan views of this patient showed the presence of calcific foci.



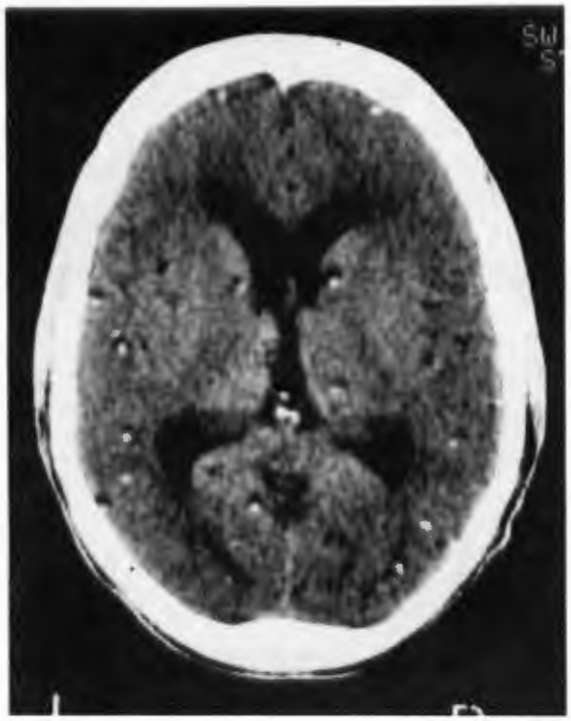


Radiology 3
CT scan demonstrating the presence of generalised atrophy with scattered calcific foci.

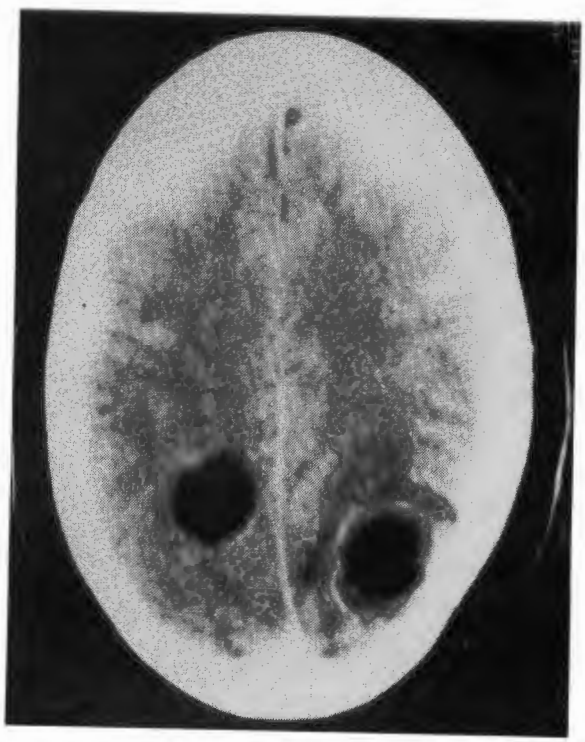
With the advent of CT scanning more extensive classifications were proposed and Rodriguez-Carbajal et al using their wide experience classified a large series of patients with anatomopathological and CT correlation (Carbajal and Duran 1982).

1. **Meningeal cysticercosis** manifesting in the acute phase with meningeal enhancement followed by hydrocephalus in the chronic phase. Cerebral infarction due to involvement of basal and perforating blood vessels was also described. 17.6% of their cases fitted into this category (Radiology 1 and Radiology 2).
2. **Intraventricular cysticercosis.** Only 2.3% of their cases were so classified.
3. **Parenchymal cysticercosis** was the most frequent localization involving 66.6% of their cases. Three different forms were identified:
   a. calcific foci solitary or multiple (Radiology 3) - these calcific foci represent dead calcified parasitic granulomata not to be confused with viable cysts containing calcified scoleces (Radiology 4)
   b. intracerebral cysts solitary or multiple (Radiology 4 and Radiology 5).
   c. 'granulomatous' cysticercosis in an acute encephalitic phase (Radiology 6). This type of lesion may also be single or multiple and occurred more frequently in children and adolescents. (As previously discussed there is pathologic evidence that many of the 'parenchymal' cyts and 'granulomata' are subarachnoid in the deep cortical sulci but even so the clinical effects result largely from parenchymal involvement).
4. **Mixed cysticercosis** where parasites were found in various combinations of meningeal parenchymal and ventricular forms. 13.5% of their cases fitted into this category.

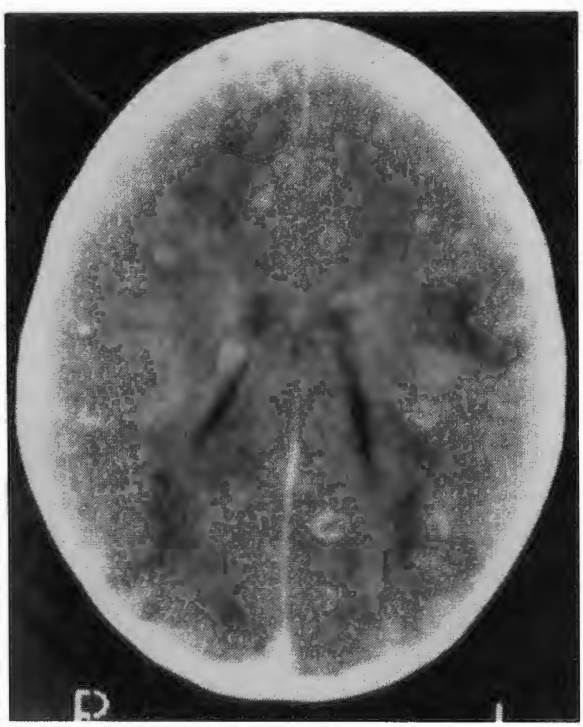
This classification highlighted the importance of the various forms of 'parenchymal' cysticercosis which because of CT scanning could now be diagnosed prior to surgery or autopsy. These parenchymal lesions comprised 66.6% of the series a figure very similar to the one produced by the sum of Groups 1 and 2 of Stepein et al study i.e. 67.4% - a presumably similar group of patients.



Radiology 4 ←
CT scan demonstrating numerous 'parenchymal' cysts many of which contain calcified scoleces.



Radiology 5 →
CT scan (with contrast) demonstrating two posteriorly placed giant cysts. One of these is undergoing degeneration with an enhancing rim and pericyst oedema. [MRI of this patient demonstrated, in addition, the presence of a few smaller cysts].



Radiology 6 ←
CT scan (with contrast) demonstrating the ring enhancing and homogeneously enhancing lesions of granulomatous cysticercosis (multifocal cysticercal encephalitis).
Note the oedema of varying degree in the surrounding white matter.

A classification of 753 patients integrating CT and CSF findings with a view to identifying 'active' and 'inactive' forms of neurocysticercosis for the purposes of therapeutic trials and research into the immunology of the disease was proposed by Sotelo et al (Sotelo et al 1985; Sotelo 1987):

1. **Active disease**
    a. Parenchymal cysts - 14.2%
    b. Encephalitis and vasculitis - 2.3%
    c. Arachnoiditis - 46.2%
    d. Intraventricular cysts - 0.7%
    e. Spinal cysts - 0.7%
2. **Inactive disease:**
    a. Granulomas and calcifications - 57.6%
    b. Basal fibrosis - 3.8%.

This classification although extensive and derived from a very large experience is unfortunately confusing especially with regard to assessing therapy in relation to the natural history of the disorder. It does not allow, in particular, for clear understanding of the term 'active disease'. 'Viable' enlarging parenchymal cysts which elicit no inflammatory reaction and are quiescent and asymptomatic may continue to actively enlarge without producing an active inflammatory response in the host. These viable cysts may require different management from 'dying' cysts. The 'dying' or 'dead' cysts are actively eliciting an inflammatory response in the host with the producion of enecephalitis, vasculitis and arachnoiditis i.e. active disease on the part of the host despite an inactive dead parasite.

Another excellent paper by Stern attempts to surmount the inherent difficulties associated with an all-encompassing clinico-pathological classification. Although managing to reveal these the author does manage to categorise the various forms in an understandable if somewhat cumbersome and lengthy classification (Stern 1981). A summary of this classification follows.

Category I - Diffuse Parenchymatous disease - larval death with inflammatory reaction producing toxic encephalopathy and meningitis

Category II - Calcified larval form with seizures.

Category III - Basilar adhesive and racemose form with arachnoiditis and hydrocephalus.

Category IV - Ventriculitis and hydrocephalus.

Category V - Intra-parenchymal cysts as mass lesions - solitary or multifocal.

Category VI - Subarachnoid and cysternal cysts - focal symptomatology.

Category VII - Intra-ventricular cysts - solitary or multiple.

Category VIII - Spinal forms.

The author includes mixed and overlapping types in categories III, IV, VI and VII in a somewhat random fashion which only serves to stress the varied pathological findings that are possible in any one patient.

However, many publications on the subject of neurocysticercosis confirm that despite the numerous possible pathological changes and protean clinical features the majority of patients present with problems related to seizures, to raised intracranial pressure, to localizing neurological deficits, to psychiatric disorders or to combinations of any or all of the above (Trelles and Trelles 1979; Sotelo 1988; Grisolia and Wiederholdt 1982 Lombardo and Mateos 1961; Earnest et al 1987; McCormick et al 1982; Torrealba et al 1984; Bittencourt et al 1988; Shasha and Parmenter 1989; Loo and Braude 1982; Zenteno-Alanis 1982). Autopsy series (Rabiele-Cervantes et al 1982) have shown that many people infected with neurocysticercosis are asymptomatic and the wide use of CT scanning in endemic areas is increasingly confirming this fact.

PART II

NEUROCYSTICERCOSIS - TEACHING HOSPITALS, UNIVERSITY OF CAPE TOWN

METHODS:

Cases diagnosed as having neurocysticercosis while attending the University of Cape Town Teaching Hospitals between and inclusive of the years 1975-1989 were identified by review of:

1. The discharge diagnosis obtained from the Groote Schuur Hospital medical records.
2. The listed diagnosis obtained from the records of the Groote Schuur Hospital Department of Neuroradiology. All the patients attending Somerset Hospital and those attending the Red Cross War Memorial Children's Hospital from 1975 to 1987 were traced in this way.
3. The discharge diagnosis obtained from the Red Cross War Memorial Children's Hospital medical records for the years 1988-1989 as CT scanning became available on these premises during this period.

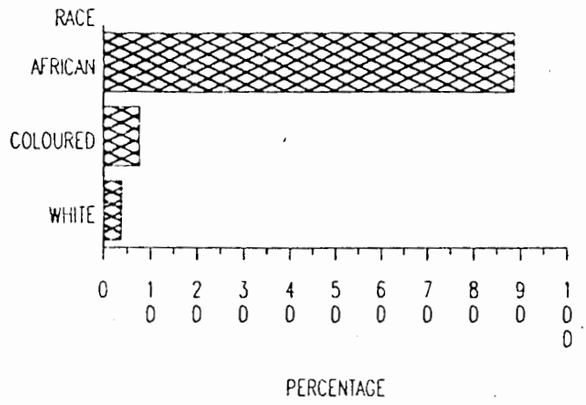
From amongst the case records that were still available for review 239 patients were accepted as having neurocysticercosis. The following diagnostic criteria for the diagnosis of neurocysticercosis were used.

1. **Diagnosis definite:** (For a definite diagnosis at least one of the following criteria had to be present)
   a. Histologic confirmation of cysticercosis from biopsy or autopsy specimens.
   b. Positive titres of cysticercus antibodies in serum and or CSF of patients with compatible clinical and characteristic radiological features

2. **Diagnosis probable:**
   Diagnostically characteristic CT scan features in patients from endemic regions in whom the evolution of the clinical and radiological features was compatible with such a diagnosis.

Graph 1

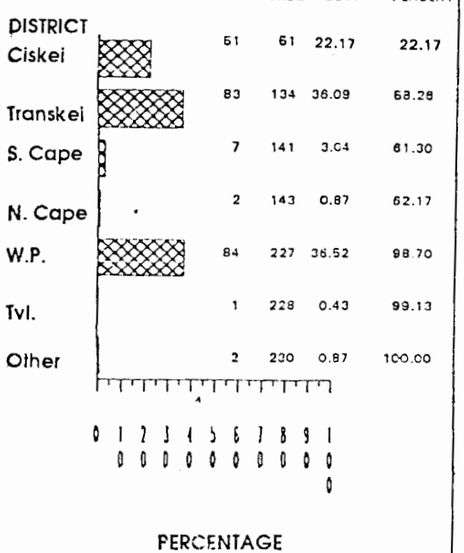
DISTRIBUTION OF RACE



	FREQ	CUM. FREQ	PERCENT	CUM. PERCENT
AFRICAN	212	212	88.70	88.70
COLOURED	18	230	7.53	96.23
WHITE	9	239	3.77	100.00

Graph 2

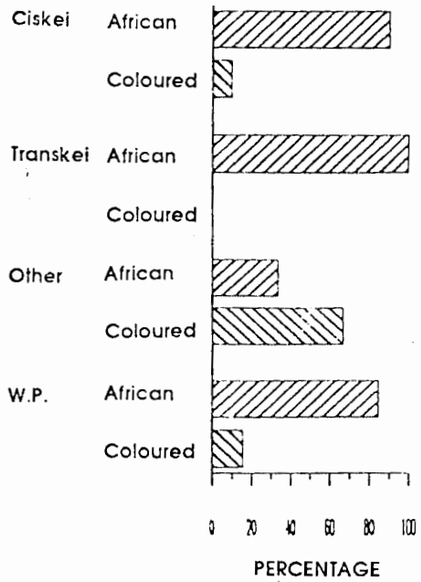
DISTRIBUTION OF DISTRICT



	FREQ	CUM FREQ	PER CENT	CUM PERCENT
Ciskei	51	51	22.17	22.17
Transkei	83	134	36.09	58.26
S. Cape	7	141	3.04	61.30
N. Cape	2	143	0.87	62.17
W.P.	84	227	36.52	98.70
Tvl.	1	228	0.43	99.13
Other	2	230	0.87	100.00

Graph 3

DISTRIBUTION OF RACE BY DISTRICT



DISTRICT	RACE	FREQ	CUM FREQ	PER-CENT	CUM PERCENT
Ciskei	African	46	46	90	90.20
	Coloured	5	51	10	100.00
Transkei	African	83	83	100	100.00
	Coloured	0	83	0	100.00
Other	African	4	4	33	33.33
	Coloured	8	12	67	100.00
W.P.	African	71	71	85	84.52
	Coloured	13	84	15	100.00

The charts of these selected patients were reviewed and data collected and stored regarding race, district of origin, age, sex, clinical features, cerebrospinal fluid findings, full blood counts, serum chemistry, radiologic investigations, electroencephalographic findings and serologic findings.

Initially all these patients were classified according to the clinical format mentioned above i.e.: 1) those with seizures with or without other neurological problems; 2) those with symptoms and signs of raised intra-cranial pressure; 3) those who were 'asymptomatic' but were found to have neurocysticercosis on CT scan done for other reasons e.g. trauma.

RESULTS

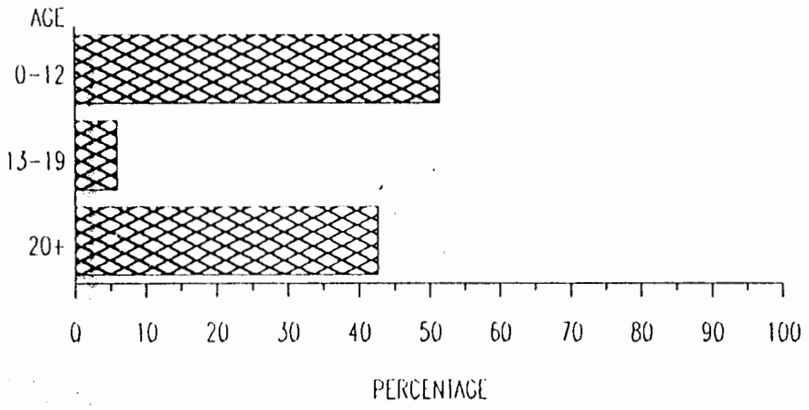
Between and inclusive of the years 1975 - 1989 two hundred and thirty nine patients who attended Groote Schuur Hospital and the associated teaching hospitals of the University of Cape Town have been identified as having neurocysticercosis. From Graph 1 it can be seen that 88.7% of these patients were African. Graphs 2 and 3 delineate the districts from which these patients came. 58.46% of the patients were referred directly from the rural regions of the Transkei and Ciskei. Another 36.52% came from the Western Cape. These patients were migrant labourers residing in the African townships and squatter camps of Greater Cape Town and its environs. Occasional African patients were referred for neurological investigation from as far afield as for example Malawi.

From Graph 4 it can be seen that 51.46% of the patients were children, again largely Africans as shown in Graph 5.

Prior to this review i.e. prior to 1975 only a few adult patients presenting with neurological problems had been diagnosed at Groote Schuur Hospital as having neurocysticercosis. However, in this series during 1975-76 although only four cases were diagnosed all were children. With the advent of CT scanning at Groote Schuur Hospital towards the end of 1977 there was a

Graph 4

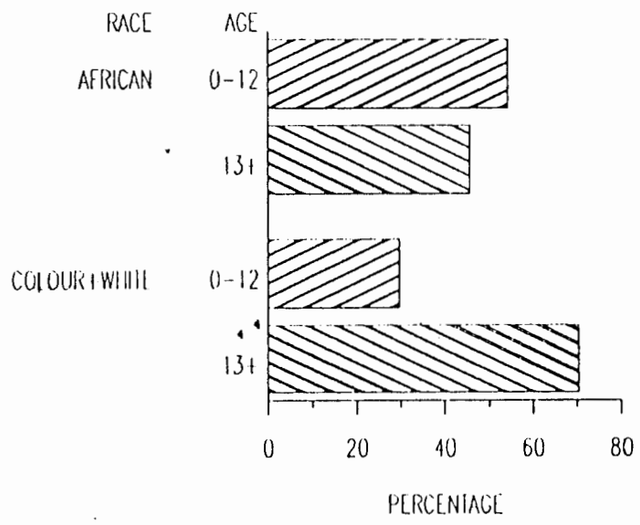
DISTRIBUTION OF AGE



	FREQ	CUM. FREQ	PERCENT	CUM. PERCENT
0-12	123	123	51.46	51.46
13-19	14	137	5.86	57.32
20+	102	239	42.68	100.00

Graph 5

DISTRIBUTION OF AGE BY RACE



		FREQ	CUM. FREQ	PERCENT	CUM. PERCENT
AFRICAN	0-12	115	115	54.25	54.25
	13+	97	212	45.75	100.00
COLOUR/WHITE	0-12	8	8	29.63	29.63
	13+	19	27	70.37	100.00

marked increase in the number of patients diagnosed as having neurocysticercosis. From Graph 6 it can be seen however that it was only from 1986 that per annum more adults than children were diagnosed with the disease. 1989 showed a massive increase in the number of adult patients.

In this series there was no significant difference between the number of male (48.54%) and female (51.46%) patients.

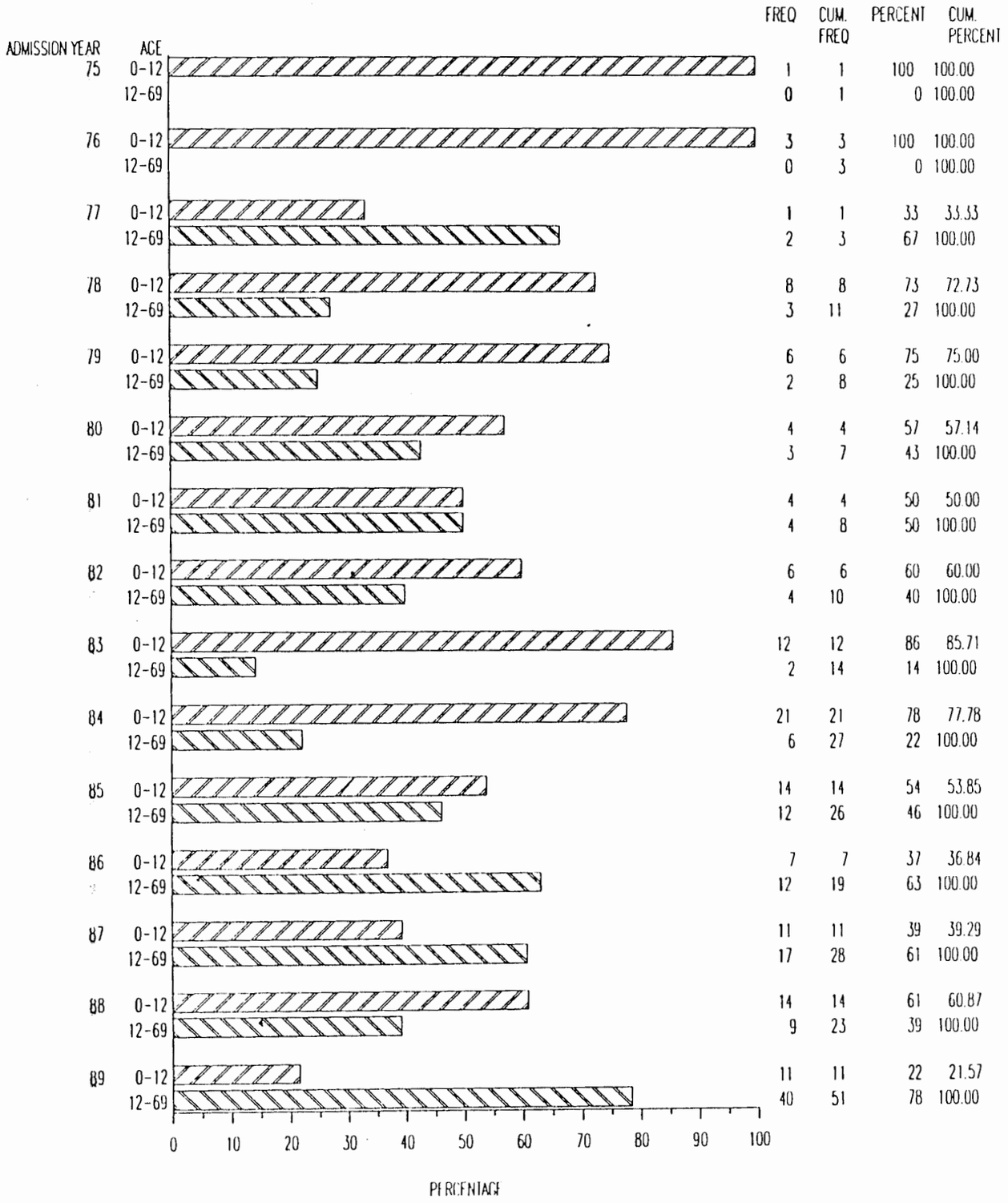
The clinical division of these 239 patients into 3 groups is tabulated below (Table I). Some of these patients were classified as belonging to both the seizure and the raised intra-cranial pressure groups.

TABLE I : CLINICAL GROUPS

GROUP I SEIZURES:	**= 190**
This group consists of patients presenting either with recurrent seziures (epilepsy) or recent onset of seizures ('acute seizures' i.e. initial seizure within the week prior to admission).	
Epilepsy only (adult 27, children 24)	= 51
Epilepsy + focal neurology / dementia (adult 13, children 21) / psychiatric	= 34
Epilepsy + raised ICP (adult 8, children 22)	= 30
Acute seizure (adult 24, children 25)	= 49
Acute seizure + raised ICP (adult 4, children 22)	= 26
GROUP 2 RAISED INTRACRANIAL PRESSURE	**= 86**
Hydrocephalus (adult 26, children 6)	= 32
Space demanding mass lesion (adult 4, children 0)	= 4
Multifocal cysticercal encephalitis (adult 6, child 44)	= 50
GROUP 3 ASYMPTOMATIC (adult 10, children 0)	**= 10**

GRAPH 6

DISTRIBUTION OF AGE BY YEAR



DISCUSSION

The great majority of these patients (88.7%) were African. They came from amongst the different Xhosa speaking tribes of the Ciskeian and Transkeian homelands. In these rural areas free range pig farming is practised and sanitation is largely non-existent. It is therefore no wonder that cysticercosis is so commonly found amongst the Xhosa people of the Eastern Cape Province (Sasha and Pammenter 1989; Campbell and Farrell 1987). The large number of patients referred from the African townships and squatter camps of greater Cape Town where migrant workers and their family members who had originated from the Ciskei and Transkei. Only 3 African patients in this series did not belong to the Xhosa nation and came from other areas - Malawi, Namibia and Transvaal respectively.

The large number of children in this series was partly due to the seriouness of the illness in many of them and until recently partly due to the absence of neurological investigative facilities at the referral hospitals in East London - Frere Hospital and Cecilia Makiwane Hospital. Presumably the presence of pica with geophagia in some of these children allowed for the very heavy infestation present in most of those referred directly from the Eastern Cape.

Initially in this series more children than adults were diagnosed annually as having neurocysticercosis. However, more recently the numbers of adult patients with the disease have increased. By 1989 the adult patient numbers had markedly increased. This was probably related to the increasing influx of African labourers into the Western Cape. This adult patient preponderance is the more usual finding in many series reported from endemic areas and quoted in extensive review articles (Earnest et al 1987; McCormick et al 1982; Loo and Braude 1982).

Seizures were by far the commonest clinical manifestation (190 patients) and presented as the only problem in 100 of these (51 adults, 49 children). That seizures are the commonest clinical manifestation of neurocysticercosis has been well documented (McArthur 1934; Arseni and Cristesau 1972; Bittencourt et al 1988). It is of interest to note that seizures plus raised

intracranial pressure and that seizures plus one or more of dementia, psychosis and focal neurological deficit occurred much more commonly amongst the children (65 children, 25 adults). The increased morbidity amongst the children in this series with seizures was probably due to the patient selection, in particular due to the selection of those children referred with raised intracranial pressure.

The next most common clinical presentation was that of raised intracranial pressure which occurred in 86 patients. It is of interest to note the significant differences in the causes of raised intracranial pressure in children as compared to adults. Amongst the adults with raised intracranial pressure 26 had hydrocephalus, 6 had multifocal cysticercal encephalitis and 4 had focal space demanding lesions. Amongst the children (12 years or younger) on the other hand 44 had multifocal cysticercal encephalitis whereas only 6 had hydrocephalus and there were no children with space demanding focal lesions large enough to produce recognised features of raised intracranial pressure. These differences in the causes of raised intracranial pressure in adults and children with neurocysticercosis have been noted previously (Hernandez and Garaizar 1982a).

Although only 10 asymptomatic adults in this series were discovered on CT scan of the brain done for other reasons, it is known from autopsy, radiologic and serologic studies done in endemic areas that there are many patients with neurocysticercosis who are asymptomatic (Rabiela-Cervantes et al 1982; Zenteno-Alanis 1982; Mazer et al 1983; Zini et al 1990).

PART III

MULTIFOCAL CYSTICERCAL ENCEPHALITIS

METHODS

From amongst the 239 patients with neurocysticercosis those with cysticercal encephalitis were selected using CT scan features which have been well described. Following contrast administration these features consist of a small ring enhancing or a small homogenously enhancing lesion (radiologically termed 'granuloma') with surrounding white matter oedema (Minguetti and Ferrreira 1983; Mazer et al 1983; Carbajal and Duran 1983; Sotelo 1987) (Radiology 6). These CT scan features have been correlated with the histologic findings of the encysted parasite surrounded by inflammatory exudate and oedema (Madrazo et al 1983; Rangel et al 1987). These 'granulomatous' encephalitic lesions may vary in number from a single lesion to many lesions, the term miliary being used to describe the latter (Sotelo et al 1985). Prior to the use of CT scanning only the severe miliary forms were occasionally diagnosed antemortem in endemic areas. Ventriculography done in these patients demonstrated symmetrically swollen brains with slit ventricles and effacement of the cortical sulcal pattern (Stepien 1962).

Using these radiologic criteria 116 patients (80 children, 36 adults) were identified as presenting the features of cysticercal encephalitis. Sixty six patients had five or less enhancing lesions on their presenting CT scans. For the purposes of this study these patients were defined as having focal encephalitis (Table 2).

TABLE 2 : FOCAL CYSTICERCAL ENCEPHALITIS **66 patients**

C T scan findings:

Granulomas with oedema (34 child, 27 adult)	=	61 patients
Enhancing cysts with oedema (0 child, 5 adult)	=	5 patients

Clinical features:

Epilepsy alone (28 child, 25 adult)	=	53 patients
Epilepsy + (focal neuro/dement) (6 child, 4 adult)	=	10 patients
Epilepsy + mass effect + ↑ICP (0 child, 3 adult)	=	3 patients

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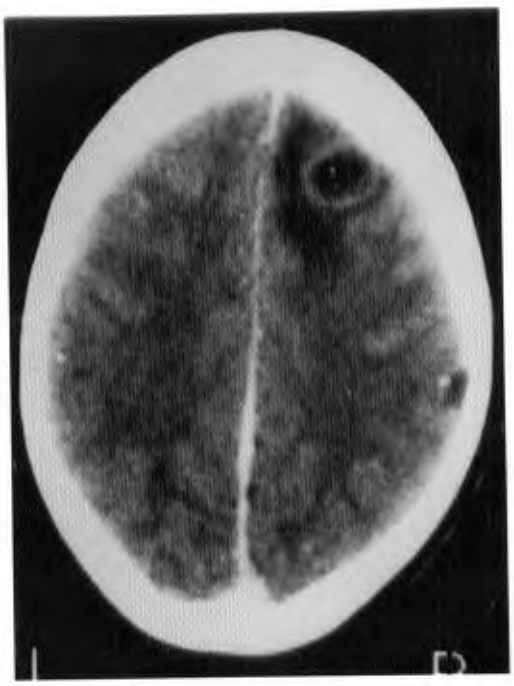


Radiology 7
CT scan (with contrast) demonstrating a single enhancing lesion with oedema of the surrounding white matter - focal cysticercal encephalitis in the right frontal region. Note the cystic lesion with a calcific scolex present in the right parietal region as well as the calcific speck in the left parietal region.

Of these 66 patients with focal encephalitis 33 had single enhancing lesions with associated oedema on their CT scans (Radiology 7). These 33 patients were clinically accepted as having neurocysticercosis for the following reasons. Twenty of the 33 had in addition to the single enhancing lesions multiple intra-cranial calcific foci on their CT scans (1 adult patient had in addition multiple non-enhancing cysts). Two the 33, both adults, had their cystic lesions biopsied with positive histologic confirmation of cysticercosis. Three of the 33 demonstrated an increase in the number of enhancing lesions following on Praziquantel therapy before these lesions all resolved over the subsequent few months. Four of the 33 had positive cysticercus antibody titres in blood and/or CSF (serological testing had only been undertaken in 16 of the 33 patients and was positive in 8 of them). The remaining 4 patients had single lesions which resolved over a period of a few months. No specific therapy was given to 2 of these patients while the remaining 2 had received a course of Praziquantel.

Fifty patients of the 116 patients with encephalitis presented with the syndrome of Multifocal Cysticercal Encephalitis. The CT scan of the brain of these patients demonstrated the presence of diffuse or extensive multifocal cerebral oedema and in addition the presence of multiple enhancing lesions well in excess of 6 and often innumerable.

TABLE 3 : MULTIFOCAL CYSTICERCAL ENCEPHALITIS **50 patients**

Radiologic findings:

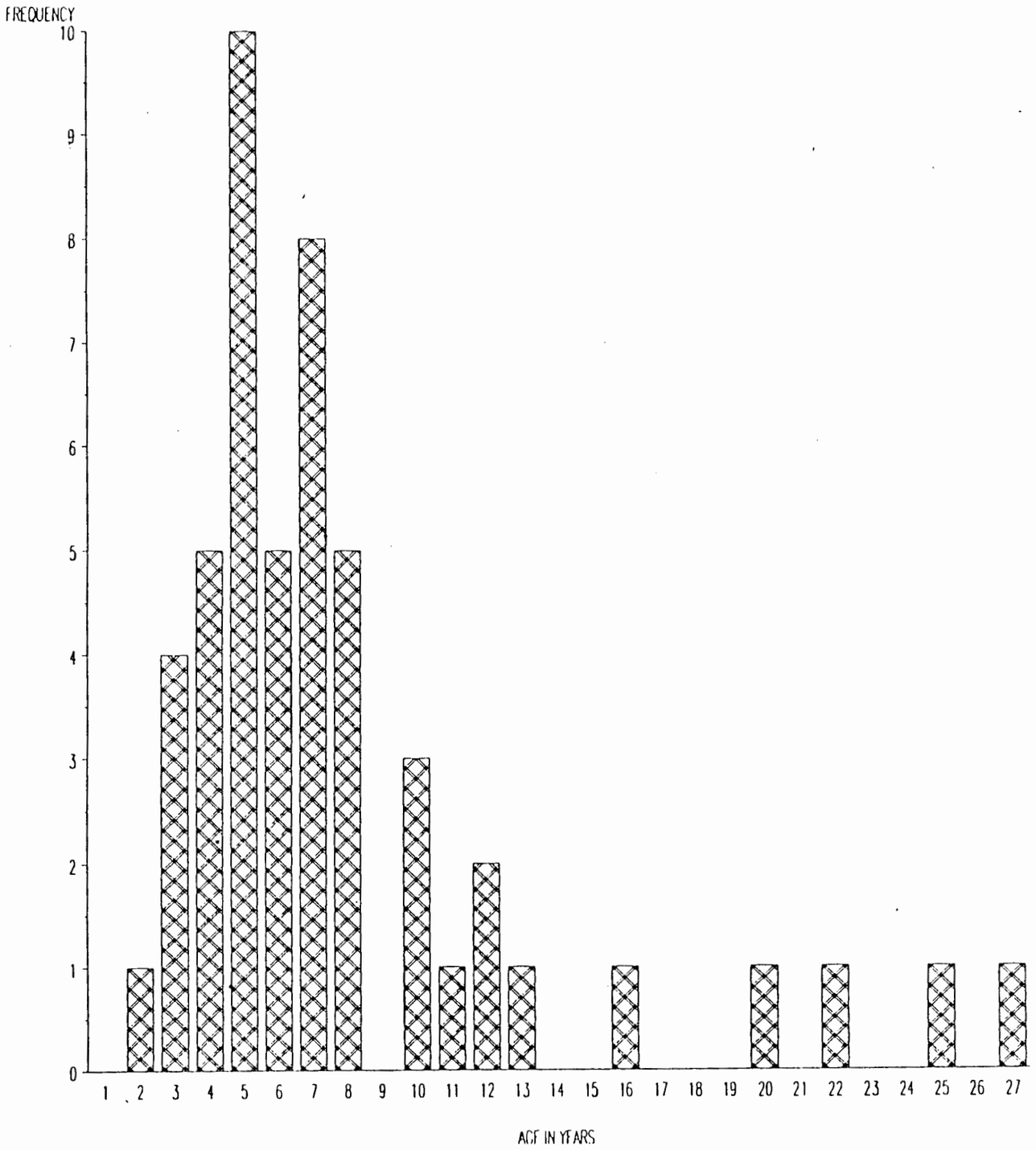
Granulomas with oedema (CT) (42 child, 2 adult)	=	44 patients
Enhancing cysts + oedema (CT) (0 child, 4 adult)	=	4 patients
Swollen brain (vent) (2 child, 0 adult)	=	2 patients

These fifty patients (20.9% of the total series) with the clinical features of generalized encephalopathy and radiologic features of acute multifocal cysticercal encephalitis form the study group for further analysis. These patients would have been classified as Group II classification of Stepein et al, Group IIIc classification of Rodriguez-Carbajal et al, Group IB and IC classification of Sotelo et al and Category I classification of Stern.

Graph 7

MULTIFOCAL CYSTICERCAL ENCEPHALITIS

DISTRIBUTION OF AGE



RESULTS

Forty-four of these 50 patients were children (< 12 years). In the total group of 123 children 35.7% were diagnosed as having Multifocal Cysticercal Encephalitis (Graph 7 - Age distribution). The ages of the 6 patients in the adult group (> 12 years) were 13, 16, 20, 22, 25 and 27 years, that is all young adults with two of them belonging to the teenage group of 14 patients. Amongst the children 26 patients were female and 18 were male, and amongst the adults 4 were male and 2 were female. Forty-eight of the patients were Xhosa, 1 white male from the South Cape (Oudtshoorn), and 1 coloured male from the North West Cape (Wuppertal).

CLINICAL FEATURES

As the adult group consisted of so few patients the clinical features of the whole group were analyzed together. The initial symptoms of the illness were convulsions in 27 cases (54.0%), headache with or without vomiting in 18 cases (36%), behaviour and cognitive disorder in 3 cases (6%) and myalgia with fever in 2 cases (4%). As the last 2 patients were more sophisticated and thus able to give more detailed histories perhaps the symptoms of myalgia and fever were more common than the available histories suggest. There was a wide range in the duration of illness prior to admission but from the available histories it was not often clear as to when the more dramatic illness began. This duration of illness varied from < 1/52 in 10 patients (20%) to < 1/12 in 11 patients (22%) to < 3/12 in 9 patients (18%) and to < 6/12 in 11 patients (22%) Nine patients (18%) were symptomatic for longer than 6/12.

Symptoms and signs on admission are presented in Table 4.

TABLE 4: CLINICAL FEATURES MULTIFOCAL CYSTICERCAL ENCEPHALITIS

PRESENTING SYMPTOMS - 50 patients

1.	Convulsions	44 cases	88%
	(Epilepsy	(22 cases	(44%
	(Acute seizures	(22 cases	(44%
	Status epilepticus	16 cases	32%
2.	Headache and vomiting	39 cases	78%
3.	Myalgia and fever	11 cases	22%
4.	Behaviour and Cognitive Disorders	9 cases	18%

FINDINGS ON ADMISSION - 50 patients

1.	Papilloedema	23 cases	46%
2.	Acute confusion /delirium	19 cases	38%
3.	Depressed level of consciousness	19 cases	38%
4.	Focal neurological signs	18 cases	36%
5.	Meningeal Signs	8 cases	16%

The commonest presenting symptom was convulsions in 44 patients (i.e. 22 epileptic and 22 patients with acute seizures). Acute seizures were definied as seizures with initial onset occurring within the week prior to admission. Amongst the 44 patients who presented with convulsions, 22 had focal onset seizures with secondary generalisation more often than they had seizures with a generalised onset, 15 had generalized tonic/clonic seizures only, 4 had complex partial seizures with secondary generalization and 3 had focal seizures only.

Headache with or without vomiting was the next most common symptom occurring in 39 cases (78%). Papilloedema was found in 23 (12 males and 11 females) of these patients with raised intra- cranial pressure. Papilloedema has been recorded as the commonest neuro-ophthalmologic sign in neurocysticercosis (Keane 1982). Depressed level of consciousness was found in 19 patients (11 males, 8 females) and the combination of depressed level of consciousness and

papilloedma was found in 11 patients (5 males, 6 females). Thus 8 patients (6 males, 2 females) had depressed level of consciousness without papilloedema. In three of these patients associated status epilepticus was noted on admission and was no doubt a contributing factor to the depression of consciousness.

Eighteen of the patients had focal neurologic signs. Most of these were the result of the markedly increased intra-cranial pressure. Except in 2 patients (1 with optic atrophy and 1 with quadriplegia) all of these signs resolved on reduction of the intra-cranial pressure. Fourteen were ataxic (12 with gait ataxia, 1 with truncal ataxia and 1 with limb ataxia). In addition 2 of these patients had nystagmus. Excluding the patients with papilloedema, 10 in addition to the 2 with nystagmus had cranial nerve involvement (1 with optic atrophy, 5 with non-localizing 6th nerve palsies, 3 with upward gaze palsies, 1 with pseudobulbar palsy). Following on papilloedema with or without abducens palsies, prectectal findings of upward gaze palsy and pupillary abnormalities have been reported to be the second major group of neuro-ophthalmological signs in neurocysticercosis (Keane 1982; Keane 1990). Motor weakness was found in two patients with hemiplegia and 1 with quadriplegia and dystonia (the patient with pseudobulbar palsy). One patient had cortical blindness. The patient with optic atrophy, an adolescent female, had the disc features diagnostic of long-standing raised intra-cranial pressure and not those of perichiasmatic compressive arachnoiditis.

LABORATORY INVESTIGATIONS

Laboratory investigations were also analyzed for the group as a whole.

Cerebro-spinal fluid findings: Forty-seven patients were lumbar punctured. In 30 of these patients, with clinical features suggestive of raised intra-cranial pressure, lumbar puncture was performed only after CT scans of the brain had been done and the raised intra-cranial pressure lowered by means of Dexamethasone therapy (+ Mannitol in 5 cases). Effective reduction of intra-cranial pressure was equated with the improved level of consciousness of the patient. In 20 patients the pressure of the cerebrospinal fluid was measured and in 14 was found to be elevated above 18 cm of water confirming the presence of raised ICP in those 14 patients. Four of these

14 patients had completely normal CSF on chemical and cellular analysis. In 32 of the 47 patients lumbar punctured analysis of the CSF was found to be abnormal. In 2 of the adult patients the abnormality may have been related to the presumed presence of other CNS infections. Therefore these two CSF's have been excluded from the analysis.

TABLE 5: CSF FINDINGS IN 45 CASES OF MULTIFOCAL CYSTICERCAL ENCEPHALITIS

CSF	Normal	= 15;	Abnormal	= 30			= 45
Globulin	Negative	= 23;	Positive	= 22			= 45
Protein	< 0.5 g%	= 33;	0.5-1.0 g%	= 7;	> 1.0 g%	= 5	= 45
Glucose	< 3 g %	= 10;	> 3 g %	= 35			= 45
Lymphs	0-5	= 15;	5-50	= 23;	50-100	= 5	= 45
	> 100	= 2					
Polys	0	= 28;	1-50	= 13;	50-100	= 2	= 45
	> 100	= 2					
Eosinophils	Not done	= 28;	Positive	= 6;	Negative	= 11	= 45

Comparative blood glucoses were not obtained at the time of lumbar puncture. To detect eosinophils in the CSF special staining techniques are required and were only requested or done in 17 of the CSFs analysed. Bacterial culture, TB culture and cryptococcal antigen were negative in all 30 abnormal CSFs.

Cysticercus antibody tests: Serologic testing for the presence of cysticercus antibodies was carried out in the sera of 40 patients and in the CSF of 37 patients. These tests were carried out at the Research Institute for Diseases in a Tropical Environment of the South African Medical Research Council, Durban. Initially an indirect haemagglutination (IHA) test was utilized but subsequent to 1983 this was replaced by the more specific enzyme-linked immunosorbent assay (ELISA) test (Pammenter et al 1987). None of these patients had sera nor CSF tested by the more recent combination of ELISA and immunoblotting which has proved to be highly sensitive and more specific than the ELISA alone in the immunodiagnosis of neurocysticercosis (Gottstein

TABLE 6: IHA AND ELISA TESTS

MULTIFOCAL CYSTICERCAL ENCEPHALITIS - 44 CHILDREN

CSF \ BLOOD	0	-	+	+ +	+ + +	
0	3			4	2	= 9
-	1	1		2		= 4
+			2	2	1	= 5
+ +		1		2	6	= 9
+ + +	2			1	14	= 17
						= 44

Blood 0	CSF 0	=	3
Blood 0	CSF -	=	1
Blood 0	CSF +	=	2
Blood -	CSF -	=	1
Blood -	CSF +	=	1
Blood +	CSF 0	=	6
Blood +	CSF -	=	2
Blood +	CSF +	=	28
			44

Key:

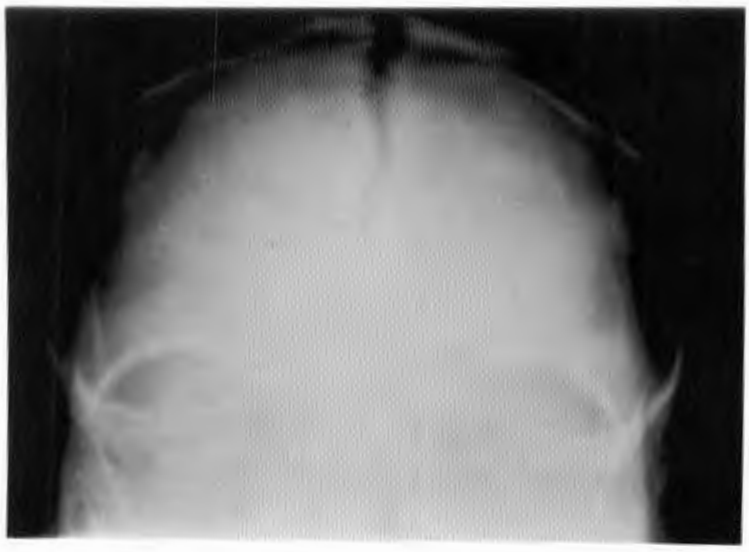
0	=	Not done
-	=	Negative
+	=	Slightly positive
+ +	=	Moderately positive
+ + +	=	Strongly positive

et al 1987; Shasha and Pammenter 1989).

However, as the CT scan findings in these patients were completely unlike the CT scan findings that would be expected in children with cerebral echinococcus (hydatid disease), the problem of possible cross-reactivity of the cysticercus ELISA test with hydatid antigen does not arise and does influence the diagnosis of these cases (Ozgen et al 1979). Thirty-seven of 40 patients whose sera were tested were found to contain cysticercal antibodies. Thirty-one of 37 patients whose CSF were tested were found to contain cysticercal antibodies.

From Table 6 which documents the results of the immunological tests (IHA and ELISA) done in the blood and CSF of the children, it can be seen that both the blood and CSF of 32 children was tested. Twenty-eight children were positive in both blood and CSF, 2 children were positive in blood and negative in CSF, 1 child was positive in CSF but negative in blood and 1 child was negative in both blood and CSF. Six children who only had blood tested were positive, 3 who only had CSF tested were positive in 2 and negative in 1 and the 3 remaining children had neither blood nor CSF tested. Amongst the 6 adult patients only 3 were tested. One was negative in both blood and CSF, one was positive in blood (CSF not checked), and 1 was negative in CSF (blood not checked).

Haematologic investigations revealed that 4 patients had haemoglobin levels below 11 g% (all children). Only 1 of these had an MCV below 72 but milder degrees of iron deficiency may have existed partly explaining the platelet counts in excess of 400 000 in 29 patients. However, the most likely explanation for these high platelet counts is the presence of infection. White blood cell counts in excess of 12 000 cells with polymorphs exceeding 70% of the differential count were found in 12 patients. Only 14 patients demonstrated an eosinophilia in excess of 5% on differential count. Erythrocyte sedimentation rate was elevated above 20 mm Westergren in 29 patients and above 50 in 11 of these patients.



Radiology 8
X-ray of a child's scull demonstrating marked sutural diastasis due to raised intra-cranial pressure

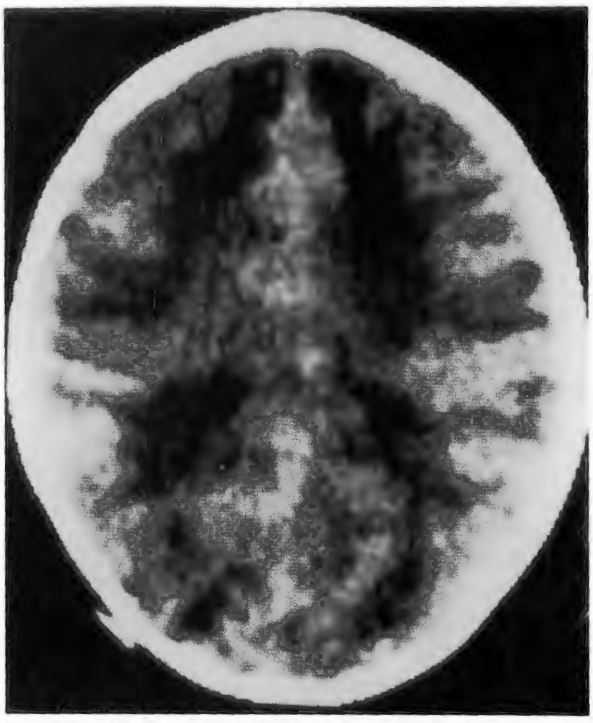
Radiology 9
Skull X-ray demonstrating the presence of numerous intra-cranial calcific foci.

Biochemical investigations: There were no abnormalities in hepatic or renal function tests in any of the patients. Calcium and glucose metabolism were also normal.

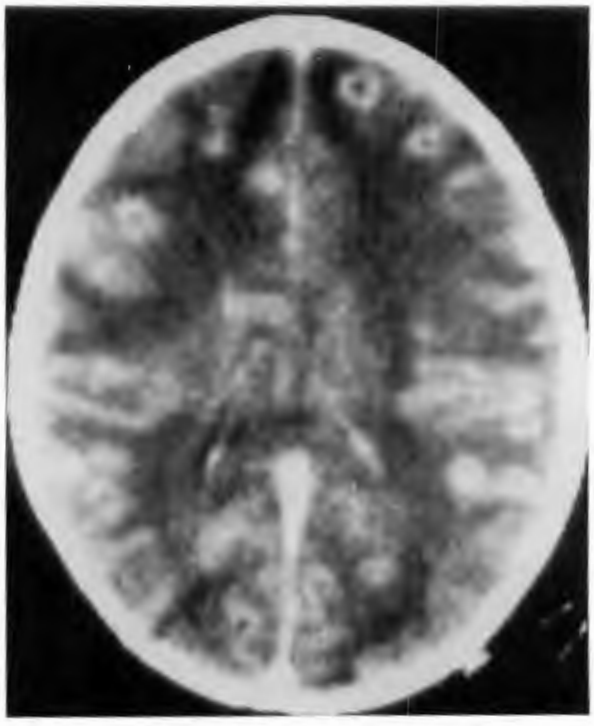
Radiologic findings: In 17 patients radiology of soft tissues (X-ray thighs) was performed and in 2 of these patients, both adults, calcific lesions were visible in the muscles and or subcutaneous tissues. X-rays of the skull were reviewed in 48 patients as there was no trace of skull X-rays in 2 of the patients. In 17 patients the skull X-ray was normal. Among the 31 patients with abnormal skull X- rays, 28 showed evidence of raised intra-cranial pressure (24 with diastasis of skull sutures, 1 with diastasis and intra-cranial calcific foci, 2 with erosion of posterior clinoids, 1 with erosion of posterior clinoids and intra- cranial calcification) (Radiology 8). The skull X-rays of the 3 remaining patients demonstrated intra-cranial calcific foci only (Radiology 9).

Using high resolution CT scanners (Elscint 905 and 1800) CT scans of the brain were done in 48 of these 50 patients initially. Two patients were diagnosed prior to the availability of scanning at Groote Schuur Hospital and only 1 of these was subsequently scanned at the 1 year follow-up. On admission forty scans were done with and without contrast, 6 with contrast only and 2 without contrast only. Among the 48 abnormal scans 11 demonstrated generalized oedema with compressed ventricular system (Radiology 10), 29 demonstrated generalised oedema with compressed ventricular system and multiple ring enhancing lesions following contrast administration (Radiology 11), 5 demonstrated multifocal oedema with multiple enhancing lesions following contrast administration, and 3 demonstrated multifocal oedema with multiple cystic lesions which enhanced following contrast administration (Radiology 12). The CT scans of 13 of these patients demonstrated the presence of calcific foci as well. Magnetic Resonance Imaging was performed in 2 patients and was abnormal confirming the CT scan findings. Ventriculography was performed in 2 patients prior to the availability of CT scan facilities at GSH. Both were performed with some difficulty revealing extensive brain swelling with compressed ventricles.

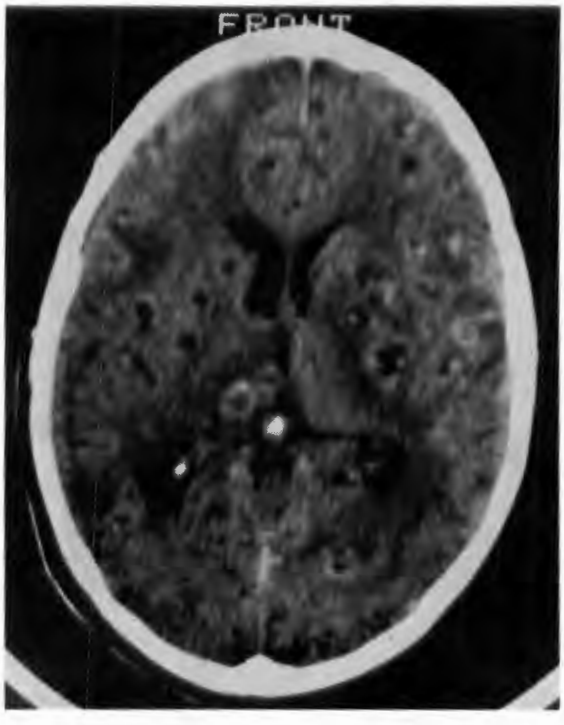
Electroencephalography was done in 39 patients and was found to be abnormal in 34. Thirty-one of these patients had EEG's with generalized slowing and 3 had EEG's with focal slowing and focal spikes.



Radiology 10
CT scan (with contrast) demonstrating generalised oedema in a child with multifocal cysticeral encephalitis and severe raised intra-cranial pressure.



Radiology 11
CT scan (with contrast) demonstrating generalised oedema and ring enhencing lesions in the same patient on steroid therapy 1 month later.



Radiology 12
CT scan (with contrast) in an adolescent patiant demonstrating enhancing cysts with varying degrees of multifocal oedema.

DISCUSSION

The earliest reference to patients with multifocal parenchymal neurocysticercosis was from Poland (Stepien and Chorobski 1949). These patients presented with features of raised intracranial pressure and at ventriculography were found to have symmetrically swollen brains. Some of these patients came to autopsy and were noted to have diffuse or extensive multifocal oedema in relation to the many intracerebral parasites. Further experience was published from the same medical centres (Stepien 1962). Subsequent reports relating to neurocysticercosis prior the the advent of CT scanning did on occasion make reference to cerebral oedema complicating multifocal parenchymal neurocysticercosis. These reports emanated from Rumania (Arseni and Samietea 1957), India (Balasubramaniam et al 1971; Vinayan et al 1977) and Mexico (Cardenas 1962; Goni 1962).

Two such children from the present series presented with clinical features of raised intracranial pressure and were found to have diffuse cerebral swelling on ventriculography. Subsequent studies confirmed the diagnosis of multifocal parenchymal neurocysticercosis. The clinical and radiologic findings of these two patients have been reported previously (Thomson 1984; Handler 1983). With hindsight, it is reasonable to presume that in the pre-CT scan era, children from endemic areas with the syndrome of Diffuse Encephalopathy due to multiple parenchymal neurocysticercosis were often misdiagnosed. They were probably diagnosed as cases of either 'toxic'/'metabolic' encephalopathy or viral para/post-infectious encephalitis or even in the milder cases as benign intracranial hypertension.

With the widespread use of CT scanning in endemic regions a flurry of papers reporting and highlighting this multifocal parenchymal form of neurocysticercosis have appeared from Latin America (Minguetti and Ferreira 1983; Maser et al 1983; Rodriquez-Carbajal et al 1987; Carbajal et al 1983), India (Wadia et al 1988), and South Africa (Thomson et al 1984; Handler and Mervis 1983). With few exceptions most of the patients reported in these 2 South African papers were referred from the Eastern Cape territories of the Ciskei and the Transkei both known as highly endemic regions.

Forty four of the 50 patients with multifocal cysticercal encephalitis were children 12 years of age or younger. Of the remaining 6 patients 2 were adolescents and 4 adults who were all in the 3rd decade. Thus only 4 of 102 adult patients (3.9%) had multifocal cysticercal encephalitis whereas 2 of 14 adolescents (14.3%) and 44 of 123 children (35.7%) of 12 years or younger were so diagnosed. These figures certainly confirm previous reports that multifocal cysticercal encephalitis is much more common in children referred to hospital (Stepien 1962; Balasubramaniam et al 1971; Hernandez and Caraizar 1982a&b). The reported incidence of this form of neurocysticercosis in childhood varies quite widely and is dependent on the nature of the centre reporting the patients. Most of the patients in this series were referred from secondary/tertiary care hospitals for diagnosis and evaluation. Thus by no means do these figures reflect the incidence or prevalence of multifocal cysticercal encephalitis in the total paediatric cysticercosis population of the Eastern Cape. Many children infested with the cysticercal parasite may remain asymptomatic or may be only mildly and transiently ill and therefore do not present to hospital. Other children may present to hospital with the problem of seizures which if easily controlled are not referred for further investigation.

Although the distribution of acute multifocal cysticercal encephalitis was slightly more common in the female in this series (28 females to 22 males) there was no significant sex difference amongst the severely ill patients. Females did not comprise the majority of those who were very ill (13 females to 19 male). These findings are at variance with some previously reported series (Rangel 1987; Del Brutto et al 1988).

In this series the duration of illness prior to admission with the more florid signs of encephalopathy was extremely varied. Correlation of the duration of the preceding illness with the initial symptomatology and admission CT scan findings was not possible. However, it was obvious that the 3 patients with histories longer than 6/12 and the 6 patients with histories longer than 12/12 presented with epilepsy as the main problem until episodes of raised intracranial pressure precipitated admission. Of interest only 4 of their 9 CT scans manifested

calcific foci in addition to the findings of multifocal cysticercal encephalitis (1 with a history of > 6/12 and 3 with histories of > 12/12). Thus 5 patients with long histories had no evidence of intra-cranial calcification on their CT scans.

Twenty CT scans were performed on the 21 patients who presented with relatively brief preceding illnesses (10 < 1/52, 11 < 1/12) manifesting with headache with or without vomiting and with recent onset of seizures (6 with status epilepticus). Five of these scans showed calcific foci in addition to cysticercal encephalitis. The other one of these 21 patients only had ventriculography performed which demonstrated marked bilateral cerebral swelling.

The 20 patients with histories longer than 1/12 but less than 6/12 presented with epilepsy and/or fluctuating episodes of headache and vomiting. Three of these patients were, in addition, reported to have shown a marked decline in cognitive function. As 1 patient, prior to availability of CT scanning, had ventriculography which demonstrated bilateral cerebral swelling, only 19 scans were done. In 3 of these scans calcific foci were seen in addition to the usual features of cysticeral encephalitis.

Thus 12 patients in this group of multifocal cysticercal encephalitis had evidence on CT scan of calcific foci. Five of these CT scans were found in patients with brief preceding histories suggesting previous asymptomatic disease in these patients and only 4 CT scans of 9 patients with lengthy histories had calcific foci suggesting that the evolution of the disease process varies widely in different patients and possibly may not always terminate in calcification (Miller et al 1983).

Although 11 (22%) of these patients were recorded as having myalgia and high fevers during their initial admission only 2 (4%) admitted to myalgia and fever as their initial symptom. One of the patients had a very observant trained nursing sister for a mother and the second patient was a sophisticated teenager. Of interest, both these patients were initially considered to have rheumatic fever by the referring doctors. It is very likely that as most of these patients came

from unsophisticated families of poor socio economic standing the symptoms of myalgia and fever were considered minor and not reported or forgotten in relation to the seriousness of the other more dramatic symptoms.

One of the adult patients was, on examination, found to have 3 sub-cutaneous nodules. Excision biopsy of one of these was performed. Histological examination confirmed the presence of cysticercus cellulosae. In the experience gained from this series the presence of sub-cutaneous nodules was extremely uncommon, unlike the findings from other series (MacArthur 1934). Perhaps the clinical search required to establish their presence was not diligent enough. We certainly have not seen patients with the pseudohypertrophy of muscle as reported in series from India (Sawhney et al 1976; Venkataraman et al 1982; Wadia et al 1988).

The clinical picture of multifocal cysticercal encephalitis has been well described and although not diagnostic is sufficiently characteristic to suggest the diagnosis in patients from endemic areas (Rangel et al 1987; Hernandez and Garaizar 1982a). These 50 patients clearly comply with this clinical picture except for the previously noted female predominance (Rangel et al 1987; Del Brutto et al 1988). The patient is almost always a child or occasionally an adolescent or rarely even a young adult. However, a report from mainland China describes 33 patients aged from 13 - 55 years with intra-cranial hypertension due to cerebral cysticercosis. Twenty one of these patients had general or focal oedema with 'allergic' changes in the CSF. It seems that 4 had diffuse oedema and 8 had multiple 'nodules' but unfortunately the ages of the patients are not given (Feng 1987). The symptoms are dominated by seizures (not infrequently by status epilepticus) which are commonly associated with complaints of headache and vomiting. The more ill the patient the more florid are the manifestations of raised intracranial pressure with findings such as papilloedema and depressed levels of consciousness. In a few patients the development of cerebral oedema and the resultant increase in intracranial pressure was so dramatic that depressed levels of consciousness without the development of papilloedema were produced. This circumstance occurred in 5 of these 50 patients. However, it is more usual for the cerebral oedema to develop more slowly with the associated development of papilloedema.

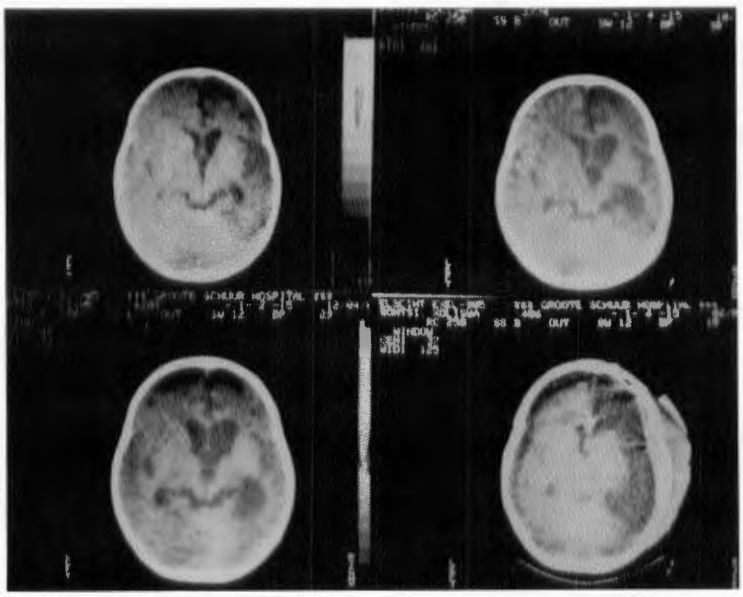
Associated features such as fever, myalgia and meningeal irritation tend to be less prominent and are therefore eclipsed by the dramatic features of seizures and raised intracranial pressure. That only 9 of the 50 patients presented with a history of behaviour or cognitive disorder is of interest. This finding may reflect either inadequate history taking due to language difficulties or may reflect that almost all of these patients came from unsophisticated rural communities and therefore these more subtle signs were possibly not observed. However 19 (38%) of these patients were noted to have an apparently obvious confusional state on admission with bizarre behaviour and occasional hallucinations. As mentioned previously it is apparent from the histories of some of these patients that the bouts of encephalopathy may fluctuate and vary in intensity over some months.

Of the 45 patients lumbar punctured, 15 patients had completely normal cerebrospinal fluid findings confirming that at least in one third of these patients there was no florid meningeal involvement and that 'all' of the detectable host parasite interaction was intraparenchymal and indeed 'purely' encephalitic. However, 30 patients had abnormal CSF's associated with their florid encephalitic picture suggesting that in the majority (two thirds) a meningo-encephalitis is present. The commonest abnormal finding in the CSF was the presence of cells, a pleocytosis in 17 cases and a pure lymphocytosis in 13 cases. The CSF globulin was abnormal in 22 cases although the total protein was only elevated in 12. CSF glucose was reduced below normal in 10 cases - unfortunately concomitant blood glucoses were not obtained. The presence of CSF eosinophilia is stated to be a common finding in neurocysticercosis (Arseni and Cristesau 1972; Goni 1962). However the finding of only 6 positives amongst the 17 cases, who had special staining of the CSF sediment for eosinophils, does not confirm this statement but rather supports the opposite finding of others (Vinayan et al 1977; Miller et al 1983). The CSF abnormalities in the cases of cysticercal meningoencephalitis are most commonly those of an aseptic meningitis although very occasionally the changes of a bacterial meningitis may be mimicked (Loo and Braude 1982; Miller et al 1983).

The high rate of positive serology in this group of patients with multifocal cysticercal encephalitis

with or without overt meningitis is to be expected and has been reported (Miller et al 1983; Miller et al 1983; McCormick et al 1982; Sotelo 1985a). However, this has not been the finding in all reports (Rangel et al 1987). Both blood and CSF were tested simultaneously for antibodies to cysticercal antigen in 33 patients. Twenty eight of these patients demonstrated positive titres in both blood and CSF, 2 positive titres in blood only, 1 positive titre in CSF only while 2 patients had neither antibodies in blood nor CSF. Seven further patients who had only blood serology done were positive as were 2 of 4 patients who only had CSF testing done. Thus 37 of 40 sera tested were positive and 31 of 37 CSF's tested were positive, suggesting that a significant response to cysticercal antigens occurs in this form of neurosysticercosis and the titre of antibody may correlate to the degree of inflammatory response present. Although intra-blood-brain barrier IgG synthesis occurs in neurocysticercosis (Miller et al 1985) and although it has been suggested that the CSF antibody titres are more likely to be positive than the blood titres (Sotelo 1988; Miller et al 1983; Rosas et al 1986) this has not been confirmed in this series. Presumably this is because of the system then in use at the Research Institute for Disease in a Tropical Environment of the South African Medical Reserarch Council, Durban (Pammenter et al 1987). Of interest, 6 of the CSF's which had positive titres of cysticercal antibodies were completely normal on routine examination whereas only 1 CSF documented with pleocytosis had negative antibody titres. In a recent report high cysticercus antibody levels in blood and CSF of patients correlated well with those who had active malignant disease i.e. multiple granulomata, hydrocephalus, vasculitis and cerebral infarction (Zini et al 1990).

The radiologic findings were indeed interesting. Only 2 of 17 patients in this group had evidence of extracranial calcification on radiology of the soft tissues. The paucity of this radiologic finding was also noted in the other clinical groupings of this series. Both of these patients were adults. The skull x-ray was found to be a useful examinaton as features of raised intracranial pressure such as sutural diastasis or erosion of the posterior clinoids were found in 28 of these patients. Two of these 28 skull X-rays also showed evidence of intracranial calcification. A further 3 of the patients' skull X-rays showed intra-cranial calcification as the only abnormality.



Radiology 13
Serial CT scans of a young child with an extensive right cerebral infarct and intractable epilepsy. These scans spanned a one year period and did not demonstrate the presence of multifocal neurocysticercosis which was found at hemispherectomy.
(see Figuras 3 and 4).

It was of interest to note that the CT scan appearances of 4 of the adult/adolescent group differed from those of the paediatric patients. These 4 CT scans, besides the features of oedema, demonstrated the presence of well demarcated enhancing cysts. However, none of the paediatric patients with cysticercal encephalitis, had well demarcated cystic lesions on their scans. These paediatric CT scans demonstrated ring enhancing or miliary enhancing lesions in addition to the extensive oedema. In fact 10 of the children's CT scans only showed extensive oedema initially and follow-up in 5 showed the development of ring enhancing lesions at 1-2 months in 4 and at 3-4 months in the 5th. This difference between the CT scan findings in children and adults with multi-focal disease has been commented on previously (Mitchell and Crawford 1988). However, in an earlier report from the same centre in Los Angeles 3 children less than 12 years of age are listed as having focal cystic lesions (Mitchell and Snodgrass 1985). In our experience with children, who present with multifocal or paucifocal cysticercal encephalitis, the parasitic cyst prior to the encephalitic phase has not yet evolved into a size large enough to be detected by CT scanning. It seems that it is only when the pericyst blood-brain barrier breakdown occurs with the resultant host inflammatory reaction that the parasite becomes detectable in the patches of oedema as a ring enhancing and later as a miliary enhancing lesion. Pathological correlation with MRI findings has suggested that the parasitic cysts which are viable with intact scoleces and cyst walls are too small to be detected by CT scanning or even by present MRI (Lotz et al 1988). Our experience with a 2 year old child confirms this finding. She presented with acute hemiplegia due to a large infarct in the territory of the right middle cerebral artery and later developed severe intractable epilepsy. Three CT scans done over a 12 month follow-up period failed to demonstrate the numerous cysticerci found in both the infarcted and non-infarcted hemispheres at right hemispherectomy which was done for the intractible epilepsy in this patient (Radiology 13) (Figures 3 and 4).

The CT scan finding of 'parenchymal' cystic lesions in children resembling those usually found in adults or less commonly in adolescence has been reported (Hernandez et al 1982a; Byrd et al 1982). However, it is not clear from either of these reports whether the few patients with cystic lesions were adolescents or were indeed pre-adolescent children. Although there are case reports

of symptomatic children with intra-ventricular cysts and we have treated one such child, this must be a very rare occurrence (Tasker et al 1979; Woody et al 1984). It would seem to be as rare for children under the age of 12 years to become symptomatic with viable chronic cysts involving the brain parenchyma. In an excellent paper correlating serial CT scan findings of the brain in patients with neurocysticercosis an attempt was made to document the natural history of parenchymal cerebral cysticercosis (Kramer et al 1989). Of interest these authors correlated the presence of visible non-enchancing cysts (chronic cysts) on CT scan with cysts containing viable invaginated larvae bathed in clear fluid as determined by pathological examination. This finding is at variance with that of a recent MRI correlative anatomo-pathological study where the enlarging cysts visible on MRI although consisting of viable capsules had either hyalinised or calcified scoleces on histological examination (Lotz et al 1988). It appears therefore that for cysts (cellulosae or racemosae) to enlarge the cyst capsule must continue to function in order to evade the hosts immune surveillance. However, the scoleces in these enlargings cysts are no longer viable being either hyalinised, calcified or even resorbed.

Many facets of the evolution of the parasitic larval phase in the host are not understood. What are the mechanisms that allow the parasite to evade the host defence system and consequently to enlarge for perhaps 30 years or more forming massive giant cysts? The finding of giant cysts has been reported previously (Berman et al 1981; Joubert and Van As 1990) (Radiology 5). Why at the opposite end of the spectrum do some larvae invoke a severe host inflammatory response probably within a year or two of infestation while the cystic lesions are still at a stage too small to be detected by present imaging methods?

Parasites are obviously able to evade the hosts immune system. Some of these mechanisms are known and others are presumed. Parasites such as trypanosomes and plasmodium are able to vary their surface antigens and thereby form a changing buffer coat around the organism thus preventing lysis of the parasite by host antibodies. Schistosomela can acquire immunity to the host by appropriating host molecules including histocompatibility antigens onto their surface layer and thus can mimic the antigenic structure of the host and remain undetected by the host's

immune surveillance system. Trypanosomes and Leishmania can learn to live with macrophages by not fusing with macrophage lysosomes, by evolving resistance to the specific selected host macrophage and by escaping from macrophage lysosomes and residing in the cytoplasm of the macrophage. Plasmodium, Leishmania and Trypanosomes are known to suppress the immune response directly by causing non-specific polyclonal response of B-lymphocytes and possibly a suppression of T-cells as well (Bloom 1979; Nussenzweig 1982). That some of the above mechanisms are available to the cysticercus are supported by the absence of demonstrable antibodies in many cases of neurocysticercosis (Rosas 1986; Flisser et al 1980). It has been suggested that the larvae may survive for long periods in the brain because the brain provides an environment which is relatively protected from the immune response (Miller 1983). This long survival of the cysticercus occurs mainly in the larger subarachnoid spaces as well as the ventricular system and appears to depend on the viability of the cyst wall and not the viability of the scolex which is either hyalinsed, calcified or destroyed and absent in these larger cellulosae or racemose cysts.

However, in some patients particularly in children with 'parenchymal' disease a massive inflammatory reaction is mounted against the parasitic cyst despite the parasites inheritant ability to evade immune detection. This reaction manifests with inflammatory cell infiltration and vasculitis in the pericystic tissue. An extensive oedema of the brain parenchyma and a meningitic response manifesting in the cerebro-spinal fluid as a pleocytosis results. It has been postulated that the eventual death of the larvae after about 2 years in the more confined spaces of the cortical sulci and parenchyma of the host's brain results in a leak of parasitic antigens and promotes a massive antibody response on the part of the host i.e. that the death of the parasite sparks off the inflammatory response. Destruction of the parasite by the use of parasitocidal drugs has been reported to cause a similar inflammatory response and a marked rise in the antibody titres of the host (Miller 1983).

An interesting report from Mexico draws attention to a number of autopsies performed in children with neurocysticercosis (Sanz 1987). The children who were presumed to be immunologically

normal demonstrated evidence of cysticercal encephalitis whereas children who died due to the effects of malignant disease or who were markedly immnosuppressed for other reasons evidenced viable cysticerci with no inflammatory response in their brains. These findings may lend support to the suggestion that the hosts immune system in some way is activated sufficiently to bring about the initial damage to the parasitic capsule thus destroying the parasites ability to evade immune detection (Rabiela-Cervantes et al 1982).

The cases with multifocal or diffuse cysticercal encephalitis in this series, had without exception, many parasitic lesions in the brain. An autopsy was done in one patient who had been treated with Praziquantel and who died of disseminated chicken pox due to prolonged steroid immune suppression. Examination of the brain showed that the many degenerated cysts with pericyst inflammatory cells, vasculitis and oedema were in the cortical mantle or related subarachnoid spaces of the deeper cortical sulci. Most reports in the literature correlate extensive or multifocal oedema with numerous parasitic lesions (Minguetti and Ferreira 1983; Mazer et al 1983; Handler and Mervis 1983; Rangel et al 1987; Hernandez and Garaizar 1982a&b). However, one report from India described patients with diffuse cerebral oedema related to single viable or non-viable parasitic cysts and suggested that some form of massive allergic response to the parasitic antigen was the cause of the fatal cerebral swelling (Srinivas et al 1980). Although, for their stated reasons, an associated viral encephalitis in an endemic cysticercotic region was felt to be unlikely, this probability cannot be excluded. Amongst the patients seen at Groote Schuur Hospital those children with focal degenerating parasites manifested only focal oedema and no cases as described in the above report were seen.

Some points of interest relating to these patients with extensive multifocal cysticercal encephalitis are unfortunately not available for discussion. Firstly, the history of pica was not specifically elicited and was recorded only in the occasional case report. Therefore, no comment can be made about the possible link between pica and an increased risk of extensive multifocal neurocysticercosis. Secondly, only very occasional stools from these patients were examined for the ova of Taenia solium so again no comment can be made about the possible risk of heavy

infestation in patients harbouring the adult worm. Reports documenting the presence of Taenia solium ova in the stools of patients with all forms of neurocysticercosis conclude that a minority of about 25% of the patients have the adult worm in their bowel (Loo and Braude 1982; Arseni and Samitca 1957; Dixon and Hargreaves 1944; Heinz and Klintworth 1965; Stepien 1962; Bia and Barry 1986). However, a report from Brazil noted that all but one of 19 patients with acute multifocal enhancing lesions and oedema on CT scan had the ova of Taenia solium in their stools (Minguetti and Ferreira 1983). This finding suggests that auto inoculation (i.e. anus to mouth or even possibly retrograde peristalsis) may be the cause of such extensive infestation.

PART IV

MULTIFOCAL CYSTICERCAL ENCEPHALITIS - FOLLOW-UP

INTRODUCTION

Follow-up of all 50 patients with multifocal cysticercal encephalitis was only possible for the first 4 weeks following on their presentation. Twenty one patients had been treated symptomatically and their case records were all reviewed retrospectively. Twenty nine patients had formed part of a prospective open therapeutic study using Praziquantel in addition to supportive therapy. However, beyond the first month comparison of the outcome of the 2 groups is impossible as the numbers, especially amongst the retrospective group, are too few for any valid conclusions. However, as the follow-up notes in some of the case reports were extensive and available the findings were considered worth reporting. A few personal observations regarding the outcome of the 2 groups will be made but it is important to note that no valid conclusions regarding the effect of Praziquantel on the outcome or 'natural history' of this form of neurocysticercosis can be reached.

METHODS

For this part of the study the outcome of these 50 patients with multifocal cysticercal encephalitis were reviewed where it was possible. Twenty-one (19 children, 2 adults) of the 50 patients were treated symptomatically only and did not receive a course of Praziquantel. These patients were all reviewed retrospectively. Twenty-nine patients (25 children, 4 adults) were treated with Praziquantel in addition to the symptomatic therapy. These patients formed part of a prospective open therapeutic study (Thomson 1988). Praziquantel which is a pyrazinoisoquinoline derivative provides the first truly broad spectrum antihelminthic agent (Mahmoud 1987).

In both groups the first priority in treatment had been the reduction by, medical means, of clinically significant raised intracranial pressure in 30 of these patients (13 from the retrospective group, 17 from the prospective group). Initially Dexamethasone (Decadron) was given

intravenously and then subsequently orally in a dose of 0.5 mg/kg/day in 8 hourly divided doses. Five of these patients with severely depressed levels of consciousness had required intravenous Mannitol in addition in order to effect a more rapid reduction in the raised intracranial pressure. A further 12 patients from the prospective group who had not required therapy for symptomatic raised intracranial pressure were placed onto Dexamethasone therapy 24-48 hours prior to commencing Praziquantel.

All in all 42 patients were treated with Dexamethasone for varying periods of time. Potassium supplements were given to all patients on steroid therapy. In the prospective study group, Dexamethasone was continued at a dosage of 0.5 mg/kg/day for the full two weeks of Praziquantel therapy, then reduced to 0.25 mg/kg/day for the subsequent 7 days before changing to Prednisone 1 mg/kg/day in divided doses. Prednisone was then gradually tapered and tailed off as soon as possible. The change to Prednisone was effected as the half-life of Dexamethasone is long and it may therefore be difficult to wean patients off Dexamethasone after therapy lasting more than a few days. Our previous experience with steroid therapy in children with multifocal cysticercal encephalitis had highlighted the difficulty of weaning some of these patients off the steroids (Thomson et al 1984).

Praziquantel was administered to 29 patients with multifocal cysticercal encephalitis as a single 14 day course at a dosage of 50 mg/kg/day given in three divided doses. Prior to commencing therapy all these patients had the following investigations done: CT scans, chest x-rays, intradermal Mantoux tests, full blood counts, erythrocyte sedimentation rates, serum chemistries, electroencephalograms and lumbar punctures when this procedure was considered safe. Where possible cysticercus antibody tests were performed on blood and cerebrospinal fluid. All these tests were repeated serially after about 1 month, 3 months, 6 months, 9 months and 1 year in all compliant cases.

In addition to Praziquantel, steroids and anti convulsant therapy, 9 patients received anti-tuberculous drugs because of strongly positive intradermal Mantoux tests. One patient was

treated with antifungal drugs because of probable cryptococcal meningitis and 2 patients received a course of antibiotics for a urinary tract infection in one and diarrhoeal disease in the other.

RESULTS

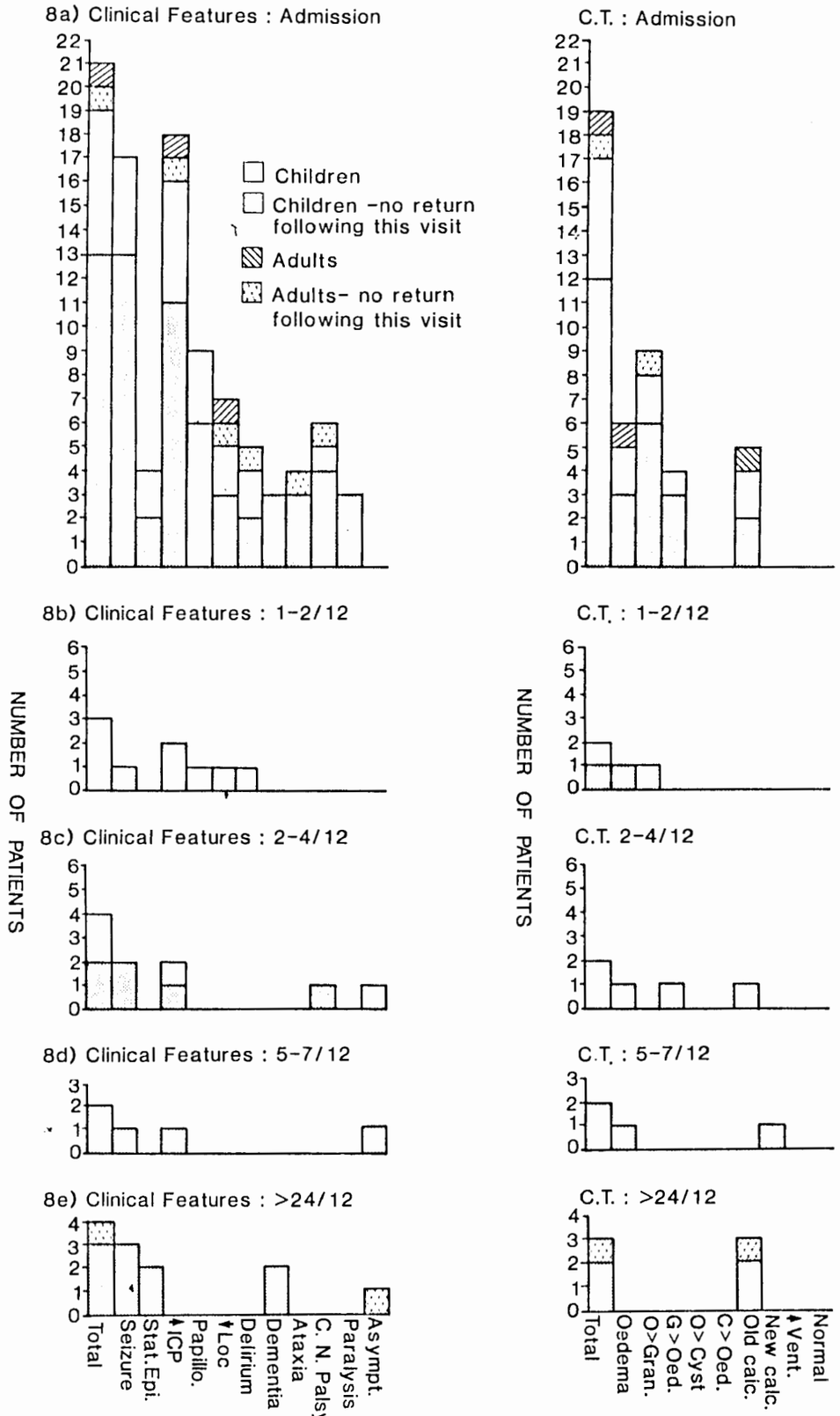
Steroid therapy

Forty two of the 50 patients were treated with steroids. Steroid therapy was discontinued within 8 weeks in 24 patients (10 of the restrospective group and 14 of the prospective group), within 16 weeks in 9 patients (1 retrospective group, 8 prospective group), within 24 weeks in 7 patients (2 retrospective group, 5 prospective group) and only after 24 weeks in 2 prospective group patients. However, one of these last 2 patients required placement of a lumbar peritoneal shunt before steroids could be withdrawn. All the patients on steroid treatment developed varying degrees of Cushingoid facies and truncal obesity but manifested no serious complications such as hypertension, diabetes mellitus or electrolyte abnormalities. However, one patient did develop uncontrollable infection, related to prolonged high dose steroid therapy given for his cerebral oedema prior to diagnosis and admission. On completion of his two week praziquantel course he developed an 'acute abdomen' and only after about 36 hours of illness did he develop the rash of varicella. Despite belated acyclovir therapy he died and at autopsy the findings were those of disseminated chicken pox lesions in addition to the many degenerating cerebral cysticerci.

Praziquantel therapy

In none of the 29 patients treated with Praziquantel were any toxic effects noted in haematologic, hepatic and renal function during or following on Praziquantel therapy. Likewise no abnormalities of glucose, calcium and phosphorus metabolism were noted. A few of the patients on concomitant tuberculous therapy developed mild elevation of hepatic enzymes but not severe enough to warrant withdrawal of the anti-tuberculous drugs. However, within the first 3 to 5 days of commencing Praziquantel therapy six patients developed a significant acute pyrexial illness with severe myalgia - arthralgia, general malaise and an exacerbation of headache,

GRAPH 8 : Clinical Features and C.T.; 21 Patients Symptomatic RX



vomiting and drowsiness. In two of these patients the associated ocular palsies were exacerabated. This illness resembled a Herxheimer reaction with clinically apparent increases in intracranial pressure. The addition of antipyretics and analgesics to the therapy partially improved the symptomatology. As the symptoms and signs of raised intracranial pressure stabilised the dose of Praziquantel was not reduced and other more active attempts to reduce intracranial pressure were not required. These symptoms all gradually improved over the subsequent week.

Clinical Picture and CT Scan Follow-up

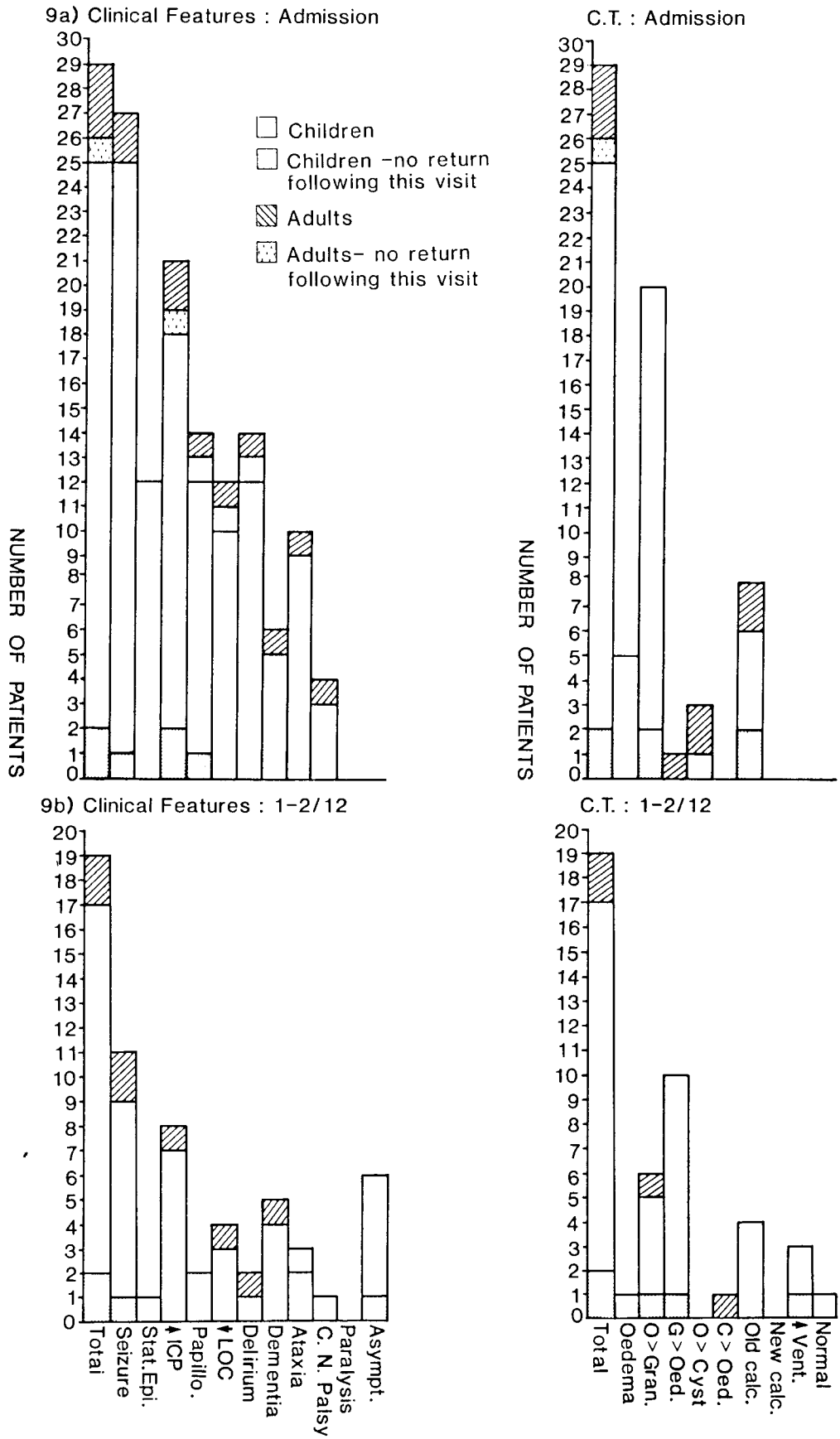
Retrospective Group

Of the 21 patients (19 children, 2 adults) who were treated symptomatically and did not receive a course of Praziquantel, only 7 (6 children, 1 adult) were followed after their initial presentation. Their subsequent course is shown in Graphs 8a-e where the clinical features and CT scan findings are depicted.

Early follow-up :- Fourteen patients did not return following discharge. Ten of these had cerebral oedema with features of raised intra-cranial pressure which were well controlled by corticosteroid therapy. They were well at discharge and were on treatment schedules of reducing steroid dosage. The steroid therapy was to be gradually withdrawn by the referring doctors.

Four children were followed between 1-4 months and 2 of these again at 5-7 months post admission. All 4 children had features of cerebral swelling on radiologic study (2 on ventriculography and 2 on CT). Three presented with clinical features of raised intra-cranial pressure and two of these had markedly decreased levels of consciousness. The fourth was admitted in status epilepticus without clinical evidence of raised intracranial pressure. Except for the latter the other 3 all demonstrated fluctuating signs and symptoms of raised intra-cranial pressure (related to attempts at steroid withdrawal) for a period of 3-4 months in 1 patient and for periods of 4-5 months and 5-6 months respectively in the other 2. CT scans done at monthly intervals in 1 of these patients showed varying degrees of cerebral oedema. Subsequent to 4 months 2 were discharged

GRAPH 9 : Clinical Features and C.T. 29 Praziquantel RX



well and subsequent to 5 and 6 months the other two were also discharged well. All of these 4 patients at the time of discharge were no longer on steroid therapy.

Late follow-up:- Three of these early follow-up children subsequently failed to return but 1 who had presented prior to the availability of CT scanning at Groote Schuur Hospital returned 1 year later with problems of epilepsy and dementia. CT scan done at this visit demonstrated multiple 'granulomata'. He was seen subsequently at 2 years, 3 years and 4 years after his original admission. His clinical picture was that of a static encephalopathy with mental retardation but easy to control seizures. His sequential CT scans were all identical demonstrating multiple calcific foci.

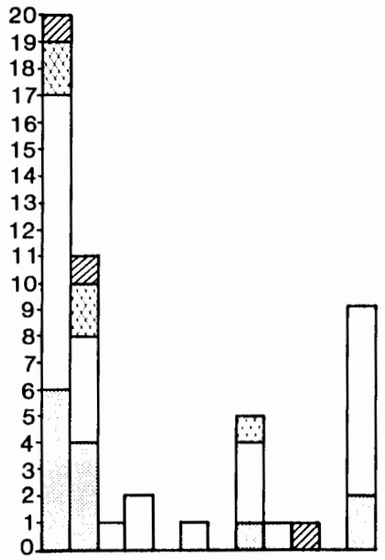
Two further children and one adult who all had clinical features of raised intra-cranial pressure and cerebral oedema on CT scan initially but were well on discharge were only seen again at 2 years, 4 years and 7 years respectively. The 2 children returned with a history of epilepsy and status epilepticus whereas the adult returned because of an intercurrent illness and was neurologically asymptomatic. All 3 demonstrated multiple calcific foci on CT scan.

So the 4 patients seen at follow-up after some years all had multiple calcific foci on CT scan although the clinical picture was varied. One with the longest follow-up was asymptomatic, 1 was epileptic with frequent seizures, 2 were demented (1 with easy to control epilepsy and 1 with frequent seizures).

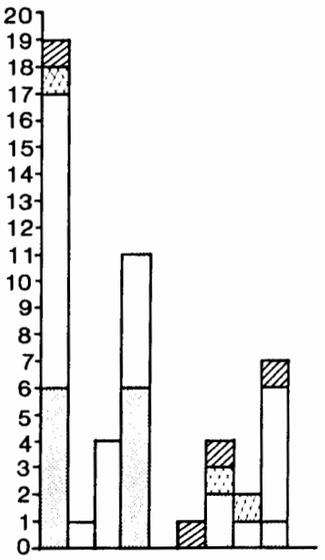
Prospective Group

Of the 29 patients (25 children, 4 adults), who were treated with Praziquantel in addition to symptomatic therapy, 18 children and 3 adults had symptoms and signs of raised intracranial pressure. However, all 29 patients had generalised or multifocal oedema on CT scan with, in addition, multiple 'granulomata' in 20 children and 1 adult and multiple enhancing cysts in the remaining 3 adults. Their subsequent course is shown in Graphs 9a-f where the clinical features and CT scan findings are depicted.

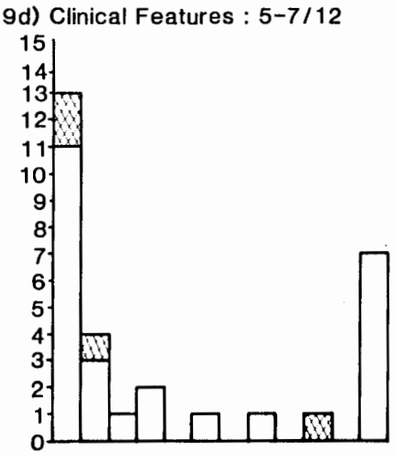
9c) Clinical Features : 2-4/12



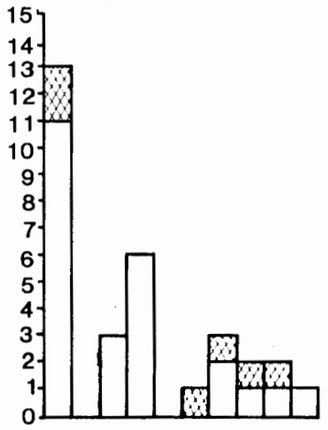
C.T. 2-4/12



9d) Clinical Features : 5-7/12

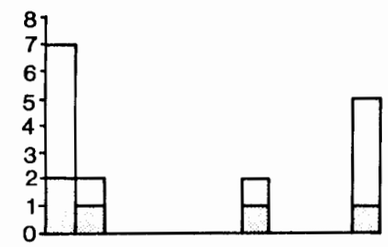


C.T. : 5-7/12



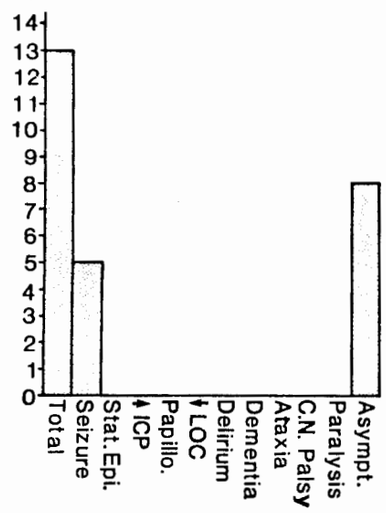
NUMBER OF PATIENTS

9e) Clinical Features : 8-10/12

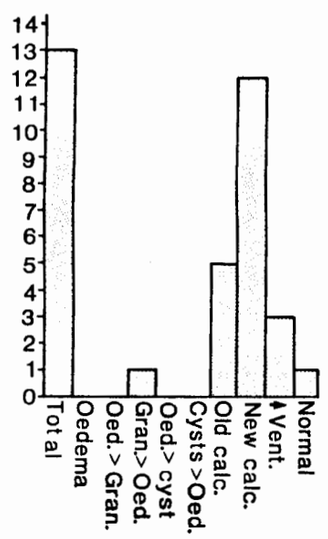


C.T. : 8-10/12

9f) Clinical Features : 12-16/12



C.T. : 12-16/12



Early follow-up:- At the 1-2 month follow-up 9 children and 1 adult had clinically improved with resolution of the signs of raised intra-cranial pressure and marked decrease in the amount of cerebral oedema on CT scanning. Two children and 1 adult had not returned for follow-up but had been clinically well on discharge.

By the 5-7 month follow-up period the problems of fluctuating raised intra-cranial pressure and fluctuating cerebral oedema on CT scan (in relation to attempts at steroid withdrawal) had been resolved in 5 of the remaining children. However, two young girls were still plagued by steroid dependent cerebral oedema causing significant morbidity six months after admission and initiation of therapy. The problem was of such magnitude in one of these girls that a lumbar peritoneal shunt was placed before steroids could gradually be withdrawn.

Late follow-up:- Two children were followed until 10 months post admission. One was demented and epileptic with a CT scan demonstrating multiple enhancing granulomas plus multiple calcific foci. The other was asymptomatic and had a normal CT scan. At the 12-16 month follow-up 13 children were seen. Eight were asymptomatic and 5 had epilepsy. Of the 13 CT scans 11 showed multiple intra-cranial calcific foci (3 of these had in addition ventricular dilatation), 1 showed enhancing granulomas and calcific foci and 1 was normal.

EEG and Epilepsy Follow-up:

Serial follow-up EEG's were obtained in 4 children from the retrospective group of 21 patients and in 19 children and 2 adults from the prospective group of 29 patients.

Retrospective Group

The 4 from the retrospective group had diffusely slow EEG's on admission. One of these EEG's had returned to normal by 5 months and the others remained diffusely abnormal at 4 months, 2 years and 4 years when these patients were respectively last seen.

Prospective Group

The 21 patients from the prospective group were found to have diffusely slow EEG's in 18 and

normal EEG's in 3 patients.

Of the patients with diffusely abnormal EEG's 8 had reverted to normal by 4-6/12 but 3 were again abnormal on longer follow-up (2 diffuse slow, 1 focal abnormality). Ten remained persistently abnormal with diffuse slowing and 3 of these developed in addition persistent focal abnormalities.

The 3 patients with initial normal EEG's had all developed diffuse slowing at 3/12 follow-up.

At 12-16 months, 11 of the patients who were still attending follow-up had EEG's. Five of the EEG's were normal, 4 showed diffuse slowing and 2 showed focal abnormalities.

Initially forty-two patients from both groups were treated with anticonvulsants. The initial therapy was Phenobarbitone in 35 patients (all almost exclusively childen), Phenytoin in 4 patients (all adults) and Carbamazepine in 3 children. Due to inadequate seizure control in 13 patients Phenytoin was added to the primary therapy in 6 of them, Carbamazepine in 4 of them, Clonazepam in 2 and Primidone in 1. In most of the children the seizures were effectively controlled by the initial drug therapy and by the measures employed to reduce intra-cranial pressure.

At the long-term follow-up of more than 12 months 17 patients were reviewed. These 17 patients consisted of 16 children and 1 adult with 13 coming from the prospective group while 4 came from the retrospective group. Seven (5 prospective and 2 retrospective) still complained of recurrent seizures despite therapy. Their compliance as regards drug therapy was difficult to assess. Of the 10 patients who were now seizure free 4 had not been taking anti-convulsant therapy for some time while the other 6 were well controlled on therapy.

CSF follow-up:

Retrospective Group

The CSF's from 19 of the retrospective group of patients were examined during their initial admission. Five and 14 were found to be normal and abnormal respectively.

Only 3 patients, all from the abnormal group had repeat CSF studies done. Two of these CSF's were still found to be abnormal, in one case at the 1-2 months follow-up and in the other at the 5-7 month follow-up. CSF in the 3rd patient had reverted to normal by the 5-7 months follow-up.

Prospective Group

Twenty six patients from the prospective group had CSF studies done during their initial admission.

Ten of these patients were found to have normal CSF's. From amongst these 10 patients 2 did not return after initial discharge. One patient at 5-7 months follow-up still had a normal CSF but then subsequently failed to return as did 2 patients with normal CSF's following the 8-10 months follow-up and 4 patients with normal CSF's following the 12-16 months follow-up. Only one patient demonstrated conversion of the CSF to abnormal both at the 1-2 months and 2-4 months follow-ups.

Sixteen patients had abnormal CSF findings on initial admission. Four of these patients failed to return. Amongst the others the CSF's remained persistently abnormal in 9 until they absconded from follow-up which was after the 1-2 months visit in 3 patients, after the 2-4 months visit in 1 patient, after the 8-10 months visit in 2 patients and after the 12-16 months visit in 3 patients. The CSF findings in the other 3 patients fluctuated from normal to abnormal as demonstrated in Table 6.

TABLE 7: CSF FINDINGS - FOLLOW UP 3 PATIENTS

	ADMISSION	1-2/12	2-4/12	5-7/12	8-10/12	12-16/12
Patient 1	Abnormal	Normal	Abnormal	-	-	-
Patient 2	Abnormal	Normal	Abnormal	Abnormal	-	Abnormal
Patient 3	Abnormal	Abnormal	Abnormal	Abnormal	-	Normal

TABLE 8: SEQUENTIAL BLOOD ANTIBODY TITRES IN 12 CHILDREN TREATED WITH PRAZIQUANTEL

	PATIENTS											
	1	2	3	4	5	6	7	8	9	10	11	12
0	0	+++	+++	0	+++	+++	+++	++	0	++	+	-
1/12	0	+++	0	0	0	0	++	+	0	0	0	-
3/12	+++	0	+++	+++	+++	0	+	0	+	++	+++	-
6/12	0	0	+++	0	0	+++	0	+	++	0	0	0
9/12	0	0	0	+++	0	0	0	0	-	0	0	0
12/12	+++	+++	0	0	+++	-	0	0	0	+++	0	++
	5 titres 1 S Q (In Status Quo)					4 titres ↓				3 titres ↑		

TABLE 9: SEQUENTIAL CSF ANTIBODY TITRES IN 11 CHILDREN TREATED WITH PRAZIQUANTEL

	PATIENTS										
	1	2	3	4	5	6	7	8	9	10	11
0	+++	+++	++	0	++	+++	+++	0	++	+++	-
1/12	+++	0	0	+	0		0	0	0	0	-
3/12	0	+++	0	++	+++	+	+++	+++	0	0	0
6/12	0	0	+++	0	0	-	++	0	0	0	-
9/12	0	0	0	0	0	0	0	++	0	0	0
12/12	+++	0	+++	0	0	0	0	0	-	-	-
	2 titres 1 SQ		3 titres ↑			5 titres ↓					1 titre -ve 1 SQ

TABLE 10: SEQUENTIAL BLOOD ANTIBODY TITRES IN 2 CHILDREN NOT TREATED WITH PRAZIQUANTEL

PATIENTS

1			2		
0	=	+++	0	=	+++
1/12	=	0	1/12	=	0
3/12	=	0	3/12	=	0
6/12	=	+	6/12	=	0
12/12	=		12/2	=	+++

CSF Eosinophilia follow-up

Prospective Group

Special staining for eosinophils was only done on the CSF's of 11 patients prior to treatment with Praziquantel.

Four of these CSF's stained positive for eosinophils. Only 1 of these 'positive' patients had further CSF's examined and these were repeatedly positive for eosinophils at 1-2 months, 5-7 months and 8-10 months.

Two patients whose CSF's were initially negative for eosinophils became positive subsequent to Praziquantel therapy at 2-4 months in 1 patient and at 5-7 months in the other patient. In the latter patient the CSF eosinophilia had cleared by the 12-16 month follow-up.

In 5 patients the CSF's were only examined for eosinophils after Praziquantel therapy had been commenced.

In only one of these CSFs was eosinophils found. This cerebrospinal fluid no longer demonstrated the presence of eosinophils at the 8-10 month visit.

Retrospective Group

Amongst the patients not treated with Praziquantel 2 of the 6 CSF's examined at the initial presentation were found to contain eosinophils. One of these reexamined at the 1-2 month follow-up was still positive. Two further patients whose CSF's were examined after the initial presentation were not found to contain eosinophils.

Follow-up of Immunological tests:

Table 8, 9 and 10 delineate the sequential titres of antibody to cysticercus antigen in the blood of 12 children treated with Praziquantel, in the CSF of 11 children treated with Praziquantel and in the blood of 2 children not treated with Praziquantel. Although these sequential titres are by no means complete no definite pattern could be determined following treatment with Praziquantel. Some patients showed no change in antibody titres, others showed an increase in the titres and yet others showed a decrease in the titres. Similarly one of the patients not treated with Praziquantel showed a decrease in the titres at follow-up and the other showed no change in the

TABLE 11: AGE/SEX DISTRIBUTION MULTIFOCAL CYSTICERCAL ENCEPHALITIS RETROSPECTIVE AND PROSPECTIVE GROUPS

	NO OF PATIENTS	
AGE DISTRIBUTION	RETROSPECTIVE	PROSPECTIVE
0-3 years	2	3
4-6 years	8	12
7-9 years	5	8
10-12 years	4	2
13-15 years	0	1
16-20 years	1	1
20-25 years	0	1
25-30 years	1	1
	14 male 7 female	10 male 19 female

titres at follow-up.

Summary of Clinical Follow-up

In summary 2 patients died during their admission. One adult from the retrospective group died shortly after admisison from cryptococcal meningitis. No autopsy was done. The other a child from the prospective group died from disseminated chicken pox following on prolonged high dose steroid therapy. Forty one patients were assessed as being clinically improved when last seen - 15 (11 retrospective, 4 prospective) at 0-2 months, 12 (3 retrospective, 9 prospective) at 3-6 months, 1 prospective at 6-9 months and 13 (2 retrospective, 11 prospective) at more than 1 year. It is important to note that the number of clinically improved patients recorded at the above intervals is related to the time of discharge and not to the time of initial clinical improvement. Five patients were assessed as being clinically in status quo when last seen - 2 retrospective at 0-2 months, 1 prospective at 6-9 months and 2 prospective at more than 1 year. Two patients, both retrospective were assessed as having deteriorated clincally at long-term follow-up of more than 2 years.

DISCUSSION

This study is partly a retrospective one and although the two groups of patients i.e. Praziquantel 'treated' (prospective) and 'untreated' (retrospective) are with the exception of the sex distribution matched in regards to age (Table 11), race, clinical presentations and radiologic findings, the follow-up number especially of the retrospective cases is too small for adequate comparison. Indeed the high drop-out rate of the patients from the prospective open therapeutic study exposes the difficulty experienced in conducting long-term follow-up drug trials in developing countries.

Follow-up assessment at 1-4 months of the retrospective patients consisted of only 4 as compared to the 26 prospective patients. As all retrospective patients were clinically improved at discharge it is possible that only those that became steroid dependent returned for early follow-up. Three of these retrospective patients manifested a fluctuating encephalopathy which was related to variations in steroid dosage as attempts were made to withdraw this therapy. In 1 case the fluctuating encephalopathy continued for as long as 6/12 post initial admission.

Amongst the prospective patients, most of those with the clinical features of raised intra-cranial pressure had resolved their clinical problems by 1-2 months but 5 remained with fluctuating encephalopathy and cerebral oedema on CT scan for a longer period. Three of these patients resolved between 2-4 months while another 2 only resolved between 5-7 months. Of note one of the latter 2 patients had not resolved adequately and was judged to require a lumbar-peritoneal shunt at 6/12 because of recurrent severe symptomatic cerebral oedema. Of interest the 3 most ill cases in the prospective group were females whereas in the retrospective group the two most ill cases where males. This finding does not confirm the observations of others that the most marked inflammatory reactions invoked by the parenchymal parasite occur in females (Rangel et al 1987; Del Brutto et al 1988).

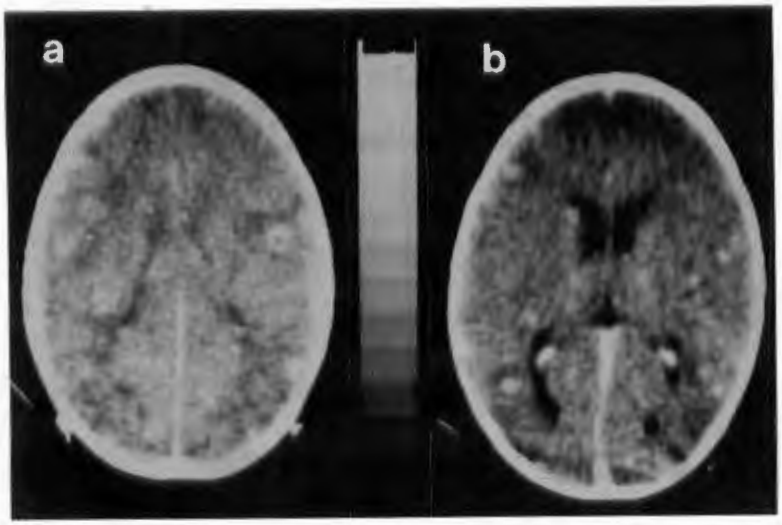
Although early deaths among the 'rapid responders' of the retrospective group cannot be excluded, it might be reasonable to presume that the majority of these patients followed the same course as those who responded more rapidly amongst the prospective group. The marked variation in the time to resolution of symptoms and in particular the fluctuation in the degree of the cerebral oedema on CT scan of steroid treated patients with multifocal cysticercal encephalitis has been commented on previously (Rangel et al 1987; Carbajal et al 1983). It seems therefore that in the early follow-up of patients with serve multifocal cysticercal encephalitis the addition of Praziquantel to the therapy does not appear to lessen the severity or the duration of the acute encephalopathic illness in these patients. In fact in some patients the addition of Praziquantel exacerbated their symptoms transiently despite 'adequate' steroid cover. This possible exacerbation of symptoms would be expected and has often been previously documented (Wadia et al 1988; Sotelo 1987).

In cases of multifocal cysticercal encephalitis with symptomatic raised intra-cranial pressure the mainstay of therapy is cortisone. Therefore there can be little argument about prophylactic steriod use when Praziquantel therapy is contemplated in these patients even if they do not have overt raised intra-cranial pressure. However, the use of prophylactic steroids prior to commencing and during Praziquantel therapy in neurocysticercosis is a controversial issue. Some authorities maintain that it is mandatory to use steroids in conjunction with Praziquantel therapy

as the dangers of increased inflammation and cerebral oedema are significant (De Ghetaldi et al 1983; De Ghetaldi et al 1984; Ciferri 1984). Others have shown, that it is not necessary to use prophylactic steroids in all patients with neurocysticercosis on Praziquantel therapy and recommend that steroids be used only if the patients develop significant symptomatic cerebral oedema (Sotelo 1987). Also the use of steroids in conjunction with Praziquantel has been shown to lower the serum levels of the latter (Vasquez et al 1987). Whether this impairs the therapeutic efficacy of Praziquantel is not known but in the light of the following report the loss of efficacy appears to be doubtful. A report on 2 patients treated with Praziquantel and Prednisone daily for 3 weeks demonstrated that Praziquantel still penetrated rapidly into the CSF despite the concomitant use of steroids. It entered the parasite more slowly but still more rapidly than the plasma half-life of the drug (Overbosch et al 1987).

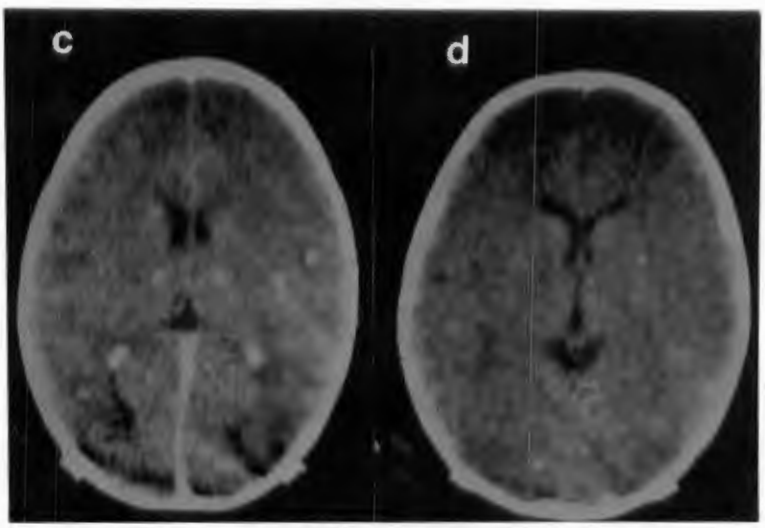
When comparing the late follow-up of retrospective and prospective patients there is the same problem as mentioned above. Only 4 of the retrospective patients were followed for 2 or more years post-admission. All 4 had similar CT scans findings i.e. multiple calcific foci, but they had variable clinical outcomes. One patient was well and asymptomatic while 3 were epileptic, two of whom had bouts of status epilepticus and 2 of whom were demented. Thirteen patients of the prospective group were followed for 12-16 months. Eleven showed the presence of multiple calcific foci on CT scan while 1 in addition showed occasional enhancing 'granulomata' and one had a normal CT scan. Eight of these patients were reported to be asymptomatic while 5 still complained of recurrent seizures. As the length of follow-up was not the same and the numbers of retrospective patients too small it is impossible to arrive at any valid conclusions. However, it does not appear that there was any great difference in the long-term outcome of the two groups especially if it is noted that one prospective patient who failed follow-up after 10 months was both demented and epileptic. No specific pattern of change following Praziquantel therapy was definable in the serial CSF findings and in the serial antibody titres in both blood and CSF. It is difficult to draw any conclusions from the serial electroencephalographic findings except to note

Radiology 14
CT scans of a child with multifocal cysticercal encephalitis



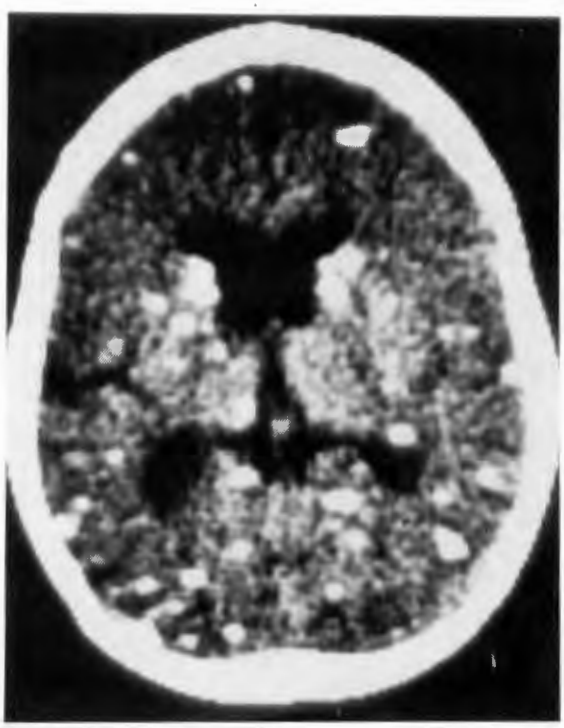
a. CT scan (with contrast) demonstrates multi-focal oedema with ring enhancing lesions at initial presentation of patient

b. CT scan (with contrast) demonstrates multi-focal homogeneously enhancing lesions 3 months after Praziquantel therapy



c. CT scan (with contrast) demonstrates marked reduction in the number of enhancing granulomata 6 months after Praziquantel treatment

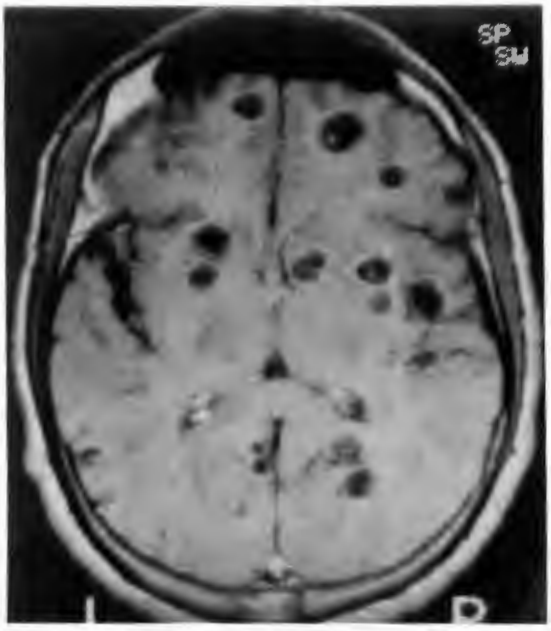
d. CT scan (with contrast) is now almost normal with very occasional granulomata still present 12 months after Praziquantel treatment



Radiology 15
CT scan demonstrates atrophy and multiple calcific foci. This was the end result of multifocal cysticercal encephalitis 1 year after initial admission (refer earlier CT scans of same patient Radiology 10 and 11).

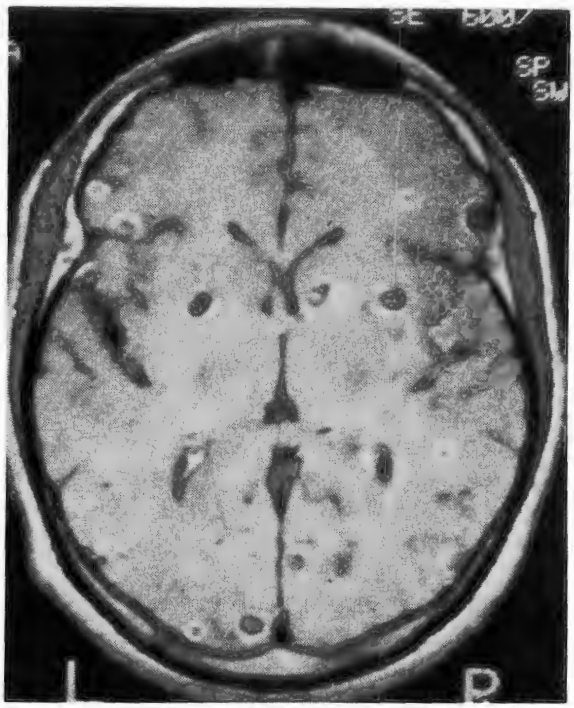
that the presence and degree of bilateral slowing was related to the presence of diffuse cerebral oedema and encephalopathy. The EEG abnormality improved with Decadron therapy but in the prospective group was occasionally exacerbated by Praziquantel therapy in these patients. The EEG findings at the 12-16 months follow-up in the prospective group show no specific trend.
The initial clinical response in both groups was due to the reduction of cerebral inflammatory oedema with the use of steroids. The clinical course and outcome of the few comparable cases in both groups was very similar as were the CT changes which have been described (Handler and Mervis 1983). Initial multifocal oedema with or without ring enhancing lesions evolves at a varying speed over a period of 2-7 months into enhancing miliary lesions with decreasing surrounding oedema. These enhancing lesions gradually decrease in intensity and may disappear by 10-12 months or more usually be gradually replaced by radiologically detectable calficic lesions from 12 months onwards (Radiology 14 a-d and Radiology 15).

The lack of demonstrable therapeutic effect is probably to be expected in this form of the disease. In our experience and in the experience of others this is most unlike the findings in some adult patients with other forms of the disease. These particular adults present with non-enhancing parenchymal cysts on MRI or CT scan and when treated with Praziquantel rapidly develop a pericystic inflammatory-allergic response which manifests on MRI or CT scan as contrast rim enhancement of the cysts (Radiology 16 a-c). These enhancing cysts then depending on their size disappear at variable rates and might or might not be replaced by calcific foci (Vascoucelos et al 1987; Robles et al 1987; Sotelo et al 1984; Sotelo et al 1985; Joubert and Van As 1990). The parasitocidal effect of Praziquantel has been well shown in a number of different parasitic diseases including neurocysticercosis and has firmly established Praziquantel as the first truly broad spectrum anti--parasitic drug (Mahmoud 1987). It should be noted however that spontaneous evolution and healing of 'parenchymal' parasitic cysts may occur and has been documented (Miller 1983b). It has also become clear from our experience and from that of others that the cysts in the ventricles and to a lesser extent those in the larger subarachnoid spaces are not usually damaged by Praziquantel and persist despite repeated courses of the drug

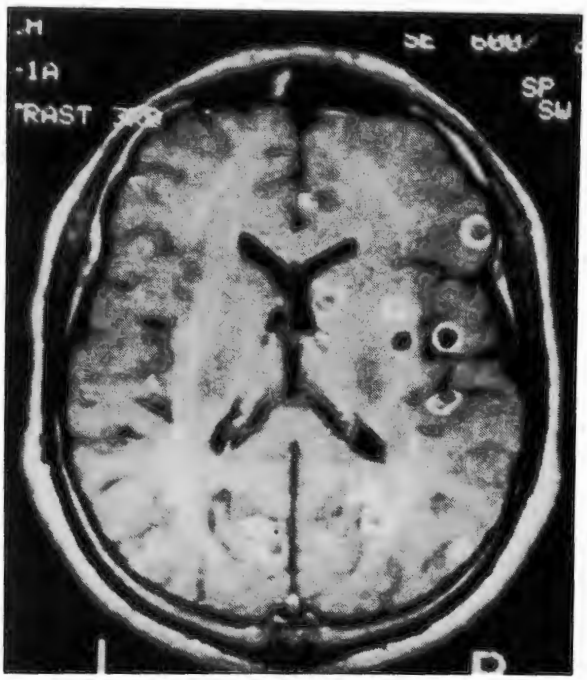


Radiology 16
MRI of an adult patient with parenchymal cysts

a. MRI (with gadolinium) prior to Praziquantel therapy demonstrating minimal or non-enchancement of the cysts.



b. MRI (with gadolinium) 3 days after commencing Praziquantel therapy. Many cysts now demonstrating marked rim enhancement



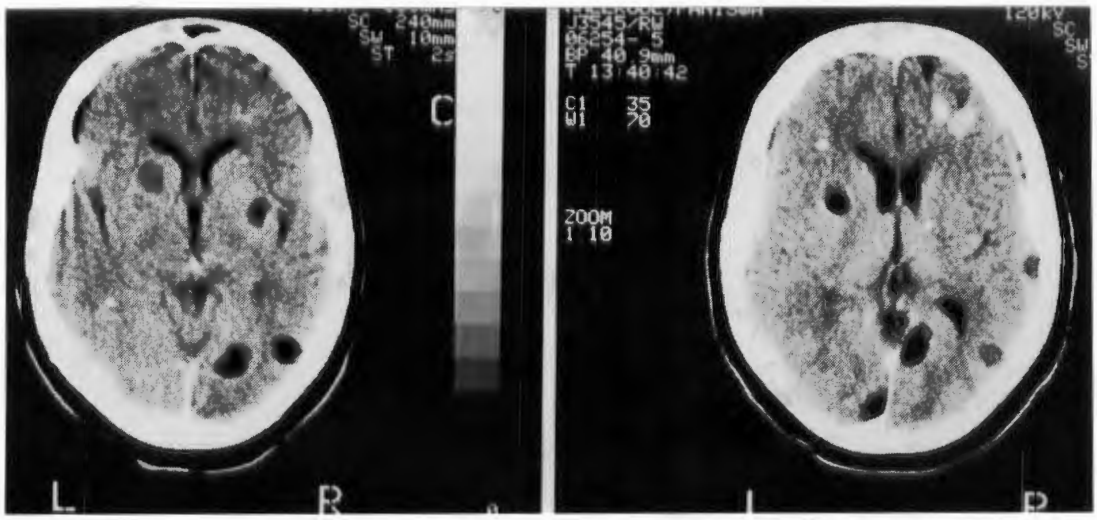
c. MRI (with gadolinium) 7 days after commencing Praziquantel therapy demonstrates further increase of rim enhancement.

(Sotelo 1988; Sotelo and Del Brutto 1987, Joubert 1990).

In the young patients presenting with multifocal cysticercal encephalitis, the triggering factors responsible for the host's inflammatory response are already operative. Therefore it has been suggested that the use of Praziquantel in these patients is perhaps rendered unnecessary or even dangerous. This latter suggestion is leant credence by a report from India of a small series of patients with severe extensive disseminated cysticercosis. These very ill patients had serious even fatal reactions due to 'massive cyst breakdown' following on Praziquantel therapy despite steroid cover (Wadia et al 1988). A report from Hong Kong also highlights the possible danger of Praziquantel therapy in these heavily infested patients. A patient with extensive neural parasitic cysts developed cerebral infarction following on Praziquantel therapy, again despite steroid cover (Woo et al 1988). This however has not been our experience. The use of high dose steroid cover has apparently successfully suppressed the more serious complications caused by the extensive inflammatory response in our patients whether it was spontaneous or Praziquantel induced.

The suggestion that the use of Praziquantel is unnecessary in cases of focal or multifocal cysticercal encephalitis is supported by the experience gained in California. It was, however, pointed out that their patients were not as ill or as extensively infected as those from the Third World regions (Mitchell and Crawford 1988; Goldberg 1984). In this present series the small numbers of patients with multifocal cysticercal encephalitis who were not treated with Praziquantel and who were followed for long enough seemed to have the same clinical and radiological outcome as those followed from the Praziquantel group. The outcome of both of these groups is perhaps comparable to the quoted experience of the few similar though less ill patients who were followed in California (Mitchell and Crawford 1988).

The use of Praziquantel for the treatment of 'intraparenchymal cysticercosis' has also been queried following on the experience gained by some investigators in Natal, South Africa. In these

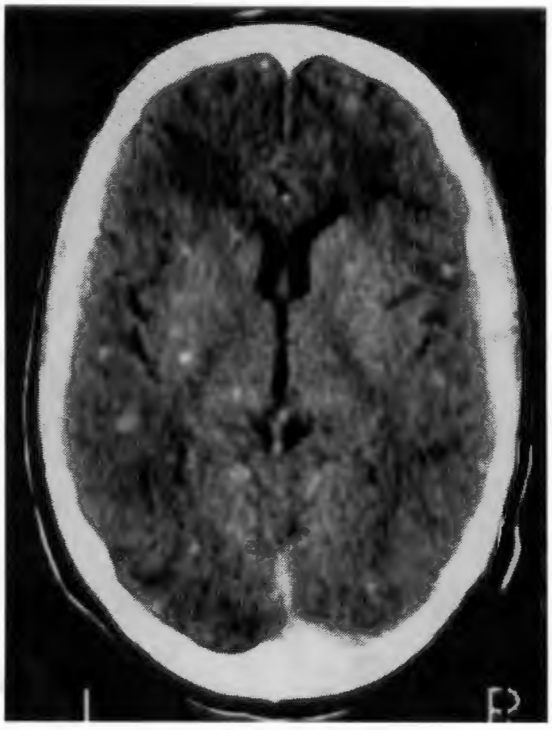


Radiology 17

CT scans (with contrast). Different views of the same patient demonstrating the presence of non-enhancing cysts, enhancing cysts, occasional granulomata and calcific foci

authors experience this form of the disease is usually self-limited (Moodley and Moosa 1989). However, this is strongly at variance with the opinion based on the experience of others from Natal (Van Dellen and McKeown 1988). It must be reemphasised that it is important to differentiate between patients with CT findings of non-enhancing parenchymal cysts and patients with CT findings of cysticercal encephalitis (Mitchell and Crawford 1988). The former are found in adult patients and occassionally in adolescents and not in children in our experience. These cysts may persist for many years growing to large sizes with possible space demanding effects. With the onset of spontaneous inflammation in these cysts the risk of increasing mass effect and of serious complications developing prior to resolution is a very real one. These cysts are however very sensitive to destruction by Praziquantel, with a rapid onset of the inflammatory response following on initiation of therapy. Thus if the 'natural history' of cyst resolution can be hastened while under medical surveillance presumably the risk of complications developing prior to that resolution will be much reduced. Therefore, their seems to be a good reason for the use of Praziquantal in this 'parenchymal' cystic form of the disease. However, the presence of cysticercal encephalitis with either enhancing cysts or with enhancing 'granulomata' indicates that the parasites are already damaged and therefore do not require Praziquantel therapy to hasten their destruction and resolution.

Some authorities however still recommend Praziquantel therapy for patients with multifocal cysticercal encephalitis (Vascoucelos et al 1987; Sotelo and Del Bruto 1987). In support of this recommendation a number of observations are worth noting. Firstly, at any one time some patients are infested with parasites at markedly different stages of their life cycle. On the CT scans of some children coexistence of patches of oedema, 'granulomata' and calcific foci have been observed. In adolescents and adult patients some CT scans have shown the coexistence of non-enhancing cysts, enhancing cysts, granulomata with oedema and calcific foci (Radiology 17). These CT scan findings suggest that either the patient has had a number of episodes of exposure to the parasite or that if only a single exposure occurred, not all the cysts mature at the same rate and become vulnerable to the hosts' defences at the same time. Secondly, in some of these patients with multifocal cysticercal encephalitis addition of Praziquantel to the therapeutic

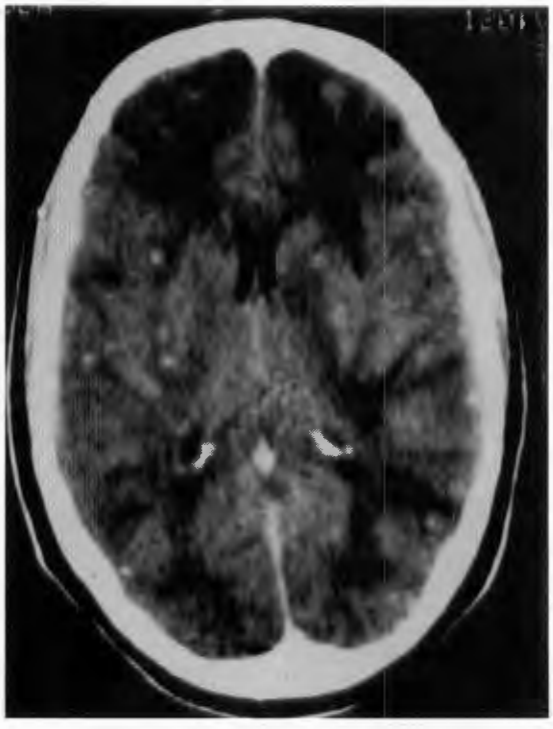


Radiology 18

CT scans (with contrast) of the same patient:

a. demonstrating the presence of enhancing granulomata, with minimal oedema prior to Praziquantel therapy. Occasional frontal cysts present

b. Demonstrating increased numbers of granulomata with marked increase of white matter oedema following on Praziquantel therapy. Note enhancement of left frontal cyst



programme resulted in a severe exacerbation of the symptoms and signs suggesting that there was an increase in cyst destruction and in the amount of cysticercal antigen being released following the cysticidal effects of the Praziquantel (Radiology 18). Thus it appears that even in these patients, with the development of marked spontaneous inflammatory reactions during the natural course of events, not all the cysticerci become vulnerable at the same time. Thirdly, a few of these patients who gave a history of prolonged or recurrent bouts of encephalopathy had associated prolonged status epilepticus and survived with residual cognitive dysfunction as a result of their hypoxic-ischaemic damage. Hopefully the complication of prolonged status epilepticus could be avoided if the patients were under medical supervision at the time of cyst destruction and encephalopathy.

Although there is no conclusive evidence that Praziquantel is effective or even necessary in patients with multifocal cysticercal encephalitis we have continued to treat such patients with Praziquantel despite the unresolved controversies. It is therefore suggested, that even in the presence of encephalitis, 'parenchymal' cysticerci be treated by Praziquantel under controlled conditions in hospital (Thomson 1990). This may ensure that the parasites may all be destroyed at the same time and thus perhaps the occasional spontaneous development of severe sequaelae be avoided or at least treated appropriately in the hospital situation. Of note those of our multifocal encephalitic patients with obvious severe dementia had had episodes of encephalopathy with status epilepticus prior to admission and therapy.

PART V

CONCLUSIONS

1. The majority of the patients in this study were Africans. With few exceptions they originated from amongst the Xhosa speaking people of the eastern regions of the Cape Province. This high incidence of neurocysticercosis amongst the Xhosa people has been noted previously (Campbell and Farrell 1987). The patients came from socio-economically deprived rural communities. The practice of free range pig farming associated with the lack of sanitation and poor education amongst these people renders their homelands one of the largest endemic cysticercal regions in South Africa. For the foreseeable future eradication of the disease by preventative measures such as education, improved sanitation and improved farming methods is unlikely to be attained rapidly in the present socio-economic climate.

2. Amongst these symptomatic patients with neurocysticercosis epilepsy was by far the commonest presenting symptom. This has frequently been the finding in other series (Subianto et al 1978; Arseni and Cristesau 1972; Powell et al 1966; MacArthur 1934; Bittencourt et al 1988; Campbell and Farrell 1987; Naidoo et al 1987). Seizures as an isolated neurological problem occurred as commonly amongst the children as amongst the adults, however, seizures plus other neurological complications were much more frequently found amongst the children. Therefore, the following axiom applies, that any patient from an endemic area who presents with a neurological problem in particular epilepsy should be regarded as having neurocysticercosis until proven otherwise.

3. The next most common neurological manifestation of neurocysticercosis in these patients was that of raised intra-cranial pressure. A large number of the patients were children and 40.6% of the children presented with features of raised intra-cranial pressure either clinically or radiologically. Of these 88% were found to have multifocal cysticercal

encephalitis whereas only 12% were found to have hydrocephalus. These findings are in direct contrast to the findings amongst the adult patients with raised intra-cranial pressure. These adults comprised 31% of the total adult group and whereas 73.3% presented with hydrocephalus only 16.6% had multifocal encephalitis and 11.1% had focal cystic space demanding lesions. This marked difference in the pathology of intra-cranial hypertension due to neurocysticercosis in adults and children has been documented previously (Hernandez and Garaizar 1982a).

4. In our experience multifocal cysticercal encephalitis is a very serious illness and gives rise to significant morbidity. Although none of these patients died due to the effects of the disease case fatalities are not infrequent (Rangel et al 1987). The raised intra-cranial pressure produced by the disease may be critical and give rise to transtentorial herniation which presumably because of the aggressive medical therapy did not end fatally in these patients . The added complication of status epilepticus in many of these patients increases the already dangerously raised intra-cranial pressure and may produce further anoxic-ischaemic damage to the brain with mental retardation as a result.

5. Most of these patients with multifocal cysticercal encephalitis require admission to hospital for treatment of their significant intra-cranial pressure problems. Steroid therapy is quite dramatic in its ability to reduce inflammation and cerebral oedema in these patients with rapid improvement in their symptomatology. A few patients with early transtentorial herniation had to be given Mannitol as well. Although there is an initial good response to steroid therapy in these patients a few of them developed a prolonged degree of steroid dependence.

6. In our patients with raised intra-cranial pressure due to cysticercal encephalitis the CT scan demonstrated the presence of many parasitic lesions. No patients with diffuse cerebral oedema on CT scan were found to have only single or infrequent parasitic lesions. Therefore, to some extent the severity of the cerebral oedema depends on the

number of the infesting parasites. Why in some patients the parasite loses its ability to evade the hosts immune system and thus invokes a massive inflammatory response in the host is largely unknown. However, this presumably depends to some extent on the competence of the hosts immune system. We have not found that females are more likely than males to develop a more severe form of cysticercal encephalitis.

7. The course and outcome of the patients with multifocal cysticercal encephalitis who were treated with Praziquantel was very similar to that of the few followed from the retrospective group and to the experience previously reported in the literature (Thomson et al 1984; Mitchell and Crawford 1988). Praziquantel produces its therapeutic effect by damaging the viable 'quiescent' cysts which had previously evaded the hosts immune system. These damaged cyst capsules then can no longer continue to evade the host inflammatory response. However, in patients with cysticercal encephalitis the inflammatory response has already been initiated spontaneously and therefore the addition of Praziquantel to therapy is probably unlikely to make any obvious difference to the outcome. A carefully controlled drug trial is the minimum prerequisite for the assessment of drug efficacy in a disease process, especially when the natural history of the disease is as variable and is as inadequately documented as in neurocysticercosis. However, the difficulty of conducting controlled double blind drug trials in third world populations is well recognised and has again been highlighted by the incomplete follow-up of the patients in the trial described in Part IV of this dissertation.

The parasitocidal efficacy of Praziquantel in adult and adolescent patients with 'parechynmal' cysts has been well documented and therefore its use in selected patients is indicated. Perhaps some of these patients with small numbers of non-life threatening cysts could be carefully followed in the absence of Praziquantel therapy so as to observe the natural history of this form of the disease. On the other hand Praziquantel has in our experience and that of others (Joubert 1990) been shown to be ineffective in the therapy of intraventricular and subarachnoid racemose cysts and may even be contraindicated in

some of the latter cases.

The decision whether or not to use Praziquantel in patients with cysticercal encephalitis is not clear cut. In the absence of a properly controlled double-blind drug trial an attempt to trace more of these patients for late follow-up assessment may provide a clearer answer to the natural history and to the indications for use of Praziquantel in patients with multifocal cysticercal encephalitis.

8. However, for a number of reasons we have continued to treat with Praziquantel those patients who have multifocal cysticercal encephalitis:

   a. Praziquantel and subsequently Albendazole have been shown to be effective in the treatment of neurocysticercosis (Sotelo et al 1988; Alarcon et al 1989) (Albendazole is not as yet available in South Africa)

   b. There is no conclusive evidence that all the 'parenchymal' cysts are involved at the same time in the spontaneous encephalitic process. Moreover, our experience suggests that not all the cysts are involved at the same time in this process. There is an exacerbation of symptomatology in some of these patients as well as an increase in the size and number of the enhancing lesions and the degree of oedema on CT scan following on Praziquantel therapy (Radiology 18). These findings therefore suggest than there maybe some quiescent cysts undetected by the hosts immune system which are damaged by Praziquantel therapy in these patients.

   c. Praziquantel has shown no toxic effects in these patients with regard to haematologic, hepatic or renal function. In the patients in this series who developed severe Herxheimer reactions after commencing Praziquantel therapy, all were well controlled on high dose steroid and no fatalities nor complications resulted. If life-threatening complications appear imminent Praziquantel should be withdrawn from therapy and possibly recommenced carefully at a lower dosage.

   d. Most if not all of these patients with multifocal cysticercal encephalitis require

d. Most if not all of these patients with multifocal cysticercal encephalitis require hospitalization and steroid therapy. Therefore the use of Praziquantel or Albendazole (which is reported to be relatively inexpensive) would seem to be of value under these controlled circumstances.

Guidelines outlining the indications for Praziquantel or Albendazole therapy have been carefully tabulated from years of experience (Sotelo 1987; Sotelo an Del Brutto 1987; Sotelo 1988). The need for Praziquantel and/or Albendazole therapy must be carefully assessed for each individual patient. Our experience is indeed very similar to that reported from South and Central America.

9. Of course prevention is better than cure. The final solution to the problem of neurocysticercosis rests with the education of the affected rural populations and hopefully a resultant improvement in their socio-economic status, farming methods and sanitation. In countries such as South Africa, endemic cysticercal regions with high rates of population infectivity, result in significant costs to the economy. To the high cost of hospitalization and medication must be added the economic losses incurred by absenteeism from work as well as by the wastage of large quantities of infected 'measly' pork.

It would be appropriate and of some priority to undertake a cost-effective study comparing the cost of educating the indigenous people (regarding the life cycle of taenia solium and the dangers of neurocysticercosis) with the cost already incurred by the existing situation. Should education of the involved communities be found to be a feasible economic proposition, it would be of prime importance, to ensure that these communities understand, that the disease can in the first instance be largely eradicated by prevention of 'free range human defaecation' and by the use of 'pit toilets'. They should also understand that pigs should be denied access to such areas and that as their economy improves free range pig farming should be replaced by more modern methods.

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