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## Cysticercosis: immunology and immunotherapy

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**SUMMARY**

*Taenia solium* cysticercosis is an important cause of human neurological disease in many developing countries. Porcine cysticercosis contributes to economic hardship and completes the parasite life-cycle. In humans and pigs cysticerci usually live within host tissues without causing inflammation or disease. The mechanisms of immune evasion by living cysticerci may include sequestration within immunologically privileged sites; antigenic shifts; molecular mimicry of host-like antigenic determinants; masking of cysticercal antigens by host immunoglobulins; and modulation of host immune responses. However, the degeneration of one or more cysticerci is associated with granulomatous inflammation which in humans may result in transient or progressive symptoms.

Cysticercosis is a disease of poverty. Public health and animal husbandry measures have eradicated the disease from developed countries but are difficult to apply in endemic regions where pigs are usually reared on a subsistence basis. In contrast to preventative measures, an inexpensive *treatment* for infected pigs may be an effective way of controlling the parasite and preventing human disease because it may double the value of cysticercotic pigs, providing an incentive for widespread use. Immunotherapy with cysticercal antigens may cause degeneration of cysticerci, potentially curing porcine cysticercosis. Our blinded randomised placebo-controlled study assessed the efficacy and safety of immunotherapy in 28 naturally parasitised pigs. Four weight-matched groups were inoculated with purified cysticercal antigen, crude cysticercal antigen with Freunds adjuvant, adjuvant alone or saline alone. Immunotherapy was well tolerated but had no effect upon the macroscopic appearance or histology of cysticerci. Most of the pigs given crude antigen plus adjuvant developed new antibody bands on electro-immuno transfer blot and the crude antigen caused a significant increase (from 10% to 34%, $p<0.04$) in the proportion of cysticerci that failed to evaginate and were therefore not viable for causing human infection. Although immunotherapy with cysticercal antigens caused a statistically significant fall in the viability of cysticerci, this immunological reaction was not great enough to be of value in preventing human disease.

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## 1. INTRODUCTION

Cysticercosis is a parasitic disease that results from ingestion of *Taenia solium* tapeworm eggs. These microscopic eggs contaminate the environment in endemic areas and when pigs ingest them porcine cysticercosis develops, reducing the animal's weight and value. In the Andean region of Peru up to 50% of pigs have cysticercosis, contributing to economic hardship and malnutrition (Gonzalez et al 1990). When humans eat infected pork they may develop tapeworms that release further eggs, completing the parasite life-cycle. When humans ingest *T. solium* eggs they develop cysticercosis, an important cause of neurological disability and mortality in many developing countries including 0.5 to 2% of people in Peru (Garcia et al 1991) and Mexico (Flisser et al 1982a).

## 2. IMMUNOLOGY OF ASYMPTOMATIC CYSTICERCOSIS

Symptomatic human cysticercosis is associated with inflammation around at least one degenerating cysticercus most importantly and commonly within the brain, as revealed by autopsy examinations of neurological patients. However, autopsy series of victims of warfare and pedestrians in road traffic accidents have revealed that a large proportion of neurocysticercosis infections are asymptomatic, discovered incidentally at necropsy (reviewed by Gemmell et al 1988). In addition, living cysticerci may occasionally cause disease through local pressure effects or by obstructing the flow of cerebro-spinal fluid, despite the absence of a host inflammatory response

A study of 450 British soldiers who acquired cysticercosis whilst stationed in India (Dixon & Lipscomb 1961) provided an opportunity to study the time course of disease. Few soldiers returned from India with epilepsy, the majority developed seizures 2-8 years after infection. The longest interval between infection with cysticercosis and appearance of symptoms was 30 years. This is remarkable because studies in pigs and humans have shown that cysticerci take only 60-70 days to reach maturity after infection (reviewed by Grove 1990). To explain this, MacArthur (1935) suggested that a biologic objective of cysticerci while in the tissues of the intermediate host is to remain quiescent, with obvious evolutionary advantage, and that the death of the parasite may liberate toxins, causing irritation. Alternatively, the death of cysticerci may end active immune evasion by the parasite allowing immunologically mediated inflammation to develop and cause symptoms.

The pig is the usual intermediate host and tolerates living cysticerci well. In some endemic regions examination of the pig's tongue is routine practice before purchase for slaughter since this reliably diagnoses cysticercosis (Gonzalez et al 1990). The usual absence of apparent illness is surprising considering that thousands of cysticerci are often found at autopsy, scattered throughout neurological and other tissues. Since *T. solium* cysticerci may live and actively evade immunity for many years, the fact that pigs are usually slaughtered in their first year of life may explain the absence of neurological disease, pigs usually dying before any cysticerci degenerate and cause inflammation.

Asymptomatic human cysticercosis may be diagnosed serologically or by biopsying subcutaneous lesions. Although circulating anticysticercus antibodies have access to the surface of cysticerci, as illustrated by imaging studies with radio-labelled antibodies (Skronne-Kadlubik et al 1977), hundreds of 8mm cysticerci may live within human tissues, evading immune destruction and symptomatic inflammation. However, a single low dose of praziquantel given to treat intestinal parasitosis may cause sufficient damage to latent



asymptomatic cysticerci that inflammation and epilepsy results, providing evidence for active immune evasion or suppression by living cysticerci (Johnson 1986).

### 2.1. MECHANISMS OF IMMUNE MODULATION BY CYSTICERCI

The propagation of *T. solium* depends upon successful survival of cysticerci within the intermediate host. Our understanding of the complex mechanisms employed by helminths to prevent immune-mediated destruction is increasing rapidly (reviewed by Maizels et al 1993) and several of the mechanisms employed by cysticerci have been elucidated (reviewed by Flisser 1994).

***Sequestration***. After a brief period of migration in tissues, *T. solium* larvae lodge in host tissues and form cysticerci. The site at which they settle and the nature of their relationship to the encapsulating host may contribute to sequestration of the parasites from immune attack. The unequal distribution of cysticerci throughout body tissues does not mirror regional blood flow but may result from selective invasion by the parasite or differential survival and encystment of larvae in different tissues. In humans, cysticerci occur commonly within the brain, spinal cord and eye, all of which may be considered to be 'immunologically privileged sites'. The central nervous system differs from other tissues in the presence of the blood brain barrier which prevents conventional lymphocyte recirculation; the inducible rather than constitutive expression of major histocompatibility class I and II molecules; and the presence of specialised cells that execute immunological effector functions. These features may explain the unique interaction between the central nervous and immune systems (reviewed by Fabry et al 1994) and the resistance of the brain parenchyma to leukocyte diapedesis (Andersson et al 1992). However, we are not aware of systematic study of the number of cysticerci in human brain compared with non-neurological tissues and the apparent prediliction for the brain may simply reflect the severe symptoms which result from lesions in this organ. The firm, fibrous encapsulation which surrounds some cysticerci, particularly in non-neurological tissues, is unlikely to form a physical barrier to immunity since humoral factors do gain access to the internal fluids of cysticerci (Willms & Arcos 1977) and chemotherapeutic challenge or death of cysticerci is followed by immediate intense inflammatory cell infiltration (Rickard & Williams 1984).

***Antigenic shifts***. In concomitant immunity, hosts are protected against newly invading larvae whilst tolerating an established worm infection. This may result from shifts in the antigens expressed by parasites as they develop through different stages of their life-cycle. Alternatively, or additionally, adult larvae may be able to counteract those immune effector mechanisms that kill immature forms. Concomitant immunity has been demonstrated for *T. saginata* and *T. hydatigena* where vaccine derived live cysticerci exist in animals resistant to egg challenge, but not in *T. solium* cysticercosis. It may explain the lack of overwhelming cysticercosis in hyperendemic regions since animals may only be able to acquire cysticercosis for 1 or 2 weeks after primary exposure to the parasite. Thereafter, the animal may be resistant to re-infection despite the survival of viable cysticerci resulting from the primary infection (Gemmell et al 1988).

***Molecular mimicry*** by parasites is the evasion of immune recognition by the synthesis of host-like antigenic determinants. Willms et al (1980) detected immunoglobulin G (IgG) on the surface of *T. solium* cysticerci by immunoelectronmicroscopy but after purification this IgG showed no specificity for antigens on the cysticercus, so the possibility that it was synthesised by the parasite was tested *in vitro* by translation of parasite-derived RNA. One of the protein

products was precipitatable with rabbit anti-pig IgG, providing evidence that the cysticercus itself synthesised host-mimicking antigens. The occurrence of homologous genome sequences in host and parasite may explain the selectivity of cestodes for particular hosts, for example *T. solium* for pigs and humans.

***Masking of cysticercal antigens by host immunoglobulins.*** The presence of host antibodies has been studied in fresh cysticerci obtained from human surgery compared with host serum and CSF. Although circulating human IgG was present with the same frequency as IgG on the surface of the parasite; IgM, IgA and IgE were present only on the surface of the parasite and could not be detected in the serum or CSF. Furthermore, *T. solium* cysticerci have recently been shown to express an Fc receptor for IgG. These results suggest that cysticerci may be masked by host immunoglobulins, although the importance of this potential mechanism of immune evasion has not been established (reviewed by Flisser 1994).

***Modulation of host immunity.*** Some evidence suggests that *T. solium* cysticerci may not only 'hide from' the host immune system, but may also actively suppress host immunity. A secretion product of living cysticerci, antigen B, has been shown to bind to and inhibit C1q, the first component of the complement cascade (Laclette et al, 1992). As yet unidentified secretory products of cysticerci also have a suppressive effect on cultured human lymphocytes stimulated with phytohemaglutinin (Molinari et al 1990). Similarly, viable cysticerci implanted into the peritoneal cavity of mice release factors which depress rather than enhance lymphocyte reactivity (Willms et al 1980).

## 3. IMMUNOPATHOLOGY OF SYMPTOMATIC CYSTICERCOSIS

The immune response to cysticerci has been studied mainly because of the need for a diagnostic blood test. Although the literature is confused by numerous different serologic tests evaluated with varying degrees of scientific rigor, it is clear that virtually all cases of symptomatic cysticercosis are associated with a detectable humoral immune response. Furthermore, sero-epidemiological studies in endemic regions have revealed a similar rate of antibody positivity in healthy people to the prevalence of asymptomatic cysticercosis in autopsy series (Garcia et al 1991).

Studies of the experimental treatment of 'asymptomatic' cysticercotic pigs showed that while parasites had no macroscopic or histopathological evidence of damage prior to treatment, praziquantel lead to accumulation of eosinophils around cysticerci followed by lymphocytes and macrophages which appeared to phagocytose cysticercal material and cell debris. The macroscopic (and radio-imaging) disappearance of killed cysticerci took 2 months (reviewed by Flisser 1994). We have observed similar results with albendazole (Gonzalez et al, submitted) and other cestocidal drugs.

The cause of degeneration of untreated cysticerci in human tissues is not known but it has been proposed that death of the parasite may simply occur at the end of its natural life-expectancy. Cumulative damage from chronic host inflammation is an alternative possibility. The human tissue response to a degenerating cysticercus is granulomatous, consisting of plasma cells, lymphocytes, eosinophils and macrophages enclosed in a network of connective tissue. In later stages host cells penetrate into the remnants of the parasite. After 1-2 months a glial or connective tissue scar remains, which may then calcify (Gemmell et al, 1988). This relatively benign natural history is often reported from Southern India where patients with epilepsy resulting from degeneration of a solitary parenchymal cysticercus are routinely treated symptomatically until inflammation and resultant symptoms resolve. In contrast, one



or more degenerating cysticerci may cause chronic, progressive granulomatous inflammation which often proves fatal despite steroid and or surgical therapy, a clinical syndrome which appears to be more common in South America. It is not clear whether variations in the parasite or the host response explain these variable clinical features of neurocysticercosis.

## 4. PREVENTION AND CONTROL OF CYSTICERCOSIS

Cysticercosis is a disease of poverty and social under-development. Human cysticercosis may be prevented by provision of sanitation and treatment of tapeworm carriers. The parasite life-cycle may be broken by enforcing meat inspection, freezing/adequately cooking pork or by large scale commercial pig rearing which denies pigs access to human faeces. Such improvements in public health and animal husbandry have led to the virtual eradication of human and porcine cysticercosis in wealthy countries but these measures are currently of limited relevance in less developed rural areas (Gemmell et al 1988).

### 4.1. PROTECTIVE VACCINATION TO PREVENT CYSTICERCOSIS

Human vaccination to prevent cysticercosis has not been widely considered as an appropriate intervention in endemic regions because little is known about the immunology of human cysticercosis and symptomatic cysticercosis is greatly under-diagnosed (Garcia et al 1991). It has been suggested that cysticercosis occurs with greater than expected frequency in immunologically deficient children (Flisser et al 1982b) but this uncontrolled observation may reflect a chance association or diagnostic bias rather than an effect of immunodeficiency on susceptibility. Cysticercosis has not been noted to be common in immunosuppressed or immunodeficient adults. In common with most other human cestodes, protective immunity against the adult tapeworm does not appear to occur and adult tapeworm carriage does not appear to protect against cysticercosis. However, there is evidence in experimental animal models that a definitive host can reject a tapeworm or cause it to destrobilate and that antibody may be present (Gemmell et al 1988).

Vaccination of pigs to prevent porcine cysticercosis has been proposed as a possible way of improving animal health, meat yield and of breaking the parasite life-cycle, potentially preventing human disease. Molinari et al (1983) showed that vaccination of healthy pigs with cysticercal antigen caused partial protection against the subsequent development of porcine cysticercosis. Likewise, immunisation of pigs with excretory-secretory products of *T. solium* oncospheres caused a decrease in the number of cysticerci which developed from subsequent challenge infection (Pathak & Gaur, 1990). Similar protective vaccination has been developed for other *Taenia* species (Flisser, Perrez-Montfort & Larralde 1979, Johnson et al 1989). Oral vaccination against *T. solium* has not been attempted. Prophylactic vaccination may not be practicable in areas where cysticercosis is common; where pigs are typically free-roaming and are reared by individual families on a subsistence basis (Gemmell et al 1988).

### 4.2. IMMUNOTHERAPY FOR PORCINE CYSTICERCOSIS

In contrast to preventative measures which are difficult to apply in endemic regions, an inexpensive treatment for porcine cysticercosis may be of practical value in the poorer areas where the disease is most common. Such a treatment may be sought after and used by owners of infected pigs if it improved animal health, meat yield and especially if it caused the degeneration of cysticerci that are easily visible in infected 'measly' pork, halving its value (Gonzalez et al 1990). Such a treatment for porcine cysticercosis may, therefore, be a cost-

effective way of breaking the life cycle of the parasite, preventing human as well as animal disease. Our group are investigating treatments for porcine cysticercosis with drug therapy (Gonzalez et al, submitted) and immunotherapy (Evans et al 1994). Immunotherapy may have the advantages of being effective after only one or two doses and may increase protection against re-infection.

**4.2.1. Previous Research**

Cysticerci may be destroyed by immunological processes. Herbert & Oberg (1974) infected 9 pigs with cysticercosis at the age of 2 months and re-infected 4 of these pigs 2 months later. Paradoxically, autopsy revealed significantly fewer cysticerci in the pigs that had been infected twice; suggesting that re-infection accelerated cysticercus degeneration and absorption. Similarly, re-infection of cows infected with *T. saginata* and of sheep infected with *T. hydatigena* caused degeneration of established cysticerci (Gallie & Sewell 1972, Sewell & Gallie 1974, Gemmell 1970).

Most significantly, Molinari, Meza & Tato (1983) reported that immunotherapy caused the resolution of porcine cysticercosis. Inoculation of naturally parasitised pigs with cysticercal antigen caused eosinophilia and autopsies at 4 and 8 weeks revealed increasing macroscopic degeneration of cysticerci. There was an intense inflammatory reaction around cysticerci with eosinophilic infiltration and more than 90% were 'degenerating'. However, only 12 cysticerci were examined from each of 2 inoculated and 1 control pig and no assessment was made of the viability of cysticerci for causing human infection. This immunotherapy was also evaluated in a field trial (Molinari et al 1993). Although the prevalence of cysticercosis fell significantly in 2 villages where 447 pigs were vaccinated repeatedly with 1,076 doses of immunotherapy, there was no control group and cysticercosis was diagnosed by tongue palpation only, limiting interpretation of these results. 7 cysticercotic pigs given immunotherapy were studied in more detail and 73% of cysts excised from them failed to evaginate vs. 5% in 7 untreated cysticercotic pigs. These encouraging results led us to further investigate the effect of immunotherapy on porcine cysticercosis in a prospective, randomised, controlled and blinded study.

**4.2.2. Recent research in Peru**

28 privately reared naturally parasitised pigs that were being sold for slaughter were purchased from a city in the Peruvian Sierra and were randomly divided into 4 weight matched groups: *(1) Purified Antigen (5 pigs)* was prepared from 2,000 cysticerci by the method of Molinari, Meza & Tato (1983) and the same amount of antigen was administered: a subcutaneous injection of 0.25mg of protein (in 0.1ml saline) behind the ear on day 1 and 7. *(2) Crude Antigen + Adjuvant (9 pigs)* was prepared by the method described by Estrada & Kuhn (1985): the supernatant from several thousand homogenised, sonicated centrifuged cysticerci. The concentration was adjusted so that 2.4mg was given in 1ml of Freund's adjuvant (Sigma). This preparation was split into 5 equal volumes that were injected into different subcutaneous sites and this was repeated on day 14. *(3) Adjuvant Alone (7 pigs):* Freund's adjuvant alone administered in the same way as for group 2. *(4) Saline (7 pigs):* sterile saline administered in the same way as for group 1. Two pigs developed a transient limp following vaccination in the forelimb but no other adverse reactions were noted.



***Haematology & Serology.*** There were no significant differences in differential white cell count or cysticercosis antibody ELISA (Estrada & Kuhn 1985) between early and late values and between groups. An electro-immuno transfer blot (EITB) (Tsang et al 1983 & 1986) using glycoprotein antigens to detect infection-specific antibodies in serum was interpreted with reference to the 7 glycoprotein bands (glycoproteins 50, 42-39, 24, 21, 18, 14 & 13) commonly recognised by antibodies from serum in human and porcine cysticercosis (Tsang et al 1989 & 1991). EITB with purified antigen did not change but in the crude antigen EITB some pigs developed new antibody bands during the study (12-13KD, 19KD & 24KD). Only one control pig developed new bands in contrast to 9 of the 14 vaccinated pigs ($P<0.01$). The presence or development of one or more of these bands was not significantly related to white cell count, eosinophilia, evagination rate nor histological injury.

***Necropsy.*** Pigs were anaesthetised and sacrificed 10-12 weeks after the first vaccination. The mean (SD) number of cysticerci per kg dissected from the tissues of all pigs were: muscle 256 (418); tongue 70 (65); & brain 14 (18). The number of cysticerci per kg varied considerably between pigs but the mean was similar for each intervention group. The macroscopic examination of cysticerci revealed only 6 clearly degenerated cysticerci and all of these were found in 2 pigs that had been given the crude antigen. At least 3 cysts from 3 tissues for every pig were examined histologically but host inflammatory reactions were very variable and did not correlate with viability or vaccination. Macrophages were the commonest cell, especially when >1,000 inflammatory cells were seen. Eosinophils predominated in less than a quarter of cases, most commonly in the presence of <100 inflammatory cells. Lymphocytes and plasma cells were seen in much smaller numbers.

***Evagination.*** Cysts were incubated in 1% pepsin then evagination medium (Canedo et al 1982). The percentage of 'dead' cysticerci that failed to evaginate and were therefore not viable for causing human infection was calculated for each tissue from each pig (table). Significantly fewer of the cysts from pigs given crude antigen were viable compared with the adjuvant (or saline) control group ($P<0.04$). Adjuvant alone had no effect upon viability compared with saline. The effect of purified antigen was not significant when compared with adjuvant, saline or combined control groups. The effect of vaccination appeared greatest for tongue tissue, less so for muscle and was not significant for brain tissue. There were relatively few cysticerci in brain tissue and these were of low viability.

***Table: effectiveness of vaccination.*** The percentage of cysts which failed to evaginate and were therefore not viable for causing human infection was calculated for each pig. The mean (SD) of these percentages for each intervention group is shown in the table.

| | n | Muscle | Tongue | Brain | All Cysts |
|---|---|---|---|---|---|
| Purified Antigen | 5 | 15 (14) | 13 (15) | 48 (37) | 17 (16) |
| Crude Antigen + Adjuvant | 9 | 28 (29) | 46 (36) | 44 (41) | 34 (28) |
| Adjuvant | 7 | 7 (8) | 8 (11) | 53 (40) | 10 (9) |
| Saline | 7 | 7 (8) | 13 (21) | 41 (39) | 18 (19) |

## 5. CONCLUSIONS

This study confirmed that when pigs naturally infected with *T. solium* cysticercosis were inoculated with cysticercal antigen the viability of cysticerci was significantly reduced. The percentage of cysticerci that showed no evidence of viability was more than doubled in the group of pigs given crude antigen and most of these animals developed new EITB bands suggesting an antibody response to the immunotherapy. However, all of the pigs remained macroscopically heavily infected and most of the cysticerci in the majority of the treated animals appeared viable for causing human disease.

Molinari, Meza & Tato (1983) reported marked inflammation and degeneration of cysticerci in naturally parasitised pigs following inoculation with purified cysticercal antigens. However, we administered the same dose of purified antigen prepared in the same way but this had no apparent effect upon the appearance of cysticerci nor their viability. None of the pigs in our study showed the eosinophilic response to immunotherapy that Molinari et al reported in the 2 pigs they inoculated. Molinari et al did not assess the viability of cysticerci in this study and their histopathological findings may have been biased by the small number of pigs and cysticerci studied.

Alternatively, the lack of effect of purified antigen in our study may be explained by cysticercal heterogeneity if the cysticerci used to prepare the immunotherapy differed antigenically from those infecting the pigs treated. This would also explain the surprisingly variable inflammatory changes seen in adjacent cysticerci. Morphological heterogeneity (Correa et al 1987) and antigenic diversity (Yakoleff-Greenhouse et al 1982) have been noted between cysticerci dissected from different naturally infected pigs and DNA probes have revealed genetic variation between different geographic isolates of porcine cysticerci (Rishi & McManus 1988). However, antigenic heterogeneity is unlikely to be relevant because the crude and purified antigens were prepared from several thousand cysticerci obtained from multiple pigs reared in the same area as the animals given immunotherapy.

The statistically significant effect of immunotherapy on parasite viability illustrates the active nature of the host-parasite interaction and the potential for manipulating this relationship for possible control of parasitic infection. However, a considerable increase in efficacy would be required for immunotherapy to be of practical value. Genetically engineered monoclonal vaccines have been shown to cause a greater degree of immunity against other tapeworm species (Johnson et al 1989, Rickard et al 1995) and identification and synthesis of the appropriate antigens for porcine cysticercosis may allow more effective immunotherapy. If it were possible to achieve complete or near-complete destruction of naturally contracted porcine cysticercosis with an inexpensive vaccination then the implications for increasing usable meat yield and preventing human disease by breaking the life-cycle of the *T. solium* parasite may be of considerable socio-economic and medical importance.

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# Nervous system dysfunctions in African trypanosomiasis

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African sleeping sickness is caused by subspecies of the extracellular parasite *Trypanosoma brucei (T.b.)*. The course of the disease is rapidly progressive during infection with the Eastern African *T.b. rhodesiense*, but more protracted and heralded by symptoms from the nervous system during Western African *T.b. gambiense* infections. The parasites are spread by tsetse flies, which are hematophagous insects of the genus *Glossina* belonging to the *G. palpalis* and *G. morsitans* groups. Flies belonging to the *G. palpalis* groups primarily transmit *T.b. gambiense* (Western Africa and Uganda), while flies belonging to the *G. morsitans* group inhabit the dry savannah of central and Eastern Africa[1]. More than 55 million people live in areas of sub-Saharan Africa with a risk of becoming infected. Only 10% of the population is under surveillance, by which 25.000 new cases are detected each year; the actual number of cases may therefore be considerably higher. The disease has been divided into two stages: stage I (or blood-lymph phase) with no or minor effects on the central nervous system (CNS) and stage II (or meningo-encephalitic phase) with CNS involvement verified by cerebrospinal fluid changes[2]. Signs of nervous system disease include a severe pain syndrome, extrapyramidal disturbances, neuropsychiatric changes and alterations in the sleep pattern. Arsenic salts are still used for treatment of nervous system symptoms and this results in arsenic encephalopathy in up to 10% of the patients. In this presentation symptoms from the nervous system in human patients will be compared with those observed in experimental animals and molecular mechanisms behind nervous system dysfunctions highlighted.

## 1. SENSORY DISTURBANCES

Early during infection signs of hyperalgesia appear both in humans and experimental animals. In the latter, parasites are localised to dorsal root ganglia. From observations *in vitro,* we have obtained evidence that the parasites and sensory neurones interact through the release of molecules. This molecular interplay may be involved in eliciting the sensory disturbances *in vivo*.

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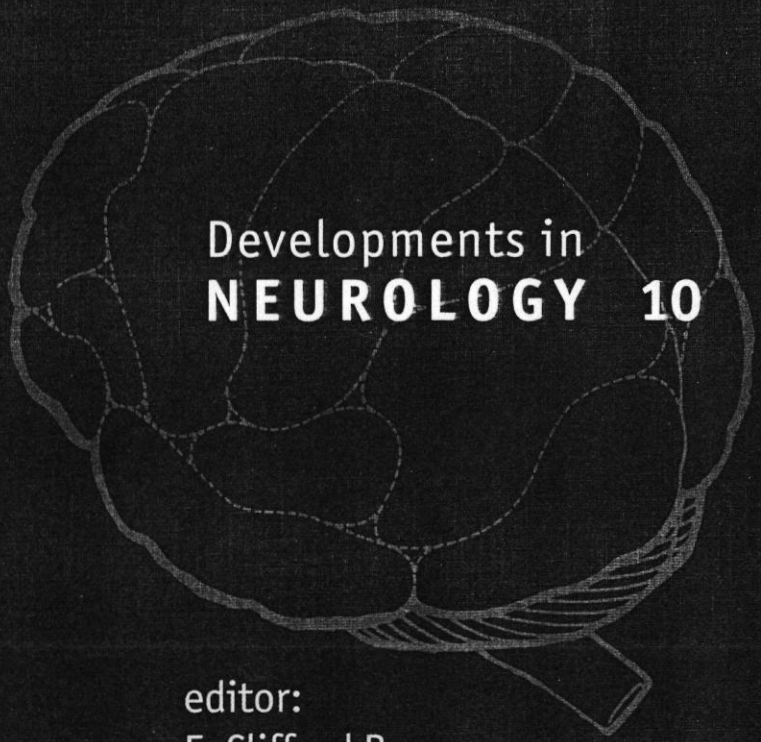
*Recent Advances in Tropical Neurology*



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