

Historical Perspective: The British Contribution to The Understanding of Neurocysticercosis.

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ABSTRACT

Neurocysticercosis, or brain infestation with the larval stage of *Taenia solium* is the most common risk factor for epilepsy in many endemic regions of the world. Hardly any cases are seen in western developed countries including Britain. However, a sizeable number (n=450) was seen among British soldiers returning from deputation to India, then a British colony, first reported by Col. MacArthur at the Queen Alexandria Military Hospital in 1931. Here, we review the influence of the perceptive observations of the British army medics on the understanding of the parasitic disorder. The majority of these people presented with epilepsy. Among the contributions of the army medics were establishing the diagnosis, initially by histological examination of subcutaneous and muscular infestation, and later by radiography, clarifying the prognosis and the role of medical and surgical treatments and uncovering the close relationship between the larval (cysticercosis) and adult (intestinal tapeworm) stages of *T. solium*.

Key Words: *Taenia solium*; cysticercosis; epilepsy; military medicine

Introduction

Cysticercosis denotes the infestation of living human tissue with the larval stage of the pork tapeworm, *Taenia solium*. When the cysts lodge in the brain, the infestation is termed neurocysticercosis (NCC). The presence of the adult tapeworm in human intestines is known as intestinal taeniasis, which is linked to the occurrence of larvae in pigs, known as porcine cysticercosis. Humans accidentally develop NCC by ingesting eggs excreted by the adult tapeworm.

The estimated number of people infested with NCC worldwide is between 2.6 and 8.3 million (WHO, 2018). It is the *main* preventable risk factor for epilepsy, but, is particularly endemic across resource-poor settings in Latin America, South and Southeast Asia and sub-Saharan Africa (Garcia, Del Brutto & Cysticercosis Working Group in Peru, 2005). It accounts of nearly a third of all epilepsies in these regions (Montana et al, 2005). Until recently, the infestation was rarely encountered in affluent societies but increasing immigration and travel have resulted in mounting numbers of imported cases among immigrants and natives (O'Keefe et al, 2015). This has possibly scaled up attention on the parasite to an extent that may not have occurred if the infestation were confined to resource-poor countries.

A substantial number of NCC cases have been reported in the United States but reports have also emerged from other affluent countries, albeit in more modest numbers (Wadley, Shakir & Rice Edwards 2000; Thaker, Tacconi & Snow 2001; Choksey & Hamid, 2002; Del Brutto, 2012 a, b, c; Fabiani & Bruschi, 2013). From 1970 to 2011, 26 cases were identified from Great Britain, mostly in people of Asian origin (Wadley, Shakir & Rice Edwards 2000; Thaker, Tacconi & Snow 2001; Choksey & Hamid, 2002; Del Brutto, 2012). Prior to these recent reports, however, a number of cases were described from Britain in the early part of the twentieth century (MacArthur, 1933, 1934 a, b; Dixon & Smithers, 1934; Dixon & Hargreaves, 1944). Notwithstanding the few cursory allusions to this remarkable British contribution in scientific literature, we revisit a series of historical papers to ascertain the evolution of views relating to the pathophysiology, clinical presentations and course of NCC. (Wadia & Singh, 2002; Del Brutto & Garcia, 2015)

Methods

We extensively searched the Wellcome Trust Library for the History of Medicine archives in London. Articles published in the BMJ and Lancet were available from the publishers' digital archives while some of the other journals were accessed at the National Library of Medicine at New Delhi, India. Retrieved articles were hand-searched for further references. We also reviewed the case notes of two individuals with NCC, who were perhaps the earliest admissions with this condition at the National Hospital for Neurology and Neurosurgery, Queen Square, London. These were sourced from the hospital's archives.

Results

NCC in Britain prior to the 19th century

The earliest accounts of NCC were in the fifteenth century (Wadia & Singh, 2002). Subsequent descriptions of large case series were mostly from Germany and France with scarcely any British report (Virchow & Notizen, 1860; Vosgien, 1911). Meat hygiene was enforced in England by an Act of Parliament as early as 1482, when the sale of "measly pork", i.e., likely contaminated by cysticerci, was banned. It is unclear whether prevailing conditions prompted this but enforcement of this may explain why despite being endemic in mainland Europe, NCC was virtually non-existent in Britain through the seventeenth and nineteenth centuries. We identified only two reports of cysticercosis in British natives, proven by chance at post-mortem examination prior to 1900 (Ottley & Frobese, 1843; Brittan, 1859). One was a woman who was variously diagnosed at different times as "gastric irritation disorder" due to frequent bouts of vomiting (with headaches) and hysteria but had a sudden death and in whom, an autopsy revealed cysticercosis in the fourth ventricle. The other report also of a woman who died of "convulsions lasting for nearly 24 hours", i.e., status epilepticus in whom brain cysts were found. Both cases were sufficiently unique in their presentations but seem to have been written

up largely due to the rarity of NCC in Britain. Another British report in the nineteenth century refers to a coolie in India, found to have multiple cysticerci at autopsy (Armstrong, 1888).

NCC in Britain in the early 19th century

In the first two decades of the twentieth century, the number of NCC cases reported from Britain was limited to a trickle (Galbraith, 1904; Lunn, 1912). This clearly changed in the 1930s when large numbers were reported by physicians of the Royal Army Medical Corps (RAMC) working at the Queen Alexandra Military Hospital at Millbank by the Thames River. The hospital was commissioned in 1902 to serve military personnel with non-combat-related ailments. It was built at the site of Millbank Prison, a convicts-holding facility before transportation to Australia, which had closed in 1890. The hospital operated until 1970 when it was decommissioned and now its main building houses part of Tate Britain, one of the leading British art museums. The first report of NCC was of five former soldiers, by Col. (later, Lieutenant-General) William Porter MacArthur (1884-1964) (Box 1; Fig. 1) (MacArthur, 1933). A very few contemporary reports described the diagnosis of cysticercosis in life by radiography and biopsy of intra-muscular cysticerci, perhaps the earliest to document diagnosis during life (Roth, 1926; Aitken, 1928; Broughton-Alcock, Stevenson & Worster-Drought, 1928). Subsequently in 1933, MacArthur presented eight cases of cysticercosis to emphasize its relationship to epilepsy (MacArthur, 1933). The number of reported cases from the British Army rapidly grew from eight to 20 cases, to 71 cases by 1934 (Dixon and Smithers, 1934), to 284 and eventually to over 450 cases by 1961 (MacArthur, 1933, 1934, 1935; Dixon & Smithers, 1934, 1935; Dixon & Hargreaves, 1944; Dixon & Lipscomb, 1961). While most reports were from Millbank, many centres in London and elsewhere also sporadically catered to the disorder, some to stray walk-in military pensioners and others to cases referred in need of specialized care. We identified two cases through the archives of Queen Square in the early twentieth century including one who was operated (Fig.2). In addition, cases which were discussed at clinical meetings chaired by Denny-Brown and Critchley in the 1930s are documented (Critchley, 1934; Denny-Brown, 1934).

Epidemiology of human cysticercosis and intestinal taeniasis

Large numbers of people with epilepsy at Millbank were first noted in the late 1920s. This amounted to 100 cases in the preceding five years but it cannot be ascertained if this represented an unusual increase in incidence over the prevailing rates. Other unusual epidemiological features were quickly recognized (Table 1). MacArthur noted that the disorder occurred exclusively in former servicemen, mostly those of healthy stock who had served in India (MacArthur, 1933, 1934, 1935).

Another feature was that there were hardly any affected Officers or Sergeants; instead they were mostly from the lower ranks. Systematic investigations which followed not only established cysticercosis as a risk factor for epilepsy but also of the close relationship of NCC with intestinal infestation with adult *T. solium*. Indeed, perusal of military records allowed an estimation of the incidence of intestinal taeniasis among British military personnel (Table 2). Compared to the numerous reports of cysticercosis in British military personnel relocating from India, reports among native Indians were few and far apart (Krishnaswami, 1912; Dogra & Ahern, 1935; Alexander, 1937; Minchin, 1937; Menon & Veliath, 1940; Ashton, 1943; McRobert, 1944; Subramaniam, 1946; McGill, 1947; Gault & Balasubrahmanyam, 1948).

Clinical manifestations

Most cases presented with seizures (Table 3). Different semiologies including somatosensory auras, visual auras, aphasic seizures, Jacksonian march, *petit-mal* type of seizures, convulsions and multiple seizure combinations were described (Dixon & Lipscomb, 1961). Status epilepticus was the cause of death in a few and in these, post-mortem examination revealed NCC (Dixon & Hargreaves, 1944). A number of cases were diagnosed as hysteria. MacArthur (1934) noted that “Apart from a diagnosis of epilepsy, cerebral cysticercosis has been passed as hysteria, cerebral tumour, disseminated sclerosis, acute encephalitis, acute mania, delusional insanity and dementia praecox” Headaches of the “migraine-type” and “cerebral tumour type” often co-existed (Dixon & Hargreaves, 1944). A

certain proportion presented with temporary or permanent insanity. It was earlier stated that mental retrogression and insanity invariably occurred, sometimes to the extent of requiring institutional segregation (MacArthur, 1934). Subsequent observations over several decades, however, did not confirm this (Dixon & Hargreaves, 1944).

Establishing the diagnosis

The difficulties in establishing a diagnosis of NCC were clearly underscored (MacArthur, 1933). Initially, the diagnosis was based on the detection of subcutaneous and intramuscular cysts. It was, however, stated that the temporal relationship of palpable cysts with neurological symptoms was variable (MacArthur, 1934). In some people, cysts could be palpated at seizure onset, while in others, cysts were detectable several years or never after the first seizure. Repeated examination of suspected cases at six-monthly intervals was advocated (MacArthur, 1934). A variety of laboratory tests, often in combination, were used to confirm evidence of cysticercosis (Table 4). Attempts at immunological diagnosis were made and an intradermal (skin) test and a complement fixation test developed (Dixon & Smithers, 1934). Among 14 proven cases, the skin test was positive in six (43%) and complement fixation positive in only five (36%) (Dixon & Smithers, 1934). Likewise, peripheral blood eosinophilia was a rare, albeit important finding, as it was mostly seen in the acute stages of infestation while seizures often occurred much later. While MacArthur could not ascertain a history of intestinal taeniasis (passage of proglottids of tapeworm in stools) in the majority of his subjects, others subsequently appreciated the significance of tapeworm infestation in establishing a diagnosis of cysticercosis (MacArthur, 1933, 1934; Dixon & Hargreaves, 1944; Dixon & Lipscomb, 1961). In a later series of 284 cases, intestinal *T. solium* infestation was detected in 77 (37%) (Dixon & Hargreaves, 1944). Hence, the importance of obtaining a history of taeniasis in contacts of subjects was emphasized (Dixon & Lipscomb, 1961).

Radiography

The first account of the utility of radiography in the diagnosis of cysticercosis was presented in 1926 (Roth, 1926). Cigar shaped calcifications were detected in the limbs of an individual with long-standing epilepsy but contemporaneously, a discharging sinus. Biopsy of one of the cysts confirmed a diagnosis of cysticercosis. Later, spotty calcification/s were observed in skull roentgenograms (Fig. 4a) of individuals with cysticercosis and these findings were linked to those of typical calcifications in limb radiographs (Fig. 4b) (Morrison, 1934; Brailsford JF, 1941). It was, however, later emphasized that the yield of calcifications on skull x-rays (seen in two out of 14 cases) was much less frequent in comparison to limb radiographs. (Dixon & Smithers, 1934; Dixon & Hargreaves, 1944). It was also stated, somewhat regretfully, that x-rays allowed for the diagnosis at a time when the parasite had died, *i.e.*, relatively late in the course of disease (MacArthur, 1934). Skull x-rays often failed to detect calcifications early during disease, hence, it was advocated to repeat radiographs at six-monthly intervals. A standard radiological protocol comprising of lateral skull view, root of the neck and all limbs was recommended, possibly to increase the diagnostic yield (Budd, 1850; Morrison, 1934). Another RAMC radiologist stated that calcifications could also be found in asymptomatic people. Of the 1944 series, 28 (10%) were diagnosed incidentally when limb radiographs were performed for other reasons (Dixon & Hargreaves, 1944)

Treatment

There were no known medical treatments for the parasite although a variety of agents including parenteral antimony tartrate were tried (Budd, 1850; Carma, 1931; Evans, 1939). It was observed that treatment was generally ineffective (Dixon & Smithers, 1934). It was also recognized early on that attempts to eliminate the parasites were often fraught with seizures and other adverse effects (Dixon & Smithers, 1934). In a single case, seizures occurred soon after treatment for intestinal taeniasis was given (MacArthur, 1933). It was also stated that treatment with certain pharmaceutical agents only led to exacerbation of symptoms presumably by causing death of more parasites (Dixon & Hargreaves, 1944). Seizures were mostly treated with bromides and phenobarbital but phenytoin was

used in some cases in the 1940s (Dixon & Hargreaves, 1944). Overall, the impact of anti-epileptic drugs on the outcome was not felt to be impressive though in some cases seizures were controlled (Dixon & Smithers, 1934; Dixon & Hargreaves, 1944). Those who required surgical management were often referred to the specialist neurological centres, e.g., Maida Vale and Queen Square (Critchley, 1934; Denny-Brown, 1934). The limitations of surgical treatment were, however, soon recognized. MacArthur stated that none in his series justified surgical intervention even though there were reported cases of successful localization and removal of solitary brain cysts. In his view, the widespread distribution of cysts across different brain regions in three cases in his series precluded successful surgery (MacArthur, 1934). Over time, 14 people with NCC had brain surgery for either diagnostic or therapeutic indications. In two, who had decompressive surgery, the outcome was satisfactory (Dixon & Lipscomb, 1961). Three people had unsuccessful surgery to control seizures (Dixon & Hargreaves, 1944).

Prognosis and outcome

MacArthur concluded from his observations that cysticercosis was a retrogressive disorder with dismal prognosis in terms of cognitive status and seizure control, even though seizures could occasionally cease (MacArthur, 1934). Subsequently, systematic follow-ups, however, seemed to suggest that the prognosis was “better than previously thought” (Dixon & Smithers, 1934; Dixon & Hargreaves, 1944). Seizures continued till death in three-quarters of those who had died (n=43) by 1944 but remitted in the remaining (Dixon & Hargreaves, 1944)

Discussion

Credit goes to MacArthur for creating interest in the disorder as a cause of new-onset epilepsy and other neurological symptoms in British army personnel. (MacArthur, 1933, 1934, 1935). His views were contrary to the prevailing beliefs of the largely here do-familial nature and relationship to lunacy, of epilepsy. His reports presented serially in the early 1930s served to prompt formal and

systematic investigations in the form of screening and following up all those who developed epilepsy after service in India. The large number of cases reported at the RAMC was in sharp contrast to only a handful of cases reported in native Indians (Krishnaswami, 1912; Dogra & Ahern, 1935; Alexander, 1937; Minchin, 1937; Menon & Veliath, 1940; Ashton, 1943; McRobert, 1944; Subramaniam, 1946; McGill, 1947; Gault & Balasubrahmanyam, 1948). This does not mean that NCC did not exist among native Indians; only it was unrecognized (or unreported) in the early twentieth century. The advent of computed tomography in the 1980s established NCC as the main risk-factor for seizures and epilepsy in India. (Veerendrakumar, 1986; Dhamija et al, 1990; Chandy et al, 1991). Despite the difficulties in confirming a NCC diagnosis, the medics were able to establish algorithms for approaching suspected cases and these were effective, useful and persuasive (Dixon & Hargreaves, 1944). The consideration of NCC in previously-healthy people developing neurological symptoms after service in India was a significant conclusion (Dixon & Smithers, 1934). This added to considerations of rank and residence could a *priori* lead to a high diagnostic suspicion (Dixon & Lipscomb, 1961)

In the 1920s, the only means of diagnosing NCC was histopathology, either in life by biopsy of subcutaneous and muscular cysticerci in people with neurological symptoms or at post-mortem. (Armstrong, 1888; Galbraith, 1904; Lunn, 1912; Roth, 1926; Aitken, 1928; Broughton-Alcock, Stevenson & Worster-Drought, 1928). Army medics deserve credit for establishing radiology as a means of diagnosing cysticercosis and from 1930s onwards, radiographs became a standard in the diagnostic workup (MacArthur, 1933; Brailsford, 1941; Dixon & Hargreaves, 1944; Gault & Balasubrahmanyam, 1948). The medics clearly understood, however, these approaches were indirect and at best presumptive (Dixon & Hargreaves, 1944). The travails of making a diagnosis of cysticercosis and the persistence and assiduousness required in doing so were emphasized.¹² Currently, the availability of modern neuroimaging represents a major advance in the diagnosis of NCC allowing for a quick and confident diagnosis. (Del Brutto et al, 2017; White et al, 2018). The army medics incorporated rigorous methods in the investigation of adult *T. solium* infestation

(intestinal taeniasis) in all suspected cases of NCC. (Dixon & Smithers, 1934, Dixon & Hargreaves, 1944; Dixon & Lipscomb, 1961). They advocated the demonstration of adult tapeworm eggs as a diagnostic element, possibly in recognition of the association between adult *T. solium* carrier status and cysticercosis. This seems to be the only effort to estimate the incidence of intestinal taeniasis on a large scale. This was possible as all people with intestinal taeniasis at that time were admitted to hospitals for treatment (Dixon & Lipscomb, 1961). The frequency of intestinal *T. solium* infestation in the British military cohort is considerably higher than the yield reported in most current series of cysticercosis (McCormick, 1985, Allan et al, 1996; Gilman *et al*, 2000).

The identification of adult *T. solium* carrier status in NCC cases is currently often neglected largely due to a poor yield of stool examinations for *Taenia* eggs and the technical difficulties in testing (Allan et al, 2003). Demonstration of *Taenia* eggs in stool samples provides the most definitive diagnosis but is unreliable due to the intermittent nature of egg excretion. Immunological methods, including coproantigen detection in faecal samples and immunoblot in serum are more sensitive and specific but are not widely available (Wilkins et al, 1999; Allan & Craig, 2006). High yield of 82% was recently described in people with exceptionally heavy infestation using a combination of techniques of evaluation including history, conventional stool examinations and coproantigen assays but most contemporary studies report a yield of less than 5% in people with NCC (McCormick, 1985; Allan et al, 1996; Garcia & Del Brutto, 1999; Gilman *et al*, 2000). From a field perspective, the determination of levels of transmission of *T. solium* in a community is based on the assessment not only of the burden of human cysticercosis, but also porcine cysticercosis and human taeniasis. Recent studies using GIS mapping have shown the presence of human cysticercosis “hotspots” as well as heavily infested pigs in close spatial relationship to adult tapeworm carriers (Lescano et al, 2007; Morales et al, 2008; Pray et al, 2017). The incidence of cysticercosis in pigs in a community can be easily estimated due to the short life-span of pigs (Gonzalez et al, 1994; Sarti et al, 1999). This was not undertaken by the army medics as their subjects returned to a non-endemic environment after initial exposure in India and hence it was not possible to sample pigs. Nevertheless, the rigorous detail

with which they investigated their subjects to establish the close relationship between human cysticercosis and taeniasis is commendable. To date there is still not a report of the ascertainment of the incidence of NCC and adult taeniasis at the scale performed in the British military cohort. While obviously, accurate estimation of the incidence of cysticercosis would not have been possible due to the insensitive screening tools at that time (absence of modern neuroimaging and specific serological tests), the investigators were able to determine the burden of symptomatic infestation. On this and many other accounts, some of the controversies that continue to beset our understanding of cysticercosis even today might be resolved by perusing the collection of these insightful reports.

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LEGENDS TO FIGURES

Fig. 1: Image portrait of Sir William MacArthur, Bromide print, 936, by Walter Stoneman. Courtesy, National Portrait Gallery, UK.

Fig. 2 a) Skull X-ray, antero-posterior view of a recent patient with NCC showing a calcified blemish and (b) the corresponding appearance on MRI and (c) Limb X-ray of another patient showing multiple calcification in the thigh. The illustrations are from the personal collection of the authors.

Box1.

William Porter MacArthur was born in 1884 and was commissioned into the British Army in 1909 soon after graduating in medicine. In the early part of his career, he served in Mauritius, France and China but oddly never in India. Yet, he made an outstanding contribution to the understanding of *Taenia solium* cysticercosis, a disorder which seemed highly prevalent in India. This he accomplished by astute observations at the Queen Alexandria Hospital, Millbank on army personnel returning from India with new-onset epilepsy. He inspired a generation of military physicians to continue several series of investigations in to the disorder. Unsurprisingly, he went to become the Director General of the Army Medical Services (1938-41) and President of the Royal Society of Tropical Medicine (1959-61). He died in 1964 at the age of 80 years.

Table 1. Epidemiological characteristics of the British military cohort with cysticercosis.

S. No.	Characteristic	Numbers (%)
1.	Gender (n=450)	Males: 441 (98%)
		Females: 9 (2%)
2.	Occupation (n=450)	Armed forces: 444 (99%)
		Civilians: 6 (1%)
3.	Geographic location of service (n=450)	India: 440 (98%)
		Other: 10 (2%)
4.	Rank within the armed forces (n=285) (Dixon and Hargreaves, 1944)	Officers: 2
		Sergeants: 4
		Corporals/Private: 279 (98%)

Table 2. Incidence data for cysticercosis and human taeniasis derived from the original papers (Dixon and Smithers, 1934; Dixon and Hargreaves, 1944; Dixon and Lipscomb, 1961).

S. No.	Item	Numbers
I	Average annual strength of British troops posted in India 1920-30s	56,377
II	Average duration of posting in India	5 years
III	Number at risk over 3-4 years	169,000– 225,000
IV	Total number of cases with cysticercosis the in British military cohort	450
V	Number of cases of cysticercosis diagnosed between 1928 and 1937	335
VI	Incidence of symptomatic cysticercosis (1928-1937)	3/10,000 person years
VII	Taeniais in the entire British military cohort (n=450) a) Documented b) Historical reports Total	48 49 97 (2.6%)
VIII	Number of British army personnel admitted to hospital for treatment of taeniasis	774
IX	Incidence of taeniasis	5/1000 person years

Table 3. Clinical presentations in the British military cohort (n=450) (Dixon and Lipscomb, 96)

S.No.	Clinical presentation	Numbers (%)
A) Neurological disorders		
1	Seizures and epilepsy	413 (92%)
2	Focal neurological deficits	12 (2.7%)
	- With seizures and epilepsy	11
3	Neuropsychiatric symptoms	39 (9%)
B) Extra-neural manifestations		
1	Ocular cysticercosis	8 (2%)
	- With seizures	8
2	Lingual cysticercosis	8 (2%)
3	Subcutaneous nodules	242 (54%)
4	Muscular symptoms	15 (3%)
C) Asymptomatic		15 (3%)