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Editorial comment

Anthony J. Raimondi, Executive Editor

The following papers were presented to the "Seminar on Infections in the CNS in Children" held in Bombay, India in 1983. These papers were considered significant enough to be published together in *Child's Nervous System.*

The pathology and pathogenesis of tuberculous encephalopathy and myeloradiculopathy: a comparison with allergic encephalomyelitis

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Abstract. The pathology and pathogenesis of tuberculous encephalopathy are reviewed. They confirm the findings in a smaller series previously published. The main features were: (1) diffuse brain edema and myelin pallor in the majority of specimens; (2) microvascular distension or necrosis with perivascular macrophage reaction and greater demyelination; (3) focal glial nodules in the white matter; (4) less frequently, hemorrhagic lesions in the presence of mild-to-moderate tuberculous meningitis (TM), but in the virtual absence of the commoner brain-damaging mechanisms. Focal demyelinating lesions in the nerve roots are now added to the above pathology in the brain in some of the cases of spinal tuberculous meningitis. In addition, a picture similar to that in human postinfectious allergic or experimental allergic encephalomyelitis (EAE) has emerged. The spinal cords from one case of the former condition and from four animals with EAE are described to illustrate this similarity. The pathogenesis of tuberculous encephalopathy and myeloradiculopathy is believed, as before, to be due to delayed hypersensitivity, i.e., cell-mediated immunity (CMI) to tuberculoprotein. Experimental confirmation of this demyelination as a nonspecific consequence of CMI to various forms of tubercle bacillus proteins has recently been published. In a proportion of our cases, where two episodes of TM had occurred, the possibility of a hypersensitivity reaction to the brain's own myelin protein is also considered.

Key words: Tuberculous encephalopathy – Myeloradiculopathy – Neurotuberculosis – Allergic encephalomyelitis – Cell-mediated immunity – Experimental allergic encephalomyelitis.

An unusual form of tuberculous meningitis in children was first briefly reported on clinical grounds alone by a colleague of mine who is senior pediatrician of the J. J. Group of Hospitals [19]. In this form, the meningitis is not severe, but severe diffuse brain damage, rapid progression, and death frequently ensue. Tuberculous encephalopathy is the most interesting and still the least understood aspect of tuberculosis of the central nervous system even 15 years after its clear dilineation by Dastur and Udani [9], Udani and Dastur [20] and Dastur and Lalitha [7]. In those three papers, we suggested that in the absence of extensive or copious tuberculous meningitis, border-zone encephalitis, vascular involvement with extensive ischemia or infarction, severe hydrocephalus, or large tuberculoma, which are the usual mechanisms producing pathologic changes in brain parenchyma in neurotuberculosis [5], the most likely mechanism is an allergic or hypersensitivity type of reaction to tuberculoprotein and/or the brain's own myelin protein in cases which have a history of an earlier, more usual type of tuberculous meningitis that had been inadequately treated [7].

Our hypothesis of pathogenesis was strikingly confirmed by the experimental work of Wisniewsky and Bloom [22] on demyelination following tuberculous infection in sensitized animals. Over the years, I have also been impressed by the fact that tuberculous encephalopathy is even more similar to some forms of human allergic encephalomyelitis and demyelination in the spinal nerve roots amid the exudate of tuberculous spinal meningitis than was mentioned in our earlier publications.

Another reason for studying the pathology of any aspect of tuberculosis of the central nervous system is that it is still very prevalent, even though the rate has been reduced during the last two decades of tuberculous meningitis compared to tuberculosis of all organs. This can be seen from the records of the J. J. Group of Hospitals [14] and by the proportion of brain tuberculomas versus other intracranial space-occupying lesions that have been examined histologically in the neuropathology unit of that hospital [13].

In the present communication a brief outline will be given of our own observations and conclusions on the pathogenesis of tuberculous encephalopathy, to be follwed by a consideration of the findings of Wisniewsky and Bloom. Some very recent relevant data on the role of lymphokines, lymphocytes, and macrophages in tuberculosis [4] will also be included.

Materials and methods

The brains for this study were obtained mainly through Professor P. M. Udani, and a few specimens also came from other pediatricians and neurologists. The patients had been children and young adults between the ages of 2 and 22 years. In all, about 30 brains were studied during the period 1962–1972. The spinal cords (about 25 in all) and the clinicopathologic correlations on spinal tuberculous meningitis were studied mainly on patients of Professor N. H. Wadia from 1958 to 1968 [11].

Brain biopsy specimens from the nondominant frontal lobe, extending from the surface to just outside the ventricular wall, i.e., including the full thickness of grey and white matter, were obtained from about a third of the patients. These were obtained usually by Professor S. N. Bhagwati. In the remaining cases autopsy material was available. All specimens were fixed in formalin, blocked in paraffin and the sections stained appropriately for cells, myelin, glia and occasionally for axons.

Results

The gross morphologic appearance of the fixed brain slices, in most of the cases where autopsy material was available, was consistent with that of diffuse brain edema. This was characterized by generalized pallor and bulkiness of the white matter and corresponding thinning of the cerebral grey matter. This feature was noticeable even in brain biopsy specimens, in most of which the full thickness of the white matter, was included, almost up to the wall of the anterior horn of the lateral ventricle. This "gross" appearance of edema was lacking in two specimens.

In a female child aged 4 years with miliary tuberculosis and a long history of inadequately treated tuberculous meningitis (TM), there were dense basal leptomeninges and miliary tubercles in the lungs. In the edematous and pale white matter, microscopy revealed diffuse myelin pallor with depleted oligodendroglia and distended venules (Fig. 1 a). A number of small perivascular or paravascular necrotic lesions containing small and large mononuclear cells (including astrocytes and microglia) were seen almost throughout the cerebral white matter (Fig. 1 b). There were also focal areas of demyelination in the deeper white matter of the cerebrum and cerebellum in this patient, shown as a periventricular bleached lesion in Fig. 2 a. Even in cases with diffuse edema, such as in this child, the perivascular space was particularly distended and contained a few glial cells and strands (Fig. 2 a). The neurons also suffered in such cases, with the large neurons of the cerebral cortex and the Purkinje cell layer tending to be depleted, possibly on account of anoxia as a result of pressure of the edematous white matter. This, too, was obvious in the brain of this particular child. The dentate nuclei showed a striking loss of neurons, as well as fiber elements, and were very pale and very sparsely cellular (Fig. 2 b). About a third of our cases showed such focal necrotic lesions in the midst of the white matter with diffusely depleted myelin.

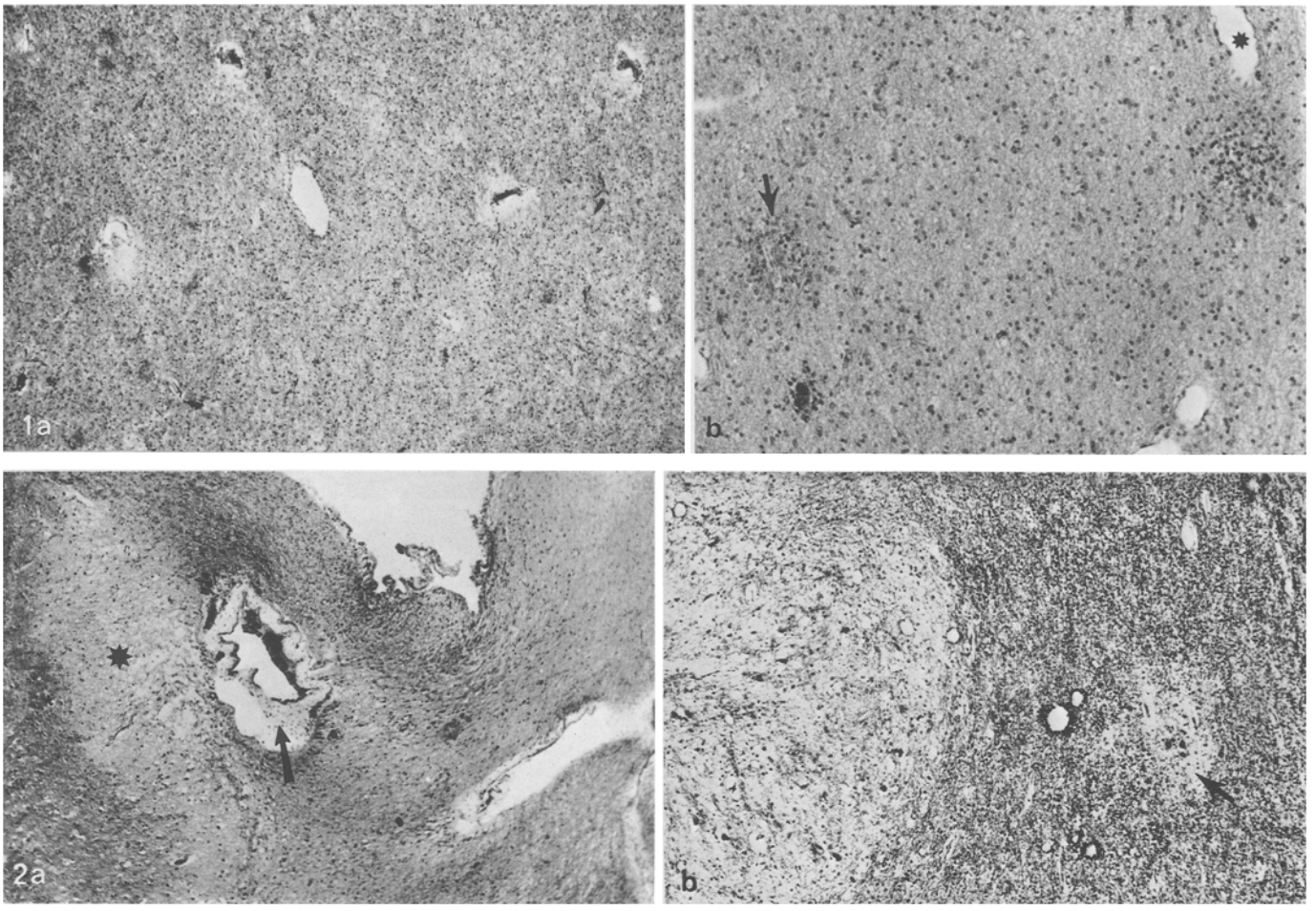
In contrast to the majority of patients was a boy 9 years of age who had had signs of meningitis, spasticity, and hydrocephalus on ventriculography. He had improved with antitubercular treatment but had shown persistent quadriparesis, hydrocephalus, and mental retardation. At brain biopsy the leptomeninges were found to be thickened and after fixation, instead of the diffuse pallor of the white matter, the specimen showed punctate congestion. At microscopy, foci of perivascular demyelination (Fig. 3 a), each with the demyelinated area full of large and small mononuclear cells (Fig. 3 b), were encountered in otherwise well-myelinated white matter. However, the deeper white matter showed pallor and an increase in astrocytes.

A still more unusual case, the only one of its kind, was a 17-year-old girl who was not treated for pulmonary tuberculosis despite her symptoms fever and cough, and detection of acid-fast bacilli in the sputum, 6 months before the terminal event. The last illness was sharp and severe, lasting only 4 days, with unconsciousness and decorticate flexor posture of the limbs. At autopsy, in addition to bilateral extensive pulmonary tuberculosis, there was miliary diffuse dissemination, and a striking hemorrhagic leukoencephalopathy of both cerebral and cerebellar hemispheres (Fig. 4 a). Microscopy showed the expected discrete and confluent recent hemorrhages in the white matter, with very little cellular reaction, plus exudation of plasma from the more outlying blood vessels and some perivascular focal areas of myelin loss (Fig. 4 b).

An unusual case was that of a 22-year-old student nurse who was admitted with signs of increased intracranial pressure of 3-week duration. There was severe bilateral papilledema with retinal hemorrhages, but plain radiography and ventriculography did not reveal any intracranial mass. Subtemporal decompression was carried out; the brain was under tremendous tension, pale and edematous. Despite mannitol, steroids, and antitubercular therapy, the patient died after 3 days. At autopsy, besides the severe diffuse cerebral and cerebellar edema, a small (1.5 cm) tuberculoma was found on the surface of one cerebellar hemisphere. There was compression of the ventricular system by edema, but no meningitis or any other lesion was detected. Histological examination confirmed the severe, diffuse edema with ballooned oligodendroglia in the white matter and prominent congested veins [17].

Two of our cases of spinal TM are included, as focal demyelination was seen in some of the nerve roots that were in the meningeal exudate but not infiltrated by it. This is seen in Fig. 5 a where the darker areas with retained myelin contrast with the paler areas (arrows) with loss of myelin within some of the nerve roots. Figure 5 b illustrates another case with entrapped spinal roots, at least one of which shows an area of perivenous demyelination.

One case of postinfectious allergic encephalomyelitis is included here that was a patient of Professor B. S. Singhal. This case was selected because (1) there was predominant involvement of the spinal cord and (2) the preceding infection appeared to have been bacterial with extensive infected burns (rather than the usual viral infection). This



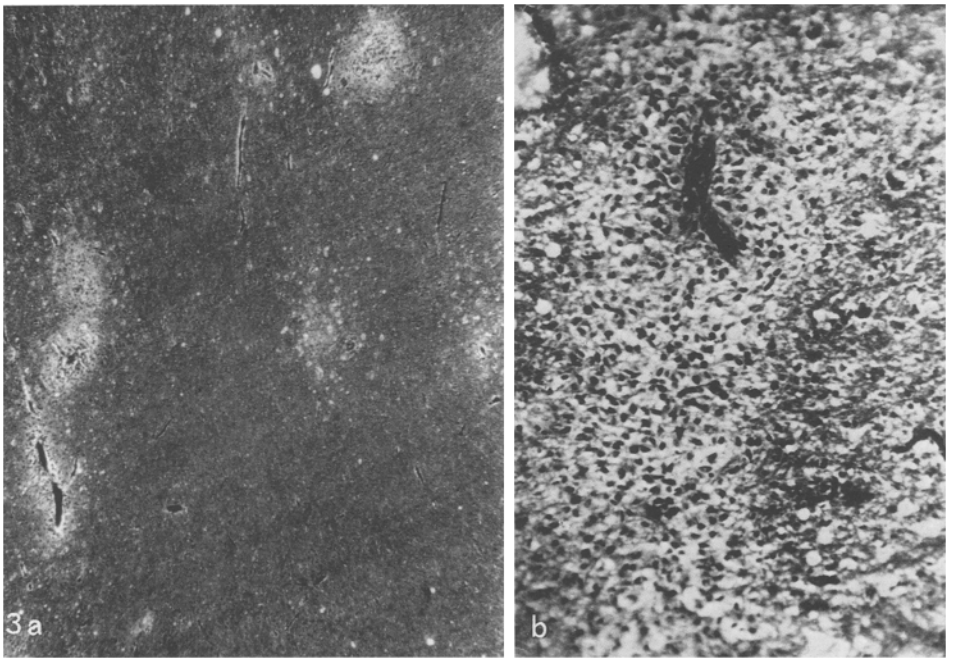
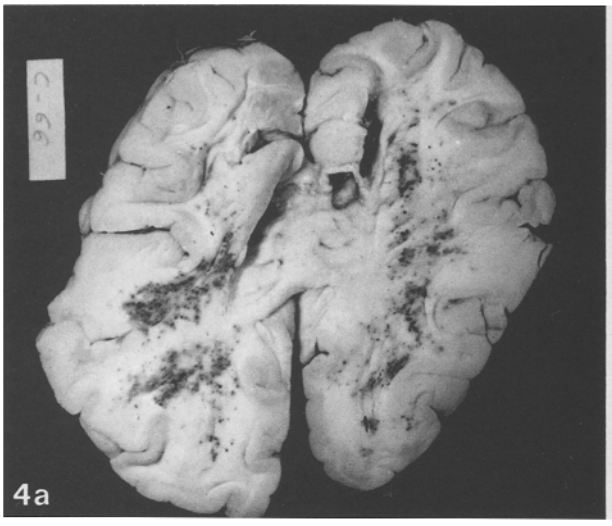
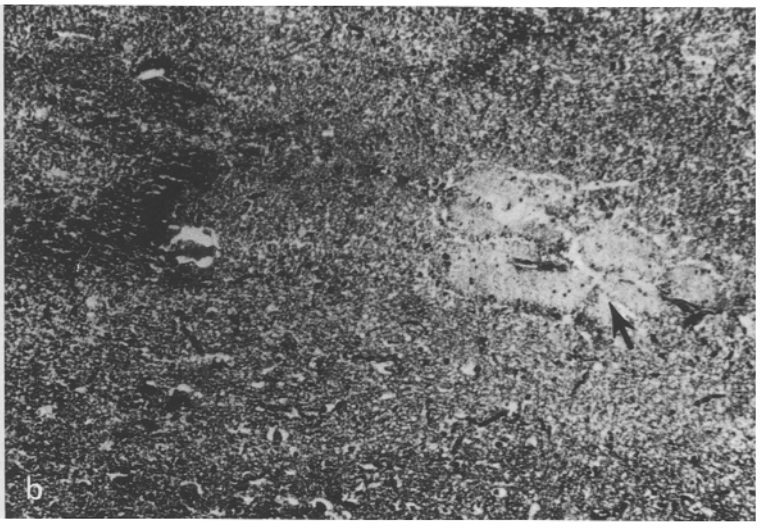


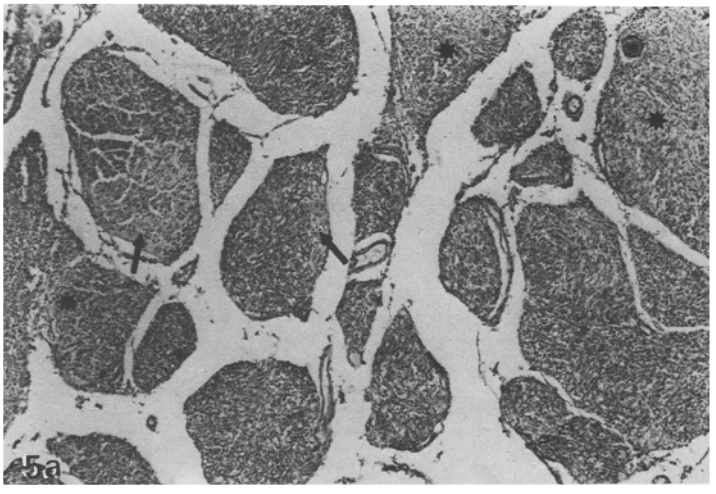
Fig. 1. **a** Diffuse myelin pallor and distended venules in the edematous white matter. Note some preservation of myelin along the left border (representing cortical "U" fibers). **b** Closer view of cerebral white matter, showing diffuse prominence of astrocytes and two necrotic foci, the larger on the right beneath a distended venule (*) and the smaller on the left (*arrow*) around a very small blood vessel. **a** Heidenhain's myelin stain, ×29; **b** hematoxylin and eosin, ×87

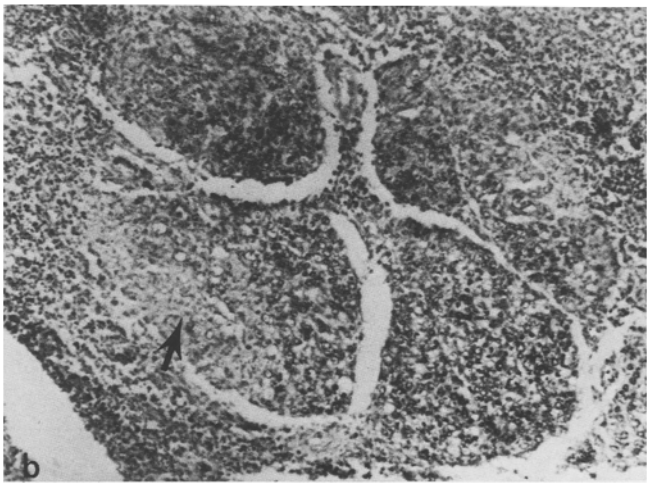
Fig. 2. **a** Bleached area of demyelination (*) to the left of the blood vessel with perivascular edema (*arrow*) in subependymal zone of the same brain. **b** Loss of fibers and neurons in the very pale dentate nucleus along the left side and a small perivascular demyelinating lesion (*arrow*) in the cerebellar white matter. Heidenhain's myelin stain, **a** ×64, **b** ×58

Fig. 3. **a** Many small foci of perivascular demyelination in otherwise well-myelinated white matter. **b** Closer view of one such focus, showing large and small mononuclear cells in the area of demyelination. Myelin stains, **a** ×27, **b** ×160









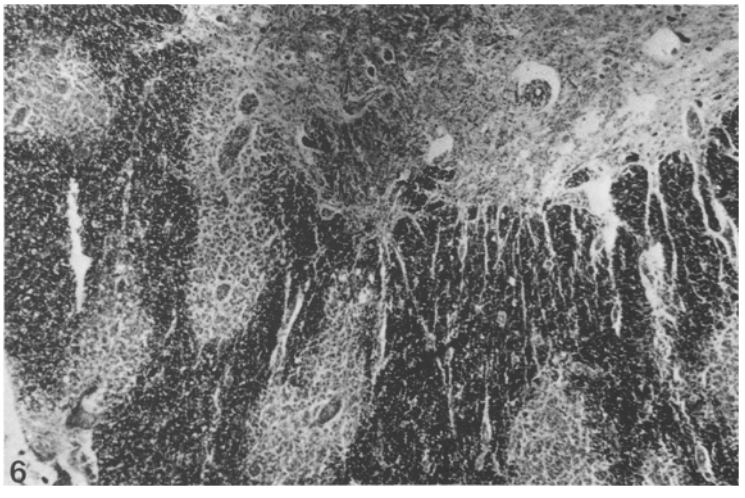


Fig. 4. **a** Petechial and confluent hemorrhages in the white matter of both cerebral hemispheres, constituting hemorrhagic leucoencephalopathy. **b** Part of the white matter showing hemorrhage on the left side and a perivenous demyelinated lesion (*arrow*) on the right, Myelin stain ×81

Fig. 5. **a** Lumbar spinal nerve roots, some showing patches of demyelination (*arrows*). The roots are entrapped amidst granulomatous inflammatory exudate (*); note the single giant cell at the top right. **b** Similar nerve roots entrapped amidst exudate and showing one clear area (*arrow*) of perivenous demyelination. Kluver-Barrera myelin stain, **a** ×44, **b** ×89

Fig. 6. Many foci of perivascular demyelination and cell reaction in the anterior column of cervical spinal cord in a case of postallergic encephalomyelitis. Kluver-Barrera myelin stain, ×34

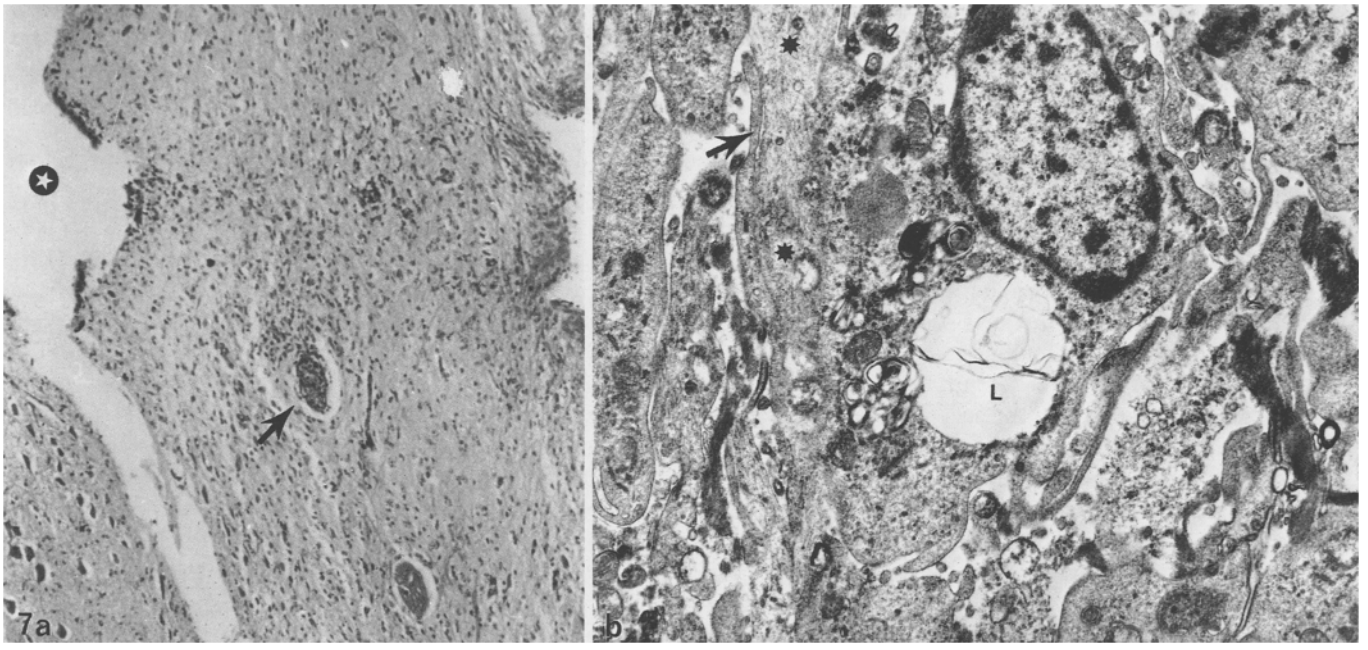


Fig. 7. a Subependymal part of cerebral hemisphere of guinea pig with EAE, showing vascular congestion, one paravascular cellular nodule (*arrow*) and diffuse glial cell reaction throughout. The lateral ventricle is indicated (*). **b** Electron micrograph of part of necrotic reaction in spinal cord of same animal. Note the large macrophage in the center with a vacuole (?-lysosomal, *L*) and the demyelinated axon (*between asterisks*) being engulfed by a tongue of macrophage cytoplasm (*arrow*). **a** H&E, ×102, **b** osmicated, thin araldite section, stained with uranyl acetate and lead citrate, ×7,000

case was a young woman aged 20 years, with a febrile illness of 10 days and neurologic disorder (mainly quadriplegia) of 8 days duration. The classic foci of perivenous demyelination packed with large mononuclear macrophages can clearly be seen in Fig. 6 which shows the cervical spinal cord, which was soft and swollen at autopsy.

In a more recent fine structural study of EAE induced in guinea pigs by injecting whole brain extract and complete Freund's adjuvant, we observed [15], as other have [1], various stages of demyelination, mononuclear cell reaction, phagocytosis, perivascular edema, and general tissue destruction, particularly in the spinal cord of paralyzed animals. The necrotic and phagocytic reaction is illustrated in Fig. 7 a, where a subependymal perivascular lesion is seen amidst white matter with diffuse increase of glial cells. Figure 7 b shows an electron micrograph of a vacuolated macrophage in severely necrosed tissue, including broken-down nerve fibers and a demyelinated axon that is actually being phagocytosed (between the arrows).

Discussion

The main clinical and neuropathologic features that argue in favor of the proposed pathogenesis of tuberculous encephalopathy and myeloradiculopathy are as follows. Certain patients, mostly children and infants, have had an acute-to-subacute course of neurologic illness, with relatively mild signs of meningitis and evidence of severe diffuse brain involvement in the form of rapidly developing drowsiness which has progressed to coma. This is often accompanied by generalized convulsions or decortication, leading to decerebration prior to death, against a background of overt or latent pulmonary tuberculosis. On histopathologic examination, there was severe diffuse brain edema and pallor of myelin affecting the cerebral and cerebellar white matter, which was accompanied by few to many perivenular foci of demyelination or tissue necrosis and microglial, i. e., macrophagic reaction. There was no evidence of severe border-zone encephalitis, large tuberculoma, extensive infarction or established hydrocephalus, which are the commoner brain-damaging mechanisms in neurotuberculosis [5, 7, 9]. Occasionally, however, such mechanisms may be in evidence, together with terminal edematous encephalopathy, in a child who has received irregular and inadequate antitubercular treatment for a long period (several months to over a year), after an initial attack of typical TM. We have recently reported one such case [10].

We have generally attributed this form of encephalopathy to an allergic or delayed hypersensitivity type of reaction to tuberculoprotein, on the basis of the predominant involvement of the white matter, the frequent focal perivascular demyelination, necrosis and microhemorrhages, and the clinicopathologic similarity to human or EAE. Sensitivity to the brain's own myelin protein has also been proposed as a possible additional or alternative allergen in these cases in the listed references. This

argument is now reinforced by the further evidence of demyelinating changes in the spinal nerve roots among the exudate of spinal TM, in children or young adults manifesting this less common form of neurotuberculosis. Originally, we had thought [11] that the pallor of compressed nerve roots was caused by edema. However, even though the circumferential pallor and vacuolation of the compressed spinal cord in such cases could, indeed, be caused by venous congestion and edema, the nerve root change is patchy and dissociated and is at times located around small blood vessels, most probably as a result of demyelination. In an earlier publication, we stressed the "microangiopathy" in the two main expressions of tuberculous encephalopathy, i.e., the severe vascular distension and thinning leading to vasogenic edema and the vasculitis with perivascular macrophage reaction and demyelination [7]. It is, therefore, not surprising that recent investigators have coined the term "disseminated vasculomyelinopathy" to mean the perivascular demyelination, hemorrhagic leukoencephalopathy, or even the Guillain-Barré-like picture seen in other postinfectious or post-immunization syndromes [16].

The meticulously planned experiments of Wisniewski and Bloom [22] have provided very impressive evidence in favor of a hypersensitivity mechanism producing the demyelinative and necrotic changes seen in our patients. Using different groups of animals previously sensitized with Freund's complete adjuvant and nonsensitized control animals, they injected one of the following four types of tuberculoprotein material at various sites: live tubercle bacilli, killed tubercle bacilli, old tuberculin, and PPD. By means of light and electron microscopy, they demonstrated clear demyelination in the vicinity of mononuclear cell reaction in the brain, the spinal cord, the nerve roots, and the nerves of the sensitized animals. They concluded that such primary demyelination was a nonspecific consequence of cell mediated immunity (CMI), expressing itself as hypersensitivity directed to a non-nervous antigen, i.e., mycobacterial protein. They further concluded that their work provided experimental proof of the allergic hypersensitivity type of mechanism we had suggested for our patients, also on the basis of CMI to tuberculoprotein. They, too, were impressed by the similarity of the changes in patients with tuberculous encephalopathy or myeloradiculopathy to those in human and EAE. Wisniewski and Bloom also noted the identity of cell reaction, i.e., the epithelioid type of macrophage in tuberculoid leprosy and tuberculosis, which the authors also pointed out [6].

New thinking on the concept of "delayed hypersensitivity" in tuberculosis is now called for on the basis of some current work in a few laboratories in the United States and the United Kingdom. The most striking contribution has been published by Crowle and his colleagues in Denver [4]. Based on their work and that of others, Crowle et al. have postulated that in human tuberculous infection, the bacilli destroy the polymorphonuclear cells that ingest them. They multiply slowly, but regularly in macrophages that come to the site of infection; some of these infected macrophages reach draining lymph nodes where they present the tubercle bacillary antigens to T lymphocytes. Specifically responsible clones of T cells become activated, replicate, leave the lymph nodes in large numbers, circulate in the blood throughout the body, and provide the infected subject with the two hallmarks of tuberculous infection: (a) tuberculin hypersensitivity (T cells reactive to tuberculoproteins) and (b) tuberculoimmunity (T cells reacting to immunizing antigen). They have explained the chain of complex cellular and molecular events constituting human tuberculoimmunity by demonstrating that the immunizing antigen (the immune lymphokine or growth inhibiting factor), immune T lymphocytes (from human peripheral blood), macrophages, and tubercle bacilli may be made to interact in vitro to produce specific expression of tuberculoimmunity in man.

Extrapolation of these events to those occurring in human tuberculous encephalopathy and myeloradiculopathy would imply: (1) that delayed type-IV hypersensitivity responsible for pulmonary or any other form of neurotuberculosis is dependent upon the "T lymphocytes reactive to tuberculo-proteins"; (2) that the lymphokines produced by such lymphocytes activate macrophages, confirming the older notion of lymphocytes transferring their immune capacity to macrophages as postulated by Kabat [12]; (3) that these activated macrophages kill replicating tubercle bacilli that they have ingested; and (4) that in the process the macrophages also produce focal host tissue destruction. In this case, the destruction is necrotic or demyelinating lesions in the CNS, possibly caused by the liberation of the somatic protein of Mycobacterium tuberculosis, which has an antigenic property [3] (an essential constituent of complete Freund's adjuvant and responsible for production of EAE-like lesions [21]). This postulate is supported by the comment of Crowle et al. [4] that "hypersensitivity T cells are mainly destructive to the subject and may produce a predominance of growth enhancing factor, in addition to causing tissue damage and tubercle formation." This is in agreement with the classic study of Burn and Finlay [2] in 1932, in which the necrotizing reaction in sensitized guinea pigs was rechallanged with intracisternal tubercle bacilli. It is also in agreement with the later experiment in monkeys by Tandon et al. [18] which resulted in meningitis and diffuse brain swelling. In addition, the experimental demyelination produced by various types of tuberculoprotein, introduced in the vicinity of brain, spinal cord, and nerves in sensitized animals, by Wisniewski and Bloom [22] and the "sensitized" human beings reported by us as tuberculous encephalopathy between 1965 [8] and now also confirm this hypothesis.

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