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The Roles of TNF in Brain Dysfunction and Disease

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Abstract

Certain cytokines, the prototype being the highly pleiotropic TNF, have many homeostatic physiological roles, are involved in innate immunity, and cause inflammation when in excess. These cytokines have long been accepted to have central roles in the pathogenesis of systemic or local non-cerebral disease states, whether acute or chronic, and whether or not caused by infectious agents. Over the last decade they have also been appreciated to be broadly important in brain physiology. As in other organs, excessive levels in brain are harmful, and its physiological complexity leads to correspondingly complex dysfunction. This review summarizes the burgeoning literature on this topic, and how the functions of these molecules, particularly TNF, are influencing the outlook of researchers on the pathophysiology of these diseases. Basic brain physiology is thus informing knowledge of the brain dysfunction that characterizes such apparently diverse states as Alzheimer's disease, trauma (mostly, but not only, to the brain), and Parkinson's disease, severe systemic infectious states, including malaria, sepsis, viral diseases and major depression. The implication is that the anti-cytokine therapies now in use, typically directed at TNF, warrant testing in these diseases in circumstances in which the therapeutic agent enters the cerebrospinal fluid. Routinely administering such drugs to patients exhibiting the neurological changes discussed in this review would simply add another organ system to what is already a very successful strategy in the treament of inflammatory disease at other sites, such as joints, skin and gut. Clearly, the most relevant research is focussed on Alzheimer's disease, but the principles may also apply to other encephalopathies.

Keywords
Alzheimer's disease, cerebral malaria, septic encephalopathy, viral encephalopathy, brain trauma, major depression

Abbreviations

Aβ, amyloid beta; AGE, advanced glycation end products; AMPA, alpha- amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; APP, amyloid β (A4) precursor protein; CO, carbon monoxide; CORM-3, tricarbonylchoro(glycinato)ruthenium (II); CSF, cerebrospinal fluid; GABA, gamma -aminobutyric acid; H_2S, hydrogen sulfide; HMBG1, high mobility group box 1 protein; HO-1, hemoxygenase-1; i. c. v., intracerebroventricular; IL-1, interleukin-1; iNOS, inducible nitric oxide synthase; IFN-γ, interferon-γ; LPS, lipopolysaccharide; LTP, long-term potentiation; lymphotoxins, LTs; NMDA, N-methyl-D-aspartate; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; mtDNA, mitochondrial DNA; RAGE, receptor for advanced glycation end products; SIRT, sirtuin; TAPI-2, TNF protease inhibitor-2; TACE, TNF converting enzyme; TGFs, transforming growth factors; TLR2, toll-like receptor 2; TNF, tumor necrosis factor.

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1. Introduction – why link cerebral malaria and Alzheimer's disease?

Several years ago, driven by the conflict between the traditional mechanism in the literature on human cerebral malaria and the logic of physiology (and therefore pathophysiology), we were searching the outer reaches of its literature for a way to describe the cul de sac the field had entered. This uncovered what we regarded as a particularly clear article (Castellani *et al.*, 2008) on the same problem in Alzheimer's disease: a well-entrenched conventional approach born of an ancient histological observation being argued to have outlived its usefulness – indeed, in Castellani's words, having become somewhat of a nuisance to what should be the real focus, invisible molecules and subcellular damage that cannot be verified by direct observation.

This sounded familiar for some of us in the human cerebral malaria world. This form of encephalopathy rivals Alzheimer's disease in the scale of the problem, either condition being much more common than other similar diseases. Untreated malaria infection in naive individuals can best be described as fitting in with the systemic infectious diseases that are liable to exhibit an associated encephalopathy. Over a hundred years ago, and for want of any other leads, pathologists were attracted to red cells containing parasites often seen in sections from brains of fatal coma cases caused by the parasite *Plasmodium falciparum* (Marchiafava & Bignami, 1894) when seeking a mechanism for the neurological aspects of malaria, and mechanical blockage of microcerebral vasculature soon became the accepted explanation for this condition. Thus the disease caused by this species of malaria, which dominates most of the malarial world, parasitized red cells adhering to the walls of small cerebral blood vessels became the primary cause of abnormal brain function. This is referred to as the parasite sequestration argument of malarial disease, in which physically restricted blood flow is believed to deprive brain cells of oxygen and nutrients. It is still commonly championed as the primary cause of the encephalopathy seen in human malaria, although, as discussed later, emerging information on vivax malaria is making this allegiance difficult to sustain.

As reviewed (Castellani *et al*., 2008), those searching brain sections from cases that included what is now called Alzheimer's disease described neurofibrillary tangles (NFTs) (Fuller, 1907) – later found to be comprised of tau protein – and plaques, later realized to be formed of amyloid beta (Aβ). As with adherent parasitized red cells in malaria, these obvious physical structures became the centre of attention for investigators trying to understand Alzheimer's. The earlier literature on the apoE4 association with Aβ (Section 5.2.5.) undoubtedly reinforced case for amyloid being the primary cause of this disease. Assumed to be directly harmful, NFTs, plaques, and the molecules that formed them became the target of science-based interventions. It seems that in both fields, therefore, histological hallmarks have somehow been allowed to evolve into primary mechanisms that researchers were comfortable with, perhaps, in part, because they could point them out with the aid of a microscope.

Over 60 years ago, a malaria researcher with sepsis research experience summarized the accumulated scepticism in the malarial literature, and suggested that inflammation was a more likely explanation for the mechanism of the disease (Maegraith, 1948). The parallels with the scientific challenge at the core of cerebral

malaria and Alzheimer's disease are striking, not least because the key inflammatory cytokine, tumor necrosis factor (TNF), is appearing with increasing frequency in both literatures. The link between TNF and any non-tumor disease actually began with malaria.

In the late 1970's, when TNF had a small new literature restricted to the tumor killing, one of us (IAC) began collaborating with the group who first described TNF (Carswell *et al.*, 1975). This original TNF-systemic disease link thus made has been reviewed recently (Clark, 2007). Our joint research was directed at understanding host protection against malaria parasites as well as malarial pathology. By 1995, these same inflammatory mediators were argued to be relevant to the pathogenesis of Alzheimer's and other neurodegenerative diseases (McGeer & McGeer, 1995). Some years later, tissues from malaria brains were stained for amyloid β (A4) precursor protein (APP) (Medana *et al.*, 2002) and cerebral malaria CSF was assayed for tau (Medana *et al.*, 2005). In the same year it was reported that excess Aβ would not alter an important neurological function in mice lacking the gene for TNFR1 (Wang *et al.*, 2005), and later cerebral malaria severity was correlated with CSF levels of TNF (John *et al.*, 2008b). In the following year it was reported that TNF induces tau accumulation (Gorlovoy *et al.*, 2009). Clearly, acquiring a decent working knowledge of of the science behind Aβ and tau, the histological hallmarks of Alzheimer's disease, is necessary for research into malarial disease, and competence in Alzheimer's research increasingly requires reasonable literacy in TNF. Only then can the considerable congruency between cerebral malaria and Alzheimer's disease be appreciated. Indeed, such an interaction was the genesis of the collaboration represented by this review, with a TNF researcher with a cerebral malaria background reading a review on the link between neurogenesis and cytokines (Abdipranoto-Cowley *et al.*, 2009).

The major theme developed in this review is that the development of the basic literature on TNF and neurophysiology (and hence neuropathophysiology) appears to apply to cerebral malaria and Alzheimer's disease. Although these two diseases differ greatly in the age group affected and rapidity of onset and duration of clinical change, Alzheimer's might be usefully viewed, in pathophysiological terms, as a much less acute, but more insidious, version of cerebral malaria and its sequelae. This contrast should not deter us from this view, any more than should the chronicity AIDS dementia conceptually separate it from the more acute viral encephalopathies. All encephalopathies discussed here show evidence of the same pattern of events, albeit with different severities and durations. Cytokine-mediated diseases in particular are inevitably multifactorial, and much can be lost if each is considered in isolation. Our hope in this review is that by considering these diseases together perspectives that might have otherwise lain dormant will surface, and bring about a consensus that leads to useful treatment.

2. TNF and the other cytokines, and the innate immune system

As well as discussing the inflammatory cytokines themselves, a brief overview of the innate immune system, which is evolutionarily older than adaptive immunity, is warranted here. Activation of the innate immune system leads to the production of TNF and similar cytokines, and depends on them. The past decade has witnessed considerable conceptual advances in our understanding of how innate immune responses, which dominate the CNS (Section 4.5), are initiated. New inclusive terminologies have accompanied this. PAMPs, or pathogen-related molecular

patterns (Janeway, 1992), on viruses, bacteria and fungi are now joined by DAMPs, (danger-associated molecular patterns) found on proteins, released from damaged cells (Matzinger, 2002) as entities recognized, or sensed, by pattern recognition receptors (PRRs). Gram-negative bacterial cell wall lipolysaccharide (LPS), also called endotoxin, and discussed variously throughout this review, is an example of a PAMP, and HMGB1 (Section 4.3) can be regarded as a DAMP. The most intensely studied PRRs are the Toll-like receptors (TLRs) comprising a superfamily of at least 11 members expressed by a wide range of cells. As reviewed (Beutler & Poltorak, 2001), the Drosophila Toll protein has a fascinating lineage stretching from insect dorso-lateral polarity, through insect innate immunity, to its homologs being important for mammalian innate immunity. Once activated, TLRs induce signalling cascades that predominantly lead to release of inflammatory cytokines, chemokines, and anti-microbial peptides (AMPs). This is discussed in more detail in Section 5.2.3).

More recently, other families of PRRs have been described. Unlike most TLRs, which are membrane-bound, the newer PRR families consist of soluble proteins that provide cytoplasmic surveillance in order to detect intracellular invaders. They include NLRs, or NOD-like receptors. NLRs, and other proteins such as NALP3, form cytoplasmic complexes termed inflammasomes that activate caspase-1, thus generating IL-1β and IL-18 from their precursor proteins (Martinon *et al.*, 2002; Martinon *et al.*, 2009). IL-18 is a well-known inducer of TNF (Tsutsui *et al.*, 1997; Dinarello, 1999). TNF in turn promotes activation of caspase-1 induced by other agents, such as ATP (Franchi *et al.*, 2009), logically enhancing IL-1β and IL-18 production, and hence reinforcing itself, even in the absence of microbial infection.

Cytokines have many functions, and are generated by many cell types. Many are classified under the general term of interleukins (Aarden & others, 1979), which currently extend from interleukin-1 (IL-1) to IL-34. Some, but not all, earlier cytokines, such as the interferons (Isaacs & Lindenmann, 1957) the lymphotoxins (LTs) (Ruddle & Waksman, 1967), TNF (Carswell *et al*., 1975), and the transforming growth factors (TGFs) (Moses *et al.*, 1981) did not conform to this terminology. Cytokines have primary roles in physiology, including neurophysiology, innate and acquired immune responses and wound healing. as well as disease pathology. They operate in networks and cascades, and regulate cellular activity in an autocrine, paracrine and hormonal manner. For example IL-1 is induced by TNF, and shares many of its activities, including the capacity to induce IL-6. This cytokine is often used as a marker for systemic inflammatory reactions because it appears in the circulation conveniently later, when illness is undeniable, and stays high for longer. As another example of the complexities, both TNF and IL-1 induce IL-8, the prototype chemotactic cytokine, or chemokine, terms given to cytokines that attract cells along their concentration gradients. Many cytokines are now arranged in families with similar structures and functions. Some cytokines, such as TNF, LTs and IL-1 are pro-inflammatory, whereas others such as IL-4, IL-10 and the TGF family, are anti-inflammatory, being subsequently induced to inhibit these changes. These anti-inflammatory cytokines are established, from the work of Schwartz's group (see Section 6.2.2.), to be central in understanding how macrophages of systemic origin control brain injury and degeneration.

A number of more newly discovered interleukins, such as IL-12, IL-17 and IL-22 are increasingly linked with TNF (Yamaguchi *et al.*, 2007). This group of interleukins need to have their roles in innate immunity and inflammation explored further, but since they are as yet little studied in the brain they largely remain outside

the scope of this review. In passing, we note that the original term,TNF (Carswell *et al*., 1975) , is identical to TNF-α, the commonly-seen suffix being a now meaningless relic from when LT, now LTα, was, for a limited period some years ago, referred to as TNF-β.

Some cytokines, the prime example being TNF, are highly pleiotropic. It is, for example, an *in vitro* tumor killer, a common regulator of normal physiology, including of synapses, a homeostatic agent in cell proliferation (see Section 3.3), a key mediator of innate immunity (Clark *et al.*, 1981), and the master cytokine that precipitates the inflammatory response (Charles *et al.*, 1999). Our proposal that the pathology of malaria and salmonella infections is caused by over-exuberant production of the mediators of innate immunity (Clark *et al*., 1981), coupled with its recent linkage to the role of TNF in neurogenesis following neurodegeneration (Abdipranoto-Cowley *et al*., 2009) led this review to be largely about this cytokine. Not only does TNF possess the multiple roles outlined above, but the hugely successful biotechnology industry based on antagonizing it (some $20 billion in sales in 2010) provides excellent experimental tools to explore diseases further, as well as to treat patients. Also TNF has by far the largest literature of the cytokines, allowing more comprehensive sets of useful implications. Several negative feedback loops of cytokines and their products have been shown to limit TNF generation. An example is hemoxygenase-1 (HO-1), which generates carbon monoxide (CO), which in small amounts is anti-inflammatory (Lee *et al.*, 2003), because it inhibits TNF. This, and a functionally similar molecule, hydrogen sulfide (H_2S), are discussed in more detail in Section 3.4.

3. Roles of TNF in the brain

Is TNF an initiator, or merely a marker, of brain disease? In practical terms, does intrathecal inflammation, of which TNF is the prototype mediator, precede the onset of Alzheimer's, or is it a reaction to its presence? To approach this question, TNF levels were assayed in CSF from 56 individuals who had mild cognitive impairment (MCI), a condition that can develop into frank Alzheimer's disease, and 25 age-matched controls. When levels were tracked over a period, MCI cases were much more likely to develop into Alzheimer's if they had higher TNF levels (Tarkowski *et al.*, 2003a). Newer studies continue to reaffirm this principle, with markers of inflammation showing in serum and CSF before any indications of increased Aβ or tau (Laurin *et al.*, 2009; Schuitemaker *et al.*, 2009). This is consistent with data in Sections 5.2.1 and 5.2.2. Another group took advantage of the increased sensitivity of assaying for soluble TNF receptors rather thanTNF itself. They found good evidence for levels of these receptors in serum and CSF predicting, over a 4-6 year period, conversion to clinical Alzheimer's disease (Buchhave *et al.*, 2009).

Others have studied plasma levels of acute phase proteins, which are widely used as general indicators of inflammation that are upregulated by TNF or IL-1. For example C-reactive protein (CRP) and α1-antichymotrypsin (ACT) (Engelhart *et al.*, 2004), or CRP alone (Laurin *et al*., 2009; Schuitemaker *et al*., 2009), are present in serum and CSF before any indications of increased Aβ or tau. These studies have now been extended and confirmed by an impressive new report of plasma levels of another acute phase protein, clusterin (apolipoprotein J), being intimately associated with onset, progression, and severity of this disease (Thambisetty *et al.*, 2010). A novel and impressive proteomic neuroimaging paradigm was employed.

Unfortunately, the authors refer only to the amyloid chaperone function of clusterin, and seem to have been unaware of its role as an acute phase protein (Hardardottir *et al.*, 1994), and therefore a marker, as surely as are CRP and ACT, of inflammation. One of their more telling findings was that clusterin was raised 10 years earlier than fibrillar Aβ deposition. Taken together, these acute phase reactant arguments are an impressive link between inflammation the primary instigation of Alzheimer's disease.

Basic knowledge of the roles of cytokines such as TNF in the brain has expanded greatly in the last decade. For instance, as discussed in Section 5.2, TNF is associated at several levels in the amyloid pathway: before APP, in the conversion of APP to Aβ, and after Aβ has been generated. For some time TNF has been realised to be generated not just by microglia, as their macrophage-like character would predict, but also by neurons and astrocytes. In the light of its original tumor-killing capacity, brain-origin TNF was initially thought of purely in terms of causing cell death, but nowadays it is widely appreciated to be a physiological gliotransmitter concerned with normal communication, particularly between astrocytes and synapses, microglia and synapses, and thus synapse regulation. Indeed, TNF fits nicely into the tripartite view of synaptic physiology (Perea *et al.*, 2009). It can also suppress adult neurogenesis, allowing net neuron numbers to reduce because of non-replacement (Abdipranoto-Cowley *et al*., 2009). TNF also influences cerebral function through acting on mitochondria. This section summarizes these functional roles of TNF.

3.1. The effect of TNF on synapse function

The synapse is a particularly dynamic part of the neuron, and one of the earliest lesions noted in Alzheimer's brains is a reduction in synaptic efficacy (Selkoe, 2002). As recently reviewed (Arendt, 2009), many studies have also reported that synaptic loss is very pronounced. Indeed it is thought to be the strongest structural correlate of cognitive decline in this disease (DeKosky & Scheff, 1990). Soluble Aβ oligomers have been shown to be a contributing factor (Shankar *et al.*, 2007). Another such factor is nitric oxide (NO) from inducible nitric oxide (iNOS, or NOS2) stimulated in response to TNF that is induced by LPS (Weberpals *et al.*, 2009), in the reasonably presumable absence of Aβ. As discussed in Section 4.5, these authors were investigating the protection provided by the long-term cognitive defects caused by LPS, and found that *NOS2* gene deficiency prevented loss of the structural synaptic proteins seen in normal mice. These two observations are quite compatible when the ability of soluble Aβ oligomers to induce TNF, and its inactivity if it does not do so (Meda *et al.*, 1995; Wang *et al.*, 2005; Rowan *et al.*, 2007) (see below), is taken into account. Additionally, these data are consistent with Aβ (Abramov *et al.*, 2009) and TNF (Domercq *et al.*, 2006) having similar effects on synaptic vesicle release.

The review referred to above (Selkoe, 2002) was written when it was beginning to be realized that the soluble naturally occuring soluble human oligomeric forms (rather than monomers or visible fibrils or plaques) of beta-amyloid were best at inhibiting long-term potentiation (LTP) (Walsh *et al.*, 2002) and *in vivo* cognitive behaviour (Cleary *et al.*, 2005). Since Aβ induces TNF (see Section 5.2.4) it is not surprising that both of these agents give the same outcomes in many functional assays, such as those done on brain slices. Paired functions of Aβ and TNF extend, for instance, to LTP, with both soluble Aβ dimers (Taylor *et al.*, 2008; Ondrejcak *et al.*, 2009) and TNF (Tancredi *et al.*, 1992; Wang *et al*., 2005) shutting it down. In addition, two synthetic agents being developed for treating Alzheimer's, Ro25-6981

and ifenprodil, were recently reported to prevent the shut-down of synaptic transmission caused by soluble Aβ dimers in rats (Hu *et al.*, 2009b). Two different specific anti-TNF agents, infliximab and a specific peptide antagonist were equally inhibitory as these GluN2B-specific drugs. In addition, they reported that Ro25-6981 prevents inhibition of synaptic transmission caused by TNF. So would, by definition, specific anti-TNF agents that enter the brain in sufficient quantities. These authors also added to the evidence that Aβ dimers act through TNF by demonstrating that synapses in apical dendrites are susceptible to both agents, and synapses in basal dendrites are susceptible to neither.

In 2005 the capacity of TNF to rapidly upregulate calcium-permeable AMPA/kainate channels on neurons, with obvious implications for it to influence synaptic transmission, was published (Ogoshi *et al.*, 2005). Soon after, the phenomenon known as synaptic scaling, in which the strength of all synapses on a cell are adjusted in response to prolonged changes in the cell's electrical activity, was argued to be mediated by TNF (Stellwagen & Malenka, 2006). In addition, TNF has been shown to control regulation of the type-1 inositol 1,4,5 trisphosphate receptor (IP_3R), which is central to calcium homeostasis, and calcium-dependent functions, of neurons (Park *et al.*, 2008). Subsequently, TNF was reported to modulate synaptic plasticity through inducing sphingomyelinase-2, and thus controlling the insertion of N-methyl-D-aspartate (NMDA) receptors into neuron membranes (Wheeler *et al.*, 2009). Additionally, TNF can be expected to alter synaptic function through its striking ability to regulate their morphology. In brief, the percentage of pedunculated spines on dendrites is considerably decreased in neuronal cultures from iRNA-mediated TRAP-1 (TNF receptor-associated protein-1) knock-down mice (Kubota *et al.*, 2009).

It has recently been more appreciated that the astrocyte, as the predominant glial cell of the central nervous system, orchestrates the whole enterprise. The processes of one astrocyte contacting tens of thousands of synapses, and controling discrete large territories (Kuchibhotla *et al.*, 2009). While astrocytes do not generate action potentials, they nevertheless have the capacity to communicate well with neurons (Haydon, 2001). TNF (which astrocytes as well as microglia and neurons can release) normally stimulates the release of glutamate from astrocytes – through selective activation of purinergic P2Y1 receptors on astrocyte cellular membranes (Domercq *et al*., 2006) – into the synapse microenvironment (see for review (Volterra & Meldolesi, 2005; Haydon & Carmignoto, 2006)).

While the research referred to directly above was performed with the goal of establishing the range of physiological roles of TNF in synapse function, it also lays the groundwork for understanding the pathological consequences of TNF excess. For instance, if the active, soluble forms of Aβ act through TNF, which has been shown to alter synaptic transmission, it becomes plausible that the same synaptic pathology (caused by TNF) explains the similarity between dementia of Alzheimer's disease and the delirium and encephalopathy in critical illness, independent of their initiating factor (Stevens & Pronovost, 2006).

It therefore seems reasonable to presume that the neurological consequences of excess brain concentrations of TNF (usually defined as cerebrospinal fluid (CSF) concentrations exceeding the upper limit of the homeostatic range required for normal physiological function) inhibit neurotransmission. Examples of this limit being exceeded include the increased brain and CSF levels of TNF reported in human (Moller *et al.*, 2005) and experimental (Barichello *et al.*, 2009) meningitis, cerebral malaria (John *et al*., 2008b), Alzheimer's disease (Tarkowski *et al*., 2003a; Tarkowski

et al., 2003b), fronto-temporal dementia (Sjogren *et al.*, 2004) and Parkinson's disease (Mogi *et al.*, 1994). Where examined, CSF and serum levels of TNF did not correlate, implying separate generation within each compartment. These concepts are examined further in the section on post-sepsis encephalopathy (see Section 4).

A dramatic example of altered functionality is the synchronous hyperactivity and intercellular calcium waves recorded in astrocytes in a mouse model for Alzheimer's disease (Kuchibhotla *et al*., 2009). These waves were did not originate near Aβ plaques or neurons, but within the astrocytes themselves. Another example is the reduced capacity of hippocampal astrocytes to release glutamate when exposed to TNF in another mouse model of Alzheimer's (Rossi *et al.*, 2005). The authors point out the potential for this defect to down-regulate synaptic activity in these mice. Similar experiments are yet to be performed in meningitis and cerebral malaria models.

3.2. Influence of TNF on the role of zinc in synapse function

For decades zinc has been realised to be necessary for normal brain function (Wallwork, 1987). Much of the brain zinc is bound in metalloproteins, as elsewhere in the body, and the remainder stored in pre-synaptic vesicles. Ionic zinc has long been argued to have a physiological role in hippocampal synaptic neurotransmission (Xie & Smart, 1991).

TNF is very involved with zinc metabolism. Zinc-deficient animals are more sensitive to TNF (Waelput *et al.*, 2001), and hypozincemia is so dramatically induced by LPS, the prototype inducer of TNF, that blood zinc level has been proposed to be a useful assay for pyrogens (Boobis & Hartley, 1981). TNF induces astrocytes to secrete S100B, a zinc-binding protein (Edwards & Robinson, 2006), and TNF (Tarkowski *et al*., 2003a) as well as S100B (Green *et al.*, 1997; Peskind *et al.*, 2001), are increased in the CSF, and, perhaps as a consequence, distributed in brain regions in proportion to degree of pathology (Van Eldik & Griffin, 1994) in Alzheimer's patients. Ionic zinc is an endogenous modulator of synaptic functions controlled by alpha- amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), NMDA and gamma -aminobutyric acid (GABA) receptors (Harrison & Gibbons, 1994; Smart *et al.*, 1994). These synaptic functions include LTP, a synaptic phenomenon widely theorized to be a correlate of memory formation (Bliss & Collingridge, 1993), which is abnormal in zinc deficient rats (Hesse, 1979). Since S100B is a zinc-binding protein (Mbele *et al.*, 2002), it is plausible that its induction (Edwards & Robinson, 2006) contributes to inhibition of synaptic activity by TNF. This is consistent with reports of impaired spatial learning memory after chelation of synaptic zinc (Frederickson *et al.*, 1990) and learning impairment after dietary zinc deprivation (Takeda *et al.*, 2000). It is also consistent with the recent report that Alzheimer’s-like pathology is exacerbated in Tg2576 mice overexpressing human S100B (Mori *et al.*, 2010).

Interactions between S100B and metallothioneines, the more widely appreciated endogenous zinc chelators, appear to have not yet been studied. The review of the roles of zinc in brain function and pathology that has recently appeared (Bitanihirwe & Cunningham, 2009) is excellent, but did not include the implications of S100B in this context.

3.3. TNF and adult neurogenesis

A decade ago, when much scepticism still surrounded the evidence for neurogenesis in adults, the shrunken brains of Alzheimer's patients was simply interpreted as cell loss through neurotoxicity. This view will no doubt be revised by the discovery of stem cells in the adult human, primate and rodent hippocampus (Zhao *et al.*, 2008). As recently reviewed (Abdipranoto *et al.*, 2008), such brain shrinkage can readily be reasoned to indicate an imbalance between cell loss and neurogenesis, or even the failure of an intrinsic capacity for replacement of loss through natural attrition, much the same as in other organs. Functional studies of neurogenesis in the adult mouse hippocampus support the concept that such replacement is an important regulator of long-term memory (Rola *et al.*, 2004; Aimone *et al.*, 2006; Zhao *et al*., 2008; Kriegstein & Alvarez Buylla, 2009). In particular, arguments exist that continuous neurogenesis is required for normal retention of spatial and contextual memory (Snyder *et al.*, 2005; Imayoshi *et al.*, 2008) and object recognition.

Inflammation can repress neurogenesis (Abdipranoto-Cowley *et al*., 2009). When the requirement for Aβ to induce TNF before it can influence learning and memory is considered (Wang *et al*., 2005; Ralay Ranaivo *et al.*, 2006; He *et al.*, 2007), research on Aβ inhibiting neurogenesis (Haughey *et al.*, 2002) is entirely consistent with the TNF data summarized in this section. Likewise, a series of papers on allopregnanolone and neurogenesis in Alzheimer's disease appears to have left the effects of TNF on neurogenesis out of consideration. In brief, allopregnanolone has been shown to be reduced in brains of Alzheimer's patients (Marx *et al.*, 2006), and to be a potent proliferative agent for both rodent and human neural stem cells (Brinton & Wang, 2006). Neither of these papers, nor a more recent review (Wang *et al.*, 2008), refer to the capacity of allopregnanolone, at levels detected *in vivo*, to reduce LPS-induced TNF release from macrophages (Ghezzi *et al.*, 2000), and to reduce TNF and IL-1β production in cells isolated from rats with traumatic brain injury (He *et al.*, 2004).

To our knowledge only one paper, from a group working on post-stroke neurogenesis, has examined the functional interaction of Aβ and TNF (Katakowski *et al.*, 2007). As the authors point out, stroke is a known cause of dementia, and ischemic events are thought to contribute to the progression of Alzheimer’s disease. Aβ deposits are associated with ischemic injury (Koistinaho & Koistinaho, 2005) as well as with Alzheimer’s disease. These authors found that intraventricular infusion of TNF protease inhibitor-2 (TAPI-2), which increases TNF levels, decreased proliferation of subventricular zone cells subjected to middle cerebral artery occlusion. These results are consistent with the idea that TNF reduces the number of subventricular zone progenitors. In addition, primary cultures of the ischemic subventricular zone cells, collected before TAPI-2 infusion, overexpressed tumor necrosis factor converting enzyme (TACE) and its substrates, amyloid precursor protein (APP) and TNF. These concepts, and their therapeutic implications, have been argued to warrant examination in an Alzheimer's context (Katakowski *et al*., 2007).

Neurogenesis is part of the bigger picture in which pathways directly or indirectly triggered by TNF influence cellular homeostasis throughout the body, with low levels enhancing proliferation of a cell or organelle that higher levels destroy (Bernardino *et al.*, 2008). This phenomenon extends to thymocytes (Ranges *et al.*, 1988; Hernandez Caselles & Stutman, 1993), hepatocytes (Diehl & Rai, 1996; Bour *et al.*, 1996), hematopoiesis (Clark & Chaudhri, 1988; Rebel *et al.*, 1999) and mitochondria (Suliman *et al.*, 2005; Nisoli & Carruba, 2006; Haden *et al.*, 2007).

Hence in some experimental circumstances TNF can inhibit neurogenesis (Monje *et al.*, 2003; Cacci *et al.*, 2008), and so too can inhibiting TNF with an anti-TNF antibody (Heldmann *et al.*, 2005). We propose that, in keeping with other organs, above, the effect depends on how much TNF is present. These principles extend to acute infectious disease, with a TNF-inducible enzyme, inducible nitric oxide synthase (NOS2), being implicated (Hoffmann *et al.*, 2007) in meningitis-induced neurogenesis. TNF is also implicated in the neurogenesis of stroke (Heldmann *et al.*, 2005) and, if Aβ-induced TNF (Meda *et al.*, 1995; Wang *et al.*, 2005) is accepted and taken into consideration, Alzheimer's disease (Becker *et al.*, 2007).

3.4. TNF, brain mitochondria, and the brain's high ATP requirements

Aβ is associated with mitochondrial dysfunction, in which oxygen usage by the respiratory chain complex is reduced, leading to lowered ATP generation and functional loss in brain cells (Aleardi *et al.*, 2005; Chen *et al.*, 2006). While much of this literature implies that Aβ can impair mitochondrial function directly, newer research takes into account the observation that Aβ is a ligand for RAGE, the receptor originally described for its ability to tether advanced glycation endproducts (AGE) to cell surfaces. Once occupied, RAGE activates NF-κB, a transcription factor that initiates the inflammatory cascades induced by TNF and related cytokines. RAGE-bearing cells include neurons and microglia (Yan *et al.*, 1996). TNF can apparently inhibit mitochondrial function directly (Busquets *et al.*, 2003); however, and more plausibly, does so by generating mediators, such as NO and oxygen radicals, with this capacity. This concept has expanded greatly in the basic (Sanchez-Alcazar *et al.*, 2000) and applied literature, particularly that of sepsis and heart failure (Moe *et al.*, 2004). Much research exists on the pathways involved in this bioenergetic aspect of systemic inflammation (Fink, 2001; Fink, 2004; Singer *et al.*, 2004), as well as heart (Mariappan *et al.*, 2009) and brain (Tangpong *et al.*, 2008) pathology. Hence a reasonable explanation for the mitochondrial dysfunction caused by Aβ involves TNF-initiated reactive oxygen species.

This explanation assumes that mitochondrial dysfunction in Alzheimer's disease requires Aβ accumulation. However, there is now evidence, in a mouse model bearing two mutations in APP, that lowered mitochondrial membrane potential and reduced ATP levels appear three months before Aβ deposits (Hauptmann *et al.*, 2009). Attributing this ATP reduction to intracellular Aβ (Hauptmann *et al.*, 2009) fails to consider the capacity of Aβ to induce TNF (Meda *et al.*, 1995), and of TNF to inhibit mitochondrial function (see below). Moreover, evidence of inflammation in the brain has been reported earlier than are Aβ or tau (Schuitemaker *et al.*, 2009).

In 1954 Brian Maegraith (who in 1948 was the first to view malaria as an inflammatory state, as reviewed in this journal (Clark & Cowden, 2003)), published electron micrographs of damaged mitochondria from tissues of malaria-infected monkeys. In this article it was discussed, for the first time, the possibility of functional hypoxia in malaria arising from interference with oxygen acceptance by host cells, rather than the traditional concept of insufficient oxygen reaching the mitochondria (Maegraith, 1954). Later his group wrote of serum factors producing changes consistent with this (Riley & Maegraith, 1962). In 1972 altered mitochondrial structure was also reported in experimental sepsis, and linked to functional hypoxia in the presence of adequate oxygen (Mela *et al.*, 1972).

The next advance leading to understanding how TNF influences mitochondrial function came from observations in John Hibbs' laboratory in the form of the

argument that activated macrophages kill tumor cells by inhibiting their mitochondrial respiration, and thus ATP generation (Granger *et al.*, 1980). This response was subsequently shown to require L-arginine (Hibbs *et al.*, 1987), although at the time this had no special significance. Once it was realized that NO was derived from this amino acid, however (Moncada *et al.*, 1989), the essential role of NO in tumor killing by macrophages was rapidly appreciated (Hibbs *et al.*, 1988). By 1990 it was appreciated that TNF induced NO generation (Kilbourn *et al.*, 1990). A few years later Fink embarked on a detailed study of the biochemistry behind mitochondrial functional loss in sepsis. He proposed the concept (which he termed cytopathic hypoxia) that the effects of primary hypoxia are mimicked in a range of severe infectious diseases by the mitochondrial respiratory chain becoming dysfunctional (Fink, 1997; Fink, 2000; Fink, 2001). TNF became involved in the description cytopathic hypoxia when his group found that incubating enterocytes with TNF, IL-1 and interferon-γ (IFN-γ) reduced their oxygen consumption, and thus ATP output, via NO-mediated reduction of oxidative phosphorylation (Khan *et al.*, 2002). Meanwhile, the phenomenon, and general reasoning, was extended to HIV dementia (Kruman *et al.*, 1999) and influenza encephalopathy (Yokota, 2003).

With the revival of the notion of microbial origin of organelles (Margulis & Chapman, 1998), the above mechanism is consistent with evolutionary perspectives on mitochondria, which have been proposed to arise from a common origin with Rickettsiae (Emelyanov, 2001). In parallel with what is observed with mitochondria (see above paragraph) Rickettsiae, like many other intracellular organisms are also susceptible to TNF-induced NO (Turco & Winkler, 1993). This observation is consistent with evidence that much higher TNF expression occurs in mammalian cells on exposure to microbial and free mitochondrial DNA (mtDNA) than when they are exposed to mammalian nuclear DNA, which lacks a high density of unmethylated CpG sequences common to microbial and mtDNA (Zhang *et al.*, 2009). As discussed in Section 4.3, this also rationalizes, through release of mtDNA, high TNF induction in brain trauma, as well as the encephalopathy subsequent to systemic trauma.

As well as the high energy requirement the brain has for general cellular function, it must generate additional ATP because its release by both neurons and glial cells is important in intercellular communication (Gordon *et al.*, 2005). In addition, a novel form of synaptic plasticity that is feed-forward, expressed quickly, mediated by the synaptic activation of neighboring astrocytes, dependent on release of ATP, and acting on post-synaptic purinergic receptors, has been recently described (Gordon *et al.*, 2009). If this ATP release were regulated by TNF actions on mitochondria in astrocytes, then it is reasonable to propose that this plasticity would in fact be indirectly regulated by TNF. While the proposal that TNF could regulate ATP release during synaptic plasticity remains to be proven, it is consistent with the data described above, and with the growing literature that suggests TNF regulates synaptic plasticity (Turrigiano, 2008). If TNF indeed regulates synaptic plasticity through an effect on mitochondrial ATP production, it would provide an additional reason why normal synaptic function would be at risk in diseases in which brain TNF levels are increased. This argument can be further developed in diseases such as Alzheimer's, which is currently generating an extensive literature on mitochondrial dysfunction (Ferrer, 2009; Carvalho *et al.*, 2009). As discussed in Section 5.2.2., inhibited energy production, which can be caused by TNF, also increases the rate of APP cleavage, with harmful effects (Gabuzda *et al.*, 1994; Velliquette *et al.*, 2005).

3.4.1. Carbon monoxide, TNF, and mitochondria

CO is usually discussed in medicine because of its harmful ability to out-compete with oxygen forbinding to hemoglobin, and cytochrome oxidase within mitochondria (Goldbaum *et al.*, 1976). It is now appreciated that cytochrome *c* oxidase I within complex IV, a mitochondrial enzyme responsible for the reduction of oxygen into water as the final step of the electron transport chain, is involved. For some time it has been realized that CO is generated physiologically by the action of hemoxygenase on heme, and has essential anti-inflammatory properties. The early observation that TNF induces hemeoxygenase-1 (HO-1) (Cantoni *et al.*, 1991) was later explained by the ability of TNF to induce IL-10, which in turn induced HO-1 (Platzer *et al.*, 1995) , and thus generating CO (Lee *et al*., 2003). Likewise, the anti-inflammatory effect of 15δ prostaglandin J_2, shown to be present in tissues during inflammation (Gilroy *et al.*, 1999), also operates through induction of giHO-1 and subsequent generation of CO (Leeper-Woodford *et al.*, 1991) (235).

The anti-inflammatory action of HO-1-induced CO has been demonstrated to operate through down-regulating protein release of several pro-inflammatory cytokines, including TNF, and similarly up-regulating the anti-inflammatory cytokine, IL-10 (Otterbein *et al.*, 2000). These activities have been adopted experimentally to reverse a wide range of inflammatory states, including skeletal muscle contractile failure (Taille *et al.*, 2001), experimental autoimmune encephalomyelitis (Liu *et al.*, 2001), endotoxin-induced endothelial cell activation (Bulger *et al.*, 2003), uveitis (Ohta *et al.*, 2003), focal ischemia-reperfusion cardiac injury (Giannini *et al.*, 2005), rejection of transplanted tissue (Camara & Soares, 2005), and a mouse model of cerebral encephalopathy of malarial origin (Pamplona *et al.*, 2007a). Notably, this model, discussed further in the same year (Pamplona *et al*., 2007a), employed (separately) both pharmacological HO-1 induction and CO inhalation therapy.

It has been known for some time in Alzheimer's disease that HO-1 is overexpressed in neurons and astrocytes hippocampus and cerebral cortex relative to control brains (Schipper *et al.*, 1995). Concern has been expressed by these authors that the excess free iron this produces could cause oxidative damage (Schipper, 2004). Accordingly, a therapeutic approach to inhibit HO-1 activation (Song *et al.*, 2009) has been proposed. However, it is widely accepted that endogenously increased HO-1 activity is an attempt to restore homeostasis during inflammation (Otterbein *et al*., 2000). Indeed, the immediately above papers are a compelling part of the argument for a strong inflammatory component in Alzheimer's disease. Intriguingly, in the mouse model of malaria encephalopathypamplona, in which HO-1 was overexpressed (Pamplona *et al.*, 2007b) by either pharmacologically causing additional expression or enforcing inhalation of 250 ppm of CO for 24 hours produced an excellent recovery. It seems logical that, in a chronic condition, inhaled CO might render homeostatic HO-1 activation unnecessary by providing the anti-inflammatory component, CO, without excess free iron potentially setting a harmful Haber-Weiss reaction in motion.

As outlined above, the high affinity of CO for cytochrome *c* oxidase has, until recently, been thought to inform us only about its toxicity. In 2007, however, an additional mechanism for the anti-inflammatory action of CO has arisen from evidence that the action of lower levels of CO on cytochrome *c* oxidase is actually healthy for mitochondria, increasing their membrane potential through enhancing generation of reactive oxygen radicals that mediate adaptive mechanisms that counter cellular dysfunction (Zuckerbraun *et al.*, 2007). In the same year this concept was given a practical application when CO inhalation by mice was shown to reverse the mitochondrial damage and apoptosis in myocardiocytes by doxorubicin, a frequently

employed anti-tumor drug. In this CO inhalation model mitochondrial biogenesis was promoted, and apoptosis much reduced, (Suliman *et al.*, 2007). The basic biology of this approach has been reviewed (Bilban *et al.*, 2008).

More recently these activities of CO have been applied, using the ruthenium-based water-soluble CO carrier, tricarbonylchoro(glycinato)ruthenium (II) (CORM-3), in an *in vivo* murine sepsis model (Lancel *et al.*, 2009). This agent releases CO upon injection. The authors present evidence for mitochondrial energetic metabolism being restored, and mitochondrial biogenesis being activated in septic animals. It is as yet unresolved why the CO carrier drug CORM-3 reduced TNF levels in an *in vitro* model (Sawle *et al.*, 2005) but not *in vivo* (Lancel *et al*., 2009), whereas CO itself reduced it both *in vitro* (Otterbein *et al*., 2000; Zuckerbraun *et al*., 2007) and *in vivo* (Otterbein *et al*., 2000; Pamplona *et al*., 2007b). If upheld, the *in vivo* CORM-3 data (Lancel *et al*., 2009) imply a parallel route of CO acting directly on mitochondria rather than through inhibiting TNF production.

To date CO inhalation or CO-releasing drugs have not been used to treat any encephalopathy except the mouse model discussed above (Pamplona *et al*., 2007b). Reservations have been expressed, regarding human malaria, in terms of what is known about human HO-1 distribution and the level of CO-bound hemoglobin in infected and non-infected individuals (Hunt & Stocker, 2007). Nevertheless there is wide-spread interest in using CO-releasing drugs to therapeutically managing inflammatory states in general (Foresti *et al.*, 2008). Currently the use of CO-releasing drugs has not yet been tested on human subjects beyond volunteers breathing CO (1 h/day at 100 ppm for 5 days). This treatment regimen in skeletal muscle changes consistent with increased mitochondrial biogenesis (Rhodes *et al.*, 2009). It could be relevant that galantamine, a drug in common useage because it has some activity in suppressing Alzheimer's diseases – presumably for its capacity to reversibly inhibit acetylcholine estaerase – has recently been shown to induce HO-1 (Nakao *et al.*, 2008).

3.4.2. Hydrogen sulfide, TNF, and mitochondria

A similar story is unfolding for H_2S. Although generated by different ezymes from unrelated substrates, CO and H_2S are remarkably similar in their functions, from acute rotenone-type toxicity (i.e. directed at the mitochondrial oxidative respiration) when in excess, to anti-inflammatory activity in low doses. Like CO, H_2S is part of normal physiology, including in the brain (Boehning & Snyder, 2003; Ishigami *et al.*, 2009). Again like CO, it has mitochrondrial cytochrome c oxidase as a target for normal physiology, as well as pathophysiology (Collman *et al.*, 2009). This group describe the differential effects of high and low levels of H_2S on mitochrondrial cytochrome c oxidase. These studiies are reminiscent of those on lower levels of CO on this enzyme actually improving mitochondrial energetic metabolism (Zuckerbraun *et al*., 2007). This aspect has apparently not yet been addressed for H_2S.

Like CO, H_2S protects (Li *et al*., 2005) against the LPS inflammatory response models often referred to in this review. Both gases have the capacity to inhibit LPS-induced TNF and its attendant cascade of pro-inflammatory mediators, as well as to upregulate protein of the anti-inflammatory mediator, IL-10 (Otterbein *et al*., 2000; Li *et al.*, 2009; Whiteman *et al.*, 2010). Using purpose-designed H_2S releasing agents, this cytokine-inhibiting activity has been extended to microglial and astrocytes (Lee *et al.*, 2010). This group have confirmed that astrocytes in normal human brain contain H_2S (Lee *et al.*, 2009). Another H_2S , sodium hydrosulfide (NaHS), is being

investigated as a protective agent in a Parkinson's disease model (Hu *et al.*, 2009a). The observation, in their study, of H_2S preventing the development of lesions induced by rotenone implies it possesses mitochondrial-improving activity, as found for CO (Lancel *et al*., 2009). Predictably, the pattern of investigation and possibilities for H2S, including using H_2S-releasing agents, will parallel that of CO and the pharmaceutical agents that release it. New data, in which i.p. injection of an H_2S donor protected rats from cognitive defects, cerebral NFkB inhibition and reduced TNF generation resulting from intracerebral LPS infusion (Gong *et al.*, 2010), is consistent with this.

Manipulating CO and H_2S in order to treat human inflammatory brain disease is logical, and may prove to be less expensive, as well as easier to administer, than specific anti-TNF agents. But they require much more developmental study before they are clinically useful. In contrast, anti-TNF agents, which go to the heart of the problem, and have an impressive history in treating chronic human inflammatory states for 16 years (see Section 6.2), are potentially applicable now. These two approaches to influencing essentially the same pathway may provide synergistic treatments for the range of brain diseases discussed in this review.

3.5. TNF, sirtuins, and caloric restriction

The concept of dietary (caloric) restriction extending the healthy life spans of simple life forms, as well as mammals, is well established. Inevitably, therefore, its effects on neurophysiology and mental capacity, a key aspect of the ageing process, have been examined (Mattson *et al.*, 2003). Examples of outcomes of caloric restriction include enhanced learning in aged mice (Ingram *et al.*, 1987) and rats (Stewart *et al.*, 1989), protection against age-induced deterioration of memory in rats (Pitsikas & Algeri, 1992), and enhanced hippocampal neurogenesis in mice (Lee *et al.*, 2002). It is of particular experimental interest that caloric restriction was not required when animals were young, with mice in which it was not instigated until mid-life retaining normal function well into old age (Means *et al.*, 1993). Age-associated increases in serum levels of TNF are considered physiological, and much studied in the ageing literature. It was reported in 1997, when neither caloric restriction nor TNF was yet of interest to the Alzheimer's research community, that caloric restriction prevented mouse serum TNF from rising with age (Spaulding *et al.*, 1997). A decade later it was shown in a diabetes model that caloric restriction inhibits serum TNF and other inflammatory cytokines, as well as upregulating the anti-inflammatory cytokine, IL-10 (Ugochukwu & Figgers, 2007).

A mechanism for the link between caloric restriction and suppression of circulating TNF levels has beeen constructed through the argument that SIRT1, a class III histone deacetylase that requires NAD^+ as a cofactor, causes adaptations to caloric restriction (Rodgers *et al.*, 2005). These include inhibiting NFκB activity (Yeung *et al.*, 2004; Salminen *et al.*, 2008), and thus inhibiting TNF production (Shen *et al.*, 2009). SIRT1 is the most studied member of the sirtuins (SIRT1-7) a group that share many activities. Resveratrol, a polyphenol belonging to the phytoalexin family, is found in seeds of various plant species, including grapes,and has been proposed to be an agonist of SIRT1 (Yeung *et al*., 2004), explaining why it inhibits TNF production (Bi *et al.*, 2005; Shen *et al*., 2009). Sirtuins (Albani *et al.*, 2009) and resveratrol (Anekonda, 2006) have both been argued to have potential as treatments in Alzheimer's models, but whether through TNF modulation was not addressed by these authors.

Resveratrol is a freely available and has been a self-administered agent for some time, so its literature is confused. Of relevance to Alzheimer's are the studies reporting protection in rat brain trauma (Ates *et al.*, 2007; Sonmez *et al.*, 2007) when administered i.p., and its reported capacity to reduce deficits in working memory as a dietary supplement (Abraham & Johnson, 2009). At the time of writing, the effects of resveratrol on TNF levels does not appear to have been contemplated in any of these studies. Nevertheless small molecule SITR1 agonists are being actively sought (Smith *et al.*, 2009a; Bemis *et al.*, 2006), and another group has reported screening such agents for their anti-inflammatory effects, using reduced TNF levels as a readout (Nayagam *et al.*, 2006). An opposing argument is developing that resveratrol functions through AMP-activated kinase, with SIRT1 activation data arising from an artefact (Tang, 2009; Beher *et al.*, 2009). These groups do not deny resveratrol or caloric restriction their published activities, but argue that other, largely undefined, activities rather than SIRT1 activation would be needed to be harnessed in order to find other resveratrol-like agents.

The effect of both caloric restriction and TNF (TNF the more extensively, and always independently) have been studied on basic brain function, as well as in Alzheimer's models. For instance, the literature on the effects of caloric restriction on synaptic plasticity was reviewed in detail in 2008, with no mention of TNF (Fontan-Lozano *et al.*, 2008), yet by then TNF, which caloric restriction reduces (Spaulding *et al*., 1997), already had a considerable synapse literature in its own right, as reviewed in that year (Turrigiano, 2008).

4. Encephalopathy accompanying systemic infection, trauma or burns

Historically, encephalopathies have been viewed as the presence of diffuse multifocal cerebral functional change that is not, at least in the beginning, combined with morphological correlates (Kunze, 2002). Typically, they are described by the nature of the systemic inflammatory state that induces them, septic encephalopathy being associated with severe bacterial sepsis. Severe viral diseases, hepatic failure, pancreatitis, trauma with anesthetized (e.g. surgery) or unanesthetized injury, or severe burns can also exhibit encephalopathy. These states can be clinically characterized by slowing of mental processes, impaired attention and cognition, disorientation, delirium or coma.

In passing, acute infections exhibiting delirium have been so common historically that they provide a fascinating anecdotal link from the Ancients to day-to-day life in modern Italy. Probably for millennia, lice have spread a rickettsial disease that, since the 18th century, has been termed typhus, to denote a fever accompanied by neuropsychiatric manifestations. The disease later shown to be caused by an organism that became known as *Salmonella typhi* was sufficiently typhus-like to be termed typhoid. The term typho-malaria, now outmoded, was, until relatively recently, an accepted diagnosis for a marked association between malaria parasites in blood smears and delirium. And today? Italians refer to deliriously enthusiastic supporters of a sport, or a commercial brand, as tifosi.

4.1 Malaria

We have argued (Clark *et al.*, 2008; Clark & Alleva, 2009) that malaria is best viewed as one of the cytokine-caused systemic infectious diseases that can be accompanied by encephalopathy. Nevertheless, we note that many malaria

researchers still regard malaria pathophysiology as a special case distinct from the newer cytokine-based ideas used to explain the pathogenesis of systemic infectious disease in general. Instead, these researchers prefer the traditional argument that the primary cause of falciparum malaria is obstructed cerebral microvascular flow (Beare *et al.*, 2009). Part of their argument has been that vivax malaria, a disease difficult to distinguish by traditional diagnostic methods, is rarely fatal, or a causes of neurological signs, because it does not obstruct vascular flow. See Section 5.1 for more detail. It transpires, however, that vivax malaria may have often been more harmful, with more encephalopathy in untreated cases, or cases in regions of chloroquine resistance, than previously realized. This may have been the result of confusion with falciparum malaria when using microscpoy to identify the parasite, combined with a traditional conviction that if it was fatal it must have been falciparum. Together, the systematic diagnostic precision now available through PCR in much of India (Kochar *et al.*, 2009) and publications arising from close examination of a large number of field cases in New Guinea (autonomously by two geographically separated groups (Genton *et al.*, 2008; Tjitra *et al.*, 2008)), have consolidated the view that vivax malaria encephalopathy is much more common that previously thought. In summary, each of these two research group concluded that the frequencies of neurological disease, and the fatality rate, seen in fections with *P. vivax* were essentially the same as seen in the encephalopathy of falciparum malaria, as discussed recently (Clark & Alleva, 2009). Circulating TNF can be very high in vivax malaria (Karunaweera *et al.*, 1992), although levels of TNF in the CSF, and whether they correlate with signs of encephalopathy, have never been published. Brain levels of TNF, assayed in CSF, and some downstream cytokines have been examined in falciparum malaria, and found to correlate with encephalopathy, including long-term functional loss (John *et al*., 2008b). The later, parasite sequestration-based events that complicate interpretation of the effects of late falciparum malaria on brain sections, as discussed a few years ago (Clark *et al.*, 2006), are summarised in Section 5.1.

4.2 Systemic inflammatory events and long-term cognitive defects

As well as the acute encephalopathy accompanying acute infection, as discussed above, a less severe but much more chronic version that follows systemic inflammation is important to understand. In 2005 a case-control study (with almost 10,000 individuals in each group) showed an association between infectious disease and dementia in the elderly (Dunn *et al.*, 2005). Long-term cognitive impairment, the nature of which is only now starting to be understood, can ensue (Stevens & Pronovost, 2006; Hopkins & Jackson, 2006). As discussed earlier, malaria is also noted for long-term cognitive impairment, including deficits in memory, attention, visuo-spatial skills, language and executive function. Prospective studies have documented these changes well (Boivin *et al.*, 2007; John *et al.*, 2008a). The condition has also been examined in children in other regions of tropical Africa (Carter *et al.*, 2005; John *et al*., 2008b; Kihara *et al.*, 2009), so older age is not clearly essential to the phenomenon.

In a review of apparent interactivity of systemic and cerebral inflammation, it was proposed (Perry *et al.*, 2007) that, in diseases such as Alzheimer's, with its chronic activation of the innate immune response in the brain, successive systemic inflammatory events might be expected to exacerbate the rate of neurological degeneration. This idea is consistent with a report of chronic systemic inflammation,

as measured by serum levels of IL-6, a stable cytokine induced by both TNF and IL-1 (Zhang *et al.*, 1988), being inversely related to hippocampal grey matter size in middle-aged human volunteers (Marsland *et al.*, 2008). Perry's group have since published mouse (Cunningham *et al.*, 2009) and human (Holmes *et al.*, 2009) data that fulfil this prediction (Perry *et al*., 2007). In brief, this human study (Holmes *et al*., 2009) found that increased baseline serum levels of TNF in Alzheimer's patients were of themselves associated with an increased rate of cognitive impairment. They also found that the more acute systemic inflammatory episodes associated with an increase in serum TNF the patient experienced over a six month period the more rapid was the rate of cognitive decline. The most extreme examples, those with the most frequent high TNF episodes, had a 10-fold increase in decline rate compared to those with low starting levels and no systemic inflammatory episodes.

Apart from its importance in allowing an appreciation of the relevance of TNF to move from the laboratory to the clinic, this work by Holmes and co-workers (above) has a practical consequence for testing anti-Alzheimer's agents. It rationalizes the short-term unpredictability of the rate of decline in this disease, which leads to the often-made remark that properly controlled trials are particularly essential in this disease because of its short-term clinical variability. Their work takes the argument further through implying that systemic inflammatory events should be documented and taken into account in such trials.

It does not necessarily follow, however, that because TNF of systemic origin can exacerbate Alzheimer's disease the cognitive decline and other changes in this condition originates from TNF, or TNF-secreting cells, of non-cerebral origin, and therefore can be countered by therapeutic anti-TNF agents that cannot effectively enter the CSF. In contrast, it is a reasonable assumption that the depression, and anxiety of rheumatoid arthritis and inflammatory bowel disease, both treatable with large and systemically administered specific anti-TNF agents (Uguz *et al.*, 2009; Bercik *et al.*, 2010), arise from TNF or TNF-secreting cells of non-cerebral origin that has been neutralized before it reaches the brain.

The encephalopathies accompanying sepsis, trauma (Michaelson *et al.*, 1984), burns (Mohnot *et al.*, 1982) and elective surgery (Tufo *et al.*, 1970) have been studied in parallel (Marchiori *et al.*, 2006). IL-1 is also incriminated, as in a recent study of hepatic encephalopathy, using mice deficient in receptors for either IL-1 or TNF (Bemeur *et al.*, 2010). This is not surprising, in view of the ability of TNF to induce IL-1, and the many functions they share (see Section 2). TNF has been identified as a key mediator in pancreatic (Yang *et al.*, 2004) and septic encephalopathy (Alexander *et al.*, 2008). TNF is increased in serum or plasma in all of the above predisposing conditions (Kwiatkowski *et al.*, 1990; Molloy *et al.*, 1993; Bhatia *et al.*, 2000), (Van Reeth, 2000; Hildebrand *et al.*, 2005), and is documented in the brain as well in influenza (Ichiyama *et al.*, 2003), malaria (John *et al*., 2008b) and liver failure (Jiang *et al.*, 2009) encephalopathy. Thus the conditions that predispose to encephalopathy that can mimic Alzheimer's disease, but unlike it, dissipate over time, have been reported to generate a systemic inflammatory response syndrome, in which serum levels of TNF, and the cytokines it induces downstream, are increased.

The same concepts can be predicted to apply in circumstances when the temporary trigger for TNF generation is in the brain, rather than systemic, as above. The stimulus might be an infectious agent, such as in meningitis (Moller *et al.*, 1991; Moller *et al*., 2005; Barichello *et al*., 2009), sindbis viral encephalitis (Carmen *et al.*, 2009), influenza encephalopathy (Ichiyama *et al*., 2003),neuroborreliosis (Ramesh *et al.*, 2008), and trypanosomiasis (sleeping sickness) (Kristensson *et al.*, 2009).

Neurosyphilis (Halperin, 2010) also comes to mind, but remains unexamined. Understanding the encephalopathy of trypanosomiasis along these lines is well advanced. Brain TNF and IL-1β production is high (Quan *et al.*, 1999), and various downstream mediators are increased in the choroid plexus (a site therefore worth examining in these human diseases) and elsewhere. Moreover, i.c.v. infusion of antagonists of receptors for IL-1 and TNF have been found to attenuate neurodegeneration (Quan *et al.*, 2003). In addition a recent open trial reports a positive outcome in 6 out of 7 patients with neurosarcoidosis after infliximab treatment. The seventh responded to etanercept (Moravan & Segal, 2009). See Section 6.2.2. to have these drugs explained. From this reasoning, AIDS dementia (Mastroianni *et al.*, 1990; Yeung *et al.*, 1995) mimics Alzheimer's more closely because the source of TNF and IL-1β is largely unstoppable.

4.3. Brain trauma

An obvious form of encephalopathy without an infectious or systemic origin occurs after brain trauma, a term we use to include closed head injury. Depending on severity and whether the injury is local or global, this condition can exhibit the full gamut of neurological dysfunction, including coma, impaired memory and executive function. In these patients CSF levels of TNF and other cytokines are increased (Hayakata *et al.*, 2004; Goodman *et al.*, 1990), and their manner of interacting has been compared with the same processes in Alzheimer's disease (Mattson *et al.*, 1997). For example, synaptic plasticity is reduced in closed head injury patients (Albensi & Janigro, 2003). Two plausible triggers for TNF generation, HMGB1 (Scaffidi *et al.*, 2002) and free mtDNA, exist in brain trauma. Like bacterial DNA, but unlike mammalian DNA, mtDNA is high in unmethylated CpG repeats, and therefore induces TNF release (Zhang *et al.*, 2009). In systemic trauma the level of mtDNA in plasma (predictably therefore in CSF in brain trauma) correlated with the degree of clinical severity in a group of 38 patients (Lam *et al.*, 2004). These concepts have recently been examined in more detail (Zhang *et al.*, 2010). It would be surprising if this relationship does not also exist between CSF levels of mtDNA and the degree of brain trauma, in which intracerebral TNF inhibition has been reported to be protective (Shohami *et al.*, 1996). Other evidence for a primary role of TNF in the pathogenesis

ha *et al*, 20[illegible] of brain trauma [illegible] cytokine

(Knoblach & Faden, 1998), HU-211, a post-transcriptional inhibitor of TNF

over a decade that experimental non-cerebral inflammation influences the hypothalamo-pituitary-adrenal axis via TNF signalling within the brain (Turnbull *et al.*, 1997). Awareness that i.p. injection of LPS, the prototype inducer of inflammatory cytokines, generates their transcripts within the brain also arose at this time (Pitossi *et al.*, 1997). In 2006 a mouse model of liver failure subsequent to cholestasis was used to demonstrate that TNF-secreting monocytes migrate from the periphery to the brain, and somehow microglia are also triggered to release this same mediator soon afterwards (Kerfoot *et al.*, 2006). A recent experimental example is colonic inflammation inducing cells in the rat hippocampus to generate TNF (Riazi *et al.*, 2008). This increase in TNF level was functionally significant, since infusion of TNF antibody into the cerebral ventricles prevented the seizures associated with gut inflammation, but not the degree of gut inflammation itself. Contemporary studies have shown that migrating monocytes are attracted across to the brain by a chemokine (CCL2) originating from the microglia (D'Mello *et al.*, 2009), and work demonstrating brain pericyte detachment from the basal lamina after i.p. LPS (Nishioku *et al.*, 2009) suggests a likely route. As recently reviewed (Cameron & Landreth, 2010), a literature also exists on monocyte migration to the brain in Alzheimer's models, under the influence of the same chemokine. Though sometimes interpreted in terms of Aβ plaque removal (not useful in a recent human trial (Holmes *et al.*, 2008)), these cells may also seed the brain for excess TNF production (Kerfoot *et al.*, 2006).

4.5. Short-term systemic response causing a long-term cognitive defect

In 2004 it was reported that experimental myocardial infarction, which causes a systemic inflammatory milieu, also causes sustained (still increasing after 4 weeks) generation of TNF in the hypothalamus (Francis *et al.*, 2004). Three years later others (Qin *et al.*, 2007) found that mouse brain TNF production remained high for at least ten months after a single systemic LPS injection, whereas serum levels peaked at nine hours. These studies are consistent with earlier work in which the TNF switch-off that occurs systemically after a second LPS injection (the basis of LPS tolerance) proved to be absent in the CSF (Steinshamn & Waage, 2000). Thus TNF production evidently persists in brain for much longer than in the periphery, conceivably because the cytokines such as IL-10, which control it in the periphery, are less available within the CNS. Increasing this availabilty is the basis of a therapeutic approach that appears to have much potential (Koronyo-Hamaoui *et al.*, 2009).

Collectively, these above data provide a glimpse into the profound implications, for understanding these cognitive defect diseases, of $A\beta_{42}$ being an anti-microbial protein on the innate immune response, which dominates within the brain (see Section 5.2.3). One study (Qin *et al.*, 2007) also found that microglia were chronically activated in the hippocampus and cortex after this single LPS injection. An intriguing difference between systemic and cerebral TNF generation is that TNF receptors (allowing extant TNF to function) are needed for brain, but not for liver, to generate TNF. Thus, systemic cytokines are critical for CNS effects in response to systemic immune activation. One observation this explains is experimental sepsis specifically and significantly reducing the activity of cytochrome c oxidase in brain mitochondria (d'Avila *et al.*, 2008). This has considerable implication for meeting the brain's high requirement for ATP.

A useful step in elucidating long-term cognitive deficits triggered by severe systemic inflammatory responses (or worsened by a series of milder such events

(Holmes *et al*., 2009)) was recently published (Weberpals *et al*., 2009). Using the same animal model, dose and route of LPS as above (Qin *et al*., 2007), these authors found, two months after treatment, that wild-type mice, but not others deficient in *NOS2* gene, committed significantly more working and reference memory errors. These mice are unable to make NOS2, the form of nitric oxide-generating enzyme normally induced by TNF and IL-1. In contrast, systemic LPS induced sustained levels of NOS2 in brains of wild-type mice, particularly in the hippocampus, for the full two months. Overt hippocampal neuronal loss or astrocyte activation could not be documented in either *NOS2* knock-out or wild-type mice, whereas microglial activation was present in wild-type, but not the knock-outs. Moreover, as evidence that NOS2-induced nitric oxide (NO) affects long-term cognition by influencing synaptic function, in these studies NOS2 knock-out mice proved to be protected from reduction in presynaptic and postsynaptic proteins. One conserved protein of particular note was PSD-95, known to be critical for spatial memory formation (Migaud *et al.*, 1998) in normal mice.

Taken together, these data (Weberpals *et al*., 2009) indicate that the absence of NOS2 induction protects mice from long-term microglial activation. In other words, NOS2-derived NO might contribute to the associated inflammatory reaction and long-term learning and memory dysfunction caused by systemic LPS administration. The authors suggest several possible mechanisms by which this NOS2-derived NO could contribute to these cognitive defects. These include reducing ATP levels by inhibiting mitochondrial respiration, altering synaptic structure, and reducing brain TNF and IL-1β levels (their mRNA levels were lower in post-LPS *NOS2* knock-out mice rather than controls, by an as-yet unexplained mechanism). All are plausible, and could act in concert. Clearly, reduced TNF levels are consistent with the concepts behind recent Alzheimer's studies (Tobinick, 2009; Holmes *et al*., 2009). It is relevant that human NOS2 immunohistochemistry studies we performed some years ago (Clark *et al.*, 2003) on fatal comatose malaria and sepsis cases showed identical NOS2 staining of microglia (Fig.1). Further studies in this field could examine whether the NOS2 polymorphisms shown in such African populations (Hobbs *et al.*, 2002; Burgner *et al.*, 2003) bear any relationship to a tendency to develop long-term neurological deficit after recovery from this systemic inflammatory disease (Brewster *et al.*, 1990; Carter *et al*., 2005; Kihara *et al.*, 2006; John *et al*., 2008b; Kihara *et al*., 2009).

These new data (Weberpals *et al*., 2009) will undoubtedly encourage the use of NOS2-deficient mice and specific NOS2 inhibitors in studying these encephalopathies. Moreover, it is difficult not to draw the conclusion, from the combined human (Holmes *et al*., 2009) and various animal studies, that patients with Alzheimer's and other encephalopathies above would be better off with lower serum and CSF levels of TNF, not an unattainable therapeutic outcome given the tools now available in the clinic. Different routes of administration would likely have different consequences, with subcutaeous etanercept (an anti-TNF biological) (Bohac *et al.*, 2002) having the prospect of preventing these encephalopathies from becoming worse, and a route directed towards the CSF (Tobinick *et al.*, 2006) possessing the prospect of improving the condition. Lower brain NOS2 levels would be one consequence.

In summary, the above observations are consistent with any severe systemic inflammatory activation, through generating circulating TNF, and whether protozoal, bacterial, viral, traumatic (anaesthetised or not) in origin, having the potential to cause long-term as well as acute loss of cognitive function. Moreover, these

encephalopathies are unlikely to be caused directly by toxins unique to one of the disease variants, such as LPS or similar in sepsis, glycosylphosphatidylinositol (GPI) in malaria (Zhu *et al.*, 2009), gp120 in AIDS (Tyring *et al.*, 1991), but by the TNF that all of these agents induce. Thus any TNF inducer serves the purpose, its harmfulness depending on how effectively, and for how long, it induces TNF. It follows that LPS, the prototype TNF inducer, is as relevant a model for any of these circumstances as it is to gram-negative sepsis, where it is present in the clinical disease.

4.5.1. Sundowning

It would be instructive to know whether the phenomenon of "sundowning", the late afternoon and early evening exacerbation of behavioral symptoms in mild and moderate Alzheimer's disease that has been recognized by clinicians for more than 60 years (Bachman & Rabins, 2006), has been noted of the other encephalopathies discussed in this review. It appears to have no published rationale at present. We note, therefore, that a diurnal rhythm of TNF has been documented in the rat brain, with samples taken from hippocampus, hypothalamus, cerebral cortex, cerebellum, pons and midbrain at six hour intervals (Floyd & Krueger, 1997). Tissue TNF levels at light onset were about 10-fold higher than minimal night-time levels, particularly in the hippocampus. When it is taken into account that the rat is nocturnal, it would be surprising if this 10-fold increase would not produce a regular temporary exacerbation in all TNF-induced encephalopathies. In addition, it may account for the observation that long-term potentiation, a marker for synaptic activity, is diurnal in the normal hamster (Raghavan *et al.*, 1999). This could readily be tested.

It also seems warranted to take note of what sundowning tells us about the relative importance of the possibilities for the main cause of the functional loss seen in Alzheimer's disease. It is difficult to interpret this diurnal variation in terms other than a fluctuations of a reversible change. The length of Section 3.1 on the effects of TNF on synapse function reflects both the importance others have put on synapses as the seat of this disease (DeKosky & Scheff, 1990; Selkoe, 2002; Arendt, 2009) and the size of the TNF literature on the topic. Equally, it is difficult to reconcile Aβ-based primary neuronal death theories of Alzheimer's with the presence of diurnal clinical variation.

In summary, we visualize the sundowning effect seen in milder disease as consistent with a view that Alzheimer’s symptoms are exquisitely sensitive to the acute effects of TNF on synapses, effects that would be rapidly reversible and therefore variable, in depending on diurnal TNF levels in the CNS. The chronic effect of relentless excess TNF, however, can be expected to be neuronal and axonal loss through TNF-driven APP occupying DR6 receptors (Section 5.2.1) and TNF reduced neurogenesis (Section 3.3). Over time these influences would result in the considerable loss of brain volume observed in terminal cases.

5. Malaria encephalopathy, Alzheimer's disease, depression and aggression

5.1 Malaria encephalopathy and TNF

As outlined in Section 4.1, the primary cause of abnormal brain function in falciparum malaria has traditionally been based on restricted cerebral blood flow caused by parasitized red cells adhering to the walls of small cerebral blood vessels,

depriving brain cells of oxygen and nutrients. Over the years cerebral symptoms in malaria were often difficult to align with the presence of cerebral symptoms (Maegraith & Fletcher, 1972). Cerebral hypoperfusion could not be detected (Newton *et al.*, 1996; Clavier *et al.*, 1999), and, given the stroke literature, it remains difficult to explain how recovery from deep coma without consistent and profound residual deficit is consistent with mechanical blockage of the cerebral vasculature being the primary mechanism. These parasites shed material that induces the patient's cells to release TNF, and thus the cascade of inflammatory cytokines that many now regard as the primary cause of the disease. This was first proposed in 1981as one half of a single novel concept, the other half being that these same mediators are the key to understanding innate immunity (Clark *et al*., 1981). Both arguments continue to expand, and are updated regularly (Clark & Cowden, 2003; Clark *et al.*, 2004; Clark *et al*., 2006). By 1997 TNF has been shown by immunohistochemistry to be expressed in neurons and astrocytes in a mouse model of malarial encephalopathy (Medana *et al.*, 1997) which, although criticized as largely irrelevant to the human disease (White *et al.*, 2010), does manifest cognitive defects (Desruisseaux *et al.*, 2008).

Although encephalopathy in isolation is seen in no more than a fifth of African children who are acutely ill with malaria (Marsh & Snow, 1997), its presence commonly brands all patients with neurological change as having cerebral malaria, whatever other severe pathology co-exists. Since it is this patient group in which large-scale assaying for TNF in sera from severe falciparum cases have routinely been done, the term cerebral malaria therefore tends to be used synonymously with severe falciparum malaria with coma. Hence serum TNF levels correlated well with severe malaria, but not always with what is termed cerebral malaria, i.e. a systemic disease with an encephalopathy component (Grau *et al.*, 1989; Kwiatkowski *et al*., 1990; Shaffer *et al.*, 1991).

When the problem was examined more closely, it was realised that TNF levels in the CSF, not those in the serum, correlated with the encephalopathy, as well as the residual neurological deficit that often occurs (John *et al*., 2008b). Moreover, CSF and serum levels did not correlate, implying independent cerebral generation of TNF. Many papers are published from East Africa on reduced cognitive function associated with a history of malarial encephalopathy. Several functions of TNF warrant consideration in this context, including its inhibitory effects on synapses (Section 3.1), as well as its capacity to cause periventricular white matter damage (Aden *et al.*, 2009).

As reviewed (Clark *et al*., 2006), the concept of malaria being a primary cytokine excess disease implies that the sequestration of parasitized red cells, the traditional primary disease mechanism, is a secondary event that begins in the brain once circulating TNF levels are high. The diseases caused by *P. falciparum* and *P. vivax* each present a TNF-induced, sepsis-like, encephalopathy, with the opportunity for the neurological dysfunction in falciparum malaria to become exacerbated by vascular obstructive hypoxia once the disease is already severe. The expanded experience of vivax malaria, a disease with negligible parasite sequestration, of recent years (Genton *et al*., 2008; Tjitra *et al*., 2008; Kochar *et al*., 2009) indicates that patients are sick enough, without sequestration, for a fatal outcome. Hence it has been reasoned that cerebral sequestration, severe enough to obstruct microvascular flow and cause microhemorrhages, can terminally exacerbate, but not explain, the primary pathogenesis of neurological dysfunction in falciparum malaria. This secondary phenomenon, on top of an underlying encephalopathy common, in

principle, to all of the conditions covered in this review, is of immediate practical concern to those responsible for management of patients seriously ill from this infection. Reasonable in its day as a primary mechanism, it survives as a major research discipline largely because of the application of impressive technology to understand the mechanics of adhesion of infected red cells (Maier *et al.*, 2008). Until recently, when the roles of TNF in hypoxia became appreciated (Section 5.3), and the 2008 vivax malaria papers appeared (Genton *et al*., 2008; Tjitra *et al*., 2008), the dominance of this thinking, and the tradition of attributing all malaria pathology to it, retarded developing the cytokine approach to this disease, oddly enough the one in which the cytokine concept of disease began (Clark *et al*., 1981).

As summarized in Section 5.2.1, recent publications on the role of APP in fetal brain in triggering axonal pruning (Nikolaev *et al.*, 2009), as well as the capacity of inflammatory mediators to upregulate APP (Brugg *et al.*, 1995; Buxbaum *et al.*, 1998; Goldgaber *et al.*, 1989; Schmidt *et al.*, 2008; Sommer *et al.*, 2009), make it worth considering whether the APP stained in falciparum malaria brains (Medana *et al*., 2002) reflects the presence of more of this protein, due to increased levels of brain TNF (John *et al*., 2008b). Thus it would be the cause of axonal damage, as well as an indicator of its existence. Likewise, if the cotton wool spots noted in retinas of patients with cerebral malaria (Lewallen *et al.*, 1999) are indeed manifestations of disrupted axonal flow (McLeod *et al.*, 1977; Medana *et al*., 2002) it would, from the above reasoning, make them secondary changes consequential to the TNF that raised APP levels. Being a DR6 ligand (Nikolaev *et al*., 2009), this would damage axons, causing local distensions seen as white spots. This implies that cotton wool spots, used as a diagnostic feature in cerebral malaria (Lewallen *et al.*, 1996), are simply another indicator that brain TNF is increased. The same TNF-induced pathway would also explain the increased tau levels in Kenyan children with cerebral malaria (Medana *et al.*, 2007).

5.1.1. Coma, hibernation and tau

Finally, what can the cytokine approach offer to explain the mechanism of the coma that is seen, certainly by clinicians, as the centrepiece to understanding malaria encephalopathy? As summarized in Section 3.4.2, H_2S is a normal part of physiology in brain, and other organs. Like CO, it can both subtly adjust mitochondria and inflammation, and cause gross harm, depending on its concentration. We therefore draw attention, as briefly before (Clark *et al*., 2008), to the possibility of H_2S being the primary cause of the reversible coma that can occur in both infectious (malaria, bacteria, viruses) and non-infectious (brain trauma, advanced Alzheimer's disease) encephalopathies. In mice, it can produce a reversible state of hypometabolism and suspended animation that will protect from hypoxia (Blackstone *et al.*, 2005; Blackstone & Roth, 2007). This implies that the coma of cerebral malaria is actually an attempt to protect the patients from the damaging cerebral changes already underway, which could lead to loss of neuronal function, and of neurons, laying the ground for residual cognitive defects (Idro *et al.*, 2005). In addition, the hypometabilism induced by H_2S is reminiscent of the processes of hibernation. It is therefore noteworthy that the phosphorylated tau protein that indicates axonal pruning or injury – and seen not just in normal fetal and neonatal brains (Lovestone & Reynolds, 1997) but also in brains of adults with malaria (Medana *et al*., 2002), Alzheimer's and other neurodegenerative states (Goedert, 2004) and brain trauma (Franz *et al.*, 2003) – is also present in brains of hibernating animals (Arendt *et al.*,

2003; Hartig *et al.*, 2007). We also note that, as recently reviewed (Arendt, 2009), hibernation has a literature on altered synaptic connectivity (Popov & Bocharova, 1992; Magarinos *et al.*, 2006) and impaired cognitive function (Millesi *et al.*, 2001) that is analogous to that of Alzheimer's disease. Tau has a literature of its own on inhibiting brain function (Goedert, 2004), recent research referred to on the effects of rapamycin in Section 6.1.3 (Caccamo *et al.*, 2010) being an example of concepts we have not expanded upon for space considerations.

5.2. Alzheimer's disease and TNF

Ideas on the mechanism of Alzheimer's disease appear to be undergoing a transition. A contributing factor may be that two controlled trials against Aβ have not produced a positive outcome. One, a six year follow-up of 80 patients in an $A\beta_{42}$ immunization trial (Holmes *et al.*, 2008), had no shorter time to severe dementia or improved survival, even though removal of amyloid plaque was virtually complete. Another, the first bapineuzumab passive immunisation trial against Aβ (Salloway *et al.*, 2009), had a non-significant result. These outcomes, plus a long time awareness that amyloid plaques can be present in normal aged brains – for instance, in a 2001 study (CFAS, 2001) 33% of the 109 non-demented people had equivalent densities of neocortical neuritic plaques to equal-aged affected individuals – have contributed to the sense that the field needs to reconsider its direction (Lee *et al.*, 2007; Castellani *et al.*, 2009).

Clearly, the newer concepts and literature summarized below in Sections 5.2.1 question whether Aβ is as useful a therapeutic target as was widely assumed when the various trials directed at neutralizing its presence or actions were conceived. Nowadays a considerable basic literature from a number of autonomous groups argues for increased brain TNF (Tarkowski *et al*., 2003b) having a primary role in pathogenesis of this disease (McNaull *et al.*, 2010; Gorlovoy *et al*., 2009; Janelsins *et al.*, 2008; McAlpine *et al.*, 2009; McCoy & Tansey, 2008; Tweedie *et al.*, 2007; van Gool *et al.*, 2010; Medeiros *et al.*, 2010). These data, plus the recent important and provocative identification of $A\beta_{42}$ as an arm of innate immunity, a TNF-associated event (see Section 5.2.3), indicate a need for controlled trials intended to inhibit cerebral levels of the relevant cytokines, as discussed in Section 6. The study by McAlpine and co-workers, which used novel engineered dominant negative TNF inhibitors, long term, in a mouse model of Alzheimer's disease (McAlpine *et al*., 2009), is particularly compelling. Further interest in the inflammatory cytokine approach to understanding and treating Alzheimer's arises from a recent study (Holmes *et al*., 2009) on 300 patients (see Section 4.2). These competing approaches, amyloid and the cytokines that mediate innate immunity and inflammation, can be understood only by realizing how closely their functions are intertwined. The rest of Section 5.2 summarizes this.

5.2.1. TNF and APP in fetal development and adult disease

Here we can give no more than a brief overview of this important area of research. Alzheimer's disease is intimately associated with the *APP* gene (Hardy, 1994), the product of which, APP, is metabolized to Aβ. As has recently been reviewed (Thinakaran & Koo, 2008), more that 25 *APP* mutations have been identified as being associated with the hereditary form of familial Alzheimer's disease, and APP gene duplication alone, as seen in trisomy 21, causes a high

incidence of early onset Alzheimer's. An ample literature (Meda *et al*., 1995; Wang *et al*., 2005; Ralay Ranaivo *et al*., 2006; He *et al*., 2007) leaves little room to doubt that the consequences of Aβ, downstream from APP, inducing TNF are very real for Alzheimer's disease (see Section 5.2.3). Nevertheless, an in-depth consideration of how closely TNF (and doubtlessly IL-1) are intertwined with this amyloid pathway requires us to begin by considering, in some detail, its relationship with APP, the molecule from which the hallmark Aβ plaques arise. A human gene promoter region study has indicated that APP is a risk factor for Alzheimer's disease (Guyant-Marechal *et al.*, 2007), and increased APP message is present in Alzheimer's disease brains (Moir *et al.*, 1998). Although not along the lines described below, APP dysfunction was argued ten years ago to be central to Alzheimer's disease (Neve *et al.*, 2000).

APP is one of a family of highly conserved transmembrane proteins, with homologues in *Caenorhabditis elegans* and *Drosphila melanogaster*. APP is expressed very early in fetal development (Ott & Bullock, 2001) and becomes ubiquitous. Indeed, the chick embryo is a model for basic research into its roles, and processing (Carrodeguas *et al.*, 2005), and it is expressed in human embryonic stem cells (Porayette *et al.*, 2007). Much more is present in the normal 18-22 week human fetal cerebral cortex than in the same part of the normal adult brain (Selkoe *et al.*, 1988). Likewise, it is abundant in the 18 day fetal and early post-natal mouse brain, but has largely disappeared at 30 days (Trapp & Hauer, 1994). It appears to increase in a controlled fashion, peaking in the mouse brain at about two weeks after parturition (Loffler & Huber, 1992). Within the normal brain it is an essential component of synaptic membranes, and, as recently reviewed (Arendt, 2009) over-expression and knockout studies in mice, and work with the Drosophila APP homologue, APPL, demonstrate essential physiological roles, such as synaptogenesis, axonal arborization, axonal transport, and synaptic plasticity, for these proteins during development and maintenence of the normal mature nervous system.

Some background on TNF receptors is warranted here. The original two were termed TNFR1 and TNFR2, the former becoming known as the death receptor for its link to apoptosis. The death receptors have since blossomed into a superfamily, with a terminology that renames the original TNFR1 as TNFR superfamily 1A, or TNFRSF1A. One of this series, TNFRSF21, also referred to as death receptor 6 (DR6), has been an orphan receptor (Bossen *et al.*, 2006) that is widely expressed on differentiating neurons, but until recently (Nikolaev *et al*., 2009) had no known function on these cells. Importantly, these authors have identified N-APP, a cleaved amino acid fragment of APP, as a ligand for TNFRSF1A (DR6). From their evidence, they propose that APP uses this pathway to undertake essential axonal pruning and neuronal removal in normal late fetal and early neonatal development. TNF and related cytokines have been shown to be present early in the developing nervous system (Yamasu *et al.*, 1989; Gendron *et al.*, 1991; Merrill, 1992), and proposed to have undefined roles in normal brain development. One study (Yamasu *et al*., 1989) suggested the term ontogenic inflammation to describe the concept. They found that spontaneous TNF peaked in mouse brain cells at seven days post-partum. Intriguingly, this is not long before the peak brain concentration of APP (Loffler & Huber, 1992). Induction of APP by inflammatory cytokines is a widespread phenomenon, being reported in endothelial cells (Goldgaber *et al*., 1989), skeletal muscle (Schmidt *et al*., 2008), and 3T3 L1adipocytes (Sommer *et al*., 2009), as well as brain (Brugg *et al*., 1995; Buxbaum *et al*., 1998). Only the adipocyte study employed TNF, the others using IL-1, which functionally overlaps with TNF, or

TACE, an esterase that acts on the transmembrane form of TNF to release the extracellular domain as soluble TNF. In addition, upregulation of promoter activity of the *APP* gene by several cytokines, including TNF, has been documented (Ge & Lahiri, 2002). All of this entirely consistent with the capacity of LPS, the prototype TNF inducer, to accelerate the production of APP and acceleration of its pathway in two different APP transgenic mouse models (Qiao *et al.*, 2001; Sheng *et al.*, 2003).

These actions of inflammatory cytokines are reminiscent of the capacity of TNF and IL-1 to induce a related molecule, serum amyloid A (McAdam *et al.*, 1982), the precursor of AA amyloid, which can accumulate as fibrils in parenchymatous organs during certain chronic human systemic inflammatory states (Marhaug & Dowton, 1994). A promising human open trial with anti-TNF therapy has been reported (Kuroda *et al.*, 2009).

From the data summarized above it can be proposed that during healthy fetal and neonatal development physiologically normal increases in cerebral TNF (and other pro-inflammatory cytokines) increase APP, which acts through the TNFRSF21 (DR6) receptor to reduce the excessive density of neurons, axons, and therefore neuronal connections down to the levels required for a normal post-natal existence (Nikolaev *et al*., 2009). The high TNF and thence APP (which these authors clearly appreciate, but in isolation from its TNF association) of Alzheimer's disease could thus, through an aberration of normal physiology, cause the brain to mistakenly read the signals that saw it so well through its fetal and neonatal development. Thus, for as long as TNF and associated cytokines persist in the brain, they would, via the APP they induce, slowly but eventually, pare down synaptic function to fatal levels. In a sense, therefore, the onset and progression of Alzheimer's disease relives the normal and at the time necessary changes that occurred, decades earlier, in the patient's late fetal and early neonatal brain in response to physiologically increased TNF. It will be very informative to know what switches TNF production on and off in the normal fetal and neonatal mouse brain (Yamasu *et al*., 1989). These principles also provide a lead into how excessive fetal brain TNF levels might cause the white matter damage that leads to cerebral palsy (Dammann & Leviton, 1997; Bell & Hallenbeck, 2002).

These arguments are reinforced by a recent report that mice overexpressing non-mutant human APP had functional changes consistent with Alzheimer's disease (Simon *et al.*, 2009). These mice also lost a series of synapse-associated proteins, including AMPA and NMDA subunits, and phosphorylated tau, an indicator of axonal damage, was increased in the hippocampus. Remarkably, $A\beta_{42}$ was barely detectable. This questions the centrality of $A\beta_{42}$, the historical focus of much research and major patient trials. In addition, the loss of synapse proteins and accumulation of tau in these mice is entirely consistent with the neuronal loss and axonal pruning reported to be caused by APP/DR6 activity (Nikolaev *et al*., 2009). Mice expressing a mutant human APP demonstrated an entirely different picture, with no signs of neurodegeneration and much $A\beta_{42}$.

It seems clear that awareness that cerebral TNF upregulates cerebral APP, and the consequences of APP being a ligand for TNFRSF21 (DR6), will help us understand the pathogenesis of all of the conditions in which excess cerebral TNF can be linked with brain dysfunction. This includes (see Section 4.2) the encephalopathies that can accompany infectious diseases caused by bacterial, viral and protozoal organisms (including malaria), burns, and trauma, particularly brain trauma. Clearly, degree and continuity of TNF and therefore APP upregulation would determine acuteness and reversibility of the pathology. The principles outlined in Sections 4.2, 4.4 and 4.5 seem, at least at present, to be the most likely contender to

explain the high cerebral TNF in Alzheimer's disease, although further insight is required to rationalize its persistence and enhancement. Our proposal, a positive feedback of APP enhancement from Aβ42-induced TNF, is summarised in Section 5.2.3.

5.2.2. TNF is also a driver of APP cleavage to generate $A\beta_{42}$

Normal metabolism of APP generates Aβ, the major focus of much of the present research into the pathogenesis of Alzheimer's disease, and recent evidence (Section 5.2.3.) indicates that physiological levels are not harmful, but a useful part of innate immunity. Logically, toxicity arising from its rate of production, rather than the total amount represented in plaques, is a plausible explanation for large aggregations, generated slowly, being common in healthy brains (Schmitt *et al.*, 2000). Generation of $A\beta_{42}$, a potentially harmful form, occurs through the proteolysis of APP by the sequential actions of β- and γ-secretases. In 2004 it was shown that IFN-γ, IL-1β, and TNF specifically stimulate γ-secretase activity, concomitant with increased production of Aβ (Liao *et al.*, 2004). Since TNF inhibits mitochondrial oxidative respiration (Busquets *et al*., 2003), these data were consistent with inhibition of energy metabolism having earlier been shown to enhance APP cleavage (Gabuzda *et al*., 1994). Subsequently (Yamamoto *et al.*, 2007) IFN-γ and TNF were shown to enhance Aβ production from APP-expressing astrocytes and cortical neurons, and the numbers of astrocytes expressing IFN-γ was increased. In addition, TNF directly stimulated β-site APP-cleaving enzyme (BACE-1, or β-secretase) expression and thus enhanced β-site processing of APP in astrocytes. Again, this is consistent with the energy inhibition that increases the rate of APP cleavage operating through enhancing β-secretase levels (Velliquette *et al*., 2005). In addition, TNFR1 depletion reduced BACE-1 activity (He *et al*., 2007). Logically, therefore, anti-TNF agents should, among their other actions, be effective APP cleavage inhibitors. Results obtained in mice with long-term inhibition of TNF are functionally consistent with this (McAlpine *et al*., 2009), although these authors conclude that their data are in part consistent with APP induction, as discussed in Section 5.2.1.

From these studies it is conceivable that one role for physiological levels of TNF in the brain is to maintain APP and Aβ homeostasis, with excessive TNF generation, from whatever origin, upsetting this to the detriment of synaptic function because it generates Aβ too rapidly. Once generated excessively, $A\beta_{42}$ induces more TNF (Section 5.2.3.), which, as described in various sections of this review, opens the way for much subtle pathology associated with Alzheimer's disease to be generated directly from this and functionally related cytokines.

5.2.3. $A\beta_{42}$ shown to be an anti-microbial mediator of innate immunity

It is warranted to pause here and consider what might have been the evolutionary advantage of conserving the capacity of TNF to induce APP and enhance its cleavage to form amyloid forms including $A\beta_{42}$, a protein that, until recently, had a reputation only for harmful effects. In keeping with everything else induced by TNF, a normal physiological role for $A\beta_{42}$ would make these pathways much more likely to be functionally significant *in vivo*. Evidence consistent with this has recently been extensively documented in a report that $A\beta_{42}$ is a potent antimicrobial peptide (AMP), with activity equal or greater than the prototype AMP against seven common human pathogens (Soscia *et al.*, 2010). AMPs are part of the

innate immune response (Scott & Hancock, 2000), and a number of them, including defensins (Seo *et al.*, 2001; Hao *et al.*, 2001), as well as the new recruit, $A\beta_{42}$ (Section 5.2.2.), are induced by TNF, one of the pillars of innate immunity (Ortaldo *et al.*, 1986; van der Meer, 1988). Therefore these new data (Soscia *et al*., 2010) greatly strengthen the logic and plausibility of Section 5.2 of this review as a whole. Credit should also be given to the Chilean grojup who two years ago had reasoned the logic of a hyperactive cerebral innate immunity being central to Alzheimer's disease (Fernandez *et al.*, 2008). The strengthening of this notion by the above observations (Soscia *et al*., 2010) has particular interest for our group, in that we argued the case in a malarial context, decades ago, that overexpression of mediators of innate immunity causes pathology as well as host protection (Clark *et al*., 1981; Clark, 1987).

The reported antimicrobial activity of $A\beta_{42}$ implies, should it be readily reproduced by others, that the goal of much of the last decade's mainstream Alzheimer's research – to permanently remove, by vaccination, as much of this material as possible – could have had long-term unfortunate consequences. Regularly suppressing TNF could also (through inhibiting APP induction (Section 5.2.1.) and cleavage (Section 5.2.2.)) reduce $A\beta_{42}$ levels below what is needed for innate immunity to function normally , but dosage of anti-TNF can be adjusted should infection occur, whereas vaccination aspires to be permanent.

As noted above, Aβ appears, from this detailed new publication, to have a unique role in innate immunity, for as well as being a mediator of its effects it also perpetuates the response. Indeed, the NALP3 inflammasome (Section 2) has recently been shown to be involved as a sensor of Aβ, including in TNF production (Halle *et al.*, 2008). The researchers who first made this connnection, and the consequences of their data, are summarized in the next Section.

5.2.4 TNF is also generated by $A\beta_{42}$

About five years ago it was demonstrated that the ability of Aβ to induce TNF, a cytokine shown earlier to alter transmission in hippocampal slices (Tancredi *et al*., 1992), was a likely reason why these soluble forms of Aβ altered synaptic function (Wang *et al*., 2005; Rowan *et al*., 2007). By 2005, several laboratories began reporting influences of TNF on aspects of synaptic transmission (Pickering *et al.*, 2005; Stellwagen *et al.*, 2005). Several years later it was reported that the impaired memory induced in mice by Ab could be prevented by i.c.v. injection of an anti-TNF antibody (Alkam *et al.*, 2008). The capacity of Aβ to act as a ligand for CD14 and TLR2 (Fassbender *et al.*, 2004; Jana *et al.*, 2008; Tukel *et al.*, 2009) and TLR4 (Reed-Geaghan *et al.*, 2009) gives these findings (Cleary *et al*., 2005; Wang *et al*., 2005; Rowan *et al*., 2007) authority from basic immunology, since for about a decade it has been accepted that occupying these receptors is how the standard bacterial and protozoal-origin inducers of TNF operate (Beutler *et al.*, 2001). Unfortunately, some groups studying the role of soluble Aβ on synaptic function still fail to incorporate this dependence of TNF in their study designs, even though it is predictably (Fassbender *et al*., 2004; Jana *et al*., 2008) present in the *in vitro* model they explore (Smith *et al.*, 2009b). It will be instructive to learn whether PBT2, the metal-protein attenuating compound that targets pathology caused by Aβ (Lannfelt *et al.*, 2008) reduces the capacity of Aβ to induce TNF.

Thus TNF appears to have three interlocking pathogenic roles in encephalopathies in which its brain levels are raised. The first upregulates APP levels to what they were during early neonatal life, fooling physiological reflexes to cause

pathology, the second participates in driving APP to $A\beta_{42}$, and the third, induced by $A\beta_{42}$, apparently mediates many of its harmful effects. Clearly, all of these actions of TNF are attractive therapeutic targets, as discussed in Section 6. Logically, this $A\beta_{42}$-induced TNF can be expected to add to pool inducing APP (Section 5.2.1) as well as cleaving it (Section 5.2.2.). This would provide a positive feedback loop to combine with TNF from over-expression of innate immunity, providing a mechanism for the usual inevitable worsening of untreated Alzheimer's disease (Fig. 2).

5.2.5. What apolipoprotein E4 tells us about Alzheimer's

Apolipoprotein E protein (apoE) is expressed in humans as three common isoforms, E2, E3, and E4, and *apoE4* is a susceptibility gene with a highly significant linkage with late-onset and familial Alzheimer disease (Strittmatter *et al.*, 1993). Some Alzheimer's researchers have regarded apolipoprotein E4 itself as the causative factor (Mahley *et al.*, 2006), and a few saw its implications for understanding the pathogenesis of the disease in terms of inflammatory cytokines (Lynch *et al.*, 2001; Ophir *et al.*, 2005), but most rationalized the association in ways allied to traditional thinking about this disease. The reduced levels of total brain apoE seen in carriers of *apoE4* (explained in terms of astrocytes preferentially degrading apoE4 (Riddell *et al.*, 2008)) is argued by these authors and others to imply that useful functional roles argued for apoE, including transporting the cholesterol needed for synaptic repair would not be operating effectively in carriers of this gene. The same is still said for apoE binding to Aβ in order to promote its clearance and degradation (Riddell *et al.*, 2008), although the recent revolution in the role of Aβ (Section 5.2.3.) now questions whether clearing Aβ is the worthy goal it was once thought. Nevertheless, it is largely through its association with Aβ that the apoE4 allele literature has become part of the argument in favor of the amyloid theory of Alzheimer's pathogenesis.

It is instructive to read of apoE4 outside the Alzheimer's literature. Head trauma , a condition acknowledged to be mediated through cytokines such as TNF that have been most probably induced by triggers other than LPS (Section 4.3)) has been part of the apoE4 - Alzheimer's equation for some time. While Aβ increases in this condition, it has never been taken to be the prime mover of it, as it has been in Alzheimer's. In 1995 it was reported that apoE4 positive patients who had experienced head trauma were 10 times more likely to develop Alzheimer's disease, whereas apoE4 positives with no head trauma history have double the risk (Mayeux *et al.*, 1995). In their study head trauma alone carried no perceptible increased risk. Given the link between head trauma and TNF, this synergy is reminiscent of the report, in the same year, of a significant association of the rs1799724 SNP within the promoter of the TNF gene exhibiting synergy with apoE4 in conferring risk of Alzheimer's disease (Laws *et al.*, 2005). Experimentally, apoE (-/-) mice exhibit more severe neurological and cognitive deficits after closed head injury (Chen *et al.*, 1997), and transgenic animals bearing human E3 fared better in function recovery than did those bearing E4 (Sabo *et al.*, 2000). It has also been reported that apoE4 positivity causes excess dementia in HIV infection (Corder *et al.*, 1998), which is not the Aβ and tau disease that Alzheimer's is (Gisslen *et al.*, 2009), instead being closely associated with the main inflammatory cytokines (Xing *et al.*, 2009). Likewise, the apoE4 genotype doubles the duration of delirium in severely ill patients in intensive care (Ely *et al.*, 2007), a field associated, for some time now, with TNF and IL-1.

In 1999, researchers attempting to explain their observation that apoE (-/-) mice were very readily killed by *Klebsiella pneumonia* reported that these animals, on

i.v. injection with LPS, produced 4-5 times higher plasma levels of TNF than did normal mice (de Bont *et al.*, 1999). They rationalized this in terms of apoE, lacking in these mice, being a potent detoxifier of LPS. These principles have recently been investigated more closely, by another group, using transgenic mice expressing human apoE3 or apoE4 instead of the mouse equivalents. Those expressing hu apoE4 proved to be much more susceptible to gut bacterial sepsis (Wang *et al.*, 2009b). The study includes a protective effect, with associated reductions of TNF and functionally similar cytokines, of an apolipoprotein E mimetic that plausibly will prove useful to treat many of the diseases discussed in this review. This same group, previously focussed on apoE isoforms and the regulation of NO production by microglia (Brown *et al.*, 2002), have recently reported on neuroinflammatory responses, including TNF levels, in cells from these same mouse strains (Vitek *et al.*, 2009). In brief, cultured microglia from the hu E4 mice that had received LPS and IFN-γ had an appearance classically associated with activated microglia, and produced much more NOS2 message, nitrite (a marker for NO) and more TNF, IL-6 and IL-12 than did microglia from hu E3 mice. Admixing with E2 demonstrated that the E4 effect was dose dependant for this allele, not total apoE.

These authors therefore argue the case for apoE4 being causally linked to enhanced neuroinflammation in a range of neurological diseases, including Alzheimer's disease. Given the additional evidence summarized in this review incriminating TNF, and the capacity of TNF to induce APP (Section 5.2.1.) as well as push its cleavage to Aβ (Section 5.2.2.), *apoE4* is inevitably also a marker for Aβ. But the direct linkage that rationalizes its association with Alzheimer's disease is evidently with TNF. It should be noted that the data from brain trauma, above, tells us that other TNF triggers, as well as LPS, can be function in this disease.

5.3 Involvement of TNF in any contributions from ischemic hypoxia in 5.1 and 5.2

Some malaria (Maier *et al*., 2008) and Alzheimer's disease (Napoli & Palinski, 2005; Thal *et al.*, 2009) researchers place emphasis on ischemic hypoxia making an important contribution to the disease they study. Indeed, in falciparum malaria the parasite sequestration that concentrates in the cerebral vasculature in severe cases (see Section 5.1) could well do this, through the ability of TNF to upregulate endothelial molecules (Wenisch *et al*., 1994), as well as, once sequestration has occurred, provide a local hot spot of further TNF (Ho & White, 1999) and NOS2 (Clark *et al*., 2003). As noted earlier, NOS2 has important implications for long-term cognitive loss (Weberpals *et al*., 2009) after systemic infection.

In Alzheimer's disease a cerebral angiopathy characterized by Aβ deposition within the walls of cerebral arteries and capillaries, is of major concern, and a target of experimental therapies based on reducing Ab deposition (Weller *et al.*, 2009). Unfortunately, this publication makes no reference to the ability of Aβ to induce TNF (Meda *et al*., 1995; Wang *et al*., 2005; Ralay Ranaivo *et al*., 2006; He *et al*., 2007), nor to the vasculature changes seen in the rat hippocampus after injecting Aβ into this site being significantly reduced by administering thalidomide, an anti-TNF agent, i. p. for 7 days (Ryu & McLarnon, 2008). This is consistent with a recent human study in which the inflammatory arthropathy that tends to accompany rheumatoid arthritis was assessed (by measuring aortic pulse wave velocity) with and without the usual commercial TNF antagonists with which such patients are treated. Vascular pathology was significantly reduced by this treatment (Angel *et al.*, 2010).

As well as these arguments for the involvement of TNF in causing hypoxia in

Alzheimer's disease and rheumatoid arthritis, this cytokine has been demonstrated to be central to primary hypoxia-induced brain pathology (Barone *et al.*, 1997). Others have confirmed this experimentally by administering anti-TNF antibody i.c.v (Liesz *et al.*, 2009) or etanercept i. p. (Aden *et al*., 2009). The latter study, in rats, is of particular interest. It shows how prior systemic inflammation predisposes neonatal brains to a subsequent, hypoxic/excitotoxic, insult, in a model for the sequence of events that leads to the brain damage known to cause early learning difficulties and cerebral palsy. If etanercept was administered after (but not before) the excitotoxic insult, when the blood-brain barrier was damaged, it greatly decreased brain TNF and reduced cerebral damage by 50%. As the authors note, this is consistent with the concept that systemically administered etanercept cannot normally reach the brain.

5.4 Major depression and TNF

Nearly 20 years ago clinical depression was suggested to arise from cytokines released from activated macrophages (Smith, 1991). This state is sometimes observed in Alzheimer's disease, and argued to be a constituent of the syndrome itself, rather than an understandable secondary consequence of realizing that one has a diagnosis of Alzheimer's disease (Gohier *et al.*, 2009; Korczyn & Halperin, 2009; Sierksma *et al.*, 2010). Likewise, cognitive impairment is recognized to be associated with major depressive disorder, with poor cognitive performance sometimes outlasting the period of depression (Baune *et al.*, 2010). Consistent with a functional link between the two states, there is, as reviewed (Raison *et al.*, 2006; Dantzer *et al.*, 2008; McAfoose & Baune, 2008; Khairova *et al.*, 2009), a considerable literature connecting cytokines such as TNF with the pathogenesis of major depression. Increased serum levels of a range of inflammatory cytokines, including TNF, have been documented in patients (Hestad *et al.*, 2003; Kim *et al.*, 2007; Himmerich *et al.*, 2008). So too have serum levels of soluble TNF receptors, which are less labile, and therefore more reliable, markers of enhanced TNF activity (Himmerich *et al*., 2008; Grassi-Oliveira *et al.*, 2009; Diniz *et al.*, 2010). Work on documenting TNF increase in this disorder has since been extended, with the same conceptual outcome, to samples of various brains regions collected at autopsy (Dean *et al.*, 2010). Indeed, a recent meta-analysis covering 24 studies has reported significantly higher concentrations of TNF and IL-6 in depressed subjects compared with control subjects (Dowlati *et al.*, 2010).

Although depression can reasonably be viewed as a manifestation of brain function, it is, as noted (Smith, 1991), significantly associated with coronary heart disease, rheumatoid arthritis, stroke and other diseases, systemic or cerebral, where macrophage activation occurs. This harks back to aspects of Section 4 of this review, in which we note the ways in which systemic and cerebral consequences of macrophage activation are linked. Serum vs CSF levels of TNF appear not to have been studied systematically in major depression, although a recent publication reported CSF levels of IL-6, a cytokine downstream of TNF and IL-1β (i.e. induced by them), was higher in depressed suicide attempters than in normal controls (Lindqvist *et al.*, 2009). Among their data was an intriguing parallel with the much more acute condition of cerebral malaria (John *et al*., 2008b). While, in each case, plasma cytokine levels were higher than those in the CSF, the two did not correlate, implying independent origins.

It is therefore instructive to consider what is known about the inhibitory effects of some established anti-depressant drugs on TNF and related cytokines. Moclobemide, in clinical use in many countries for this purpose, and widely known as

a reversible inhibitor of monoamine oxidase A, significantly suppresses the unstimulated *in vitro* production of TNF and IL-8 in monocytes from human volunteers (Lin *et al.*, 2000). Another example is bupropion, an aminoketone used as an anti-depressant, largely because it inhibits re-uptake of norepinephrine and dopamine. But in addition bupropion demonstrates, arguably through increasing cyclic AMP, an ability to suppress TNF and IL-1β production so strongly that it protects mice against an otherwise lethal dose of LPS (Brustolim *et al.*, 2006). Furthermore, imipramine, the first tricyclic antidepressant to be developed, and known to influence much cerebral biochemistry, strongly inhibits TNF and IL-1β production from human monocytes (Xia *et al.*, 1996). In the light of present knowledge linking these cytokines and cognitive performance, this inhibition could explain a report that imipramine enhanced learning and memory while being used to treat patients suffering from major depression (Peselow *et al.*, 1991). A recent animal study consistent with this outcome describes imipramine, concomitant with its capacity to prevent Aβ-induced increases in cortex and hippocampal TNF levels, influenced APP processing (see Section 5.2.2.) and long-term memory impairment caused by Aβ treatment (Chavant *et al.*, 2010). For these reasons the authors propose that imipramine should be trialed in patients as an anti-Alzheimer's agent. Thus this agent joins tacrolimus and sirolimus (Section 6.1.4) and rosiglitazone (Section 6.1.5) as pharmaceuticals at present in widespread use for purposes other than their documented capacity to inhibit TNF production, that have been advocated to warrant human Alzheimer's trials.

In keeping with this anti-TNF interpretation of the actions of these drugs usually regarded as anti-depressive agents, a recent publication has reviewed evidence from clinical trials evaluating the efficacy of TNF antagonists in routine clinical use (i.e. adalimumab, etanercept, and infliximab) on depressive symptoms and mental health-associated quality of life measures (Soczynska *et al.*, 2009). While concerned with bipolar disorder (bipolar depression), more than major depression (sometimes termed unipolar depression), the theme of this extensive review is the importance of increased levels of TNF in causing these disease states, and of restoring homeostasis as a basis for their treatment – in other words, returning this cytokine and therefore its downstream mediators to physiological levels.

5.5 Aggression and TNF

Anger and aggression are well-documented aspects of Alzheimer's disease (Ballard & Walker, 1999), brain trauma (Rao *et al.*, 2009), major depression (Keilp *et al.*, 2006) and the post-cerebral malaria syndrome (Bangirana *et al.*, 2009). Indeed, a recent malaria paper describes a proportion of such patients attacking their peers and throwing stones at people and cars with little or no provocation (Idro *et al.*, 2010). TNF has been experimentally associated with aggression in human subjects (Suarez *et al.*, 2002; Suarez *et al.*, 2004) and mice selected for non-aggression express lower levels of inflammatory cytokines (Petitto *et al.*, 1994). In addition, aggression in Alzheimer's is more pronounced in patients expressing APOE4 (Craig *et al.*, 2004; van der Flier *et al.*, 2007), an apolipoprotein J variant associated with more TNF generation (see Section 5.2.5). Moreover, the well-known outcome, in a proportion of patients, of anger and aggression when interferon-α is used to treat hepatitis C (Kraus *et al.*, 2003; Preau *et al.*, 2008) has recently been associated with possession of the A allele in the -308 promoter region of the TNF gene (Lotrich *et al.*, 2010), which causes higher TNF production (Sallakci *et al.*, 2005).

Although, as referred to throughout this review, the above disease states in which anger and aggression can occur are circumstances in which TNF is increased, and sometimes have shown positive associations between the two (Suarez *et al*., 2002; Suarez *et al*., 2004), until now no firmer evidence has been available. However, a recent report has documented the absence of standard measures of aggressive behavior in double TNF receptor knock-out mice – i. e., animals quite unable to use TNF – with aggressive posturing (sideways posture and tail rattling) and bouts of fighting totally lacking when confronted by previously unseen mice (Patel *et al.*, 2010). Clearly, this has implications for understanding and treating all of the diseases noted in this section.

6. Treating TNF encephalopathies

6.1. Indirectly inhibiting TNF production

A rationale for neutralizing TNF indirectly, through inhibiting the pathway that generates it, depends on potential advantages based on either cost, administration by a more convenient route, or both. Disadvantages include having other actions as well, and not being as potent as agents that specifically neutralize TNF itself. Nevertheless the approaches summarized in Section 6.1 are extremely important, since the direct-acting biological therapies discussed in Section 6.2, though likely to be more efficacious, are beyond the means of millions who suffer from cerebral malaria and Alzheimer's disease. Moreover, these biologicals probably require administration by more highly skilled staff than are available. Therefore it is hoped that Section 6.1 might encourage more developmental work with the agents discussed below.

6.1.1. Thalidomide

While thalidomide is notorious for its teratogenic effects, its potential usefulness as an anti-inflammatory agent in patients other than child-bearing age women has been widely explored. Its major property of interest is its capacity to reduce TNF levels (Moreira *et al.*, 1993; Bauditz *et al.*, 2002), and it protects mice against LPS shock (Moreira *et al.*, 1997), largely a TNF-mediated phenomenon. There is considerable research on generating thalidomide derivatives to focus and refine its anti-TNF properties (Hashimoto, 1998; Greig *et al.*, 2004; Alexandre-Moreira *et al.*, 2005), chiefly for use in conditions such as graft-versus-host disease (Holler *et al.*, 1995), rheumatoid arthritis (Ossandon *et al.*, 2002) and Crohn's disease (Facchini *et al.*, 2001), in which anti-TNF biologicals are successful human treatments. Its application in neurodegenerative diseases is also being explored (Tweedie *et al*., 2007). In particular, thalidomide has been shown to inhibit development of a range of harmful changes caused within 7 days in mice receiving a single injection of $A\beta_{42}$ directly into the hippocampus. This short-term model, also used by others (Dinamarca *et al.*, 2006), is acknowledged to be less than ideal for the realities of Alzheimer's disease, but it is widely accepted to be central to the process (but see Simon *et al*. in Section 5.2.1). The pathology inhibited by thalidomide included vascular abnormalities, microgliosis and astrogliosis, a greatly increased message signal for TNF in microglia, and neuronal death (Ryu & McLarnon, 2008). As well as making a useful argument for this agent and its variants continuing to be developed in this context, these data add further weight to the rationale of treating

Alzheimer's diseases by directly inhibiting TNF. We are aware of only one instance of thalidomide being tested in malaria encephalopathy, in a mouse model (Muniz-Junqueira *et al.*, 2005). It was reported to improve survival.

6.1.2. CO and H_2S donors, resveratrol,and curcumin

As discussed (Sections 3.4.1 and 3.4.2) CO and H_2S donors act on the same mitochondrial enzyme, and through it are toxic in large doses, while having a host of useful modulatory functions, yet to be appreciably explored, in lower doses. It is part of the nature of inflammatory mediators, among which these two gases must be counted, that they are essentially homeostatic, but decidedly harmful in excess. Nevertheless, the concept of these agents as treatments has its genesis in a highly exciting and relatively untouched area of basic biomedical research, capable of producing concepts often able to surprise us. For example these gases are an excellent window on the function of mitochondria, to which much of the pathogenesis of cytokine-induced brain dysfunction is, in our view, ultimately bound.

Resveratrol is an intriguing polyphenol of plant origin reported to inhibit TNF production in microglia (Bi *et al*., 2005) and monocytes (Shen *et al*., 2009), and its association with SIRT1 in these studies (see Section 3.5) suggests that it mirrors how caloric restriction reduces TNF and enhances brain function. Since the literature on caloric restriction influencing brain is so impressive, resveratrol warrants close examination in an Alzheimer's context. Moreover, there are two recent reports of its efficacy in brain trauma (Ates *et al*., 2007; Sonmez *et al*., 2007), a condition linked to TNF excess, as is Alzheimer's (see Section 4.3).

Curcumin, an extract of the Indian spice, tumeric, has been mooted as a general anti-inflammatory agent for some time. In terms of Alzheimer's disease, proposed mechanisms of action have been as an anti-oxidant (Calabrese *et al*., 2003), protecting against Aβ because it is a metal chelator (Baum & Ng, 2004), preventing Aβ fibrils from forming (Ono *et al*., 2004), and suppressing NFκB (Aggarwal & Shishodia, 2004). We have included it here because of this last-listed property, which ensures reduced generation of certain cytokines, including TNF. This is consistent with, for instance, its capacity to inhibit Aβ-induced neurotoxicity (Park *et al*., 2008b), which the literature points to being TNF mediated (Wang *et al*., 2005; Ralay Ranaivo *et al*., 2006). Nevertheless, a 12 month, randomized, placebo-controlled study of oral curcumin for mild-to-moderate Alzheimer's disease was reported to have failed to show benefit (http://www.clinicaltrials.gov/ct2/show/NCT00099710). In passing, it might be an interesting exercise to see if populations renown for tumeric consumption have a lower incidence of Alzheimer's disease.

6.1.3. Intravenous immunoglobulin

Much plasma collected by blood banks is under-utilized, so immunoglobulin preparations have a long history of being administered intravenously to see if they ameliorate disease states. These include not just the hypo- and agammaglobulinemia disorders, but conditions such as disseminated intracellular coagulopathy and severe inhibition bacterial and viral diseases have been been treated "off label". As reviewed (Rosen, 1993), it was soon realized that as well as providing more total immunoglobulin, this therapy caused changes to the mediatiors common to innate immunity and inflammation through containing natural autoantibodies against IL-1 (Gallay *et al.*, 1991), IFN-γ (Toungouz *et al.*, 1996) and TNF (Simon & Spath, 2003).

Of particular relevance to this review, TNF was found to be reduced (Achiron *et al.*, 1994; Andersson *et al.*, 1996; Darville *et al.*, 1997; Sharief *et al.*, 1999; Gupta *et al.*, 2001; Kishimoto *et al.*, 2003; Asakura *et al.*, 2006). Another group reported an increase of IL-10 and soluble TNF receptor, which would have the same outcome as a fall in TNF (Gullestad *et al.*, 2001).

Unfortunately, these cytokines, the mediators of both innate immunity or inflammation, were still under the radar for most Alzheimer's researchers when the above studies were published. Therefore, when intravenous immunoglobulin began to be used to treat this disease, the accepted paradigm for this disease (Weksler *et al.*, 2005) simply required Aβ levels to be reduced to produce a positive outcome (Dodel *et al.*, 2004; Relkin *et al.*, 2009). Some clinical efficacy may have been apparent in preliminary trials, and a larger trial is currently recruiting patients (http://www.clinicaltrials.gov/ct2/show/NCT00812565), but the anti-TNF effects (above) of these agents do not yet appear have been taken into account. Nevertheless, the goal of reducing Aβ levels has been thrown into question by the two concepts discussed earlier: that TNF-induced APP can be expected to cause harm before Aβ forms (Simon *et al*., Section 5.2.1.), and that Aβ, once formed from APP cleavage, may actually be a useful mediator of cerebral innate immunity (Soscia *et al*., Section 5.2.3.). If reappraised in cytokine terms intravenous immunoglobulin might, in theory, be a useful way to indirectly reduce TNF, but it has renal toxicity (Graumann & Zawada, 2010), and its cost structure to contend with.

6.1.4. Tacrolimus (FK506) and sirolimus (rapamycin)

Tacrolimus is a widely used clinically as an immunosuppressive agent, chiefly to prevent rejection of organ transplants. It is thought to function through inhibiting the activity of calcineurin (protein phosphatase 2B), a widespread enzyme that, apart from involvement in T cell activation, is the most abundant phosphatase in the central nervous system (Mansuy, 2003). The activity of calcineurin most relevant to the purpose of this review is its capacity to active a transcription factor termed nuclear factor of activated T cells (NFAT) (Clipstone & Crabtree, 1992). Thus tacrolimus inhibits the accumulation of IL-2 mRNA, as well as the mRNAs of other early phase T cell activation genes such as IL-3, IL-4, GM-CSF, TNF alpha, IFN-gamma, and c-myc in activated human peripheral blood T cells (Tocci *et al.*, 1989). NFAT activation also occurs in the brain, with inflammatory mediators such as TNF recruiting astrocyte calcineurin to stimulate an inflammatory pathway involving this transcription factor (Fernandez *et al.*, 2007). In addition expression of TNF in neurons has been reported to involve the calcineuron-NFAT pathway (Canellada *et al.*, 2006). Thus, by suppressing calcineurin, tacrolimus predictably inhibits TNF production. Indeed, this inhibition is a widespread phenomenon (Kawano *et al.*, 1992; Goldfeld *et al.*, 1992; Sakr *et al.*, 1993; Kawano *et al.*, 1994; Squadrito *et al.*, 1999; Sakuma *et al.*, 2000). In addition, inflammatory cytokines, including TNF, induce various calcineurin-dependent activities (Grunnet *et al.*, 2009), so inhibiting calcineurin can be expected to inhibit these down-stream functions of TNF.

Hence the use of tacrolimus and anti-TNF agents in order to produce the same clinical outcomes is logical, with graft-versus-host disease (Jacobsohn & Vogelsang, 2002), inflammatory bowel disease (Legnani & Kornbluth, 2004), organ transplant (Pascher *et al.*, 2005), rheumatoid arthritis (Miyata *et al.*, 2005) being examples. In a limited comparative literature, tacrolimus appears to be slightly less efficacious than anti-TNF agents, in that infliximab proved to rescue only about a quarter of ulcerative

colitis patients refractory to tacrolimus (Herrlinger *et al.*, 2010). Tacrolimus shares with the anti-TNF agents a long history of patient use, but as noted above (Tocci *et al*., 1989) it inhibits a number of important cytokines in addition to TNF, the implications of which would require exploring before considering long-term use. It could be counterproductive, for instance, to downregulate the anti-inflammatory cytokine IL-4 (Tocci *et al*., 1989) during a chronic inflammatory disease, but acceptable in a more acute event such as brain trauma or septic encephalopathy.

Nevertheless, of all the possibilities for inhibiting TNF indirectly , tacrolimus appears to be the most promising on current data. Of particular relevance to this review, it has been reported to restore associative learning and memory (Dineley *et al.*, 2007) and reverse novel object recognition memory deficits (Taglialatela *et al.*, 2009) in a murine Alzheimer's disease model. Certainly, from a basic science perspective the tacrolimus data are important because they add further weight to TNF being a prime therapeutic target. However, as recently reviewed (Naesens *et al.*, 2009), it is well documented that the use of tacrolimus carries a risk of nephrotoxicity, presumably limiting its long-term use.

Siromilus, a macrolide antibiotic generated by *Streptomyces hygroscopicus*, was first identified as an immunosuppressant about a decade ago (Kahan *et al.*, 1991), and, as reviewed (Weir *et al.*, 2010), has been used alone or in conjunction with tacrolimus in recent years in order to lower overall toxicity. Sirolimus has been shown to possess a range of effects that interfere with activation of the immune system, and crosses paths with tacrolimus in the complexity of the immunoregulatory functions of mTOR (mammalian target of rapamycin) inhibition (Thomson *et al.*, 2009). In outline, both tacrolimus and sirolimus are ligands for FKBP12, (FK506 binding protein 12), an isomerase involved in a range of basic cellular processes as well as immunosuppression. In addition, it is involved in LTP, memory, and perseverative behaviors (Hoeffer *et al.*, 2008). One of the many consequences of these shared actions is that sirolimus, like tacrolimus, inhibits TNF production (Gabryel *et al.*, 2004; Adkins *et al.*, 2004; Lorne *et al.*, 2009; Wang *et al.*, 2009a; Krakauer *et al.*, 2010; Weir *et al*., 2010). Again like tacrolimus, sirolimus has recently been reported to rescue cognitive deficits in mouse models of Alzheimer's disease (Caccamo *et al*., 2010; Spilman *et al.*, 2010). In the light of the literature we have summarized, it seems a logical extension of these data to propose that the reduction in TNF caused by these two agents could be sufficient to explain their *in vivo* activities in these Alzheimer models. Thus tacrolimus and sirolimus, two agents presently in use for their immunosuppressive activity, join imipramine, an anti-depressant (Section 5.4), as drugs already in clinical use that, though their TNF-suppressing qualities, possess plausible cases for testing against the encephalopathies discussed in this review.

As discussed (Krakauer *et al*., 2010), toxicity might well preclude the use of siromilus (rapamycin) in states requiring long-term treatment, but short-term treatment in brain trauma and certain encephalopathies induced by infectious agents show brighter prospects. However, these indirect approaches to inhibiting TNF production approaches are unlikely to approach the efficacy of specific TNF inhibitors. Thus they are likely to be hard pressed, in life-threatening encephalopathies, to equal the outcome possible by targetting pre-formed TNF directly, as discussed below.

6.1.5 Rosiglitazone, a PPAR-γ agonist

The peroxisome proliferator-activated receptor -gamma (PPAR-γ) is a member of the nuclear receptor superfamily of ligand-dependant transcription factors. They have naturally occuring, as well as synthetic ligands, the latter having been developed for therapeutic use. Rosiglitazone, a thiazolidinedione, is one such agent, and is commonly used to counter the insulin resistance seen in type 2 diabetes. This property was recognized (Oakes *et al.*, 1994) a few years after TNF had been reported to cause insulin resistance (Lang *et al.*, 1992), but the notion of these PPAR-γ ligands might act through inhibiting TNF release had to wait another six years, when they were shown to down-regulate macrophage activation (Ricote *et al.*, 1998) and impair the production of inflammatory cytokines, including TNF, from monocytes (Jiang *et al.*, 1998). This activity of these agents were soon reported to extend to the brain (Heneka *et al.*, 2000). In that same year this class of drugs, the glitazones, were demonstrated to reduce the ability of both LPS and Aβ to activate monocytes and microglia, and inhibit TNF production from cells of this lineage (Combs *et al.*, 2000).

While these researchers subsequently argued the case for glitazones as possible Alzheimer's therapies through their anti-inflammatory properties (Sundararajan *et al.*, 2006), others began mouse experiments (Pedersen *et al.*, 2006) and human trials (Watson *et al.*, 2005; Risner *et al.*, 2006) simply on the rationale that these drugs reverse insulin resistance, their originally described property, without any role attributed to TNF. In the same year as Risner's publication appeared, insulin resistance in rheumatoid arthritis patients proved reversible by treatment with a standard dose of specific anti-TNF drug (Gonzalez Gay *et al.*, 2006). This confirmed the earlier *in vitro* observation (Lang *et al*., 1992), and implies that rosiglitazone can safely be regarded as a TNF inhibitor in an insulin context, as well as more generally (Sundararajan *et al*., 2006). Indeed, the observation that apoe4 positive individuals did not respond (Risner *et al*., 2006) is easier to rationalize through activities of TNF (see Section 5.2.5) than its influence on insulin metabolism. Another group (Escribano *et al.*, 2009) have recently that rosiglitazone rescued memory impairment in a transgenic mouse model of Alzheimer's disease, and, like Landreth and co-workers (Combs *et al*., 2000; Sundararajan *et al*., 2006) have argued the outcome in terms of inhibiting expression of pro-inflammatory cytokines, such as TNF, for which they assayed. The changes they observed in Aβ and tau can be accounted for, through TNF reduction, in observations summarized in Sections 5.1.1 and 5.2.2. Likewise, recent data on roziglitazone improving survival in malaria (Serghides *et al.*, 2009) is based entirely on the rationale of the observed reduction in TNF levels. We have similar data from experiments, with the same rationale, with highly virulent mouse influenza models with gemfibrozil, a functionally similar PPAR-α agonist (Budd *et al.*, 2007) and rosiglitazone (Alleva, L., unpublished). The pathogenesis of neither malaria nor influenza has, or is likely to have in future, a history of being explained in terms of Aβ-origin pathology or insulin tolerance.

A larger phase III trial of rosiglitazone is presently in progress in Alzheimer's patients (see http://www.alzforum.org/drg/drc/detail.asp?id=116), whereas imipramine (Section 5.4), tacrolimus or sirolimus (Section 6.1.4), have not yet reached this stage of testing. In summary, the property these four agents share of inhibiting TNF production means that, inadvertently or otherwise, those conducting such trials are testing the consequence of reducing levels of this cytokine. From precedences from other disease states, such as rheumatoid arthritis, outcomes can be expected to be less satisfactory, with more side effects, than when specific purpose-designed anti-TNF agents are employed, as described in the next Section.

6.2 Specifically neutralizing TNF once produced

6.2.1. Acute systemic infections

The broad evidence summarized in the preceding pages clearly points to treating encephalopathies by neutralizing excess TNF. Conceptually, at least in other organs, this is now an old idea. As has been reviewed (Clark, 2007), once TNF was sequenced (Aggarwal *et al.*, 1985), and cachectin appreciated to be the same molecule as TNF (Beutler *et al.*, 1985), there was soon no doubt that TNF is what causes death from injected LPS, since neutralizing anti-TNF antibody, given before LPS, prevents death in mice (Beutler *et al.*, 1985; Waage *et al.*, 1987). Many early studies in mice demonstrated that serum TNF peaks at 90 minutes after intravenous LPS, when the animals are not yet particularly sick. In other words, TNF rises before onset of appreciable illness (Waage *et al.*, 1987), so the best time to administer an anti-TNF agent has passed once severe illness is present. Thus it soon became evident that in acute illness the therapeutic potential of these TNF-neutralizing agents is largely limited to circumstances in which the acute cytokine-induced illness was an unavoidable consequence of necessary treatment. Accordingly, positive results in patients were reported in prophylactic OKT3 therapy, which minimizes graft rejection (Chatenoud, 1993; Eason *et al.*, 1996), and graft-versus-host disease (Holler *et al.*, 1995; Jacobsen *et al.*, 1992). Likewise, anti-TNF prevents the human Jarisch-Herxheimer reaction caused by penicillin administered to kill *Borrelia recurrentis*, an organism high in LPS, and the cause of louse-borne relapsing fever, but only provided it is given before the penicillin, i.e. before TNF is induced (Fekade *et al.*, 1996). Given this background, it is not surprising that administering anti-TNF antibody disappointed those using it against falciparum malaria (Kwiatkowski *et al.*, 1993; Van Hensbroek *et al.*, 1996; Looareesuwan *et al.*, 1999) or human sepsis (Abraham *et al.*, 1998; Dinarello, 2001).

6.2.2. Chronic non-cerebral and cerebral inflammatory states

During the period that the disappointing outcome of anti-TNF antibody in treating acute infections was emerging, a group in London working on rheumatoid arthritis found that TNF might be a more important mediator than IL-1 in this context, since *in vitro* anti-TNF antibody reduced IL-1 as well as TNF (Brennan *et al.*, 1989). The implications of this for treating rheumatoid arthritis (Feldmann *et al.*, 1990) led to a successful open trial being published a few years later (Elliott *et al.*, 1993). This was opportune timing, in the sense that the pharmaceutical company with which they were involved was one of many looking for new uses for a product that had become an orphan due to its failure as a treatment for sepsis. Not surprisingly they readily funded a blinded trial, the successful outcome of which appeared the next year (Elliott *et al.*, 1994). This paved the way for the interest of others in treating other non-systemic chronic states with anti-TNF agents, and nowadays patients suffering from Crohn's disease, psoriasis, and ankylosing spondylitis as well as rheumatoid arthritis are treated with infliximab (Remicade), a monoclonal murine-human chimeric antibody to TNF, etanercept (Enbrel), a fusion protein of two p75 chains of the TNF receptor II and the Fc portion of IgG1 and adalimumab (Humira), a fully human anti-TNF monoclonal antibody, on a success and scale, and with financial gain on the part of the patent owners and manufacturers, unique in the biotechnology industry. It has not all been plain sailing, with exacerbation of some, but by no means all, pre-existing

infections (Section 6.3). Details of this, and differences between the molecules and their mode of action, have recently been reviewed extensively (Tracey *et al.*, 2008; Esposito & Cuzzocrea, 2009; Furst *et al.*, 2010). Other anti-cytokine agents under development for this purpose are also discussed in these reviews.

It seems that the distinctively long duration of TNF increase in the brain during systemic inflammatory responses (Section 4.5) is a reflection of the dependence of the health of the central nervous system on the innate immune response. Thus diseases of this organ are a prime target for anti-TNF therapeutic agents should its normal surveillance by cells of bone marrow origin (Butovsky *et al.*, 2007b; Butovsky *et al.*, 2007a; Ron-Harel *et al.*, 2008), with anti-inflammatory activity that is mediated chiefly through IL-10 (Koronyo-Hamaoui *et al*., 2009), fail. This surveillance has recently been reviewed (Ron-Harel & Schwartz, 2009; Schwartz, 2010).

6.2.3 Getting anti-TNF to where it is needed in encephalopathies

Since anti-TNF agents are administered parenterally in the non-cerebral diseases discussed above, they unsurprisingly encounter no particular anatomical barrier preventing access to the site of pathology. Clearly, a drawback with testing these agents against putative TNF-driven encephalopathies is that they are about as large as albumin and globulin, so cannot be expected to pass the blood-brain barrier efficiently, where, as discussed in various Sections of this review, much evidence is consistent with excess TNF being harmful. One group has addressed the challenge of brain access through adapting a lesson from the basic aviation medicine literature, in which the effects of 5 minutes of head-down positioning allows appreciable albumin and globulin to enter the CSF, probably though the choroid plexus (Wen *et al.*, 1994). Indeed, these authors suggested this manoeuvre as a way to get large molecules in to the brain for therapeutic purposes. Combined with an injection route for etanercept that drains into Batson's plexus, this has been used with the intention of accessing the CSF via the choroid plexus. In 2006 an open trial with etanercept injected by this route, in which 15 Alzheimer's patients were treated for 6 months, was published (Tobinick *et al*., 2006), as have case reports since (Tobinick & Gross, 2008). Etanercept administered in this way has recently been shown to reach the cerebral ventricles in the rat (Tobinick *et al.*, 2009). This argues that this route is much less invasive but functionally equivalent to i. c. v., which is routinely used for anti-TNF biological agents of this size to access the CSF in basic animal studies on roles of TNF in brain function (Medeiros *et al.*, 2007; Riazi *et al*., 2008; Galic *et al.*, 2008; Liesz *et al*., 2009). We note that a similar challenge is addressed when treating brain-sited lymphoma with rituximab, a monoclonal antibody effective against non-Hodgkin lymphoma, which expresses CD20, the target of the antibody. Unfortunately its normal intravenous route for non-cerebral lymphomas is ineffective (Rubenstein *et al.*, 2003), so intraventricular administration was seen as the logical alternative. It was successful in a Phase I trial (Rubenstein *et al.*, 2007), but it would be of practical interest to establish whether the less invasive Batson's plexus route, above, will prove to be equally efficacious. Arguments in favour of this route in neutralizing brain TNF have recently been reviewed (Tobinick, 2010).

Despite the direction of the literature, calls for a double-blind human Alzheimer's trial using etanercept by this route (Tobinick *et al*., 2006) have not yet attracted industry or government funding. This is in marked contrast to the readiness, in 1993 (see Section 6.2.2), of the manufacturers of another of the above anti-TNF

agents to expand a very similar open trial on rheumatoid arthritis (Elliott *et al*., 1993) into a double-blind study (Elliott *et al*., 1994). We note, however, that an essentially identical trial except it is to employ etanercept subcutaneously, is soon to begin (see http://www.clinicaltrials.gov/ct2/show/NCT01068353). In view of the albumin-like size of this biomolecular construct, and a previous blinded trial (fewer subjects, but over 24 weeks) employing this route having a negative outcome (Bohac *et al*., 2002), giving funding precedence to a trial using this route is surprising. The challenge in getting etanercept to where it matters in Alzheimer's disease is, in addition to the rituximab example (previous paragraph), also addressed by studies in which intravenous infliximab, a similar sized molecule, can be presumed not to have entered the CSF because TNF levels in this compartment remained unchanged (Andersson *et al.*, 2006; Kikuchi *et al.*, 2008).

In 2003 a promising high-affinity inhibitor of human TNF was discovered to be secreted by Tanapox virus (Brunetti *et al.*, 2003). From its molecular weight (Rahman *et al.*, 2006), its inability to pass the BBB will still be a concern for using this protein to treat cerebral conditions, but its extraordinarily high activity compared to neutralizing specific antibodies against TNF has encouraged commercial development as VT-346, with Alzheimer's disease as well as rheumatoid arthritis and Crohn's disease the stated targets (March 16 2010 press release at www.vironinc.com). Others (see http://www.bionity.com/news/e/107293) are developing TNF neutralizing antibodies, of a type (Harmsen & De Haard, 2007) small enough to pass the blood brain barrier, for systemic use in human disease. These nanobodies are an attractive second generation drug, but like VT-346 are some years away from clinical trials. In contrast, infliximab, etanercept and adalimumab, already administered to millions of people annually in relative safety, have an immediate attraction for dealing with the large-scale clinical challenge already present, particularly in Alzheimer's disease, provided it actually gets into the CSF.

6.3. Avoiding exacerbating infections

Over 25 years ago, when working with purified TNF in the days before recombinant proteins, our laboratory argued that TNF was central to both disease and cell-mediated immunity (Clark *et al*., 1981), as recently reviewed (Clark, 2007). For example, TNF inhibits malaria parasites (Taverne *et al.*, 1981; Clark *et al.*, 1987), *Mycobacterium* spp. (Bermudez & Young, 1988), *Salmonella typhimurium* (Degre & Bukholm, 1990), *Leishmania* spp.(Titus *et al.*, 1989), *Toxoplasma gondii* (Chang *et al.*, 1990), *Coxiella brunetii* (Tokarevich *et al.*, 1992), and *Listeria monocytogenes* (Rothe *et al.*, 1993). It was always inevitable, therefore, that dormant infections with these organisms had the potential to flare when anti-TNF agents were chronically administered to, for example, rheumatoid arthritis patients (Keane *et al.*, 2001; Slifman *et al.*, 2003; Rijkeboer *et al.*, 2007). Hence patients are nowadays tested, monitored, and if necessary treated for these conditions before and while undergoing anti-TNF therapy. While this is a real phenomenon, it should nevertheless be kept in perspective, in that a recent consensus document puts the risk rate for all bacterial diseases for TNF neutralizing agents as 0.07-0.09 per patient year, compared to 0.06 for all other disease modifying anti-rheumatic drugs (Furst *et al*., 2010). As reviewed in 2008 (Domm *et al.*, 2008), the influence of anti-TNF therapy on concomitant viral diseases seems to have been surprisingly mild, and there are as yet very few guidelines on whether or not to screen, and for what conditions. Outcomes of monitoring for hepatitis B, hepatitis C, HIV, herpes, E-B virus, cytomegalovirus,

varicella zoster virus are discussed by these authors. Since this publication single cases of cytomegalovirus retinitis (Haerter *et al.*, 2004) and, of more concern, H1N1 influenza (Kling *et al.*, 2010) have been reported. Since the total number of people receiving regular dosage with these agents probably now approaches 10 million, individual cases are inevitably difficult to interprete.

The degree of this concern in other encephalopathies depends, of course, on the circumstance. Neurodysfunction after brain trauma or myocardial infarct would present the least risk, whereas after surgery or burns opportunist TNF-sensitive organisms are a more of a possibility. An encephalopathy associated with a known systemic infection (Sections 4.4 and 4.5) caused by an agent sensitive to an antimicrobial, in the widest sense, need not be as much concern as an unsuspected dormant infection when long-term treatment is envisaged. For example, the point has been made that anti-TNF did not reduce the rate of parasite clearance after antimalarial treatment (Looareesuwan *et al*., 1999). This implies that anti-TNF agents could be safely administered, along with antimalarials, in trials against long-term malaria-induced cognitive defects (Kihara *et al*., 2006). Alzheimer's disease would be expected to have the same need for testing and monitoring for dormant infections such as tuberculosis and salmonellosis, as does rheumatoid arthritis.

7. The perceived advantages of normalizing exacerbated cerebral levels of TNF

The evidence summarized in this review indicates that the advantages of reducing pathologically increased brain levels of TNF in the brain dysfunctions and diseases we have discussed are manifold. Most topically, cerebral APP can be expected to be reduced, so it does not reach levels expected to be harmful in adults because they activate TNFRSF21 (DR6) and thus thin out neurons and axons (Nikolaev *et al*., 2009), as is normal in early neonates. The rate of cleavage of APP to $A\beta_{42}$ can also be expected to be reduced (Liao *et al*., 2004; Yamamoto *et al*., 2007), and, through reducing the effects of TNF induced by $A\beta_{42}$ (Wang *et al*., 2005; Ralay Ranaivo *et al*., 2006), so too would be many of the effects of $A\beta_{42}$ on synapses and small cerebral blood vessels. In addition, inhibitory functional effects of excessive TNF on the interaction between glial cells and neurons can be expected to be inhibited, neurogenesis enhanced (Wu *et al*., 2000), synaptic zinc availability increased (Section 3.2), and effects of cerebral hypoxia minimized (Aden *et al*., 2009).

In contrast, 17 years ago, when rheumatoid arthritis treatment with infliximab was tested in a blinded control trial, very little, inevitably seen as simplistic by today's literature, was appreciated about how it might work, and key mechanisms actually came to light later (Feldmann & Maini, 2003). The same will inevitably be true for the encephalopathies, but we can safely say we know a lot more to begin with.

Finally, we again draw attention to the views expressed by two clear thinkers that their respective fields, cerebral malaria (Maegraith, 1948) and Alzheimer's disease (Castellani et al., 2008) were being led astray by what was historically obvious down a microscope, and that, in their words, invisible molecules and subcellular damage are probably what matter more. Eureka moments can often be quietly unwelcomed by many researchers because of the death knell they sound for popular paradigms, but in the long run they are very necessary. Just as work from New Guinea served that purpose in cerebral malaria (Genton *et al*., 2008; Tjitra *et al*., 2008), the combined implications of the APP/DR6 (Nikolaev *et al*., 2009) and innate immunity/Aβ (Soscia *et al*., 2010) studies promises to do so in Alzheimer's disease.

We trust that our background in the roles of TNF and similar mediators in physiology, pathology and innate immunity has allowed us to strengthen these cases, and thus help focus minds on rational treatment for this group of functionally-related diseases. We stress that to feel at home thinking about mediators such as TNF one must appreciate, in some depth, their primary, essential, role in basic physiology, examples relevant here being synapse homeostasis and setting the diurnal clock. From time to time, when a primitive signal is recognized, they also set innate immunity in motion. Less frequently, these signals are so strong that they provoke the host to overdo it, causing what we recognize as either organ-specific or systemic pathology, and have discussed here. Treatment is about ameliorating ths overblown response, not eliminating the cytokine as if it were some exogenous poison.

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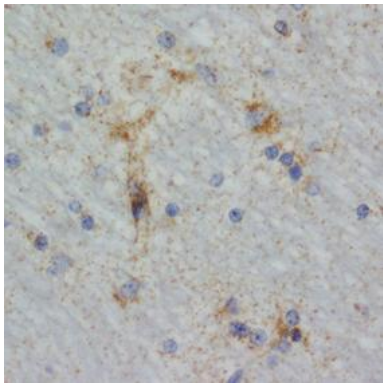
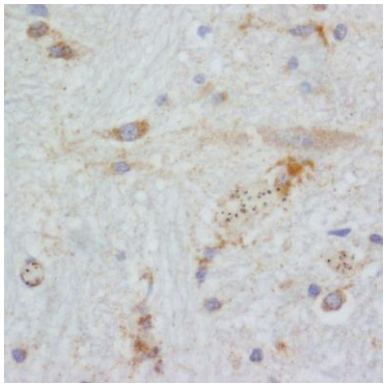
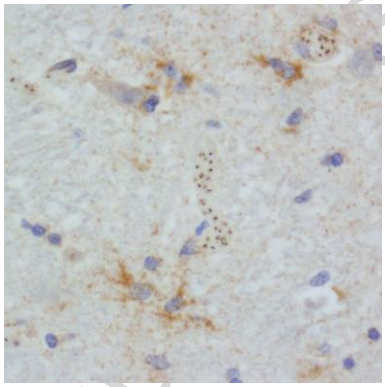
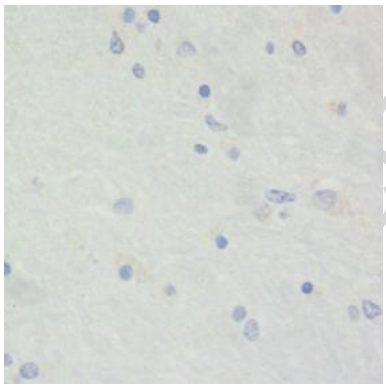


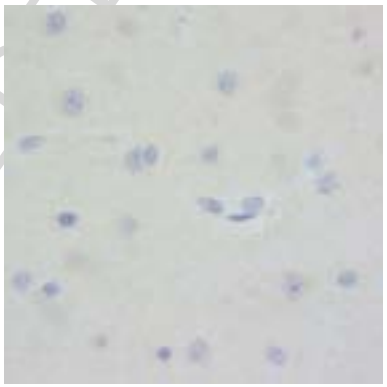
A. **Septic encephalopathy *(Salmonella enteriditis)***

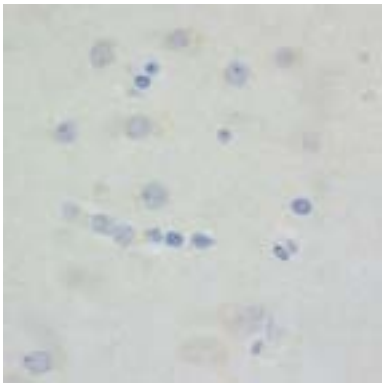




B. **Cerebral malaria *(Plasmodium falciparum)***







C. **Controls**

Fig. 1

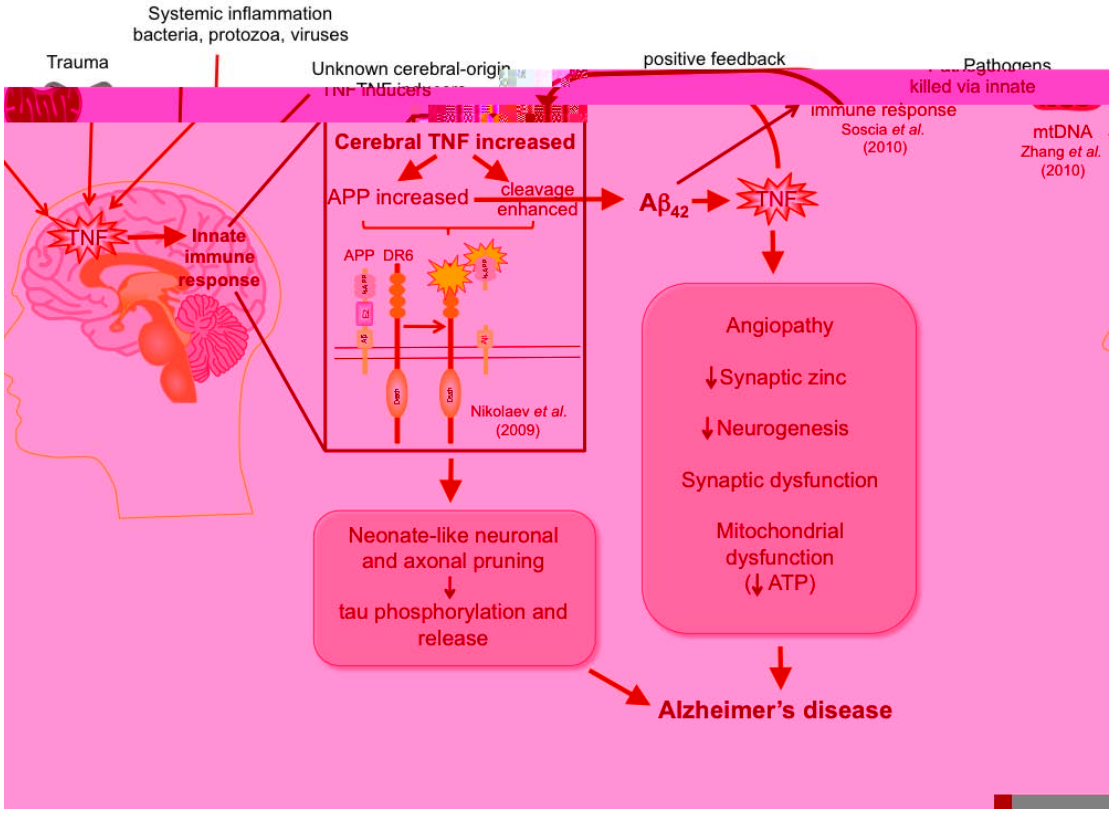


Fig. 2