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COMMENTARY

New Hope for Survivors of Stroke and Traumatic Brain Injury

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In mid-2010, an editorial marking the 40th anniversary of the *International Journal of Stroke* was signed by over 50 leaders in the field. It provided a frank commentary on what they regarded as the inability of present mainstream stroke research directions to address the needs of patients [1]. In view of what they described as a dearth of advances leading to new targets for therapy, they urged their field to break down its silo mentality and embrace new ideas and approaches from other scientific disciplines and diseases. In short, to listen to outsiders and through them learn to think outside the box.

A paper in this issue of *CNS Drugs* by Tobinick et al. might well have provided them such an opportunity. In more than 600 consecutive stroke patients, years after the initial ischaemic insult, highly significant improvements in a large range of clinical parameters were recorded at 30 min, 1 week and 3 weeks after a single dose of 25 mg of etanercept. A smaller number of patients who had suffered traumatic brain injury were treated, with similar responses. Statistically significant responses within 30 min are of particular interest, since they evidently validate a novel way to deliver large molecules into the brain non-invasively. As in Alzheimer's disease case studies [2, 3], etanercept was administered so that it enters Batson's plexus, the valveless venous labyrinth that surrounds the spine and is in continuum with the choroid plexus [4]. The patient is then tilted head-down for a short time to generate a gravitational pressure increase from the column of blood in this valveless plexus. Tilting for this period had been shown to cause albumin and globulin, two etanercept-sized molecules, to enter the rabbit CSF in appreciable amounts [5].

Etanercept is one of the specific anti-tumour necrosis factor (TNF) biological agents registered for treating rheumatoid arthritis, and this approach has been successfully used, on a large scale, for nearly 20 years. These agents are also registered to treat Crohn's disease and psoriasis, as superficially different from each other as they are from rheumatoid arthritis. Success in these clinically diverse states through lowering TNF levels by using a specific anti-TNF agent indicates they all share the one disease mechanism, inflammation, albeit exhibiting striking organ-specific manifestations.

Retrieval of function so many years after the stroke event will seem implausible to those for whom the few hours allowed by tissue plasminogen activator, a fibrinolytic enzyme with a completely different rationale, is the benchmark. Nevertheless, the years-long interval between the stroke event and rapid clinical improvement described in these patients is consistent with experimental evidence that TNF generation persists in the CSF for very much longer (10 months plus) than in the serum (gone in 6 h) [6]. Clearly, these observations will engender much further research in this area.

Although, as the authors note, randomized trials will be necessary to further quantify and characterize the clinical response of stroke patients to etanercept, in this report each patient's pre-treatment state provided an internal control. In practice, these individual pre-treatment comparisons are highly valid, since the likelihood of rapid spontaneous return of function is remote this long after a stroke event. Moreover, since no two stroke outcomes are the same, such internal controls allow precise before and after clinical comparisons in a phenotypically heterogeneous condition.

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While it has been realized for some time that TNF, a cytokine at the top of the inflammatory cytokine cascade, is important in the penumbra zone in stroke, its function has usually been thought of in terms of irreversible neurotoxicity [7]. But once the myriad physiological roles of TNF in the CNS (see Clark et al [8]. for a review) are appreciated, the functional consequences of this cytokine being above the homeostatic range for a long period can be better appreciated. As reviewed [9], the longer the period after a stroke event or traumatic brain injury the more these two conditions and Alzheimer's disease come to resemble each other. This is not surprising, since it is becoming increasingly apparent that all three are chronic inflammatory states affecting the same organ. Intriguingly, this case [9] was made as an argument that experimental brain trauma and stroke in rats might serve as useful models to test putative Alzheimer's disease treatments. Nowadays all three conditions brain trauma [10, 11], stroke [12] and Alzheimer's disease [2, 13 15] are under scrutiny for their response to agents that reduce TNF. A key finding is the reported improvement in cognition in all three conditions.

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