



## Satellite Symposium Proceedings

### The Immunomodulatory Role of Therapeutic Plasma Exchange in Peripheral Nervous System and Neuromuscular Diseases

Proceedings of a satellite symposium held  
at the 14th International Congress on  
Neuromuscular Diseases symposium,  
Toronto, Canada, 7 July 2016

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# The Immunomodulatory Role of Therapeutic Plasma Exchange in Peripheral Nervous System and Neuromuscular Diseases

Proceedings of a satellite symposium held at the 14th International Congress on Neuromuscular Diseases symposium, Toronto, Canada, 7 July 2016

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This article reports the proceedings of a satellite symposium held on 7 July 2016 at the 14th International Congress on Neuromuscular Diseases (ICNMD) symposium, Toronto, Canada. Therapeutic plasma exchange (TPE) removes pathogenic antibodies and immune complexes from the plasma. However, TPE may also impact a number of other immune-modulatory pathways that mediate cellular immunity. Data from clinical trials support the effectiveness of TPE in Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). However, to date, the use of TPE for the treatment of chronic myasthenia gravis (MG) is not supported by large clinical studies and there are discrepancies between guidelines and clinical practice. More clinical trials are needed to understand the role of TPE in MG, GBS, and CIDP, as well as other neuromuscular diseases in which it is used, or which may represent potential targets for TPE.

## Keywords

Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, myasthenia gravis, plasma exchange

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Therapeutic plasma exchange (TPE) is a valuable technique in peripheral nervous system and neuromuscular diseases: the removal of autoantibodies and immune complexes ensures a rapid onset of action, and the treatment is safe and effective for long-term use. However, the mechanism of action of TPE involves more than the removal of large molecules; studies have shown that TPE has numerous immunomodulatory effects. Despite the fact that TPE is widely used in the treatment of neurological diseases, its effectiveness has only been formally demonstrated in a limited number of conditions: myasthenia gravis (MG), Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). This article describes the proceedings of a symposium convened at the 14th International Congress on Neuromuscular Diseases (ICNMD) symposium, in Toronto, Canada on 7 July 2016. The symposium aimed to further explore the immunomodulatory role of TPE, and to discuss current clinical evidence and unmet needs. ■

## Therapeutic Plasma Exchange Mechanism of Action and Immunomodulatory Function

Presented by: Luis Querol

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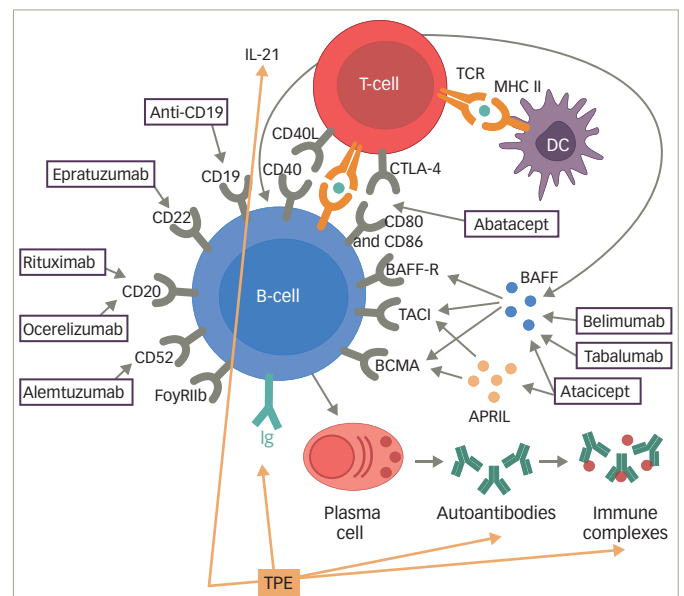
Luis Querol began his presentation by defining several terms that are often used interchangeably in the literature. Apheresis is derived from the Greek term aphaeresis, meaning to take away by force. Plasmapheresis refers to the removal of small volumes of plasma, not more than 15% of total blood volume (TBV), without necessarily replacing the volume. Therapeutic plasma exchange (the abbreviation TPE will be used in this report though PLEX, PE and PEX are also used to mean TPE) is the removal of large volumes of plasma (1 to 1.5 of patients' TBV) with appropriate volume replacement using either albumin or fresh frozen plasma (FFP).<sup>1</sup>

Separation of blood components by TPE may employ a centrifuge or membrane filtration. The major differences between the two techniques are the plasma volumes required: centrifuge techniques require lower volumes than membrane and allow a higher plasma extraction rate, which affects the procedural time and the effectiveness of the procedure. Centrifuge TPE usually employs citrate as anticoagulation factor while membrane TPE employs heparin. In addition, centrifuge-based TPE requires a lower blood flow than membrane-based TPE (<150 ml/min versus >150 ml/min). As a result, centrifuge-based TPE can be performed successfully using peripheral venous access.<sup>2</sup>

The World Apheresis Association (WAA) apheresis registry now comprises data from 50,846 procedures performed in 7,142 patients, of which 16,942 were TPE.<sup>3</sup> Most adverse events (AEs) associated with the procedure were reversible and mild in 2.4% of procedures, and included: vascular access problems (54%), device issues (7%), hypotension (15%) and tingling (8%). Moderate AEs were reported in in 3% of procedures and included: tingling (58%), urticaria (15%), hypotension (10%) and nausea (3%). In this registry, severe AEs occurred in only 0.4% of procedures: syncope/hypotension (32%), urticaria (17%), chills/fever (8%), arrhythmia/asystole (4.5%), nausea/vomiting (4%). Centrifuge-based techniques are much more commonly used than membrane filtration (16:1) and are associated with fewer AEs (6% versus 11%). Procedures performed with central venous access are associated with more severe AEs compared with peripheral access.<sup>3</sup>

Despite its use in a variety of diseases, and the fact that the use of TPE dates back to the 1950s, its mechanism of action has only been evaluated in a limited number of small studies. While the early use of TPE involved the bulk removal of pathological substances, this action does not explain all of its therapeutic effects, particularly in neuromuscular conditions.<sup>4</sup> Plasma exchange has the ability to modulate several immune mechanisms on which other drugs act individually. These are complementary to each other and include the removal of autoantibodies, immune complexes, cytokines etc. that control homeostasis and help to restore the patient's immune function to normal (see Figure 1).<sup>5</sup> In addition to the removal of pathogenic antibodies and circulating immune complexes, TPE also involves modification of immune complex structure and processing by changing the antigen/antibody ratio; modulation of immune complex solubility via complement activation; and modification of cellular components such as lymphocyte subsets.<sup>6</sup>

Figure 1: Immune modulation – inhibitors of B cells and removal of antibodies



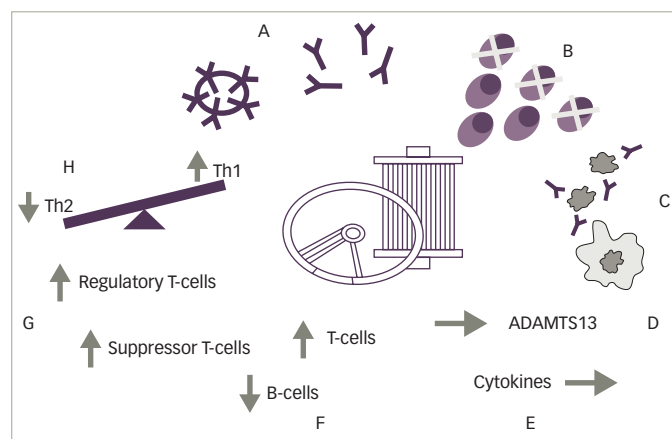
Adapted from Burmester et al., 2014.<sup>5</sup>

Alterations in cellular components of the immune system following TPE have been identified in a number of autoimmune diseases. An example is a 1999 study in which TPE was applied to the treatment of CIDP. Among 20 CIDP patients, six were treated with TPE and 14 with prednisone. After treatment with TPE, suppressor T cell function significantly increased compared to baseline in all patients (20.1% before TPE versus 39.3% after TPE).<sup>7</sup> Induction of T suppressor cells, presumably through modifications of the cytokine levels or other humoral components, might be one of the mechanisms through which TPE is effective in CIDP.

The use of TPE may also modulate cellular immunity by altering the ratio of T-helper type-1 (Th1) and type 2 (Th2) cells in peripheral blood. Th2 cells are known to facilitate the humoral immune response by facilitating antibody production by B cells. It is likely, therefore, that Th2 play an important role in autoimmune disorders due to autoantibody production.<sup>4</sup> A small study found that in two out of three patients with neuroimmunological disease, TPE altered the Th1/Th2 cytokine ratio.<sup>8</sup> In another study, patients with Miller Fisher Syndrome (MFS) were found to have an imbalance of Th1/Th2 cells with a predominance of Th2 cells; TPE shifted the Th1/Th2 balance in these patients to a Th1 dominant pattern.<sup>9</sup>

Another possible mechanism of action of TPE is sensitisation of antibody-producing cells to immunosuppressant and chemotherapeutic agents. In a study of severe systemic lupus erythematosus (SLE), Clark et al. suggested that the removal by TPE of pathogenic autoantibodies and immune complexes leads to the elimination of negative feedback on antibody-producing cells, and a rebound activation of lymphocytes.<sup>10</sup>

Figure 2: The mechanism of action of plasma exchange



A = remove antibodies; B = stimulate plasmacytes; C = remove immune complexes; D = replace missing plasma components; E = remove cytokines; F = change lymphocyte number; G = increase T-reg and T-suppress; H = alters Th1/Th2 ratio. Adapted from Reeves and Winters, 2013.<sup>4</sup>

This could increase the susceptibility of these cells to cytotoxic and immunosuppressant drugs. Other studies have reported increased lymphocyte responsiveness following TPE in patients with GBS,<sup>11</sup> and increased lymphocyte proliferation in patients with demyelinating disease.<sup>12</sup>

Therapeutic plasma exchange also removes soluble mediators of inflammation, among which are cytokines and cell growth factors. A 2009 study investigated the effect of TPE on cytokine levels in patients with MG. Following TPE, levels of interleukin-10 (IL-10), already elevated at baseline, were significantly increased.<sup>13</sup> In another study of MG patients, TPE decreased the levels of various inflammatory mediators, including acetylcholine receptor autoantibodies, soluble intercellular adhesion molecule-1 (ICAM-1), and soluble vascular cell adhesion molecule-1 (VCAM-1), though the roles of these substances in the disease are uncertain.<sup>14</sup>

Finally, TPE has an impact on the activity of natural killer (NK) cells. A study found that 20 patients with GBS had significantly decreased NK cell activity compared with patients without GBS. One month after TPE, NK cell activity had returned to the normal range.<sup>15</sup> It is not known

Table 1: Summary of evidence-based guidelines for plasma exchange in Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy and myasthenia gravis

Disease	American Society for Apheresis 2013	American Academy of Neurology 2011	European Federation of Neurological Societies 2012	Cochrane
GBS	Category I (Grade 1A) and Category III (Grade 2C) post-IVIg	Class I (Level A for severe GBS) (Level B for milder GBS)	Concurs with AAN	Grade I
CIDP	Category I (Grade 1B)	Class I (Level A for short-term treatment)	Concurs with AAN	Grade I
MG	Category I Moderate-severe (Grade 1B) Pre-thymectomy (Grade 1C)	Insufficient evidence Class III	Level A for acute exacerbation Level B pre-thymectomy	Moderate-severe (Grade II) Pre-thymectomy (Grade III)

AAN = American Academy of Neurology; CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; GBS = Guillain-Barré syndrome; IVIg = intravenous immunoglobulin; MG = myasthenia gravis

whether this increase in NK activity was a direct consequence of TPE or the resolution of the disease.

These proposed mechanisms of action of TPE are illustrated in Figure 2.<sup>4</sup> In summary, TPE can remove antibodies, and immune complexes, change lymphocyte numbers and alter Th1/Th2 ratios. The procedure can therefore have marked benefit in treating autoimmune diseases.

Dr Querol ended his presentation by summarising the guidelines for the use of TPE in autoimmune neuromuscular disorders. Clinical evidence for the use of TPE is high quality (Class 1) in GBS; this is reflected in the various clinical guidelines (see Table 1).<sup>16-18</sup> In CIDP, the strongest evidence is for short-term treatment.<sup>16,19,20</sup> However, the evidence for the use of TPE in MG is less clear;<sup>21</sup> the American Academy of Neurology (AAN) states that there is insufficient evidence for its use,<sup>16</sup> while the European Federation of Neurological Societies (EFNS) recommends that its use is limited to acute exacerbations.<sup>22</sup> ■

## Clinical Debate – the Role of Plasma Exchange in Myasthenia Gravis

Presented by: Mazen M Dimachkie

The University of Kansas Medical Center, Kansas City, Kansas, US

Mazen M Dimachkie was invited to speak on his experience with TPE in acute and chronic MG, and to describe how it relates to the current evidence, as well as to highlight the gaps in evidence and challenges for the use of plasma exchange in MG.

Professor Dimachkie began with a case presentation of a 45-year-old woman with a seven-year history of arm and leg weakness, nasal speech, dysphagia, ptosis and diplopia. She had a positive response to the acetylcholinesterase inhibitor edrophonium but tested negative for the acetylcholine receptor binding antibody titer. A repetitive nerve stimulation test showed a decrement both in the facial nerve (18%) and ulnar nerve (13%) indicative of a post-synaptic neuromuscular

junction defect. Professor Dimachkie considered that all of the following additional testing options would be appropriate:

- Muscle-specific kinase antibody (MuSK) antibody titer.
- Low-density lipoprotein receptor-related protein 4 (LRP4) antibody titer.
- Agrin antibody titer.
- Computed tomography (CT) scan of the chest.
- All of the above.

However, the LRP4 and Agrin antibody tests are not currently commercially available. The chest CT, which was suggested because 10%

of patients may have thymoma, was normal in this patient. The patient was found to be MuSK antibody-positive and was treated with pyridostigmine 60 mg QID with suboptimal response. She responded well to prednisone 60 mg/day for four weeks, then at the same dose but every other day for four weeks. However, repeated taper attempts of the prednisone failed to bring her below a dosage of prednisone 40 mg every other day without relapse. Of note, a level of below 10 mg/day is desirable to minimise complications associated with chronic corticosteroid therapy. Treatment with adjuvant immunosuppressants included sequentially azathioprine, mycophenolate, methotrexate and tacrolimus, all of which failed to reduce the required dose of prednisone. Professor Dimachkie indicated that TPE was the most appropriate treatment at this point for refractory MuSK antibody positive MG. In a retrospective study of MuSK-Ab-positive patients with MG (n=53), only 16% responded to the cholinesterase inhibitor pyridostigmine. However, 51% of patients responded to TPE.<sup>23</sup> In addition, patients usually achieve some degree of short-term remission following TPE, which makes chronic repeated outpatient TPE appealing in this disease. This patient received TPE, with good response.

In a report of the use of TPE at the University of Kansas Medical Center in an outpatient clinic setting with a dedicated TPE centre, the type and rate of complications were examined in a subgroup of 12 patients, 10 of whom had MG.<sup>24</sup> The centre was experiencing difficulties around the use of tunnelled internal jugular catheters: these included problems with thrombosis (31%) and infections (38%). They resolved this issue by the placement of arteriovenous fistulas in eight patients, and one patient received an arteriovenous graft. The authors concluded that arteriovenous fistulas and graft offered more practical access for TPE in the outpatient setting and patients received mostly anti-platelet therapy to maintain patency. However, the key message of this study was the low incidence of AEs in this cohort of patients, who underwent 91 TPE sessions. Transient dizziness occurred only in around 6% of sessions; after fluid boluses, resumption of TPE was possible on the same day in three, and on the next in two, instances. Nausea was experienced in

1%.<sup>24</sup> This study provides further evidence that chronic TPE is a benign procedure in the outpatient clinic setting.

Professor Dimachkie discussed several unpublished off-label indications for TPE in MG that are commonly used in clinical practice. Plasma exchange should be considered in patients undergoing crises such as respiratory insufficiency or severe dysphagia. It is also useful for tuning up patients prior to surgical procedures or pre-thymectomy, particularly in patients with bulbar dysfunction and in those with reduced expiratory forced vital capacity. In patients not in crisis but with severe MG symptoms or while trying to adjust dosage of prednisone and other immunosuppressive therapies, TPE allows for a more rapid response. TPE is also very useful in the treatment of refractory MG cases.

A limited number of clinical studies have investigated TPE in MG.<sup>16</sup> Investigators of a 2011 study randomised 84 patients with moderate to severe MG (Quantitative Myasthenia Gravis [QMG] score  $\geq 11$ ) who were worsening, to receive either TPE or intravenous immunoglobulin (IVIg).<sup>25</sup> The same proportion of patients improved with treatment: 69% on IVIg and 65% on TPE. The QMG score showed that there was no statistically significant difference between the two treatment groups at two, three and four weeks. Both treatments were well tolerated, and the duration of effect was comparable. The conclusion was that TPE and IVIg were both considered equally efficacious in moderate to severe MG.<sup>25</sup>

In 2013 the same group of investigators published a follow-up study to determine if the improvement in quality of life (QOL) was comparable following IVIg or TPE. A total of 62 of the original 84 patients were included in this analysis. There was no difference in improvement between both treatment groups as measured by the MGQOL-15 change between day 1 and days 14, 21 and 28, respectively.<sup>26</sup> Besides this study, no randomised clinical studies have been published to date exploring further the role of TPE in MG. Professor Dimachkie concluded by stating that TPE and IVIg both have a role in the treatment of MG, but further clinical studies are required. ■

## Clinical Debate – the Role of Plasma Exchange in Guillain-Barré Syndrome and Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Presented by: Jean-Marc Léger

*Centre National de Référence Maladies Neuro-Musculaires Rares, Institut Hospitalo-Universitaire de Neurosciences, Hôpital Universitaire Pitié-Salpêtrière and Université Pierre et Marie Curie, Paris, France*

Professor Léger commenced by highlighting the importance of TPE in neuropathies including GBS, CIDP, multifocal motor neuropathy (MMN), and neuropathies associated with monoclonal gammopathy of undetermined significance (MGUS). His presentation focused on GBS and CIDP because there is no evidence in support of the use of plasma exchange in MMN or MGUS-associated neuropathies. In MMN, plasma exchange is not recommended as it may be followed by a transient worsening of the motor deficit. Guillain-Barré syndrome is a disorder of the peripheral nervous system in which the primary pathogenesis is a presumed autoimmune attack on peripheral nerves; however, recent research has led to a redefinition of GBS.<sup>27</sup> The classical view of the disease is as a demyelinating condition, but we now know there are also other forms such as axonal forms, which are associated with immunoglobulin G (IgG) autoantibodies against the

gangliosides GM1 or GD1a, and are often preceded by infection with *Campylobacter jejuni*. IgG anti-GQ1b antibodies, which cross-react with GT1a, are strongly associated with MFS, its incomplete forms (acute ophthalmoparesis [without ataxia] and acute ataxic neuropathy [without ophthalmoplegia]), and its more extensive form, Bickerstaff's brain-stem encephalitis.<sup>27</sup> In view of the emergence of these different disease forms, there is a need to differentiate between them in clinical studies of treatment options.

Recommendations for the immunomodulatory treatment of GBS were published by the AAN in 2003<sup>28</sup> and have not progressed since then. Plasma exchange is recommended in non-ambulatory patients in the first four weeks and in ambulatory patients in the first two weeks. The use of IVIg is recommended in non-ambulatory patients in the first

two weeks. The use of TPE and IVIg are considered equally efficient. Corticosteroids are not recommended, nor are the concomitant use of TPE and IVIg.

Randomised controlled trials in the US, France and the Netherlands have provided strong evidence that TPE hastens recovery in GBS.<sup>29-32</sup> In 1993, a double-blind trial concluded that intravenous (IV) methylprednisolone was not effective in GBS.<sup>33</sup> In 1994, a trial was performed with three arms: IVIg, TPE and TPE followed by IVIg. All treatments were found to have equivalent efficacy.<sup>34</sup> In a French study, among ambulatory patients, two TPE sessions were more effective than none, while in non-ambulatory patients, four TPE sessions were more effective than two.<sup>35</sup> In 2004, a double-blind, placebo-controlled, multicentre, randomised study enrolled patients who were unable to walk independently and who had been treated with IVIg. Patients were randomised to methylprednisolone or placebo, but no differences were seen in the two treatment groups.<sup>32</sup> Two Cochrane reviews concluded that plasma exchange and IVIg were effective therapies for GBS,<sup>17,36</sup> while another concluded that there was limited evidence to support the use of corticosteroids in GBS.<sup>37</sup> In conclusion, strong evidence exists for the use of both TPE and IVIg in GBS.

The definition of typical CIDP comprises chronically progressive, stepwise or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities, developing over at least two months; cranial nerves may be affected, and there are absent or reduced tendon reflexes in all extremities. In addition to the classical presentation of CIDP, there are a number of atypical forms of the disease. Distal acquired demyelinating symmetric (DADS), pure motor or sensory presentations, asymmetric presentations, focal presentations or CNS involvement may occur.<sup>20</sup>

The use of corticosteroids, TPE and IVIg are all recommended in CIDP,<sup>20</sup> and each has been demonstrated to be superior to placebo in randomised,

double-blind, placebo-controlled studies. A considerable body of evidence supports the use of corticosteroids in CIDP.<sup>38,39</sup> The first clinical evidence in support of the use of TPE in CIDP was a prospective double-blind, sham-controlled trial, found statistically significant improvements in nerve conduction in patients who had received TPE.<sup>40</sup> Another double-blind, sham-controlled, cross-over study concluded that TPE was a very effective adjuvant therapy for CIDP of both chronic progressive and relapsing course but that concurrent immunosuppressive drug treatment was required.<sup>41</sup> The beneficial effects of plasma exchange in CIDP also have been supported by a Cochrane review.<sup>19</sup> Finally, IVIg is widely used in CIDP and its use is supported by substantial clinical evidence.<sup>42-44</sup>

New autoantibodies involved in the pathogenesis of CIDP are emerging. Antibodies against the contactin 1 and contactin associated protein 1 (CNTN1/CASPR) complex have been found in a subset of patients, and are associated with older age, more aggressive onset, predominantly motor involvement with early axonal degeneration.<sup>45</sup> Poor response to IVIGs has been reported in patients with anti-CNTN1 antibodies.<sup>46</sup> In addition, a small proportion of patients have antibodies against neurofascin;<sup>47</sup> these are characterised by severe neuropathy, poor response to IVIg, and disabling tremor.<sup>48</sup> Such autoantibodies may be useful as disease biomarkers to identify subgroups of patients most likely to benefit from TPE and eventually rituximab.<sup>49</sup>

Professor Leger concluded his presentation with a case report from his practice. A 78-year-old woman had been treated for over 15 years for hypertension and a primary immune deficiency, for which she received IVIg 30 g every six weeks. At the age of 75 she developed CIDP with motor weakness, paraesthesia in both lower limbs and areflexia in the lower limbs. Her initial treatment was an attempt to increase the IVIg regimen but no improvement was seen. She was given TPE once a week for two months, tapering to two to three times a month. The patient's condition improved and she is now in stable motor condition. This demonstrates the value of TPE where IVIg had failed. ■

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## Summary and concluding remarks

In summary, a substantial body of clinical trial data has demonstrated the efficacy and safety of TPE in GBS and CIDP. However, despite much anecdotal evidence, the use of TPE in MG is not currently supported by large clinical studies and it is clear that discrepancies occur between published guidelines and clinical practice. The use of TPE in MG is largely off-label and patients who might benefit from TPE may have limited access to the procedure. The question of how to increase access to TPE

remains unanswered. Factors limiting its use include unfamiliarity with the procedure and the lack of specialised facilities. Venous access can be an issue in many cases. In addition, reimbursement for treatment has become more problematic in the US. More clinical trials are needed to understand the role of TPE in MG, GBS, CIDP and the numerous other neuromuscular diseases in which it appears to be an effective and valuable treatment. ■

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