of trials have been disappointing.[9] Nevertheless, their potential utility cannot yet be dismissed. Some trials had to be abandoned because of side effects of the drugs and future trials would need to be continued over considerably longer periods than those performed hitherto in view of the fact that DSSP normally has a slow insidious onset over the course of several years. This also applies to other forms of metabolic intervention such as the use of agents to diminish the accumulation of advanced glycosylation end products.

NEUROPATHIES RELATED TO DYSIMMUNE MECHANISMS

The demonstration of inflammatory changes in the peripheral nerves of patients with proximal lower limb motor neuropathy or those with superimposed CIDP has raised the possibility of the use of immunomodulatory treatment. There have been reports of the successful treatment of patients with the former condition with intravenous human immunoglobulin, plasma exchange, corticosteroids, or cytotoxic drugs (cyclophosphamide, azathioprine) either alone or in combination.[24] However, the natural history of this disorder is often one of spontaneous improvement and a controlled clinical trial is now clearly needed.

Non-diabetic patients with CIDP may benefit from similar treatment and studies on limited numbers of cases have so far indicated that this also applies to CIDP in diabetic subjects.[21 24] Inflammatory lesions are known to be present in autonomic ganglia and nerve trunks in patients with severe autonomic neuropathy,[25] again suggesting a superimposed autoimmune process. Whether immunomodulatory measures would be beneficial in such cases is unknown.

POSSIBLE USE OF GROWTH FACTORS

Studies on animal models of diabetes indicate that IGF I enhances regeneration and nerve growth factor (NGF) has been shown to have a beneficial effect in other experimental neuropathies. Preliminary evidence from phase II clinical trials of human recombinant NGF has indicated that this agent may benefit symptoms related to dysfunction of small sensory fibres.[26] The results of phase III trials are therefore awaited with interest. Diabetes affects fibres of all sizes, both myelinated and unmyelinated, but the neurotrophic effect of NGF is mainly on small myelinated and unmyelinated axons. If the use of NGF is shown to be helpful, future treatment regimes may require combinations of growth factors—for example, with the addition of brain derived neurotrophic factor (BDNF)—so that the large fibre neuropathy is also targeted.

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EDITORIAL COMMENTARY

Treatment of X-linked adrenoleukodystrophy with Lorenzo's oil

Van Geel *et al* in this issue (pp 290–9)[1] provide a thorough multidisciplinary analysis of the clinical progression of 22 patients with X-linked adrenoleukodystrophy (X-ALD) who were treated with Lorenzo's oil (a 4:1 mixture of glyceryl trioleate and glyceryl trierucate). Four patients remained unchanged. One patient improved, 13 worsened, and in five some indices improved and others worsened. Mild to moderate worsening was the most frequent finding and confirms previous reports.

The introduction of Lorenzo's oil therapy 10 years ago raised high expectations, heightened by the motion picture of the same name. The expectations were based mainly on the finding that the oil normalises the concentrations of very long chain fatty acids (VLCFA) in plasma. Accumulation of

VLCFA is the principal biochemical abnormality in X-ALD and there is evidence that excess of VLCFA contributes to pathogenesis.[2] Normalisation of the plasma concentration of the "offending" metabolite is of undisputed benefit in conditions such as phenylketonuria. These considerations, coupled with the tragic course of untreated childhood cerebral X-ALD, led myself and others to conduct non-randomised rather than placebo controlled therapeutic trials. Information obtained since that time highlights drawbacks of this decision and provides a lesson for the future. The drawback is that more than a decade after the first use of Lorenzo's oil, we still do not know if it is of clinical value. Even though most symptomatic oil treated patients continue to progress, our incomplete knowledge of natural history and the lack of a control group may have masked a moderate benefit. The same concerns limit the power of a current non-randomised international study that involves 250 asymptomatic patients and aims to test whether oil administration diminishes later neurological disability. A lesson relevant to future studies is the realisation that normalisation of plasma VLCFA concentrations is not a valid marker of therapeutic success.Concentrations of VLCFA in plasma do not correlate with the degree of neurological disability,[2] and in the study of Van Geel *et al* patients worsened despite normalisation of plasma concentrations. Furthermore, erucic acid, the active principle of Lorenzo's oil, does not seem to enter the brain.[2] These data diminish the rationale for the therapy.

The continued neurological progression in most patients treated with oil, combined with a 55% incidence of side effects, supports the recommendation of van Geel *et al* that it should not be offered routinely as a therapy for patients who are already symptomatic. We do recommend continuation and completion of the important study designed to determine whether the oil can prevent later neurological disability. Patients enrolled in this study are monitored to guard against side effects and those who are candidates for bone marrow transplantation are identified. Bone marrow transplantation carries a high risk but has shown remarkable benefit in some patients with early brain involvement.[2] Two new promising therapeutic approaches have been proposed recently.[4 5] The Lorenzo's oil experience highlights the importance of developing a study design that will permit timely evaluation of their clinical effectiveness.

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EDITORIAL COMMENTARY

The Sydney multicentre study of Parkinson's disease

Natural history studies of Parkinson's disease with adequate duration of follow up are scarce and fraught with difficulty due to selection bias and retrospective assessment in hospital series, confounding effects of comorbidity and problems of diagnostic accuracy.[1] The pivotal study by Hoehn and Yahr[2] on a cohort of 672 patients with "primary parkinsonism" came up with a rather bleak prognosis, with 61% of patients severely disabled or dead after 5 to 9 years of follow up, increasing to more than 80% of those who were followed up for more than 10 years. Overall mortality was increased to about threefold the expected rate in the general population. Such poor longterm outcome is thought to reflect the history of idiopathic Parkinson's disease in the prelevodopa era with some added negative bias due to less stringent diagnostic criteria used in those days. Early postlevodopa mortality studies in Parkinson's disease indeed found mortality ratios of 1.5 or less, rising again, however, with extended follow up, suggesting that levodopa reduces excess mortality early in the course of Parkinson's disease but fails to prevent increased mortality in the long term.[3]

This general trend is also confirmed in the 10 year prospective follow up results on progression and mortality of the Sydney multicentre study of Parkinson's disease now published by Hely *et al* (this issue, pp 300–7). Regular follow up of this cohort for a maximum of 13 years has provided valuable data on disease progression and mortality in those 126 patients in whom the original diagnosis could be upheld. By 10 years 38% had died, rising to 48% by last follow up, yielding a standard mortality ratio for the whole cohort of 1.58, which is similar to many of the previously published postlevodopa studies.[3] Significant risk factors for increased mortality included old age at onset, rapid initial progression on the Hoehn and Yahr scale, and—surprisingly—initial randomisation to bromocriptine. Although this finding certainly does not support claims of possible neuroprotective effects of bromocriptine or dopamine agonists in general[4] it is of limited relevance. Only very few patients originally randomised to bromocriptine continued such monotherapy for longer than 1 year and all patients taking bromocriptine had been switched to combined treatment with levodopa by year 5. So unfortunately the longterm outcome data of the Sydney study do not allow for conclusions about differential effects of levodopa monotherapy versus bromocriptine monotherapy versus combined treatment on longterm progression and prognosis.

The biggest surprise in the Sydney study, however, is that the percentages of patients severely disabled or dead after 10 years of follow up are very similar to the figures