Gangliosides and neurological diseases

EDITOR,—Albert Figueras and colleagues' recommendation that gangliosides should be withdrawn, which is based on their experience of 17 patients diagnosed as having the Guillain-Barré syndrome and other acute motor neuropathy, is inappropriate.[1] Firstly, they give no details from which the validity of the diagnosis can be judged. Retrospectively collected data are notoriously incomplete, and even if the diagnoses were "confirmed by a neurologist" it is not clear that acceptable diagnostic criteria were uniformly applied.[2] Moreover, in nine of their cases the use of gangliosides for prodromal symptoms of the disease allegedly caused by the ganglioside could not be excluded. In addition, in at least three cases an antecedent illness that often precedes the onset of polyneuropathy was known to have been present. Thus in 12 of the 17 cases the clinical basis for implicating gangliosides as a cause is uncertain at best.

If even five cases of acute motor polyneuropathy were caused by gangliosides the risk should be calculated. To do this requires knowledge of the size of the population exposed to ganglioside. Figueras and colleagues do not give this information, stating only that the 17 reports were among 18000 reports in their database. In a recent epidemiological study in Spain no association between use of gangliosides and polyneuropathy was found.[3] An epidemiological study in Italy reported that if a risk of polyneuropathy exists at all it is less than 1 in 10000 exposed.[4] Finally, evidence is accumulating, based on well controlled clinical trials, that GM1 ganglioside may be beneficial in several types of injury to the central nervous system.[5-8]

Colleagues and I recently completed a randomised double blind, multicentre clinical trial of 287 patients with acute stroke treated with 100 mg G_{m1} ganglioside intramuscularly or placebo daily for 28 days.[9] No cases of acute polyneuropathy occurred, nor was there any significant difference in deaths or adverse effects between the two groups of patients. We found consistent benefits favouring the group treated with G_{m1} when we measured the change from baseline values in the motor component of the Toronto stroke scale at day 28 ($p=0{\cdot}02$) and day 84 ($p=0{\cdot}06$). The Fugl Meyer scale, all 10 components of the Barthel index, and four of five tests in a neuropsychological battery also favoured the patients treated with G_{m1}.

To withdraw ganglioside treatment on the basis of the evidence presented by Figueras and colleagues would be a disservice to patients who suffer from conditions for which no other effective treatment exists.

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Advice to authors

Priority will be given to letters that are less than 400 words long and are typed with double spacing. All authors should sign the letter. Please enclose a stamped addressed envelope for acknowledgment.

EDITOR,—Peter O Behan and B A G Haniffah suggest that the use of gangliosides in humans should be suspended.[1] Unfortunately, the information they present gives an inaccurate view of the state of research into gangliosides and the rationale for their therapeutic use.

Firstly, though the monosialoganglioside G_{m1} has been shown to be useful in reversing behavioural, and to a certain extent biochemical, alterations induced by damage to the nigrostriatal dopamine system, its effects may not simply be due to a neuroprotective mechanism. Whether protection against certain types of insults is provided by G_{m1} may depend on the type of insult. For example, G_{m1} may protect neurones against excitotoxicity induced by glutamate[2] but may not protect dopamine neurones in vivo[3] or in vitro[4] against damage by MPTP or MPP^+. G_{m1} does, however, apparently stimulate repair processes in damaged dopamine neurones and promote the survival of these injured neurones both in vivo and in vitro.[4,5]

Though Behan and Haniffah are correct in stating that gangliosides seem to be most effective when given shortly after injury, they are incorrect in stating that that explains their lack of efficacy in genetic disorders of the central nervous system. The evidence cited for this lack of effect is the negative results in patients with amyotrophic lateral sclerosis or Charcot-Marie-Tooth disease given low doses of ganglioside mixtures.[6] We recently showed in our laboratory, however, that treatment with G_{m1}, started shortly after birth can at least partially reverse striatal dopamine loss in homozygous Weaver mice, a genetic disorder of dopamine deficiency and incoordination (unpublished observation).

Albert Figueras and colleagues support the call to suspend human use of gangliosides,[7] but there are several problems with their short report. Though the total population from which their 17 patients with adverse effects are drawn is reported to be "over 18000," there is no estimate of how many patients may have been given ganglioside during 1989-92, when the 17 cases were reported.

It is difficult to compare recent data on pure G_{m1} ganglioside with past data obtained with ganglioside mixtures. Ganglioside mixtures (which contain only 17-25% G_{m1}) may be more immunogenic than pure G_{m1}, which is now used in most animal and human studies. The lack of immune response to pure G_{m1} is supported by results of determinations of G_{m1} antibody in serum from patients receiving G_{m1} long term for either stroke or acute spinal cord injury. To date, no antibody to G_{m1} has been detected in people treated solely with G_{m1} ganglioside.[8].

We agree that indiscriminate use of G_{m1} ganglioside should be stopped, but the call to suspend all use is too extreme. We suggest that human trials with G_{m1} ganglioside should proceed cautiously for scientifically indicated uses as animal studies continue to define the role of gangliosides in the function and repair of the nervous system.

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EDITOR,—On the basis of ample and convincing evidence obtained from experimental pathology[1] gangliosides derived from bovine brains are widely used to treat pathological conditions of the peripheral and central nervous system. Recent controlled trials conducted with the monosialoganglioside G_{m1} have indicated the efficacy of this treatment for stroke and spinal cord injury.[2,3] Concern for the safety of gangliosides, based on supposed immunogenicity causing autoimmune diseases, has been raised and the suspension of ganglioside treatment in humans has been suggested.[4] Immunogenicity of pure ganglioside derived from brains has not, however, been shown.

Gangliosides are normal constituents of the cell membrane. They are abundant in cells of the nervous system but are also present in all other tissues and body fluids. Expressed at the cell surface, they are steadily exposed to immune surveillance and recognised as self antigens. Injection of pure gangliosides does not result in antibody induction or T cell stimulation in experimental animals.[5] Immunisation with chemically modified gangliosides, in the presence of adjuvant, induces antibodies that do not crossreact with the natural gangliosides, thus indicating the mainten-

ance of immunological tolerance to these natural compounds.[6] Under conditions of autoimmunity, such as experimentally induced immune mediated demyelination of the peripheral nerves, injections of pure gangliosides do not result in the induction of antibodies to gangliosides and do not worsen the course of the disease.[7] A neurological syndrome induced in rabbits by injecting gangliosides derived from brain reported by Nagai *et al*[8] could not be reproduced and could be explained as resulting from contamination of the ganglioside preparation by myelin proteins.

Antibodies reactive with gangliosides recognise the carbohydrate portion of the molecule. These carbohydrate epitopes are not uniquely expressed on gangliosides but are also present on glycoproteins and bacterial cell walls.[9] Controlled studies in humans have proved that the prolonged administration of G_{m1} in healthy individuals as well as in patients with neurological diseases does not modify the pattern of antibody crossreactivity to glycoconjugates.[10]

In conclusion, all available data are consistent with the lack of immunogenicity of brain-derived gangliosides if purity is guaranteed. Thus, their use for therapeutic purpose should not be restricted by the present immunological knowledge.

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Venous leg ulcers

EDITOR,—A I Skene and colleagues describe a prognostic index to predict the time to healing of venous ulcers.[1] The index is based on four covariates, including an assessment of the deep veins by photoplethysmography, referred to as "deep vein involvement." This technique gives some insight into calf pump function but does not specifically indicate incompetence of the popliteal valve as the authors imply. Furthermore, no techniques for imaging deep veins were used, and thus no information regarding the presence of post-thrombotic disease is available. Post-thrombotic change in the deep veins greatly influences the natural course of venous ulceration[2,3] and should be sought with an accurate technique such as ascending phlebography in any such study.

The deep vein involvement described in this study is thus derived from an incomplete assessment of the deep veins that omitted the single most important aspect of the deep veins—namely, the presence or absence of post-thrombotic change. The failure to address this aspect of the deep veins must surely detract from the value of the prognostic index described.

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EDITOR,—A I Skene and colleagues' paper provides a useful prognostic index for healing of venous leg ulcers.[1] The authors do not comment, however, on the presence of oedema and whether this delayed healing.

Oedema represents an increase in interstitial fluid volume and is a common finding in venous leg ulcers, when it is considered to be a consequence of increased capillary filtration. It is present in 55% of patients despite graduated compression, and its prevalence is higher in patients treated in the community than in those treated in hospital.[2] It is associated with poor wound healing and may therefore be an important factor in the failure of venous leg ulcers to heal.[3] It results in increased exudation from ulcer beds, thus jeopardising the viability of surrounding skin. From the point of view of management it necessitates more frequent dressings and makes support bandages harder to apply.

If the aim of the prognostic index is to predict time to healing and help in the formulation of management decisions, the presence of oedema would probably serve as an additional prognostic factor. A yardstick by which doctors, nurses, and patients themselves could judge satisfactory treatment is the abolition of pitting on the foot and lower limb.

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AUTHORS' REPLY,—The burden of care for venous ulcers lies mainly in the community. The healing score that we described is designed to be used by trained primary care staff with an interest in and access to simple non-invasive studies. Venous function was assessed with a combination of continuous wave ultrasonography and photoplethysmography, and the patients were categorised as having deep or superficial vein involvement after appraisal of the results obtained with both techniques.

We did not attempt to resolve the controversies concerning the most accurate determinant of deep venous function. Though we acknowledge that ascending phlebography contributes anatomical detail, the invasive nature and cost were not considered appropriate in this study. Although Stacey *et al* showed many ulcerated limbs with extensive post-thrombotic change phlebographically, this finding was not associated with a delay in ulcer healing.[1]

Duplex scanning undoubtedly enhances the accuracy of ultrasound assessment and is used regularly for people attending hospital but was also not considered appropriate for a community based study. The relatively low contribution of the functional data to the prognostic index suggests that had duplex scanning been performed it would have had little effect on the outcome.

We were interested in A Prasad's comments. We recorded three variables when assessing oedema in our study but did not consider them for inclusion in the models presented in our paper. We have repeated the proportional hazards modelling to assess whether their inclusion improves the ability to predict prognosis.

The presence of oedema of the foot, ankle, or calf was not significantly associated with time to complete ulcer healing, the relative risk and 95% confidence intervals for these variables being 1·15 (0·78 to 1·71), 1·12 (0·76 to 1·66), and 1·06 (0·71 to 1·60) respectively. Oedema was, however, associated with the two principal prognostic factors, ulcer area and duration of ulceration. The mean ulcer area and duration of ulceration were 16·3 cm^2 and 38·3 months respectively for ulcerated limbs with oedema of the foot and 10·4 cm^2 and 9·8 months respectively for limbs without oedema. Attempts to assess the association between oedema and wound healing without allowing for these confounding prognostic factors can lead to incorrect inferences.

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EDITOR,—Christine J Moffatt and colleagues comment that community clinics for venous ulcers offer an effective means of achieving healing.[1] Our practice has been running a clinic for three years, with a success rate of over 80%. The keys to success are adequately trained practice nurses supported by the community dermatological nurse, close attention to achieving good compression, and open access for patients at an early stage if there is recurrence.

No special diagnostic equipment is required. In the first year of the clinic's operation the district nurses' visits for leg ulcers dropped from 24% to 8% of total visits. Whether initial aggressive management of early ulcers prevents the development of long term intractable ulceration remains to be seen.

Interestingly, although the clinic was the only one that was clearly identified as offering a health gain, it was turned down as a health promotion clinic.

Clinics for leg ulcers can easily be set up in a primary care setting; some initial extra training of nurses and attention to organisational detail are necessary. Patients' satisfaction, staff morale, and cost-benefit analysis are enhanced by a systematic approach to care.

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1 Moffatt CJ, Franks PJ, Oldroyd M, Bosanquet N, Brown P, Greenhalgh RM, *et al*. Community clinics for leg ulcers and impact on healing. *BMJ* 1992;**305**:1389-92. (5 December.)