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THE ROLE OF BETA INTERFERON IN THE TREATMENT OF MULTIPLE SCLEROSIS

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FOREWORD

Individuals or small groups in each District Health Authority in Trent have historically considered evidence on the likely effectiveness of new procedures or therapies in conjunction with their cost, making judgements on whether these should be supported. Since all or most Health Authorities face the same issues, there tends to be repetition in analysis and this can be wasteful of scarce professional expertise.

There are national attempts to remedy this situation by providing information on the effectiveness of interventions and these are welcomed. There remains, however, a significant gap between the results of research undertaken and their incorporation into contracts.

Following a request from purchasers, a network has been established in the Trent Region to allow purchasers to share research knowledge about the effectiveness of acute service interventions and to determine collectively their purchasing stance.

SCHARR, the Sheffield Unit of the Trent Institute for Health Services Research, facilitates a Working Group on Acute Purchasing. A list of interventions for consideration is recommended by the purchasing authorities in Trent and approved by NHS Executive Trent. A public health consultant from a purchasing authority leads on each topic and is assisted, as necessary, by a support team from SCHARR which provides help including literature searching, health economics and modelling. A seminar is then led by the consultant on the particular intervention where purchasers and provider clinicians consider research evidence and agree provisional recommendations on purchasing policy.

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CONTENTS

LIST OF TABLES

EXECUTIVE SUMMARY

Multiple Sclerosis (MS) is a chronic degenerative disorder of the central nervous system, leading to disability and death, on average ten years earlier than otherwise expected. To date the cause of MS remains unknown and there is no effective treatment.

There is clinical evidence to suggest that the drug Beta Interferon, though not a 'cure' for MS, does have some impact on reducing the number and severity of relapses in those MS patients in the relapsing-remitting stage. Data are restricted to a single study in North America on 372 patients in the relapsing-remitting stage of the disease. These data showed a statistically significant reduction of one third in the treatment group compared with the placebo group. The number of lesions detected by MRI scan was also significantly lower in the treatment group.

Whilst the NHS Executive in EL(95)97 has brought the issue of how to introduce Beta Interferon into the NHS to the fore of the policy debate, the costs and the benefits of Beta Interferon therapy have still not been fully explored. This paper examines the evidence for the efficacy of Beta Interferon in the treatment of MS, and utilises these data to estimate the possible magnitude of the costs and benefits from its use. Subsequently, a range of options for the implementation of Beta Interferon are reviewed and the advantages and disadvantages of each are identified.

The evidence for clinical effectiveness of Beta Interferon is limited but significant. What is unclear however is how the clinical effectiveness impacts upon the life expectancy and quality of life of individuals with MS. Preliminary analysis using available data on the effectiveness of Beta Interferon in MS suggests that the cost per Quality Adjusted Life Year (QALY) may be in the region of £1.17 million.

The introduction of Beta Interferon into the NHS should be undertaken in a way which maximises the data on outcomes and side effects to inform future policy reviews, whilst ensuring that priority is given to those patients who will, according to the existing data, benefit the most from Beta Interferon therapy. This would best be achieved through the treatment of people as part of a randomised controlled trial only.

1. INTRODUCTION

Multiple Sclerosis (MS) is a demyelinating disease of the brain and spinal cord. It may affect optic nerves and bladder function as well as sensation and stability of the limbs.

Beta Interferon was licensed for use in the treatment of MS in late 1995. Treatment is by regular injection on alternate days, and can be carried out by the patient at home.

Although not a 'cure', there is clinical evidence of a reduction in the number and severity of relapses in certain MS patients, whose disease is active and in the relapsing-remitting stage and who are treated with Beta Interferon. Therefore, the pressure through the media and from relevant pressure groups for the provision of Beta Interferon is considerable. However, the potential cost burden to the NHS is very large.

This paper explores the issues relating to the provision of Beta Interferon by the NHS; evidence for its efficacy, size of the patient group for whom it would be appropriate and the scale of the benefits from treatment. A range of possible options are set out and the pros and cons of each option are described.

2. EPIDEMIOLOGY OF MULTIPLE SCLEROSIS

There are over 80,000 MS patients in the United Kingdom, of whom some 40,000 may benefit from the use of Beta Interferon. It is estimated that there are between 5,600 and 6,600 MS patients in the Trent Region, (total population mid-1994 ~ 4.8 million) of whom some 2,600 may benefit from the drug. There are estimated to be about 240 newly diagnosed patients in the Trent Region each year.

3. EFFICACY OF BETA INTERFERON

3.1 Beta Interferon 1b (Betaferon, manufacturer Schering)

Published peer-reviewed evidence that a particular type of Beta Interferon (Beta Interferon 1b, 'Betaferon') is an effective treatment for MS is currently limited to a single reported trial.[2] [3]

In this trial 372 patients were randomly assigned to a dose of 1.6MIU or 8MIU recombinant Beta Interferon-1b administered intramuscularly once a week or a placebo, for up to two years. The primary end point of the study was a deterioration of one point or more on the Kurtzke Expanded Disability Status Scale (EDSS)[4] over a period of at least six months. The patients enrolled to the study were young (mean age 35.5 years) and had MS of short duration (mean duration of 4.4 years).

The results from this trial suggest that acute relapses or attacks can be reduced in both number and severity[2] [3] with objective evidence of a reduction in the number of brain lesions accumulating on MRI scans during the study.[5] [3] The study showed:

i) an increase in lesions of 20% in placebo vs 0.1% reduction on 8MIU after two years; a median reduction of 83% in the annual rate of active lesions in those scanned at six-weekly intervals.[5]

ii) a 30% reduction in relapses from 1.27 relapse per person per annum in the placebo group to 0.84 per person per annum in the 8 MIU treatment group after two years (with similar relative reduction at 3, 4 and 5 years, though not statistically significant).[2] [3] Relapse rates declined each year, however, in all groups in parallel so that absolute benefit in avoided relapses also declined: 0.48; 0.33; 0.26; 0.21; 0.24 in successive years (see Table 1). The cumulative avoided relapses were 1.5 at 5 years. The interpretation of this finding in terms of prognosis remains controversial.

There was no effect on disability in this trial; i.e. no statistically significant change in the Kurtzke Expanded Disability Status Scale; this may be due to a lack of sensitivity in the EDSS. [2] [3] A short extract of the scale is presented in Appendix A.

3.2 Beta Interferon 1a (Biogen, manufacturer Serono)

Reports from a second trial using a different Beta Interferon (Beta Interferon 1a),[6] which also showed a reduction in disease activity on MRI scans (acute activity), did suggest a significant, but small, delay in the progression of disability over a two year period in those treated.

The unpublished data were reported to a joint meeting of the Association of British Neurologists and the American Neurological Association in San Francisco on October 10th, 1994. This study had a functional end point represented by progression from baseline by one unit on the EDSS persisting for at least six months (though not all patients were followed up for two years).[7 8]

As in the Beta Interferon 1b trial, relapse rates were higher in the placebo group than the treatment group; i.e. the relapse rates were reduced from 0.9 per person per annum in the placebo group to 0.62 per person per annum in the treatment group (see Table 2).

At one year the proportion of patients who had progressed by one EDSS point was 20.1% in the placebo group versus 12.0% in the treatment group and at two years 36.3% versus 22.6%. Even if the evidence does support delayed progression, it should be noted that 1 point on the EDSS does not represent a great change in functional ability. The two most common scores in the original study of the scale were 3 (19.8%) and 4 (19.8%) with the scale running from 0 (no disability or neurological signs) to 10 (death due to MS).[4]

There was a higher rate of self-reported depressive systems in both treatment arms compared to placebo. However, these data were mentioned only in passing and no statistical analysis was presented.

Table 1: Average Annual relapse rates per person by year of study [3]

	Treatment group	N	Relapse rate	Significance (placebo vs 8MIU)
Year 1	Placebo 1.6 MIU 8.0 MIU	123 125 124	1.44 1.22 0.96	p<0.001
Year 2	Placebo 1.6 MIU 8.0 MIU	110 114 107	1.18 1.04 0.85	p=0.030
Year 3	Placebo 1.6 MIU 8.0 MIU	96 95 95	0.92 0.80 0.66	p=0.084
Year 4	Placebo 1.6 MIU 8.0 MIU	82 76 89	0.88 0.68 0.67	p=0.166
Year 5	Placebo 1.6 MIU 8.0 MIU	56 52 58	0.81 0.66 0.57	p=0.393

Table 2: Results from the Beta Interferon 1a Trial

	Average annual relapse rates per person	Proportion of patients who progressed by 1 EDSS point after:	
		a) one year	b) two years
Placebo group	0.90	20.1%	36.3%
Treatment group	0.62	12.0%	22.6%

4. PROBLEMS WITH THE RESEARCH DATA

The patients studied in the two trials mentioned above met strict inclusion criteria for age, disability levels and type of disease course. There is no current evidence on whether Beta Interferon would be safe and effective in patients with different characteristics. Therefore, general use of Beta Interferon should be limited to patients with similar characteristics to those entered in the trials referred to above.

The relapse rates for the placebo groups in these two trials are quite dissimilar, as are those in the treatment groups. These differences are puzzling and may reflect either the level of uncertainty in our understanding of MS and the associated trials, or significant differences in the entry criteria (see Tables 1 and 2 above).

There was a high drop out rate from the Beta Interferon 1b trial: 154 patients dropped out, evenly distributed amongst the three arms (49; 57; 48 respectively). Drop out because of continuing progression (excess steroid use, patient-perceived worsening or investigator-perceived worsening) was similar in each arm (13; 12; 13).

Long-term side-effects are unknown, whilst benefits in absolute terms show a declining trend. The 5 year follow-up paper is compromised by low numbers at 5 years (372 at start, 166 at 5 years): p values for decrease in exacerbation rate being <0.001; 0.03; 0.084; 0.166; 0.393, in each successive year.[3] The observed differences in exacerbation rate are only statistically significant for the first two years of treatment. The effects on efficacy of neutralising antibodies to Beta Interferon 1b over the longer-term is unknown.

5. NHS EXECUTIVE GUIDELINES

EL(95)97[10] asks *"Purchasing authorities and providers to develop and implement local arrangements to manage the entry of such drugs into the NHS, in consultation with other key interests, especially GPs and patient interest groups; and in particular, to initiate and continue prescribing of Beta Interferon through hospitals. In doing so, they are asked to take account of the checklist of issues in the Annex (See below 5.1) and of the attached clinical advice* on Beta Interferon."*

5.1 Beta Interferon: Prescribing Issues

Using the checklist attached to EL(95)97,[10] purchasers and providers will need to consider the following:-

Purchasing Authorities

- How many MS patients are estimated to be within the Health Authority and how many of these are estimated to be in the relapsing-remitting phase?

- What is the estimated annual incidence of new relapsing-remitting MS cases in the Health Authority?

- Are professional/managerial advisory and decision-making bodies for the introduction of new drugs (outlined in EL(94)72)[11] including Beta Interferon in their considerations?

- Are all key interests involved in discussions on proposals - e.g. hospitals, consultant neurologists, Health Authorities, GPs (through their LMCs), patient interest groups and other relevant representative bodies?

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* Clinical advice from the Standing Medical Advisory Commitee on the use of Interferon-Beta-Ib in relapsing-remitting multiple sclerosis in adults attached to EL(95) 97.

- What are the implications of the introduction of Beta Interferon on future contracting arrangements (for 1996/97 and future years)?

- Will local information be available for patients, GPs, and others on the availability and applicability of treatment?

- How will experience of treatment be evaluated and disseminated?

Providers

- What is the likely impact on resources of:-
  - -initial assessment and reassessment of patients for treatment?
  - -continued prescribing and evaluation of treatment?

In particular, what is the impact on:-

(a) waiting times?

(b) consultant availability?

(c) MRI services?

(d) nursing and other support?

(e) hospital drugs budgets?

- What are the arrangements for dispensing and supplying the drug to patients, bearing in mind issues of patient convenience (e.g. from hospital pharmacies, community pharmacies, home-health care arrangements, or others)?

- What are the arrangements for the use of patient education in administering treatment, and other matters related to the use of the drug (e.g. suitable storage arrangements) ?

- What are the arrangements for comprehensive clinical audit of this treatment.

6. NHS EXECUTIVE TRENT CLINICAL GUIDELINES

The following are extracts from the clinical guidelines attached at Appendix 1 of the Beta Interferon Steering Group's paper[1] :-

Beta Interferon cannot be recommended for widespread use. It must be used for carefully selected patients only.

All patients under consideration for this treatment should be referred to a specialist neurological centre for reassessment of the diagnosis, disease course, disability rating and suitability for this treatment.

The General Practitioner's responsibility certainly include the monthly treatment monitoring, although once stabilised after the initial six months, these intervals may be extended. Annual assessments should be undertaken at the specialist centre.

The decision to terminate treatment should only be taken after careful consideration and discussion with the patient and the referring clinician in the light of currently available information, including the possibility that deterioration may be worse after discontinuation.

7. UNRESOLVED ISSUES

The following are unresolved and require further consideration:-

***Treatment criteria*:** The documentation so far contains only referral criteria for Beta Interferon treatment to be used by GPs. It does not contain detailed criteria to be used by neurologists. The implication is that, if there are no separate criteria, GPs will effectively be deciding who will get treated. If this is the case, there is a concern whether GP records contain sufficient detail on the number of relapses. If the number of self-reported relapses is used in the absence of recorded data, desperate patients may be tempted to exaggerate in order to receive treatment.

Justification for Trent proposed investigations: i.e. reasons for glucose and thyroid function tests. These tests are not in the Standing Medical Advisory Committee (SMAC) document[9] that accompanied EL(95)97.[10] The rationale for using MRI scans is uncertain; investigations should be subject to effectiveness criteria as well as treatments.

What are the criteria for ceasing treatment? Such criteria should be very similar to the treatment criteria, with the major exception being the number of relapses, as the expectation is that treatment may reduce the relapses to below those described for the entry criteria. Such criteria for discontinuing treatment must be applied on a regular basis, possibly annually, and will need to address the evidence that absolute benefits decline each year. Paragraph 15 of the SMAC document[9] has some "suggested" criteria.

At present it is not known for how long the patient should be treated, since evidence of efficacy beyond two years is incomplete. A decision for treatment beyond this time should be made by the neurologist on an individual basis. It is suggested that treatment with Beta Interferon 1b be stopped if there are unacceptable side-effects, if there is steady progression of disability for six months or three or more courses of corticosteriods are required during a one year period.

Estimates of the proportion of MS patients likely to be treated vary widely from 10% up to 65% depending on the source. With further trials for other groups of MS patients underway, the latter figure may rise further. Purchasing authorities need to establish this

figure more clearly or they will be faced with an open-ended commitment for this extremely expensive drug. If a financial cap is imposed then two problems are likely to arise: firstly, repeated pressure from providers to increase that ceiling, and secondly a failure to target treatments at those most likely to benefit, with treatment being allocated on a first come first served basis.

8. ECONOMIC ASSESSMENT

Prevalence and incidence figures for MS would suggest an average life expectancy of around 30 years. If we assume it to be between 20 and 30 years for a relapse-remitting MS patient (RRMS), then the cost of keeping a theoretical relapse-free patient would be £250,000 (£10,000 X 25). Annual costs to the NHS of maintaining all 40,000 RRMS patient relapse free would be £400 million. This level of expenditure would have significant implications for the resourcing of all other NHS activities.

No formal economic analysis of Beta Interferon has been undertaken, however, some very *crude* figures can be generated under the following assumptions for the purposes of illustrating broad orders of magnitude:

- Assumption 1: 3.5 avoided relapses = 1 EDSS point change
- Assumption 2: 1 EDSS point change = 0.1 QoL
- Assumption 3: average number of relapses avoided = 0.3 p.a. (see table 3)
- Assumption 4: cost of Beta Interferon = £10,000 p.a.

The QoL to Relapse rate can be calculated as:

1/3.5 = 0.286 EDSS points per Relapse
0.286 X 0.1 = 0.0286 QoL per Relapse
The expected difference in QoL per Year is, therefore, the number of relapses avoided per year multiplied by the QoL 'value' of a relapse (0.0286 X 0.3 = 0.00857).
Therefore the cost per QoL, assuming drug costs of £10,000 p.a. can be calculated as:
1/0.00857 X £10,000 = £ 1,166, 861.

Table 3: Reduction in relapse rate per year [2]

	Reduction in relapse rates (from Beta Interferon 1b trial)
Year 1	0.48
Year 2	0.33
Year 3	0.26
Year 4	0.21
Year 5	0.24
average avoided relapse = (1.5 / 5) = 0.3	

The average number of relapses avoided uses data from the full five years of the trial, although there is only a significant difference in relapses in years 1 and 2. Therefore, a lower bound estimate for the number of relapses avoided per annum would be the number of relapses avoided in years one and two divided by the duration of the trial, (i.e. five years), giving 0.16 relapses avoided per annum. Using this figure, the cost per QALY rises to approximately £2.2 million. An upper bound for the number of relapses avoided per annum would equal the number of relapses avoided in years one and two divided by the effective duration of treatment, (i.e. 2 years), giving 0.4 relapses avoided per annum. Using this figure, the cost per QALY falls to approximately £863,000.

The assumption relating changes in the EDSS score to QoL is clearly vital. In support of this assumption, a 1 point change on the EDSS does not represent a large change in morbidity and published QoL valuations show that a 0.1 change in a QoL valuation does not represent a major change in morbidity. e.g. Gudex et al[12] found that a shift from a health state described as 'No disabilities with No Distress' to a health state described as 'Slight Social Disabilities with No Distress' would be a 0.1 reduction in QoL.

If it is assumed that the QoL impact of relapses is more severe, for instance a 1 EDSS point is equal to 0.2 QoL, then the cost per QALY will be less; i.e. between £430,000 and £1.1 million.

Given that it is likely that patients will go on to attain the same level of disability on treatment, but at a later stage, the total decrease in the burden of social care for these people is likely to be shifted rather than significantly reduced. There will be an initial honeymoon period during which the total burden of social care for MS patients will be reduced; however, the lifetime experience of disability is likely to remain unchanged, and may indeed be worsened by comorbidities if patients live significantly longer.

All these figures assume that the price of Beta Interferon will remain constant if its use increased significantly. Under such circumstances it is likely that the price would be reduced, but this reduction would have to be considerable for the illustrative QALY figures above to approach those generally regarded as acceptable within the NHS.

The analysis above has used the average benefit over five years to estimate the cost per QALY. An analysis based on the marginal benefits of successive years of treatment would show that although treatment in the first and second year produced QALYs at a lower price, although still extremely high, treatment beyond this point would produce QALYs which were even more expensive.

Only drug costs have been included in this analysis. The guidelines issued by the British Association of Neurologists include extensive monitoring of patients on Beta Interferon. This would increase the total cost of Beta Interferon treatment, and would need to be incorporated in to any formal economic evaluation.

9. OPTIONS FOR THE INTRODUCTION OF BETA INTERFERON IN THE NHS

The introduction of Beta Interferon in the NHS does not have to be constrained to an all or nothing choice. The following options have been identified:

(i) Beta Interferon is not funded from main NHS funds, but the NHS promotes continued randomised controlled trials to establish firm treatment criteria, long-term benefits, side-effect profile and cost effectiveness.

(ii) Beta Interferon may only be prescribed through specialist neurological centres after screening by specialist neurologists.

(iii) Prescribing of Beta Interferon is cash-limited, with random allocation of access through a first come first served system.

(iv) No specialist guidelines for Beta Interferon, leaving responsibility for prescription with General Practitioners.

(v) Beta Interferon is not prescribed within the NHS.

The major disadvantage of constraining Beta Interferon prescribing to randomised controlled trials or health technology evaluations is that those groups pressing for the provision of Beta Interferon through the NHS would not be satisfied, and would continue to press for a different policy.

This approach does have the advantage of maximising control over patient selection and total expenditure, whilst at the same time ensuring that outcomes data continue to be collected. This will allow the policy to be regularly reviewed and future decisions to be based on more and better quality data than are presently available.

Allowing Beta Interferon to be prescribed through specialist neurological centres alone will ensure that patient selection and management are optimised on the basis of available

evidence. Therefore, the health returns to the expenditure on Beta Interferon should be maximised.

Access to Beta Interferon would be made more difficult for patients who did not live close to a specialist centre. A cost implication of this might be that patients living at a distance from a specialist centre could not be assessed in an out-patient clinic. No data on longer term outcome would be generated to inform future policy decisions about Beta Interferon.

Placing a cash limit on the prescription of Beta Interferon would protect the NHS against costs which could threaten existing services. There would be no guarantee, however, that the most appropriate patients would receive Beta Interferon. Patients who started on Beta Interferon might find their treatment being stopped because money had run out before the end of the financial year. No data on longer-term outcome would be generated to inform future policy decisions about Beta Interferon.

Leaving the prescribing of Beta Interferon to General Practitioners would mean that the NHS had no control over the costs of Beta Interferon prescription. In addition, there would be a significant risk of Beta Interferon being prescribed to inappropriate patients, even patients who did not have MS. No data on longer-term outcome would be generated to inform future policy decisions about Beta Interferon

A decision not to fund the prescription of Beta Interferon would ensure that the threat of significant costs for uncertain health benefits was removed. However, once Beta Interferon has been licensed, it will be very difficult to defend a refusal to fund its prescription. Limited prescription is necessary if only to obtain the knowledge necessary to address the current concerns with regard to Beta Interferon.

10. SUMMARY

This paper has highlighted the uncertainties, unresolved issues and potential cost implications of the provision of Beta Interferon for Multiple Sclerosis patients by the NHS. It has identified the lack of reported trials investigating the efficacy of the drug and the patient grouping for which its use is most appropriate.

The key issues are whether Beta Interferon should be funded from the main NHS funds and, if so, how the system should be structured to ensure that further information on efficacy and patient criteria is made available to inform decision making, and at what level it should be prescribed, i.e.:-

(I) ***through specialist neurological centres, cash limited***; selection of patients by neurologists, the cost implication of which might be that patients living at a distance from a specialist centre could not be assessed in an out-patient clinic, although, if neurologists provide outreach clinics, this may not be a problem;

(ii) ***through specialist neurological centres, but by a protocol restricting use*** to 'new' patients and for only 2 years (then review policy);

(iii) ***cash limited with random allocation of access through first come first served system*** thus protecting the NHS against costs which would threaten existing services; or

(iv) ***through the GP***, leaving the NHS with no control over the costs of Beta Interferon prescribing.

Alternatively, how can Beta Interferon be justified, if it is not to be funded from the main NHS funds? The data suggest only marginal clinical benefit, considerable side effects and very high costs. In addition, the use of Beta Interferon is not universally supported by neurologists. Its use could be proscribed on cost-effectiveness grounds and its continued promotion may have more to do with the need to find a market for an expensive new 'high tech' drug, which will not have been developed for this specific use. Prescription from mainstream NHS funding would enable continued trials to establish firm treatment criteria, long-term benefits, side effect profile and cost-effectiveness whilst maximising control over

the total expenditure on the drug. Despite the above, the pressure for the provision of Beta Interferon by the NHS, through the media and relevant pressure groups, is considerable and will be difficult to constrain.

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Appendix A

Kurtzke Expanded Disability Status Scale

The following are the definitions for EDSS grades 3 and 4:

3 Moderate disability in one FS (one FS grade 3, others 0 or 1), or mild disability in three or four FS (three/four FS grade 2, others 0 or 10 though fully ambulatory.

4 Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively sever disability consisting of one FS grade 4 (others 0 or 1), or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest some 500 metres.

Functional Systems (FS)

Pyramidal Functions

3 Mild or moderate paraparesis or hemiparesis; severe monoparesis

4 Marked paraparesis or hemiparesis; moderate quadriparesis; or monoplegia.

Cerebellar Functions

3 Moderate truncal or limb ataxia

4 Severe ataxia, all limbs

Brain Stem Functions

3 Severe nystagmus, marked extraocular weakness or moderate disability of other cranial nerves

4 Marked dysarthria or other marked disability

Sensory Functions (revised 1982)

3 Moderate decrease in touch or pain or position sense, and/or essentially lost vibration in one or two limbs; or mild decrease in touch or pain and/or moderate decrease in all proprioceptive tests in three or four limbs

4 Marked decrease in touch or pain or loss of proprioception, alone or combined, in one or two limbs; or moderate decrease in touch or pain and/or severe proprioceptive decrease in more than two limbs.

Bowel and Bladder Functions (revised 1982)

3 Frequent urinary incontinence

4 In need of almost constant catheterization

Visual (or Optic) Functions

3 Worse eye with large scotoma, or moderate decrease in fields, but with maximal visual acuity (corrected) of 20/60 to 20/99

4 Worse eye with marked decrease of fields and maximal visual acuity (corrected) of 20/100 to 20/200; grade 3 plus maximal acuity of better eye of 20/60 or less

Cerebral (or Mental) Functions

3 Moderate decrease in mentation

4 Marked decrease in mentation (chronic brain syndrome - moderate)