Cerebrospinal fluid lactate and pyruvate concentrations in patients with Parkinson's disease and mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced parkinsonism is reportedly caused by impairment of the activity of complex I of the mitochondrial respiratory chain enzyme in the substantia nigra.^{1,2} Decreases in the activity of the mitochondrial respiratory chain enzyme complex I have been reported in the substantia nigra, skeletal muscle, and platelets of patients with Parkinson's disease.³ These results are controversial except for platelets.³ Patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) show a decreased mitochondrial respiratory chain enzyme complex I level and high lactate concentrations in CSF and blood.^{4,5}

We examined whether CSF concentrations of lactate and pyruvate were increased in patients with Parkinson's disease or MELAS.

We studied 38 patients with Parkinson's disease (five untreated, 15 treated with levodopa, and 18 treated with amantadine or bromocriptine) and four patients with MELAS. All patients with Parkinson's disease were typical and had two or more symptoms of rigidity, resting tremor, akinesia, and postural instability. The controls had headache, entrapment neuropathy, and cervical spondylosis. All patients were admitted to hospital and informed consent had been obtained. After an overnight fast and bed rest, CSF was collected at 9 00 am from patients and controls, in a lateral recumbent position. Lactate and pyruvate concentrations were determined according to the method of Asanuma *et al.*⁶ Statistical analysis was performed with one way ANOVA and Scheffé's test by StatView IV.

There were no significant differences in the CSF concentrations of lactate and pyruvate or the lactate:pyruvate ratio in the 38 patients with Parkinson's disease versus the controls (table). There was no significant correlation of lactate or pyruvate concentrations with age in either the control group or in patients with Parkinson's disease. No significant difference was found between the subgroup treated with levodopa and the untreated patient subgroup. There were no significant differences between different durations of illness or severity of disease, which was classified into three grades according to Hoehn and Yahr: mild (stages 1 and 2), moderate (stage 3), and severe (stages 4 and 5). The patients with MELAS showed significantly higher lactate and pyruvate concentrations and a higher ratio than patients with Parkinson's disease and controls (table).

In patients with MELAS, high concentration of lactate in the CSF is an important

finding for diagnosis of CNS mitochondrial impairments. Several reports showed normal blood lactate concentrations in Parkinson's disease.⁷⁻⁹ These findings are compatible with investigations of mitochondrial complex I activity in various organs.³ The decrease in mitochondrial respiratory chain enzyme complex I activity of the substantia nigra in Parkinson's disease is very likely to be a characteristic finding of Parkinson's disease.³ It may also be intimately associated with the onset of the disease. Przedsorski *et al.*¹⁰ reported that chronic levodopa treatment caused a significant reduction in complex I activity of the mitochondrial respiratory chain. But, in our study, there were no significant differences in lactate concentrations between the patients treated with levodopa and the untreated patients.

Hattori *et al.*⁹ also reported normal CSF lactate concentrations in nine patients with Parkinson's disease. Any slight decrease in complex I activity of the substantia nigra in Parkinson's disease may be localised to the substantia nigra.

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Distribution of tenascin in human malignant gliomas is not related to cell proliferation

The knowledge that radiolabelled antitenascin (TN) monoclonal antibodies are able to induce regression of human glioma xenografts prompted attempts at administration directly into tumours *in vivo*, to deliver cytotoxic radionuclides able to selectively bind to components of human gliomas.^{1,2} It has been shown, however, that TN is unevenly expressed in these tumours, with its distribution being most heterogeneous in anaplastic astrocytomas and glioblastomas.³ To evaluate whether TN expression is related to cell proliferation, surgical samples from 75 malignant gliomas (48 anaplastic astrocytomas and 27 glioblastomas according to the World Health Organisation classification) underwent double staining immunohistochemical evaluations by a procedure reported elsewhere.³ Distribution of TN was studied by using the specific monoclonal antibody BC-4, which was obtained in this laboratory⁴ and employed in clinical trials.² The monoclonal antibody Ki-67, purchased from DAKO (Carpenteria, CA, USA), was used for nuclear labelling of proliferating cells.

In both anaplastic astrocytomas and glioblastomas, Ki-67 labelled nuclei were found to occur at the same rate, with no significant differences being found in tumours strongly stained with anti-TN monoclonal antibody BC-4, compared with tumours that exhibited a weak to moderate staining (table). For TN expression, besides the definite reaction shown by the stroma and the subendothelial matrix, the only constant occurrence was a strong staining of the white matter at the periphery of the tumours. This phenomenon was not related to the presence of proliferating cells, as shown by the usual lack of nuclear labelling by the Ki-67 monoclonal antibody. As a general rule, TN expression was related to the histological texture, rather than the number of proliferating cells in different areas of a single tumour. Staining was most pronounced in areas with a compact texture, even in the presence of few Ki-67 labelled nuclei. By contrast, areas with a loose texture exhibited a less intense staining, even in the presence of several Ki-67 labelled nuclei. This reduced TN expression, unrelated to the occurrence of proliferating cells, was paramount in loosely textured areas of both anaplastic astrocytomas and glioblastomas. Enhancement of staining occasionally occurred in the perivascular conglomerates of cells, without a relation with either Ki-67 nuclear labelling of both gliomatous and endothelial cells, or TN expression in the perivascular stroma. Similarly, a consistent reaction occurring at the boundaries of necrotic areas was not related to the amount of proliferating cells.

Although TN, a polymorphic glycoprotein of the extracellular matrix, has been regarded as an exclusive component of the basement membrane of vessels in human gliomas, it is also present in stromal elements and neoplastic glial cells. However, TN expression in gliomas was found to be uneven, with the degree of anaplasia being usually associated, in immunohistochemical preparations, with a pronounced heterogeneity in both intensity and distribution of staining, which was not related to the cell type.³ The present results confirmed this heterogeneous distribution in malignant

Mean (SD) concentrations of lactate and pyruvate in CSF

Diagnosis (n)	Age (y)	Lactate (L) (mg/dl)	Pyruvate (P) (mg/dl)	L:P
Controls (25)	53.6 (17.4)	13.3 (1.0)	0.87 (0.11)	15.5 (2.3)
Parkinson's disease (38)	66.1 (9.2)	13.1 (1.9)	0.87 (0.15)	15.3 (3.4)
MELAS (4)	32.3 (18.6)	30.7 (4.4)*†	1.17 (0.21)‡	27.0 (6.6)*†

*P < 0.0001; controls v Parkinson's disease.

†P < 0.0001; Parkinson's disease v MELAS.

‡P < 0.01; MELAS v controls or Parkinson's disease.

MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes.