Canadian Association of Neuropathologists

Abstracts of papers presented at the 32nd Annual Meeting

September 17th – 19th, 1992
Toronto, Ontario

The 32nd Annual Meeting of the Canadian Association of Neuropathologists was held from September 17th – 19th at the Sheraton Centre in Toronto. The Councillors of the International Congress of Neuropathology were guests at this meeting. Local arrangements were made by Dr. L.E. Becker.

The scientific sessions included 30 platform presentations, 15 poster presentations and 11 diagnostic cases. The Royal College of Physicians and Surgeons of Canada Speaker was Dr. Hans Lassmann of the Institute of Brain Research of the University of Vienna, Austria. His lecture was entitled "Pathogenetic Aspects of Inflammation in the Central Nervous System". The Jerzy Olszewski Lecture was given by Dr. Brenda Gallie of the University of Toronto. Her lecture was entitled "Retinoblastoma: A Window to the Biology of Cancer".

The Association presents two awards annually to trainees/residents giving the best presentations. Dr. J. Provias received the Mary Tom Award for his paper entitled "Cadium Encephalopathy: A Case Report". Michael S. Pollanen received the Morrison H. Finlayson Award for his paper entitled "What are the Structural Subunits of Lewy Body Fibrils?".

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Abstracts of Papers Presented at the 32nd Annual Meeting of the Canadian Association of Neuropathologists

PLATFORM PRESENTATIONS

1.

GFAP Gene Expression in Alzheimer's Disease and Down's Syndrome

A.W. CLARK, S. BOU, P. COGGINS and C. KREKOSKI (Calgary, Alberta)

Gliosis is a conspicuous component of the pathologic changes in Alzheimer's disease (AD), and recent reports suggest that astrocytes may play an important part in early stages of pathogenesis. Better understanding of these early stages may be facilitated by studying young adult Down's syndrome (DS), since this disorder is almost always associated with development of AD-type pathologic changes by 45-55 years of age. Our laboratory has recently defined several new aspects of gene expression for a major astrocytic protein, glial fibrillary acidic protein (GFAP), in Alzheimer's disease (AD) and in Down's syndrome (DS).

We quantitated GFAP mRNA levels in neocortex from a series of DS cases ages 15 to 45 years. In the four DS cases age 15 to 34, GFAP gene expression was markedly *reduced* (0.26 ± 0.05 × control), suggesting that trisomy 21 exerts a suppressive effect on expression of the chromosome 17-derived GFAP transcript. This is the first evidence for suppression of gene expression for a well characterized brain protein in trisomy 21, although evidence of suppression of five anonymous transcripts in fetal DS brain has previously been reported (Biochem J 1984; 220: 179). GFAP immunostaining of young adult DS cases does reveal immunoreactive glia, but preliminary data from western blots in our lab suggest that GFAP is quantitatively diminished.

In the 45-year-old DS case, with severe AD-type pathology, GFAP mRNA levels were 5 times the DS baseline and 1.7 times the normal control mean value. Results from the study of DS cortex therefore support the conclusion that GFAP mRNA levels are elevated in the presence of neurofibrillary degeneration; but we find no evidence that this change precedes neurofibrillary tangles in neocortex. Delacourte (Neurology 1990; 40: 33) has shown that dramatic increases in this glial protein occur in AD even in anatomic sites with little or no neurofibrillary degeneration. We are currently pursuing studies to clarify the relationship of GFAP gene expression to the classic pathologic changes of AD.

We have also found elevated GFAP mRNA levels in cortex from subjects with AD. Preliminary data from nuclear run-on transcription assays, comparing AD and control cortex, indicate that the transcription rate of the GFAP gene is markedly elevated in AD cortex.

These studies suggest that expression of the GFAP gene, located on chromosome 17, is suppressed in young adults with trisomy 21; that this suppressed state gives way to overexpression in the presence of neurofibrillary degeneration; and that a similar overexpression of GFAP in AD cortex is referable to an increase in transcription rate of the GFAP gene.

2.

Diffuse (ßA4) Plaques in Temporal Lobectomy Specimens

I. MACKENZIE, L. MILLER and D. MUNOZ (London, Ontario)

It has been suggested that the earliest pathologic change in the development of Alzheimer's disease (AD) is the deposition of ßA4 protein in cerebral grey matter in the form of silver-positive, diffuse plaques (DP). Such DP are common in all AD brains in combination with the more diagnostic neuritic plaques and neurofibrillary tangles. Recent studies of adult Down's syndrome patients (who invariably developed AD) have shown DP to precede these other changes. DP are also a common post-mortem finding in the brains of *non*-demented individuals. It is uncertain whether the incidental finding of DP indicates a pre-clinical stage of AD or an age related phenomenon, unassociated with dementia.

In order to further evaluate the clinical significance of DP we examined surgical lobectomy specimens removed in the treatment of longstanding temporal lobe epilepsy. We restricted our examination to patients 40 years or age or older, with resections including both temporal cortex and hippocampus who had no other significant primary pathology. The 27 patients satisfying these criteria ranged in age from 40 - 61 years (average 47 years). Representative sections were screened with a modified Bielschowsky stain. Further special stains (Congo Red, Gallyas, anti-ßA4 and anti-tau) were performed on all positive cases. Six patients (22%) were found to have a significant number of diffuse plaques (DP+) within the entorhinal and temporal cortex. One patient also had a lesser number of classic neuritic plaques and congophilic angiopathy. Small focal collections of neurofibrillary tangles were seen in two patients.

A review of these patients' pre-operative neuropsychological assessments showed none to be overtly demented. However, when a blind retrospective comparison was made between the six DP+ patients and six matched controls (study patients without DP) the patients with the worst scores on tests sensitive for dementia were all from the DP+ group. Early clinical followup (1 - 4 years post-operative) in three of the six DP+ patients has shown no significant deterioration on neuropsychological testing.

We conclude that DP are a common finding in temporal lobectomy specimens of patients over the age of 40, with a frequency similar to that reported in autopsy series of non-demented patients. The number of such plaques may be very high (far exceeding the NINCDS-ADRDA criteria for the diagnosis of AD) and accompanied by some neuritic change, without being associated with clinical dementia. Neuropsychological testing shows that some of these patients may have subtle difficulties on dementia sensitive tests but longer followup is needed. We did not find any increased incidence of DP in our patients, to suggest a link between ßA4 protein deposition and epilepsy.

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3.

What are the Structural Subunits of Lewy Body Fibrils?

M.S. POLLANEN, C. BERGERON and L. WEYER (Toronto, Ontario)

The repertoire of proteins which have been immunolocalized to the Lewy body (LB) can be divided into four main groups: (1) putative structural elements, (2) elements associated with ubiquitin-mediated proteolysis, (3) kinases which phosphorylate structural components, and (4) cytoplasmic proteins which diffuse into the LB. Recently, three different proteins have been implicated as the main structural subunit of the LB fibril (neurofilament [NF], gelsolin-derived amyloid, and the microtubule associated protein tau) but no direct biochemical evidence is available on the constitutive proteins of the LB fibril. We have taken advantage of the abundant source of LBs in the cerebral cortex of patients with diffuse LB disease to prepare highly enriched fractions of detergent-resistant LB fibrils for biochemical analysis (Pollanen et al, J. Neurochem., 58, 1953 - 1956, 1992). Immunoblotting of solubilized LB fibrils revealed full length and partially truncated variants of 200 and 170 kDa NF molecules and a 68 kDa species which was labelled by an antiserum which recognized both tau and 68 kDa NF. Some NF epitopes found in solubilized LB fibrils were also detected with peroxidase-antiperoxidase labelling of *in situ* LBs. This evidence indicates that NFs are intrinsic components of the LB rather than molecules loosely associated with the fibrils. The nonstructural components of the LB may be mechanistically linked to post-translational alterations of NFs ultimately leading to their deposition as insoluble fibrils.

4.

Pathways of Lymphatic Drainage from the Brain

R.O. WELLER, A. PANTAZIS, S. KIDA and E. ZHANG (Southampton, U.K.)

Physiological studies have shown that lymphatic pathways are significant routes of cerebrospinal fluid drainage in small mammals. In the present study, tracer experiments using Indian ink, have been used to anatomically define lymphatic pathways for the drainage of interstitial fluid and CSF from the rat brain to cervical lymph nodes. Ultrastructural studies of the human brain show that similar pathways may exist in man.

Indian ink injected into the grey matter of the rat brain flows along perivascular spaces. Ink in the subarachnoid space follows a paravascular route to the circle of Willis and thence alongside the ethmoidal artery to the cribriform plate. Here, ink enters channels in the arachnoid; these channels are in continuity with nasal lymphatics through the cribriform plate. Ink thus drains into cervical lymph nodes. Although small numbers of arachnoid villi abut on to large venous sinuses and occasional lymphatics in the dura contain the ink tracer, the nasal route appears to be the major drainage pathway and the only lymphatic route for intracranial CSF in the rat.

Although tracer studies are not possible in man, scanning and transmission electron microscope studies suggest that the pathways within the brain and in the subarachnoid space exist for lymphatic drainage. Perivascular spaces within the brain are continuous with those of meningeal vessels, as the subarachnoid space is separated from the perivascular spaces by the pia mater. Compartmentalisation of the subarachnoid space may allow directional flow of CSF. Some evidence also exists for lymphatic drainage of CSF in man, particularly following subarachnoid haemorrhage.

5.

Synaptophysin Immunoreactivity Pattern in the Anterior Horn Cells in Amyotrophic Lateral Sclerosis

T. KAWANAMI, A. IKEMOTO, J.F. LLENA and A. HIRANO (Bronx, U.S.A.)

Loss and degeneration of anterior horn cells in the spinal cord are neuropathological hallmarks of amyotrophic lateral sclerosis (ALS). Extensive studies of the neuronal cytoplasm and proximal neurites have been reported but relatively less information is available regarding the synaptic alterations in ALS. To investigate synaptic alterations in ALS, we examined lumbar cords from 5 cases of sporadic ALS and 6 age-matched normal controls with a monoclonal antibody to synaptophysin (SP).

In normal controls, anti-SP antibody labeled the gray matter of the lumbar cords. The immunoreactivity was shown as small granules densely distributed in the neuropil. While proximal neurites were decorated by immunoreactive granules, only a few granules were seen around anterior horn cells. In ALS cases, although the density of SP-immunoreactive small granules in the neuropil was considerably decreased in the anterior horns, both the cell bodies and proximal neurites of anterior horn cells were intensely decorated by immunoreactive granules. These immunohistochemical features were prominent around the atrophic anterior horn cells.

Because synaptophysin is a marker protein of the presynaptic termini, our results suggest that axo-somatic and/or dendro-somatic synapses are still relatively preserved in the degenerating anterior horn cells in ALS. Another implication of this study is selective reduction of SP-immunoreactivity in the anterior horn cells in ALS. This finding is consistent with the previous report by Whitehouse et al. (Ann Neurol, 14: 8-16, 1983) of decreased cholinergic receptor density in Rexed layer IX of the spinal cords with ALS.

This work was partly supported by Amyotrophic Lateral Sclerosis Association.

6.

Use of Semithin (0.2 micron) Plastic Sections for Electronmicroscopy

K. FUJISAWA (Fuchu-shi, Tokyo)

The two cardinal mandates of electronmicroscopic neuropathological study are (1) cell pathology and (2) histopathology. By the term of cell pathology, we mean that we study morphological development of any given disease process within a

neurone (or other non-neuronal cells), beginning from a certain corner of its paricaryal cytoplasm extending and reaching to the remotest part, e.g., terminal parts of axon or dendrites. Neurones are large cells in general, and have many long cell processes, so that their domain in the tissue covers a very wide area. By the term "histopathology" we mean that we study morphological development of any given disease process among tissue components, so that we can follow stages or order of involvement among cells and search for evidence pointing to pathogenetic relationship with each other. Any given morbid process, thus, needs a certain amount of tissue space to develop itself. This amount of space must be fulfilled in a very electronmicroscopic study if one wishes to get reliable information from it. We have, therefore, studied nervous tissue as widely and extensively as possible. On the other hand, to get ultrathin sections which are large enough is a difficult task to achieve.

This task may be achieved if we compromise section thickness. We propose to double the thickness of our ordinary ultrathin sections, up to 0.2 micron. There are several reasons that we cut sections with this thickness in our daily neuropathological electronmicroscopy. They are: (1) we can cut sections as big as 1 - 2 mm wide on each side; (2) we can place them on to coarser grids (#50) for microscopy; (3) we can see sections more three-dimensionally (e.g., smooth eR system within axon); (4) although we can use ordinary electronmicroscopes with accelerating voltage of 100 kV, the quality of EM images improves substantially if we use electronmicroscopes equipped with accelerating voltage of 200 or 300 kV; (5) we can make excellent sections relatively free of knife-marks with ordinary glass knives.

The purpose of our present paper is to demonstrate with slides and/or electronmicrographs the quality of EM images taken under very low magnification (1000 - 2000 ×) or taken under more ordinary magnification (around 10,000 ×) using a Hitachi H-9000 electronmicroscope with accelerating voltage of 300 kV.

7.

p53 Mutations in Human Brain Tumors

P. KLEIHUES, R. EIBL, M. REICHEL, L. MARIANI, O.D. WIESTLER, I. PETERSEN, A. von DEIMLING and H. OHGAKI (Zurich, Switzerland)

Human brain tumors with various histologic types were analyzed for mutations in the tumor suppressor gene, *p53*. DNA was extracted from frozen or formalin-fixed, paraffin embedded material. Single strand conformation polymorphism (SSCP) analysis for exons 5 - 8 was followed by direct DNA sequencing. Astrocytic brain tumors (astrocytomas grade II, grade III, and glioblastoma multiforme) contained *p53* point mutations at incidences of 29 - 43%, suggesting that mutational inactivation of the *p53* gene may play an important role in their development. Benign pilocytic astrocytomas did not contain *p53* point mutations, suggesting a different molecular basis for this type of childhood neoplasm. Nonastrocytic brain tumors including hemangiopericytomas, oligodendrogliomas and medulloblastomas contained *p53* mutations at incidences of 11 - 14%. No *p53* mutations were detected in ependymomas, schwannomas, central neurocytomas, meningiomas, choroid plexus tumors and neuroblastomas of the sympathetic nervous system. Mutations in both human tumors were preferentially located in exon 7. Most mutations were G - >A transitions (42%), followed by frameshift mutations (26%).

Publications: Ohgaki et al., Cancer Res 51: 6202-6205, 1991; von Deimling et al., Cancer Res 52: 2987-2990, 1992.

8.

Proliferating Cell Nuclear Antigen (PCNA) Expression and Its Correlation With Biological Behavior of Astrocytomas

M. PLEWES, L.C. ANG, L. TAN, A. AGRANOVICH and D. SHUL (Saskatoon, Saskatchewan)

PCNA, an auxiliary protein of DNA-delta-polymerase at the sites of DNA replication during cell cycle, has highest concentration during proliferative phase. Since immunostaining for PCNA could be applied to tissue that is formalin fixed and paraffin embedded, it could be useful in studying archival tissue. This study involved the assessment of PCNA labelling index (LI) in 69 astrocytomas (17 low grade astrocytomas, 14 anaplastic astrocytomas and 38 glioblastomas taken from 1980 - 1990) using the ABC technique with a primary anti-PCNA antibody (Novocastra; 1:100). This histological grading correlated well with the PCNA LI as follows: low grade astrocytoma — 2.1 ± 0.3%; anaplastic astrocytoma — 10.8 ± 2.3 and glioblastoma — 15.6 ± 1.0. There are 26 tumors with LI of less than 6% and 43 with LI more than 6%. Looking at the outcome of tumors with LI < 6%; 2 patients died of causes unrelated to their tumors, 8 with tumor-related deaths and 16 were still alive at the time of study. Of the 8 tumor-related deaths, the mean survival time after diagnosis was 4.1 ± 1.1 years and of the 16 who survived they were alive after a mean duration of 5.4 ± 0.8 years. All patients with LI > 6% had died, one of unrelated cause and 42 of tumor-related causes. The mean survival time for the 42 patients was 0.6 ± 0.1 years with only one patient surviving more than 2 years. Our data indicates that PCNA LI not only has good correlation with histological gradings of astrocytomas but also with the survival of patients with the tumors.

9.

Immunohistochemistry of PCNA and p53 in Brain Tumors

D. SCHIFFER, A. CHIÒ, P. CAVALLA, R. De LUCIA, M.T. GIORDANA, A. MAURO and M.C. VIGLIANI (Turin, Italy)

PCNA (Proliferating Cell Nuclear Antigen) represents today a new tool to evaluate the proliferative capacity of tumors, since its LI correlates with that of Ki67 and BrdU. The most important advantage is the possibility of using the method in routine paraffin embedded material and therefore in archivial material.

Two hundred brain tumors were studied with PC10 Mab, including well-differentiated and anaplastic astrocytomas, glioblastomas, oligodendrogliomas, ependymomas, medulloblastomas, meningiomas and metastases. The LI was very low in astrocytomas, increased in anaplastic astrocytomas and reached the highest values in glioblastomas where, however, there were the largest field-to-field variations.

In differentiated and anaplastic oligodendrogliomas the LI was higher than in the corresponding astrocytic tumors. High values were found in medulloblastomas and metastases and low values in meningiomas, unless these belonged to the category of malignant meningioma. In ependymomas the LI correlated with the mitotic index and cell density, so that the highest values were found in the malignant variant.

All positive nuclei were counted, independently of the staining intensity; if only very intensely positive nuclei, probably corresponding more strictly to the phase-S, were computed, the correlation with malignancy was greater. In ependymomas there was a correlation with survival.

PCNA immunohistochemistry may be of value in the prognosis of brain tumors. Its main advantage was, however, the possibility of a visual analysis which permits to given an evaluation of different tumor structures from the cell kinetics point of view.

p53, evidenced by PAb 1801 did not show any correlation with cell proliferation. It was positive in some anaplastic astrocytomas, glioblastomas and medulloblastomas only, in some of which mutations have been found by PCR-SSCP technique.

10.

Glioblastoma Multiforme of the Cerebellum — Report of Three Cases

A. SAXENA and L.C. ANG (Saskatoon, Saskatchewan)

Glioblastoma multiforme (GBM) of the cerebellum are rare tumors and account for a small proportion of all GBMs (0.24% - 1.0%). We report three cases of GBM arising from cerebellum. Case 1, a 40-year-old male presented with unsteadiness and headaches and on CT examination was found to have a mass in the vermis. He was treated by surgical excision and postoperative radiotherapy. He survived twenty months and died due to recurrent tumor. Case 2, a 54-year-old female was found to have nystagmus by her ophthalmologist. CT examination could not detect any abnormality. A craniotomy was performed and following the diagnosis of GBM postoperative radiation was given. She expired five months and three weeks after presentation due to recurrent tumor. Case 3, a 74-year-old male who presented with an unsteady gait and headaches, was found to have a mass on the left cerebellar hemisphere on CT examination. Surgical removal of the tumor was followed by a rapid neurological deterioration and he expired ten days after presentation. Histologically all the tumors showed features of glioblastoma multiforme. Because of the rarity of these tumors, especially in the adults they pose diagnostic difficulties and can be thought to be metastatic tumors clinically. All the cases had cerebellar dysfunction at presentation. The prognosis was very poor especially in one of the cases where the presentation was late and the patient died within ten days of diagnosis. These tumors had an interesting pattern of spread with Case 1 showing occipital bone and skin involvement, and Case 2 with autopsy documentation of supratentorial and cervical cord infiltration. In Case 2 there was association with neurofibromatosis. As there was no previous history of pilocytic astrocytoma these cases may represent de novo GBMs.

11.

Rapid Ingestion of Serum Proteins by Astroglia Following Extravasation of Blood in the Human Brain

M.R. DEL BIGIO, G.S. DAVIDSON and J.H.N. DECK (Toronto, Ontario)

Astrocytes play a critical role in the regulation of the extracellular environment of neurons. Following injury of the brain the integrity of blood vessels may be lost and serum proteins are released into the extracellular space. Here they may alter neuronal function or slow the resolution of brain edema through an osmotic effect (Groeger and Marmarou, Acta Neurochir 1989; 101: 134-140). In the proximity of extravasated blood in human brains we have observed swollen cells with intensely eosinophilic cytoplasm appearing within a few hours of the hemorrhagic event. This is much earlier than expected for the typical reactive astrocyte with its accumulation of glial fibrillary acidic protein (GFAP) filaments. These eosinophilic cells represent a small number in comparison to the acutely edematous glial cells with empty appearing cytoplasm. They are seen within the parenchyma, along blood vessels, in the subpial regions, and in the subependymal region. We studied the nature of these cells in 13 human brains with blood collections secondary to trauma, subarachnoid hemorrhage, and intracerebral hemorrhage using a battery of immunohistochemical stains. The eosinophilic cells were moderately PAS positive and diastase resistant and were strongly immunoreactive for GFAP, IgG, and IgM. They were occasionally immunoreactive for fibrinogen or ubiquitin. The cells did not show staining for leukocyte common antigen, lysozyme, or alpha 1 anti-trypsin. We did not observe any relationship between staining characteristics an the interval from death to autopsy. This is in contrast to a recent report claiming that nonspecific immunoglobulin staining of brain cells increases with the time until autopsy (Loberg and Torvik, APMIS 1992; 100: 431-436). Electron microscopic examination of these cells showed dispersed intermediate filaments and coarse granular material in the cytoplasm. The nuclei had large clumps of peripheral chromatin and large nucleoli. We conclude that the cells are acutely swollen astroglia that have ingested serum proteins from the extracellular space. As was suggested by Klatzo (Adv Neurol 1980; 28: 359-373), astrocytes may aid in the resolution of brain edema through this mechanism. Although these glial cells have an appearance similar to that described as clasmatodendrosis, we believe that the rapid formation is more consistent with an active process than a degenerative one.

12.

Insulin Reduces MCA Infarction in Rats

R.N. AUER, M.G. HAMILTON and B.I. TRANMER (Calgary, Alberta)

Our laboratory has shown that insulin ameliorates ischemic necrosis in rat models of global brain ischemia. To now test for

a benefit of insulin in focal ischemia, 30 rats were given 2 - 3 IU/kg insulin or not treatment, prior to transient MCA occlusion for 2 hours at a blood pressure of 60 mm Hg. To clarify whether the mechanism of any insulin-induced neuroprotection requires hypoglycemia, or whether insulin acts directly, two insulin-treated groups were studied, one receiving no glucose to allow for moderate hypoglycemia, and the other receiving glucose to raise blood glucose to levels comparable with untreated animals. Animals were allowed to survive one week, to allow clear demarcation of infarction. Infarct size was assessed by quantitative neuropathology at 25 coronal planes. Pre-ischemic insulin lowered the mean intraischemic blood glucose from 8.4 mM in the control group to 3.5 mM, and reduced the volume of cortical infarction from 40.1 ± 7.4 mm^3 to 22.2 ± 3.3 mm^3. Co-administration of glucose with the insulin resulted in slightly higher mean intraischemic blood glucose value of 9.8 mM, but nevertheless reduced the volume of cortical necrosis to 30.3 ± 5.4 mm^3. In contrast, striatal infarction was reduced by insulin alone, from 19.0 ± 3.7 mm^3 to 5.0 ± 2.9 mm^3, but not by insulin plus glucose, with a volume of 24.2 ± 3.8 mm^3. Blood glucose levels, even though ranging within the physiologic range, showed an independent correlation with total ischemic damage ($r = 0.66$, $p = 0.0021$). The findings indicate that: 1) Insulin benefits transient focal as well as transient global ischemia, 2) Reducing the blood glucose from 8 - 9 mM to the range of 3 - 4 mM with insulin dramatically reduced subsequent infarction, and 3) Insulin, independent of its hypoglycemic action, also has a direct CNS effect, independent of glycemia.

Mild insulin-induced hypoglycemia may be beneficial clinically in situations where transient focal ischemia to the neocortex can be anticipated.

13.

Pathology of MRI Directed Laser Photocoagulation of Brain

P.B. LITTLE, R.A. TRACZ, R.A. TOWNER, W.A. STEWART, D.R. WYMAN, S.W. SCHATZ and B.C. WILSON (Guelph and Hamilton, Ontario)

Magnetic resonance imaging (MRI) was used to monitor the tissue necrosis created by a continuous wave Nd:YAG (1064 nm) laser. The laser irradiation was conducted interstitially in the cerebral hemisphere of six cats by a cut optical fibre. A single irradiation was performed in each of the two cats at three different powers: 2.0, 1.5 and 1.0 w. Images were correlated with histopathology. Consistent well defined target-like lesions were seen in both the images and the histopathology. Four zones were identified: 1) core with some charring, 2) dense coagulation necrosis, 3) dispersed coagulation necrosis, and 4) morphologically normal brain tissue. Lesion sizes of approximately 0.5 - 1.0 cm increased proportional to the energy. Both T1 and T2 weighted images showed the lesion but T2w had better detail. The procedure induced well controlled hemispheric lesions that produced little evidence of cerebral edema and minimal neurological signs in the postoperative period. The data indicates that the method has significant potential for application to the destruction of spontaneous brain neoplasms.

14.

The Distribution of Granulophysin in the Nervous System

W.C. HALLIDAY, V.J. FORSTER and J.M. GERRARD (Winnipeg, Manitoba)

Granulophysin (GRPn) is a 40 kD glycoprotein identified in the membranes of platelet dense granules. Monoclonal antibodies have suggested an homology to the synaptosomal membrane protein synaptophysin (Gerrard, J Blood, 1991: 77(1): 101-112). Using immunohistochemical techniques, the distribution of GRPn in the pituitary gland and nervous system is studied. Immuno-reactivity is evident in cells of the adenohypophsis, Herring bodies of the posterior gland, ependymal, choroid plexus and endothelial cells. Peripheral and central myelin show reactivity, though not as intense as that seen in the above cells. Reactive astrocytes show variable reactivity. Meningothelial cells and corpora amylacea do not stain. Usually neurons do not stain for GRPn. In the adult brain, some neurons with lipofuscin show granular, GRPn immuno-reactivity in the areas with lipofuscin. Dystrophic/swollen axons stain for GRPn, as do neurons showing the axonal reaction. This study shows that GRPn is widespread in the pituitary gland and nervous system. In some cells (e.g., choroid plexus) it is normally present; in other (e.g., neurons) it appears to be inducible and present in reactive states.

15.

Pituitary Carcinoma Mimicking a Mesenchymal Tumor: A Problem In Diagnosis

E.S. JOHNSON (Edmonton, Alberta)

The diagnosis of carcinoma of the pituitary can be frought with difficulty as exemplified by this case of a 20-year-old woman with an anaplastic pituitary carcinoma that had evoked an unusual sclerosing stromal reaction. The patient presented with a short history of amenorrhea, headache, and right ophthalmoplegia, and was shown on CT scan to have a large sellar mass with suprasellar spread. Following surgical biopsy she underwent a course of radiation therapy, but 3 months after presentation was found to have malignant tumor cells in the CSF and metastases of the right cervical lymph nodes, spleen and liver. Treatment with systemic and intrathecal chemotherapeutic agents was commenced, but the patient responded poorly. Three weeks before death she received whole brain radiation for widespread CNS metastases. She died 6 months after her first presentation. The initial sellar biopsy showed a malignant neoplasm with an obliterative hyaline stroma that mimicked a mesenchymal tumor. Immunohistochemistry and electron microscopy were of little assistance in resolving the diagnosis. Biopsy of the cervical mass, however, revealed an undifferentiated carcinoma lacking a stromal reaction or any distinctive immunohistochemical and ultrastructural features. At autopsy the eroded hypophyseal fossa was enlarged by an amorphous fibrous mass containing necrotic tumor and extending into the right cavernous sinus to entrap the contents. Within the lep-

tomeninges there was a disseminated carcinomatosis that had a predilection for the spinal nerve roots. Other intracranial metastases included both cerebellar hemispheres, the left percentral gyrus, the left lateral ventricle, and the dura of the posterior fossa. Metastases beyond the CNS were found in the spinal epidural space, right cervical region, spleen and liver. The presence of a sellar mass and absence of alternate sites for a primary tumor in the viscera was in keeping with a pituitary carcinoma. Similar to the cervical biopsy, the carcinomatous metastases consisted of sheets of small polygonal cells with sparse cytoplasms and large, round nuclei with a prominent nucleolus. Immunohistochemical studies for pituitary hormones, chromogranin, and common epithelial marker proteins were negative. As with the initial sellar biopsy, however, in occasional deposits in the brain and liver there was an accompanying sclerosing hyaline stroma, which was sparsely cellular, lacked amyloid deposits, but contained a mesh of reticulin and collagen fibers in an acid mucopolysaccharide matrix. This case is exceptional because of the aggressive behavior of the tumor with sellar invasion, the presence of combined CNS and extra-CNS metastases early in the clinical course, and the penchant of the carcinoma to induce an unusual stromal reaction that camouflaged its true nature at initial biopsy.

16.

Optic Neuropathy in Patients with Systemic Cancer

H.J. MANZ, J. KATTAH, D.G. COGAN, M. KOLSKY, L. ZIMMERMAN and G. CHROUSOS (Georgetown, U.S.A.)

Twenty-one patients with systemic malignant neoplasms were followed after presentation with visual impairment; 10 of these came to necropsy. Visual loss was acute in 11 and subacute in 10 patients and was the initial symptom of systemic cancer in 5; in the remainder, the interval between initial diagnosis of cancer and visual impairment averaged about 2 years, most often visual acuity being reduced to finger counting or light perception. By CT scan, communicating hydrocephalus and skull metastases were seen in 3 patients each, and cerebral metastases in 2. Cytologic evaluation of CSF of 14 patients disclosed meningeal carcinomatosis in 11. Patients with intraocular and intracranalicular optic nerve metastases received glucocorticoids, irradiation, or systemic chemotherapy, while those with carcinomatous meningitis received the first 2 modalities plus intrathecal chemotherapy. Partial or complete improvement of vision occurred in 9 of 19 patients, but was long-lasting in only seven. Two patients with carcinomatous meningitis developed an encephalopathy after treatment, characterized by a chronic vegetative state. Nineteen eyes of the 10 autopsied patients were examined. Grossly, 5 eyes had papilledema, 2 optic disc mass lesions, 2 optic atrophy, and one optic pallor. Microscopically, carcinomatous leptomeningeal infiltration was seen in 6 patients; also evident were optic nerve infiltration (3), vascular invasion (3), optic nerve head metastases (2), optic nerve epidural invasion, and choroidal metastasis. Additionally, axonal fragmentation and loss and demyelination were present. Optic neuropathy of intraocular, intraorbital, intracanalicular, and intracranial segments was the commonest cause of blindness by a variety of mechanisms (infiltration, vascular invasion and nerve infarction, and nerve compression). Five patients had cerebral, cauda equina, or leptomeningeal metastases, and one cerebral and spinal epidural deposits.

17.

Recurrent Meningeal Fronto-Orbital Melanocytoma: Clinicopathological Features

J.B. LAMARCHE and D. LADOUCEUR (Sherbrooke, Quebec)

We report a case of recurrent meningeal fronto-orbital melanocytoma in a 20-year-old woman. She presented with left progressive exophthalmos dating back to infancy. CT scan showed a destruction of the left orbital roof, a left parasellar subfrontal mass and a left multilobulated intra orbital mass. At craniotomy, the fronto-parietal bone showed focal brown pigmentation. The temporal fossa and the orbital roof were lined by a thickened coal-black dura which extended toward the chiasmatic region where a non pigmented frontal extraparenchymal tumor was noted. A multilobulated partially pigmented mass was found in the orbit. Some ocular muscles and the orbital fat showed areas of black discoloration. Subtotal removal of the tumor tissue including infiltrated dura and bone was carried out. Except for residual exophthalmos, she remained asymptomatic for eight years. She was then seen at 12 weeks of pregnancy because of headaches. She had marked left exophthalmos with third nerve paralysis and optic atrophy. CT scan revealed a huge left fronto-orbital mass extending into the right frontal lobe. Two weeks after delivery, she underwent partial resection of the tumor which invaded the cavernous sinus, the floor of both orbits and the middle and pterygomaxillary fossa. Surgery was complicated by a right hemiplegia and aphasia. Left partial orbital exenteration was carried out 6 weeks later. Pigmented tumor tissue filled the orbital cavity infiltrating the lacrimal gland, the ocular muscles and the sclera. Ten months after surgery, the patient's condition remained stable. Light microscopic study of tissues from the 3 operations revealed amelanotic to melanotic histologically benign tumor with patterns reminiscent of schwannoma, meningioma, blue nevus and uveal melanoma. The ultrastructural features of the tumor cells were those of melanocytes with no evidence of meningothelial differentiation. Immunohistochemistry showed positive reaction for vimentin and S-100 protein and no reaction for epithelial membrane antigen, cytokeratin, neurofilament protein and glial fibrillary acidic protein. Although the prognosis is quite good in most cases of meningeal melanocytoma, local recurrences are not uncommon. Its infiltrating potential, well exemplified in this case, can lead to severe disability.

18.

Symptomatic Intradural Adrenal Adenoma of Spinal Nerve Root

A. MITCHELL, B.W. SCHEITHAUER, H. SASANO and M.J. EBERSOLD (Rochester, U.S.A.; Sendai, Japan)

The first case of an adrenal adenoma involving spinal nerve root, and the second within the intradural spinal compartment, is

described. The lesions arose from an L-1 nerve root in a 15-year-old female who presented with a 3 month history of gradually worsening pain involving the posterolateral aspect of the right thigh; no paresthesia or weakness had been noted. The intradural, extramedullary lesion was detected by myelography. Subsequent gross total resection was curative. The well-circumscribed red-brown mass was composed of patternless sheets of large polygonal, eosinophilic cells resembling oncocytes. No medullary tissue was noted. Portions of the mass were submitted for histochemical and immunohistochemical studies, the latter including stains for adrenal cortical steroidogenic enzymes and proliferating cell nuclear antigen (PCNA). Electron microscopy was also performed. Positive staining with numerous antisera to adrenal cortical enzymes was shown, including P450-11B, an enzyme limited to adrenal cortical cells. Ultrastructurally, the cells contained abundant smooth endoplasmic reticulum, mitochondria with tubular cristae, and scattered lipid vacuoles — all features characteristic of steroid synthesizing cells. These studies confirmed the adrenal cortical nature of the lesion. The presence of a rare mitosis as well as of occasional PCNA-immunoreactive nuclei, a feature not found in five control adrenal glands, supported the neoplastic nature of the mass and its designation as a true adrenal adenoma. Despite eleven year follow-up, there have been no symptoms or evidence of recurrence.

19.

Foix-Alajouanine Syndrome: A Unique Presentation

N.B. REWCASTLE, M.G. HAMILTON, J. KRCEK and M. HUNTER (Calgary, Alberta)

The Foix-Alajouanine Syndrome (FAS) reflects a chronic progressive radiculomyelopathy resulting from a presumed diffuse vascular malformation of the spinal cord involving the thoracolumbar segments. Here we wish to document and discuss a unique example of FAS involving predominantly the cervical segments of the spinal cord that occurred in a 62-year-old male who presented with a rapidly progressive cervical radiculomyelopathy. CT, myelogram and cervical laminectomies that exposed the spinal cord from C4 to C7 gave no indication as to the etiology. Likewise, a biopsy demonstrated only gliosis. Post operative CT and myelography demonstrated adequate decompression and MRI only non-specific changes in the cord extending from C6 to the lower medulla. Unrelenting deterioration resulted in death from pulmonary sepsis five months after the initial onset. Autopsy revealed a diffuse venous malformation of the spinal cord, spinal roots and lower medulla. Sclerosis of parenchymal vessels was associated with multi-focal infarctions of varying age, the brunt of these infarctions affecting the cervical spinal cord and the lower medulla. There have been no other descriptions of FAS of the cervical cord.

Dural arterial venous malformations (AVM) that drain via root and spinal cord venous plexus may be associated with ischemic damage to the spinal cord somewhat similar to that occurring with FAS. However, few dural AVMs have been described affecting the cervical dura. Dural AVMs and venous malformations can be differentiated angiographically. Unfortunately, selective angiography was not performed in this patient because myelography, CT, MRI and direct inspection of the surface of the spinal cord at surgery gave no indication of a vascular malformation as the basis of the myelopathy. In the absence of a definable pathological process explaining progressive radiculomyelopathy, the diagnosis of FAS must necessitate further elucidation of its cause by exclusion of a dural AVM by both the clinican and the pathologist.

20.

Idiopathic Acute Necrotizing Granulomatous Myopathy

P.E. HUANG (Michigan, U.S.A.)

Granulomatous muscular disease is uncommon and is a source of particular interest to clinicians and pathologists. Possible etiology includes sarcoidosis and a wide variety of disorders. Nodular mass lesions may be seen in sarcoidosis. Myofiber necrosis with neutrophils and elevated CPK levels, however, is unusual. A previously healthy 34-year-old white female presented with acute onset of spiking fever, myalgia and cramps in the thighs, progressed to profound proximal muscle weakness with swollen tongue, a discrete sternocleidomastoid mass, and a weight gain of 10 lbs. in two weeks. The past history was negative for drug abuse, transfusion, alcohol, raw meat, shell fish, L-tryptophan consumption, or travel exposure to parasites. There were no symptoms related to other systems and no evidence of a connective tissue disease. EMG including repeated stimulation was reported to be normal. CPK was markedly elevated. All viral titers and infectious work-ups were negative. The muscle biopsy showed extensive myofiber necrosis with numerous neutrophils, macrophages, multinucleated giant cells and rare eosinophils replacing necrotic fibers, and in a perimysial distribution. No regenerative activity was noted. There was no evidence of vasculitis. Special stains for microorganisms were all negative. By electron microscopy, the multinucleated giant cells had features of histiocytes with increased number of mitochondria, membrane-bound granules and remains of degenerating myofibrils. The vascular endothelial cells also showed degenerative changes. No viral inclusions were found. She responded dramatically to steroid with CPK levels returning to normal abruptly in 48 hours. This was followed by an unexplained sudden onset of completely asymptomatic bradycardia in the range of 30's per minute, which reversed suddenly four days later. The neck mass and tongue swelling resolved, and she was discharged on steroid with some residual weakness. All known causes excluded, the pathogenesis remained elusive. The dramatic response to steroid treatment may suggest an immunologic etiology.

21.

Phosphofructokinase Deficiency: A Report of Five Cases

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Phosphofructokinase (PFK-1; EC 2.7.1.11) deficiency in infancy is rare. Reported cases have had a dismal outlook, prompting categorization of this disease among the fatal infan-

tile glycogenoses. Of the 6 cases reported in the literature, prominent findings have included arthrogryposis in three, generalized weakness in two, and neuroaxonal dystrophy in one. We report five cases of phosphofructokinase deficiency all presenting with arthrogryposis; in two patients, spastic posture of the lower extremities was detected by fetal ultrasound. Three of these cases are Canadian native infants, two of which are siblings from consanguineous parents. Two others are siblings but consanguinity is not certain; these two cases also showed hepatomegaly and cardiomyopathy. EMG findings were consistent with a myopathy. All but one infant died before two months of age. Survival to 30 months of age is noted in one case. This infant continues to do relatively poorly, with limited social development and severe neuromuscular disability despite corrective orthopaedic procedures. Muscle biopsies were examined in four, and postmortem muscle samples were available for two. Common histological findings include random variation in fibre sizes with variable endomysial fibrosis. Subsarcolemmal vacuoles, often detected in the cryostat sections, are filled with excessive amounts of morphologically normal β-glycogen particles. One case showed non-membrane bound, fine filamentous material. Biochemical confirmation was achieved in three, with increased glycogen and 0 - 5% residual PFK activity. Arthrogryposis with limited limb mobility affects the majority of these and other reported infants; this has been detected in utero in two of our cases permitting a prenatal suspicion of the diagnosis. Karyotype was normal in four out of the five patients. While our understanding of this disease and its various manifestations has broadened in the last decade, the full spectrum of the infantile phenotype is still not known until more cases are thoroughly described. Genetic heterogeneity is almost certain.

22.

Dystrophin Analysis of Fetal Muscle: Report of Three Cases Including One Case of In-Utero Muscle Biopsy

V. JAY, L. BECKER, M. HO, C. ACKERLEY, J. SUTHERLAND and P. RAY (Toronto, Ontario)

There are limited references in the literature with regard to dystrophin analysis of fetal tissues. There are no significant morphological differences between normal and Duchenne muscular dystrophy (DMD) fetal muscle. We describe three cases where fetal skeletal muscle samples were studied by dystrophin immunohistochemistry. Molecular analysis of a chorionic villus sample revealed a deletion of exon 44 of the dystrophin gene in case #1, a male fetus with a family history of DMD. Molecular analysis of a chorionic villus sample in case #2, a male fetus, revealed the same deletion in the dystrophin gene as his mother. Case #3 is a male fetus with a sister affected with DMD, with no deletion detectable.

Skeletal muscle samples were obtained from therapeutic terminations in cases #1 and #2 at 14 weeks, while an in-utero gluteal muscle biopsy was obtained from case #3 at 18 weeks. The proximal and distal muscles from both extremities (cases #1, 2) and the gluteal muscle biopsy (case #3) were studied by the following antidystrophin antibodies using the immunoperoxidase technique: "N" terminal antibody 9219, "C" terminal antibody 1461, and commercial N, midrod domain, and C terminal antibodies (Novocastra). In case #3, a continuous sarcolemmal rim of immunoreactivity was observed with all 5 antibodies. In cases #1 and #2, normal sarcolemmal staining was obtained with the "N" terminal antibody 9219 with complete absence of staining with the "C" terminal antibody 1461 and the commercial N, midrod, and C terminal antibodies. Immuno-electron microscopy confirmed absence of dystrophin in cases #1 and #2 using the "C" terminal antibody 1461.

These results indicate that although there may be no apparent morphological abnormalities in DMD fetuses, abnormalities of dystrophin are detectable by immunohistochemistry even in the fetal stage. The finding of normal staining with the "N" terminal antibody and absence of staining with the "C" terminal antibody in known DMD fetuses is of interest and underscores the importance of using antibodies with specificities to different regions of the dystrophin molecule for evaluation of fetal samples.

23.

Neuronal Changes in HIV Infection

I.P. EVERALL, P.J. LUTHERT, E. SPARGO, F. GRAY and P.L. LANTOS (London, U.K.; Cretei, France)

Although the cerebral pathology of AIDS has been extensively studied, little is known about neuronal changes caused by HIV-1. Since a high percentage of AIDS patients develop dementia, the study of the underlying cellular pathology is of paramount importance. Neuronal populations were quantitatively assessed using a stereological technique (known as the disector) in four neocortical areas of 12 AIDS patients with HIV encephalitis or with minimal pathology, and compared with controls. Significant neuronal loss of 38% was found in the frontal cortex, 30% in the occipital cortex and 18% of the superior parietal lobule, but not in the temporal cortex. This neuronal loss was not related to HIV encephalitis and also occurred in the brains with minimal pathology. Interestingly, there was no significant neuronal loss in the four regions of the hippocampus.

Neuronal populations were also assessed in asymptomatic HIV infection. In a cohort of 14 HIV-positive intravenous drug users, who did not have any evidence of AIDS, AIDS-related complex and HIV associated neuropathology, there was no significant neuronal loss in the superior frontal gyrus when compared to age-matched controls.

From these findings the following important conclusions can be drawn: 1) there is significant neuronal loss in various neocortical areas in AIDS, 2) this neuronal loss occurs irrespective of HIV encephalitis, 3) various neocortical areas show different susceptibility which may be due to particular neuronal populations using different neurotransmitters, 4) neuronal damage develops late during HIV infection, thus allowing the administration of potential therapeutic agents to asymptomatic individuals to prevent or reverse neurotoxicity before neuronal loss occurs.

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Finally the mechanism of dementia associated with AIDS is more complicated than previously thought and neuronal loss plays an important role in the cognitive impairment of HIV infection.

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24.

Subacute Panencephalitis Associated With Chronic GVHD

Y. IWASAKI (Sendai, Japan)

The CNS has been generally thought to be spared in graft versus host disease (GVHD) but CNS involvement has recently been implicated in two fatal cases of chronic GVHD. In addition, in acute experimental GVHD, strong expression of MHC class I and II antigens in the microglia and endothelial cells in conjunction with sparse infiltration of T lymphocytes have been reported in the CNS of F1 hybrid rats injected with parental lymphocytes. Thus, activation of monocyte/macrophage lineage cells and endothelial cells in accordance with infiltration of T lymphocytes into the CNS may not be so rare in GVHD as it has been thought, although it remains dormant in most cases.

Now we report the development of a unique form of subacute panencephalitis in a child with aplastic anemia eight months after an allogeneic bone marrow transplantation (BMT). Twenty-one months prior to his death at nine years and nine months, the patient received BMT from his HLA-identical, MLC non-reactive sister. Thirty-two days after the BMT, he developed systemic erythema, followed by severe diarrhea and hypoalbuminemia, which were ameliorated by continuous immunosuppressive therapy and intravenous hyperalimentation. Eight months after the BMT, a fever and systemic erythema developed suddenly, followed shortly by episodes of clonic seizures and progressive clouding of consciousness and spasticity of the four extremities. The MRI was normal one month after the onset of seizures but generalized cortical atrophy and dilatation of the entire ventricular system were evident three months later. General autopsy disclosed diffuse parenchymal infiltration of CD3 lymphoytes, a marked increase in the number of microglia strongly expressing HLA-DR antigens in both the grey and white matter, and diffuse degeneration of the cerebral white matter. Myelin sheaths were more severely affected than axons but there was no tendency towards perivenous demyelination. Cellular infiltrates in the CNS lesions were exclusively CD3 lymphocytes intermingled with a small number of monocytes labeled with CD68. There was a preponderance of cells of the CD45RB phenotype. The pathological changes in visceral organs were consistent with those of chronic GVHD.

In addition, scrutiny of immunohistochemistry disclosed sparse infiltration of CD3 lymphocytes and diffuse gliosis in the cerebral white matter of another child with chronic GVHD. This 13-year-old girl died nine months after allogeneic BMT from HLA-matched, MLC-negative brother. These cases provided solid evidence for the suggestion of the potential risk of CNS involvement in GVHD.

25.

Induction of Function-Related Morphological Changes of Microglia by Glia-Produced Cytokines in Culture

C. HAO (London, Ontario)

We have demonstrated a paracrine relationship between astroglia production of CSF-1 and the response of microglia to this cytokine in culture (Hao et al., J Neurosci Res 27: 364-323, 1990). Now we report that, after we examined the microglia in different culture conditions, we found that the cytokines, produced by astroglia as well as microglia, regulate the function and morphology of the microglia. In a purified microglia culture to which 100 U/ml of CSF-1 or 50% astroglia culture conditioned medium is added, the microglia appear as irregularly shaped cells with many processes. They are phagocytic, secrete lysozyme and have a high degree of motility and a very low degree of mitotic activity. When transferred to an astroglia colony culture which generates less than 10 U/ml of CSF-1 in the medium, these microglia lose their phagocytic ability and their high degree of motility, although they still keep their irregular shape with processes. The microglia can become long, bipolar and crescent-shaped cells with a high degree of mitotic activity, after being stimulated with 1000 U/ml of CSF-1. When simulated to 10 μg/ml of LPS, the microglia lose their processes and develop extensive lamellipodial projections and become ameboid cells. These microglia are high phagocytic, release lysozyme into medium and have a high degree of motility and zero degree of mitotic activity. In this culture medium, we can detect about 100 U/ml of CSF-1 and 0.5 μg/ml of TNF-α. The TNF-α is antagonistic to the CSF-1 effect on microglia proliferation. We speculate that these cytokine-induced changes in microglia may occur *in vivo* so that the cells can be expressed as ramified or ameboid types of microglia under different conditions.

I wish to express my gratitude to my supervisor, Dr. Sergey Fedoroff, for his valuable advice, constant encouragement and friendship throughout the course of this study.

26.

Basic Fibroblast Growth Factor Improves Recovery After Demyelination in Pure Oligodendrocyte Cultures

C. FRESSINAUD and J.M. VALLAT (Limoges, France)

In order to investigate the putative role of growth factors in remyelination, we created a model of toxic attack of myelin and oligodendrocytes (OL) in pure myelinating OL secondary cultures derived from newborn rat brain. A 24 hour treatment with 2.10^{-5}M lysophosphatidyl-choline (LPC) induced a loss of 59% of the cells in these cultures and the proliferation decreased by 64% compared to untreated control. The entire OL lineage was affected by this compound as proved by immunocytochemical studies. The remaining cells lost their processes and showed numerous intracytoplasmic inclusions and disruption of myelin membranes evidenced by transmission electron microscopy.

Daily treatment with 10 ng/ml basic fibroblast growth factor (bFGF) induced after 3 days a better recovery than in cultures treated with LPC only: the number of cells doubled and the proliferation increased. This recovery was essentially due to the proliferation of 0-2A progenitors. Ultrastructural study revealed that remyelination was in progress after bFGF treatment, nevertheless myelin appeared uncompacted. On the contrary, the cells still presented numerous cytoplasmic inclusions and myelin was absent in cultures treated with LPC only.

27.

Infantile Cerebello-Optic Atrophy in the PEHO-Syndrome

M. HALTIA and M. SOMER (Helsinki, Finland)

The PEHO syndrome (Progressive encephalopathy with Edema, Hypsarrhythmia, and Optic atrophy) is a new clinically defined entity characterized by infantile spasms, severe hypotonia, profound psycho-motor retardation, transient or persistent subcutaneous edema, and blindness (Salonen et al., Clinical Genetics 39: 287-293, 1991). The distribution of patients in the affected families is compatible with autosomal recessive inheritance. The onset of symptoms is from 2 weeks to 4 months; pregnancy and delivery are normal, and most patients have been considered normal during their first weeks of life. Extensive biochemical investigations have failed to identify specific abnormalities. The patients may live in a vegetative state up to an age of 15 years.

Uniform neuropathological changes were seen in 8 autopsied patients, including 4 familial cases. The most characteristic feature was severe cerebellar atrophy, most pronounced in the vermis. The inner granular layer was either totally absent or showed a sparse population of scattered neurons. The Purkinje cells were relatively preserved in number, but they were small in size and had either stunted or deformed, often horizontally oriented dendrites. The molecular layer was extremely thin. The optic nerves showed loss of myelinated axons.

This combination of clinical and histopathological findings is not compatible with any previously established disease and suggests a new autosomal recessive disorder with distinctive neuropathological findings.

28.

Cadmium Encephalopathy: A Case Report

J. PROVIAS, C. SMITH and L.E. BECKER (Toronto, Ontario)

A number of heavy metals are known to be toxic to the human nervous system, the best studied being lead. Cadmium is a known heavy metal pollutant which has been shown to produce neuropathologic damage in experimental laboratory animals. In addition, a number of cases of human chronic cadmium toxicity are reported, with pathologic changes documented in both bone and kidney but not brain. We present the case of a 2-year 10-month-old boy of East Indian origin who died suddenly and unexpectedly. Autopsy findings showed marked cerebral swelling with herniation and histologic evidence of marked cerebral edema with perivascular protein leakage indicating blood-brain barrier disruption. X-ray probe elemental analysis of the brain showed marked accumulation of cadmium, predominantly intracellular, both within endothelial cells and to a lessor degree neurons. Subcellular localization was predominantly intranuclear. Similar analysis also showed a significant pathologic deposition of cadmium in renal glomeruli. Although the environmental source of cadmium remains unknown, we speculate that acute cadmium toxicity led to brain capillary endothelial accumulation with resultant cell dysfunction, blood-brain barrier disruption and lethal cerebral edema.

29.

Relative Rates of Migration and Proliferation Define Histologic Patterns of Gliomas

E.C. ALVORD, JR., C.-M. SHAW and T.L. RICHARDS (Seattle, U.S.A.)

It seems obvious that the longer the interval of time between mitoses, the longer the daughter cells have not only to differentiate but also to migrate. Growth rates of solid tumors can be measured by the "tumor volume-doubling time", but the concept of a "tumor volume-doubling time" can hardly apply to most gliomas, which are usually more or less infiltrative of the surrounding brain tissue. Marked improvements in diagnostic imaging techniques have enabled clinicians and neuropathologists to see gliomas at much earlier stages, even before "mass effects" develop with displacement of vascular or ventricular structures. Especially with oligodendrogliomas, the histologic sections frequently contain mixtures of normal and reactive elements and relatively small percentages of neoplastic cells, although occasionally one sees small foci of densely packed tumor cells.

In an attempt to understand how these patterns might develop, we explored mathematical models in which various types and amounts of migration of cells were permitted between each division. Migration was considered in terms of direction (i.e., random or restricted, not towards each other) and extent (i.e., number of cell-diameters) but for simplicity was restricted to 2 dimensions with only 8 possible positions for a cell to move to from any one point. Rather surprisingly to us naifs, but predictable according to others more knowledgeable about statistics, the center of what had previously appeared to be a diffuse distribution of cells suddenly became completely filled in. The number of cell divisions necessary to produce such a solid center was directly proportional to the number of migration steps permitted between "mitoses". With a ratio of 20:1, after 13 divisions producing 8,192 cells, the solid zone had a diameter of about 100 cells and contained about 90% of the cells. Assuming 10-micron cells, one would calculate such foci to be about 1 mm in diameter *in vivo* — approximately what one occasionally observes. Once such a focus develops, the pattern of migration must change, but how? Does migration cease and these foci grow as expected of "solid tumors"? Or, does migration become directed outward, away from these foci with their presumably higher metabolic demands?

30.

Chromosome Analysis of Pediatric Brain Tumors

D.P. AGAMANOLIS, J.M. MALONE, S.A. ARNOLD, R.W. NOVAK and J.R. WATERSON (Akron, U.S.A.)

We studied chromosomes from 37 primary pediatric brain tumors; 10 pilocytic cerebellar astrocytomas, 3 low-grade cerebral astrocytomas, 5 anaplastic astrocytomas/glioblastomas, 8 cerebellar medulloblastomas, 1 cerebral neuroblastoma, 1 pineocytoma, 6 ependymomas, 1 meningioma, 1 immature cerebellar teratoma and 1 cerebellar astrocytoma with epithelial differentiation. Ten tumors showed clonal abnormalities (three cells with the same missing chromosome or two cells with the same extra chromosome or structurally abnormal chromosome), 7 had a normal karyotype and 20 showed non-clonal structural and numerical abnormalities. Among the 10 pilocytic cerebellar astrocytomas, 1 had a clonal 16q deletion, 3 were normal and 6 showed non-clonal structural and numerical abnormalities including polyploidy and losses of chromosomes 16, 17 and 22. Among the 5 high-grade astrocytomas, two showed abnormal clones including double minutes, polyploidy, gain of chromosome 7 and loss of chromosome 22. One high grade astrocytoma was normal and 2 had non-clonal abnormalities including 17p deletions. Two medulloblastomas had clonal abnormalities including polyploidy, and multiple markers and one also had a 17q isochromosome. One medulloblastoma was normal and 5 had non-clonal autosomal monosomies and deletions.

Chromosomal and molecular analysis is important for understanding mechanisms leading to oncogenesis. Our series is the second largest series of pediatric brain tumors with chromosome studies reported. The proportion of clonally abnormal tumors is smaller than in other series but non-clonal abnormalities are frequent and similar to those reported previously. However, based on our results and those reported in the literature, in the majority of pediatric brain tumors, there is no specific correlation between the karyotype and histological type of degree of malignancy.

POSTER PRESENTATIONS

P1.

Pathogenesis of Mineralization in Sturge-Weber Syndrome: Analysis of Resected Cortex, Utilizing Light Microscopy, Stem, and X-Ray Microprobe Analysis

J. PROVIAS, C.A. ACKERLEY, V. JAY and L.E. BECKER (Toronto, Ontario)

Sturge-Weber syndrome is a sporadic phakomatosis characterized by a severe seizure disorder and an underlying abnormal leptomeningeal vascular plexus and varying degrees of hemispheric atrophy, astrogliosis, and mineralization. Previous studies have been morphologic and descriptive with particular emphasis on possible abnormalities of blood vessels. Astrogliosis is often surprisingly minimal considering the extent of mineralization. There is little understanding of the pathogenesis of mineralization. An analysis was undertaken of surgical corticectomy specimens from seven patients with Sturge-Weber syndrome with intractable seizures. Scanning electron microscopy, transmission electron microscopy, and X-ray microprobe analysis indicates the presence of more extensive mineralization than is appreciated with conventional histology. Microprobe analysis showed significant deposition of aluminum in many foci, in addition to the expected calcium and phosphate. The mineralization was present in many forms including free neuropil concretions and deposits in neuronal soma, neuritic processes, and perivascular foci. Calcium was found almost exclusively in association with phosphate in the form of hydroxy apatite crystals. The co-deposition of aluminum in many foci was an unexpected finding seen in all cases examined, and absent in normal and pathologic (other diseases with calcification) controls. It is hypothesized that the altered blood flow in the abnormal leptomeningeal vascular plexus may lead to chronic low-grade cortical ischemia with subsequent tissue acidosis creating the optimum micro-environment for aluminum precipitation together with calcium phosphate deposition.

P2.

Ultrastructural Properties of Corpus Amylaceum

L. LEEL-ŐSSY (Esztergom, Hungary)

Electronmicroscopical (EM) studies afforded valuable findings considering the origin and development of the corpus amylaceum (CA) as follows: 1. A very close connection may be demonstrated between the intracytoplasmicastrocytic fibres and the early form of CA. 2. The glycogen and/or polyglucosan granules found in the border zone of CA supposed to be as a "triggering" materials in the development of CA. The granules contain mannose and glucose residues and they may be later on the component of CA which mainly consist of astrocytic fibres. 3. The origin of CA may probably be multifocal even in one astrocyte where they can fuse each other. This coalescence enlarges gradually the CA and finally it may completely destroy the cell. The glycogen and/or polyglucosan are partially derived from rough endoplasmic reticulum, the Golgi apparatus and hypolemmal cisternae. 4. The predilection sites sometimes overcrowded by a great number of CA which make impossible the identification of the original structures. The neural elements: neuron, axon, myelin, astrocyte, etc., may hardly be recognizable. It remained an unsolved question whether the tremendous quantity of CA in some regions: hippocampus, fornix, anterior medullary velum, marginal zones of the medulla and spinal cord, perivascular spaces can secondarily disturb the function of these structures or not. 5. The proximity of the CA to the brain-liquor barrieres raises the question of the increased activity in glucose turnover of these places which may be decrease or may become insufficient in different conditions: aging, chronic ischemic lesions, degenerative processes, multiple sclerosis, etc. If this insufficiency relates to a specific enzyme defect it may cause the "polyglucosan body disease" or amylopectinosis. The EM studies demonstrate the different phases of the forming of CA which have not yet been examined.

P3.

Further Immunohistochemical Study of Neurofibrillary Tangles in Parkinsonism-Dementia Complex on Guam

A. HIRANO, S. KATO, T. KAWANAMI and S.-H. YEN (Bronx, U.S.A.)

Parkinsonism-dementia complex (PDC) on Guam is characterized by abundant neurofibrillary tangles (NFTs) in the perikarya of affected neurons unassociated with senile plaques (SPs).

In previous immunohistochemical studies, NFTs were revealed using antibodies to tau protein, paired helical filaments (PHF), ubiquitin in the cerebrum, brain stem, and spinal cord in PDC on Guam. Those studies also demonstrated small number of SPs, mostly diffuse plaques, and β amyloid protein-containing NFTs (β-NFTs) in the cerebrum in some of the elderly patients with PDC on Guam.

This report confirms the absence of any amyloid deposits including β-NFTs in two younger patients with PDC on Guam below age 60, and shows absence of any amyloid deposits including β-NFTs in the brain stem which have glial fibrillary acidic protein (GFAP)-positive NFTs, and in the spinal cord. On the other hand we found β amyloid deposits in the perinuclear area corresponding to what appears to be intracellular NFTs in some of the neurons in the temporal cortex of some elderly patients with PDC on Guam.

NFTs in the dentate fascia of the hippocampus in Alzheimer's disease (AD) were already reported (Dickson et al., 1986, Kato et al., 1989). However they have not been reported in PDC on Guam. We found argyrophilic, tau-positive various shaped cytoplasmic inclusions in the dentate fascia in PDC on Guam, similar to those in AD.

Support in part by a grant from the Amyotrophic Lateral Sclerosis Association.

P4.

Superoxide Dismutase Positive Hypertrophic Astrocytes in Pathological Tissues of Human Brain

N. SHIBATA, A. HIRANO and M. KOBAYASHI (Bronx, U.S.A.; Tokyo, Japan)

It is generally recognized that every aerobic life physiologically produces toxic superoxide. It has been pointed out that superoxide may take part in several pathological states because excessive accumulation of intracellular superoxide usually disturbs normal metabolism of the cell. Superoxide dismutase (SOD) which scavenges superoxide and converts it to hydrogen peroxide, is essential for normal cellular metabolism. We investigated immunoreactivity for Mn-SOD (one type of Isozyme of human SOD) in pathological brain tissues of human autopsy cases. These included cerebral infarction, anoxic encephalopathy, multiple sclerosis and progressive multifocal leucoencephalopathy. Anti-human Mn-SOD rabbit polyclonal antiserum (provided by Dr. K. Asayama, Department of Pediatrics, Yamanashi Medical College, Japan), anti-rabbit biotinylated goat antibody and avidin-biotin complex were used in immunostaining paraffin sections of all cases. Immunoreactivity was visualized by diaminobenzidine. We clearly observed that hypertrophic astrocytes in these lesions have strong reactivity for Mn-SOD. This is shown as granular structures in their cell body and processes. Normal astrocytes far from lesions had no or only a little immunoreactivity for Mn-SOD. Some neurons, oligodendroglias, microglias, macrophages, leurcocytes and erythrocytes also showed weak reactivity for Mn-SOD in several regions. These results of this study suggest that hypertrophic astrocytes which increase the scavenging capacity of superoxide may plan a certain role in pathological processes.

P5.

The Incidence of Dysembrioplastic Neuroepithelial Tumors (DNT) in a Pediatric CNS Tumor Series

A.L. TARATUTO, G. SEVLEVER, G. GALLO, H. POMATA, J. MONGES and M. SCHULTZ (San Remo, Italy)

Overtreatment by radiotherapy and/or chemotherapy of CNS tumors in infancy and childhood may well be deleterious so that recognition of surgically curable clinicopathological entities is mandatory. DNT, first delineated by Daumas Duport at Saint Anne Hospital, Paris (personal communication, 1984), was later extensively reported in a larger series (Daumas Duport et al., Neurosurgery, Vol 23:5, 1988) as a supratentorial cortical multinodular lesion, heterogeneous in cellularity, including neurons, astrocytes and oligodendrocytes occurring in young patients and associated to intractable partial complex seizures without neurological deterioration. Histologically, more complex DNT were further reported occurring in the same clinical setting (Daumas Duport, San Remo, Italy, September 1990). We here report 9 cases, age range 2½ - 13 yrs; mean 6.83 yrs; M/F ratio: 6/3; time of onset of clinical signs ranging from 15 d - 6 yrs, mean 2 yrs. Four were frontal, 4 temporal and 1 occipital. CT scans disclosed hypodense pseudo-cystic lesions, in 2 cases showing focal post-contrast enhancement. Deformity of the overlying skull was also observed in two cases. Three out of nine were referral cases from other pediatric hospitals; the other six were from a series of 350 CNS tumors in infancy and childhood from 1988 to 1992 (Hospital Nacional de Pediatria). Tumor was suspected on clinical grounds in the last 2 out of 9 cases and intrasurgical diagnosis performed in smears in 3 cases. Within mucoid matrix in most of our cases, NSE, NF, MAP 2, synaptophysin and beta-tubulin Mab immunostaining confirmed the obvious neuronal component, while GFAP and S100 did so with the glial one. PCNA L1 ranged from 0.38% — 5.23%, mean 1.70%, S/D 2, median 1. In two cases of subtotal resection, follow-up CT scanning failed to reveal significant growth, while the other seven patients have had no recurrence to date.

Awareness of this clinicopathological entity is essential for therapeutic and prognostic purposes.

P6.

193 Surgically Removed Pituitary Adenomas: A Histologic, Immunocytochemical and Ultrastructural Study

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This paper summarizes our experience on pituitary adenomas in Mexico City. We have collected 193 surgically removed pituitary adenomas from 2 hospitals from 1987 to 1990. The tumors were investigated by histology, immunocytochemistry using the avidin-biotin-peroxidase complex technic and by electron microscopy.

There was slight female preponderance; 110 (57%) were women and 83 men (43%). The age of the patients varied from 13 years to 76 years; the average was 41 years. Two surgical approaches were applied: 164 patients (85%) were operated via transsphenoidal route whereas in 19 patients (15%), the tumors were resected by transcranial surgery. Chromophobic adenomas represented the most common histologic type; 98 tumors (51%) belonged to this group. We have identified 31 acidophilic (16%) and 9 (4%) basophilic adenomas; 57 (29%) tumors contained chromophobic and acidophilic or basophilic cells. Clinically 100 patients (52%) showed signs of hormone excess. In 93 patients (48%) endocrine alterations were not evident. Galactorrhea and/or amenorrhea was noted in 45 hyperprolactinemic patients (23%). Acromegaly was diagnosed in 43 patients (22%) and Cushing's disease in 10 patients (5%). Two patients (1%) had signs of hyperthyroidism. Immunocytochemistry revealed that 64 (33%) contained only one hormone whereas 99 adenomas (51%) were immunoreactive for 2 or more hormones. Thirty tumors (16%) were pluri-hormonal. In patients with hyperprolactinemia; 27 adenomas contained only prolactin, 10 adenomas were immunoreactive for 2 hormones and 8 were immunopositive for more than 2 hormones. In patients with acromegaly; 14 adenomas contained only growth hormone, 9 adenomas were immunoreactive for 2 hormones and 20 adenomas were immunopositive for more than 2 hormones. In patients with Cushing's disease; 8 adenomas contained only ACTH and 2 adenomas were found to be plurihormonal. By ultrastructural analysis, a strong correlation was found between electron microscopic findings, clinical presentation and immunocytochemical features. The present work is the first in Mexico which report findings on surgically removed pituitary adenomas, based on a correlative histologic immunocytochemical and ultrastructural study.

P7.

Late Onset Pineoblastoma with Pineocytic Differentiation

D.L. SCHULTZ and T.E. HUANG (Michigan, U.S.A.)

Pineoblastoma is a rare primitive neuroectodermal tumor, usually occurring in the younger age groups. It is locally aggressive with a rapid clinical course and short survival. We present an unusual case of pineoblastoma with pineocytic differentiation in a previously healthy 75-year-old woman who was found confused at home following a one day history of headache. Computed tomography revealed a large central mass with scattered calcifications, intraventricular hemorrhage, obstructive hydrocephalus, and superior distortion of the quadrigeminal plate and brain stem. It was isodense by magnetic resonance imaging and showed a brief tumor blush by cerebral angiography. Refusing a brain biopsy, a ventriculoperitoneal shunt was placed and she improved remarkably on Decadron therapy. Increasing lethargy brought her back to the emergency room one month after discharge. She became comatose with decerebrate posturing and died one month later. Autopsy revealed a massive central brain tumor with extensive hemorrhage and necrosis. Microscopically, the tumor was predominantly composed of densely packed primitive cells with extensive necrosis and small scattered foci forming pineocytic rosettes. There was local infiltration of the adjacent parenchymal structures by pineoblastomatous cells. Immunoperoxidase stains for neuron specific enolase, synaptophysin and chromogranin were positive in the pineocytomatous rosettes, but only neuron specific enolase was positive in the pineoblastomatous cells. The late age at onset and the long presymptomatic duration of the tumor were unusual. Extensive necrosis and acute hemorrhage in the tumor accounted for the rapid terminal course. The pathogenesis is to be discussed.

P8.

Neuronal Chromatolysis in a Case of Colchicine/Podophyllin Toxicity with 12 Day Survival

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Colchicine and podophyllin bind to tubulin and depolymerize microtubules. Experimentally colchicine can produce effects resembling those of axotomy (Science 1972; 177: 1116) and induce perikaryal filament accumulation (Lab Invest 1967; 17: 577). Fatal toxicity with either agent in humans is uncommon and the neuropathology poorly defined. Encephalopathy and peripheral neuropathy have been reported both for colchicine (Ann Emerg Med 1981; 10: 364) and for podophyllin (J Toxicol Clin Toxicol 1982; 19: 35). In the present case, the neuropathologic changes were dominated by neuronal chromatolysis, reminiscent of colchicine effects previously described only in experimental settings.

A 37-year-old man died 12 days after ingesting a colchicine/podophyllin solution, as well as alcohol and other drugs. The clinical course supported the diagnosis of colchicine toxicity: cardiogenic shock, acute renal failure, respiratory distress, thrombocytopenia, and rhabdomyolysis. General autopsy findings included a necrotizing pneumonia, acute renal tubular necrosis, and hepatic and splenic congestion.

Except for a focal old contusion, gross examination of the brain was unremarkable. The salient microscopic changes were swelling and chromatolysis affecting most of the lower motor neurons of the lumbosacral spinal anterior horns, a minority of those in the cervical anterior horns, occasional neurons of the posterior horns, a focus of Betz cells in motor cortex, and a few neurons of the cingulate cortex. Ultrastructurally, the spinal anterior horn cells contained markedly increased numbers of filaments resembling neurofilaments but randomly arranged and admixed with other cytoplasmic organelles.

The widespread chromatolytic changes described here are distinctive, and consistent with known neuropathic effects of colchicine. Because podophyllin and colchicine have similar mechanisms of action, both agents may have contributed to the changes. Chromatolysis, particularly in spinal anterior horn cells, may be a hallmark of colchicine or podophyllin intoxication when death is delayed for several days following exposure.

P9.

The Natural History of Childhood Hypotonia and Muscle Weakness Associated with Type I Muscle Fibre Predominance

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In the course of investigating children with muscle weakness and hypotonia, muscle biopsy of the vastus lateralis not infrequently demonstrates greater than 55% predominance of the aerobic histochemical type I fibres, or "Pure Type I Fibre Predominance" (T1FP) with no other changes. The significance of an initial biopsy diagnosis of T1FP is not well understood. At present "pure T1FP" is not regarded as a disease entity and it is known that many of the defined childhood muscle disorders such as nemaline myopathy or central core disease occur on a "background" of T1FP. In order to determine the natural history of "pure T1FP" as the presenting feature, a search was made of the records held in the Royal Perth Hospital Neuropathology Department and it was found that 27 of the 155 patients aged 0 - 20 years who were biopsied between 1980 - 1990 had T1FP. Review of their outpatient follow-up records showed that 13 of these patients subsequently had a more specific diagnosis applied (12 CNS disease: 1 muscle). These "primary" disorders became manifest subsequent to the muscle biopsy taken during infancy when the child was merely "floppy". Four patients had T1FP and were asymptomatic, biopsied because a first degree relative was susceptible to malignant hyperpyrexia (MHP); all had remained clinically normal though 3 were found to be susceptible to MHP on biochemical testing. The 10 remaining patients who had no new diagnosis applied other than T1FP, were re-examined clinically. Of these, 2 had improved to normality, 5 had improved but had persisting neuromuscular abnormality, and 2 were unchanged after mean follow-up of 5.7 years. None was more than mildly incapacitated. One could not be located for follow-up. The findings of this study provide prognostic information which may be used by paediatricians when the diagnosis of T1FP is first made in a floppy infant.

P10.

Chiari II Malformation in an Infant with Prolonged Expiratory Apnea: A Morphometric Analysis of the Brainstem

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This female with a Chiari II malformation had a lumbar meningomyelocele closed at 1 day of age and a ventriculoperitoneal shunt inserted at 4 days of age. Apneic spells led to a posterior fossa decompression at 9 days. Thereafter the child had apneic spells, which began in response to a noxious stimulus, and went into a forced expiration leading to cyanosis, bradycardia and unconsciousness. She died at age 13 months of age.

Morphometric analyses were performed on serial Nissl sections through the medulla and pons to determine the volumes of selected brainstem nuclei and the total number of neurons within these nuclei. Results were compared to 3 age-matched normal controls. The Chiari II malformation showed a 35% increase in the combined length of the medulla and pons, but there was a decrease in total volume of both the medulla (30%) and the pons (17%). On the right side of the medulla there was a 13% decrease in the cross-sectional area of the tractus solitarius (TS). On the left side the TS and the associated nucleus of the tractus solitarius (NTS) were absent. Decreases in the total volume of brainstem nuclei were detected for the inferior olivary nucleus (62%), nucleus ambiguus (NA, 39%) and nucleus pontis (25%). The volume of the dorsal nucleus of the vagus was normal. The volume of the hypoglossal nucleus was significantly increased (17%). In the Chiari II malformation the total number of neurons in the inferior olivary nucleus was decreased by 98%. Reduced neuron numbers in the NA were greater on the left (53%) than on the right (26%). In the dorsal nucleus of the vagus a normal complement of neurons was observed. In the hypoglossal nucleus there was a significant increase in the number of motor neurons (25%), although the number of interneurons was normal.

These results indicate substantial neuronal depletion in the brainstem due to hypoplasia or atrophy. We postulate that the absence of the NTS in the left side of the medulla and the reduction in neurons of the NA contributed to the expiratory apnea observed in this patient. Inspiratory bulbospinal neurons, which project to contralateral phrenic and intercostal motor neurons, are located predominantly in the NTS (dorsal respiratory group) and in the NA and surrounding reticular formation (ventral respiratory group). The asymmetrical reduction in neurons of the NA may be secondary to hypoplasia of the NTS, since a major efferent pathway from the NTS projects to the ipsilateral NA. (Supported by the MRC).

P11.

Mitochondrial Cytopathy, Complex I Deficiency: Report of Two Cases with Neuropathologic Studies

J. PROVIAS, B. ROBINSON and L.E. BECKER (Toronto, Ontario)

The mitochondrial encephalomyopathies are a heterogeneous group of disorders involving skeletal muscle and central nervous system which have been partially characterized as clinical syndromes including MERFF (myoclonic epilepsy with ragged-red fibers), and MELAS (mitochondrial encephalopathy with lactic acidosis and stroke-like episodes). There are, however, few correlative biochemical and neuropathologic studies. We report two cases, sisters, with antemortem determined complex I enzyme deficiency and subsequent neuropathologic examination at autopsy.

The most significant changes were in the brain, with sparing of the spinal cord and peripheral nerve. Both cases showed severe but patchy cortical nerve cell loss and reactive astrogliosis. One assumed a marked geographic distribution producing a "ulegyria-like" pattern. In addition, neuronal loss was marked in subcortical nuclei, chiefly caudate, putamen, thalamus, and dentate nucleus. In contrast, there was relative sparing of hippocampi and cerebellar cortex. Hemispheric tissue showed marked rarefaction with severe depletion of both axons and myelin, focal cystic change, and reactive astrogliosis. Scattered foci of dystrophic mineralization were present. Of interest were multiple foci of grey matter necrosis, chiefly cortical, of varying ages, with no vascular pathology identified. Examination of the remaining organs was unremarkable with the exception of skeletal muscle which showed patchy fiber necrosis and focal mononuclear cell infiltrates, but no ragged-red fibers.

These neuropathologic changes are likely secondary to the underlying cellular biochemical defect associated with mitochondrial complex I enzyme deficiency. The pattern of neuronal loss involving both cortex and subcortical nuclei may reflect selective vulnerability of neuronal subpopulations. The multiple discrete foci of grey matter necrosis in the absence of vascular pathology may have a similar metabolic pathogenesis and may represent the neuropathologic substrate of stroke-like episodes in MELAS syndrome.

P12.

Cerebral Infarction in a Heroin Sniffer

B. MARC, F. GRAY and M. DURIGON (Paris, France)

Cerebral infarcts complicating heroin abuse have been seldom reported and were only clinically and radiologically documented. We report a pathological case of cerebral infarct in a heroin sniffer.

A 31-year-old North African male, heroin sniffing addict for several years, with no past neurological history, was found dead one morning. The evening before he had presented usual signs of recent heroin intake. Opiates were found in large amounts in blood and urine by immunoenzymatic screening. Post mortem HIV serology was negative. Post mortem examination disclosed usual signs of heroin addiction but no cutaneous sign of IV drug use. Myocardial ischaemic lesions of various ages involved the antero-lateral part of the left ventricule; coronary arteries were normal. Neuropathological study revealed ancient, partly cystic infarcts in the right cerebral hemisphere. Those were mostly cortical with an intralaminar pattern and a watershed distribution at the boundaries between the anterior and middle cerebral territories and of the middle and posterior cerebral territories. A small cystic focus also involved the white matter between the deep anterior and middle cerebral territories. Intracerebral vessels, large intra cranial and cervical arteries were normal. There was no vascular inflammation.

This case demonstrates that pathologically documented cerebral infarcts may complicate heroin sniffing in the absence of definite neurological deficit. The mechanisms of cerebral infarction is unclear and different hypothesis may be proposed which are not mutually exclusive. In rare cases, angiograms demonstrated brain vessel occlusions (Richter et al., Bull NY Acad Med 1973; 49: 1-21; Knoblauch et al., Schweiz Med Wschr 1983; 113: 402-440) and images consistent with cerebral arteritis (King et al., Med J Aust 1978; 2: 444-445). In the present case, pathological findings were consistent with hypoperfusion lesions, likely to be due to heroin-induced hypotension either directly, or through associated myocardial infarct.

P13.

Brain Pathology in Divers — A Review of Recent Findings

A.C. PALMER and I.M. CALDER (Cambridge, England)

In continuation of our studies on the neuropathology of the brain in divers (Palmer et al., 1992) we have re-assessed our original 25 cases (12 amateur and 13 professional) and added a further 10 (5 amateur and 5 professional). Control brain material was obtained from 15 male airmen who died as a result of flying accidents. In the divers, microscopically, grossly dilated empty vessels were present in a total of 17 brains. This finding is probably related to the presence of intravascular gas bubbles from accidental rapid decompression. Lacunar spaces around vessels were observed in 10 brains and hyaline degeneration of small arteries in cerebral white matter in 12. Small foci of necrosis in cerebral grey matter occurred in 8 brains and evidence of patchy white matter changes in 10. These changes probably arose from periodical arterial obstruction by intravascular bubbles (Palmer et al., 1992, Neuropath Appl Neurobiol 18, 113-124).

P14.

Polyglucosan Body Diseases With and Without Branching Enzyme Deficiency

J.M. SCHRÖDER and R. MAY (Munich, Germany)

Polyglucosan body (PB) diseases comprise a wide spectrum of disorders that include glycogenosis type IV (Anderson's disease), Lafora's disease, adult PB disease with PNS and muscle involvement, and adult PB myopathy. PB myopathy in adults, contrary to infantile cases (Anderson's disease or amylopectinosis), is not associated with significant deficiency of the branching enzyme (= amylo-1,4-1,6 transglucosidase) (Schröder, May, Shin et al., Neuropath Appl Neurobiol 17: 517, 1991; Goebel et al, J Neuropathol Exp Neurol 51: 24, 1992).

We therefore report on a sporadic infantile case with only minor PG storage, and on two brothers with severe juvenile PG disease and complete branching enzyme deficiency comparing these cases with an earlier one without branching enzyme deficiency (Weis and Schröder: Clin Neuropathol 7: 271, 1988). The muscle biopsies in both brothers revealed extraordinarily severe deposits of PG bodies not only in muscle fibers, but also in interstitial and other cells that could be evaluated in the 19-year-old brother also in a sural nerve and an endomyocardiac biopsy, and finally, at the age of 20, at autopsy. The younger, 14-year-old brother was erroneously classified by a previous muscle biopsy as having central core disease. The older brother represents to our knowledge the first juvenile, familial case of PG body disease with total branching enzyme deficiency and

extensive glycogenosis involving skeletal, cardiac, and smooth muscle fibers as well as connective tissue cells. Peripheral axons, Schwann cells and perineurial cells were less severely involved. Abundant PGBs were noted in astrocytes but not in peripheral or central neurons.

P15.

Dentate Gyrus Molecular Layer Gliosis: A Consistent Finding in Temporal Lobe Resections for Epilepsy

T.G. BEACH and W.B. WOODHURST (Vancouver, B.C.)

Hippocampal sclerosis is the most common pathoanatomic finding in temporal lobe epilepsy. Amongst hippocampal subdivisions, CA1 and CA4, or endfolium, have been traditionally identified as most affected. Recent work, however, has uncovered an unusual neuronal sprouting response in the molecular layer of the dentate gyrus (DGML). This has been documented by abnormal Timm's staining in DGML. We have re-examined our archived temporal lobectomy cases in order to look for changes within the DGML. Timm's staining requires special fixation and is therefore unsuitable for archived paraffin material, but since fibre rearrangements in the DGML in Alzheimer's disease have been accompanied by a proliferation of fibrous astrocytes, we used immunohistochemistry for glial fibrillary acidic protein (GFAP) to assess whether a similar gliotic response occurs in epilepsy. Forty-eight consecutive temporal lobectomies, gathered over a three year time span, were initially evaluated. Of these, 23 were judged unsuitable because they did not contain sufficient tissue from the dentate gyrus. The remaining 25 had diagnoses as follows: hippocampal sclerosis (16); ganglioglioma (4); cavernous hemangioma (2); cystic encephalomalacia (1); cysticercosis (1); non-specific findings (1). Control tissue was obtained from five autopsy cases of sudden death in young subjects free of significant past medical histories. Sections were taken from the paraffin block which contained the most complete portion of the hippocampal complex and were stained with an immunoperoxidase method for GFAP. Astrocytes in DGML and other hippocampal subdivisions were counted manually using an ocular graticule at 400× final magnification. In all but two surgical cases, there was an obvious proliferation of GFAP-positive astrocytes within DGML; the mean density of labelled cells was 10.0/mm^2 (control: 1.76/mm^2). Compared to other hippocampal subdivisions, DGML gliosis was more consistently present and of greater magnitude. In conclusion, astrocytic gliosis of the DGML is a consistent finding in temporal lobe resections for epilepsy and may be related to previous reports of mossy fibre sprouting.

Titles of Diagnostic Case Presentations

1. **Cortical-Basal Ganglionic Degeneration with Neuronal Achromasia**
   K. BERRY (Vancouver, B.C.).
   G.N. HOAG (Victoria, B.C.).
2. **Desmoplastic Medulloblastoma**
   J.M. BONNIN (Indianapolis, Indiana).
3. **Cerebral Neuroblastoma**
   E. NEUMANN and K. DOROVINI-ZIS (Vancouver, B.C.).
4. **Primary Meningeal Fibromyxosarcoma**
   J.P. ROSSITER, S. NAG and D.M. ROBERTSON (Kingston, Ontario).
5. **Primary Intracranial Malignant Fibrous Histiocytoma, Multicentric with Leptomeningeal Invasion**
   P.V. GOULD and D. MUNOZ (London, Ontario).
6. **Stenosis of the Aqueduct of Sylvius caused by the Draining Vein of a Venous Angioma**
   J. MICHAUD and E. LIKAVCAN (Montreal, Quebec).
7. **Malignant Rhabdoid Tumor, Cauda Equina Region**
   K. MEAGHER-VILLEMURE, J.L. MONTES and A. O'GORMAN (Montreal, Quebec).
8. **Neu-Laxova Syndrome**
   M.G. NORMAN (Vancouver, B.C.).
9. **Lafora Body Disease**
   J.M. BONNIN (Indianapolis, Indiana).
10. **Neuronal Lipid Storage Disorder, Niemann – Pick Disease – Group II, Type C**
    O. WILLIAMS, B. CURRY and O. SUCHOWERSKY (Calgary, Alberta).
11. **Familial adult-onset Leukodystrophy with Pigmented Cells**
    A.H. KOEPPEN, D.A. KATZ, C.Y. LEE and J.A. MARTINI (Albany, New York).
    E.P. RICHARDSON (Boston, Mass.).