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Dossier EXHIBIT NEW-YORK

Dossier STEREOTACTIC DYNAMIC RADIOSURGERY

- STEREOSCOPY
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JEAN-LORRAIN VÉZINA

## PRIX ALBERT JUTRAS



Figure 2

## An unusual intracerebral tumour: dysembryo-neuroepithelioma

#### DONATELLA TAMPIERI

A 25 year-old male, suffering from epileptic seizures of unknown focus, was submitted to a CT scan. The examination showed a round hypodense lesion in the right temporal region. The intra- or extracerebral site of the lesion was not obvious on the CT picture (Fig. 1). But MR solved the problem, showing a well-circumscribed intracerebral round lesion in the right temporal lobe. The signal of the lesion has a double component in the T-1 weighted image, appearing hypointense with a thin hyperintense ring (Fig. 2 and 3). The signal becomes homogeneously hyperintense in the T-2 weighted image (Fig. 4). The diagnosis of low-grade astrocytoma was done. At pathology, the lesion was said to be a dysembryo-neuroepithelioma.

The dysembryo-neuroepithelioma is an unusual intracerebral tumour. It is a benign lesion characterized by proliferation of astrocytic and



Figure 1

oligodendroglial cells associated with a severe anomaly of the cortical architecture: the neurons do not respect their usual alignment and are dysplastic mostly due to their poverty in Nissl substance.







NEURO-IMAGE

## **Multiple sclerosis**

#### **GORDON FRANCIS**

Magnetic Resonance scans have had a major impact on imaging lesions in Multiple Sclerosis. The sensitivity of lesion detection is tenfold greater (using MRI) than CT scanning, while no lesions seen on CT are missed by MRI. Positive studies are obtained in 90-95% of clinically definite MS patients and this equals or exceeds the rate of positivity from CSF oligoclonal band studies and yet provides, in addition, anatomic information not available with Many patients diagnosed as MS pre-CSF studies.

Two projects of particular interest here have been the use of MRI to study patients with progressive MS before and after immunosuppressive treatment (cyclophosphamide) and secondly to evaluate patients with clinical myelopathies (acute transverse and chronic progressive variants).

Cyclophosphamide has been shown to arrest progression of disease for 1-2 years in 75% of patients with chronic progressive MS. Figure 1 shows the MRI of a 27 year-old

woman after several months of rapidly progressive disease refractory to steroids or ACTH. The second scan (Fig. 2) was obtained 8 months after completion of the induction phase of cyclophosphamide, at which time marked clinical improvement had occured. The MRI in this setting allows us to follow disease activity and quantitate disease volume. In addition, MRI gives objective means to assess therapy other than clinical evaluations.

sent with a chronic progressive myelopathy (CPM) without symptoms or signs above the neck. These patients present diagnostic dilemmas and often require myelography to exclude other diseases. Prior studies of CPM patients indicated 50% had paraclinical (CT, evoked potential) evidence of supra-cervical disease. Using MRI, we have found that 75% of 30 such patients have lesions detected above the foramen magnum. Figure 3 is the MRI of a patient with paraplegia yet normal arm and cranial nerve function. His MRI shows scattered cerebral lesions and an absence of spinal cord



Figure 3

compression. A myelogram done previously was normal. However, other patients with similar clinical pictures have no cerebral lesions. but have demonstrable cervical lesions consistent with demyelinating disease (Fig. 4). Patients with ATM (acute transverse myelopathy) have similar findings, i.e. some patients with a single episode of myelitis



Figure 1



Figure 2





## MR in partially sequestered fourth ventricle

#### D. MELANSON, V. WAGLE

In literature, sequestered fourth ventricle has been described as the ballooning of the fourth ventricle due to occlusion of the aqueduct of Sylvius and the foramen of Magendie and Luschka. However, in the two cases seen at the Montreal Neurological Institute, although the aqueduct was occluded, the basal foramina were patent, the basal subarachnoid spaces were normal or moderately enlarged, but the convexity sulci filled poorly following a delayed post (Metrizamide) cisternogram. Magnetic resonance in the second case showed a CSF filled large fourth ventricle and open foramina of Magendie and Luschka (SE 400/30 msecs).









## A case of midbrain AVM treated by stereotactic dynamic radiosurgery

A. OLIVIER, I. PODGORSAK, J. HAZEL, M. PLA, A. DE LOTBINIÈRE, B. PIKE, T. PETERS

Figure 1 & 2. Antero-posterior and lateral stereotactic DSA with superimposed arterial and venous phases, showing midbrain AVM fed by terminal branches of the vertebro-basilar system.

#### Figure 3.

Plates used to mark coordinates of target for radiosurgery.



Figure 3

NEURO-IMAGE 5

Figure 2

Figure 1

#### Abstract

A 35 year old female presented with a history of progressive neurological deterioration of two years duration, consisting in a left hemiparesis and ophthalmoparesis, disturbance of gait accompanied by headaches. Angiography revealed the presence of a right-sided midbrain AVM. This lesion was judged inoperable. The patient underwent treatment of the arteriovenous malformation with a 1 cm photon beam delivered by a linear accelerator. The treatment was given according to a technique termed "Dynamic Radiosurgery" implying the continuous and simultaneous rotation of both the patient and the gantry around a common isocenter in order to obtain a steep dose gradient thereby protecting surrounding normal brain tissue. This case serves to illustrate a technique developed at McGill, using modern imaging techniques done in stereotactic conditions with a linear accelerator. It also demonstrates the usefulness of such a technique in management of an otherwise untreatable deep seated brain lesion.

#### Introduction

Until recently, radiosurgical treatment of inoperable arteriovenous malformations was only possible with the help of the proton beam (5) gamma unit (12) or helium cyclotron (7). These devices were shown to be of definite help in alleviating most of the symptoms of cerebral AVMs including rebleeding. Their use, however, could not be expanded because of enormous physical and financial requirements. The introduction of the linear accelerator coupled with stereotactic techniques by Betti (1) was rapidly followed by other workers in the field (2). Along the same line we have developed at McGill University a system to interface a linear accelerator with stereotactic subtraction angiography and MRI scanning. More recently, a system of double continuous rotation of the patient and of the linear accelerator gantry around a common isocenter has permitted delivery of a uniform dose in the prescribed area with a steep fall off of the radiation outside the lesion allowing a safer treatment of deepseated lesions (9). The case of a patient harbouring an inoperable midbrain AVM is presented to demon-

strate: a) the technique of stereotactic localization; b) the technique of dynamic radiosurgery; and c) clinica results in this specific patient.

#### **Case History**

A right handed 35 year-old female without significant medical history was admitted to the Montreal Neurological Hospital on December 14, 1986. Four or five years prior to admission she first noticed clumsiness in her left hand. It had remained mild, although it had worsened in the past two years. In addition, she noted a tendency to lean to the left when walking. For the past two years she had been complaining of double vision, mainly in the horizontal plane, occuring intermittently about once a day and lasting for about a half an hour. This had increased in frequency to about three times a day. For many years she had suffered from headaches described as "pounding" in the frontal and both temporal areas, associated with photophobia. Four or five years ago her headaches had become constant and daily but no medical help was sought. Over the last year it has been felt as a constant pressure on the right side and lasting about five hours. She was



Figure 4. MRI showing location of AVM with respect to surrounding cerebral anatomy.



Figure 5





#### Hounsfield CT Prototype



EMI 1005



Empty Sella Turcica



## Looking into tomorrow with magnetic resonance imaging and spectroscopy

Multiple Sclerosis

- pH 7.01 rt affected hemisphere cd 0 200 .9 phc 220,90
   Plot file: popsbran.plot
- It hemisphere pH 6.95 cd 0 200 .9 phc 200 150
   Plot file: popsbran2.plot



Dysplasia of right hemisphere — Spectroscopy

seen by a neurologist one to two years prior to admission who found no significant abnormality. In August 1986, she was seen by another neurologist who arranged for a CT scan.

At the time of her hospitalization, she was alert and oriented. Her ocular pursuit movements were altered and she had vertical nystagmus with a marked upbeat component and a small downbeat component. A permanent 12 diopter exotropia and 20 diopter hypertropia was noted on the right. The motor examination was characterized

by some unsteadiness of gait, a left hemiparesis with decrease of the left nasolabial fold, a slight left pronotor drift and decrease in left foot tapping. A significant left dysmetria was also noted on the finger-nose test.

#### **Stereotactic Localization**

On December 16, 1986, she underwent placement of the stereotactic frame, followed by MRI and digital substraction angiography (DSA).

**Stereotactic Digital Angiography** The patient was brought to the radiology suite where transfemoral vertebral angiography was performed,



Figure 5, 6 & 7. Coronal, sagittal and transverse MRI slices showing isodose curves for a 10 mm collimated beam.



Figure 6

the frame being solidly affixed to the skull by fixation pins. The frame is equipped with four plates with metal markers. A computer software program devised at the Montreal Neurological Institute by the computer engineers (8) can be used to take full advantage of DSA, specifically substraction of the skull and selection of the optimal angiograhic phases. Furthermore, the program can be used to measure the size of the AVM, to study its relative arterial and venous components and to determine a target in its nidus or core. Superposition of arteries and veins is also possible permitting a more comprehensive study (Fig. 1, 2). AP and lateral views are done routinely in stereotactic conditions.

#### Stereotactic MRI

Following DSA angiography, the patient was transported to the MRI suite where the stereotactic DSA marker plates were replaced with the stereotactic MRI plates located on the anterior, posterior, lateral, and dorsal aspects of the frame. The Z shaped markers make it possible to establish target coordinates in the three orthogonal planes of space.

Thus, in this patient, the mid-brain AVM was visualized by angiography in two planes and by MRI in three planes. Exact correlations were made between the two techniques which are complementary. Angiography shows more precisely the location of feeding arteries and draining veins. The MRI shows better the nidus as well as the surrounding secondary changes such as gliosis or hemorrage. For stereotactic radiosurgery planning, MRI has the marked advantage of showing not only the lesion but the neighborhood anatomy. Indeed, with the focal delivery of high energy it is not only important to visualize and characterize the target zone, but to study the surrounding anatomy as well. In the present case, the avoidance of the contralateral tegmentum and cerebral peduncle was of crucial importance (Fig. 4).

#### **Dynamic Radiosurgery**

Following the anatomical study of the lesion and determination of the nidus center by MRI and DSA, and appropriate adjustments according

to the surrounding anatomy, the coordinates are transferred onto another set of plates affixed to the frame. On these plates the volume and center of the lesion is marked as seen in various planes of space (Fig. 3). Three dots representing the lesion center are used to align three laser beams in order to place the center of the lesion in the isocenter of the accelerator. During the procedure, the head is maintained totally immobilized by the stereotactic frame which is itself affixed to the treatment couch by a slot-shaped frame holder.

The simultaneous and continuous rotation of the treatment couch and of the accelerator gantry around a common isocenter permits the beam to enter the head in a multitude of different angles in order to bring a high and uniform dose of radiation in the desired area within the lesion and a minimal one to the surrounding normal brain. In this patient a total of 50 Gy were delivered by two successive sessions on December 17 and 19, each treatment lasting approximately 20 minutes (Fig. 5, 6, 7). The procedure was well tolerated without any side effects. The patient was discharged home in good condition on December 20.

#### **Results on Clinical Conditions**

The patient was seen for follow-up two months following her treatment. Her headaches have improved, her blurred vision has disappeared and her gait is more steady. The left sided-weakness has markedly improved.

#### Discussion

Arteriovenous malformations (AVMs) are congenital anomalies thought to enlarge slowly during early life (10). Their clinical manifestations can be various: intracranial hemmorhages, seizures, headaches, progressive neurological deficit, and other clinical phenomena (5).

Studies by Graff et al (4) suggest that intact arteriovenous malformations tend to rupture at a rate of 2-3% per year. The rate of rebleeding is 6% in the first year after hemmorhage and about 2% per year thereafter. About 10% die with the first hemmorhage and 20% with each rebleeding. Thus, as underlined by Drake (3), it appears that in the short term the condition is reasonably benign, but the longer the patient lives the more likely it is that serious complications will occur. It is thought that in the United States and Canada, 500 000 people are harbouring an AVM (3).

The accepted traditional surgical treatment of these lesions has been excision by craniotomy and embolization by pellets and tissue adhesives (11). This form of treatment is still associated with a significant mortality and morbidity (3, 5). Another mode of treatment has slowly emerged which is highly complementary to the other forms of treatment, namely, radiosurgery pioneered by Leksell (6) and Steiner (12) in Sweden using the cross firing of the Gamma unit and Kjellberg (5) in the United States using the Bragg peak of the proton beam. This mode of treatment is indicated in patients harbouring "inoperable" lesions located deep in the brain or located in the motor, speech, or visual areas of the brain.

Kjellberg's series of over 400 patients treated by proton beam therapy (5) clearly shows that protection against death due to hemmorhage appears to develop gradually, with no definite protection during the first years and exceptional rebleeding after two years. Total obliteration (which does not appear to be essential for protection against rebleeding) was achieved in 22% of those with follow-up arteriograms, with a further 29% with "nearly total" obliteration. Total obliteration is reported in 84% of cases by Steiner (3). This form of treatment has also been shown by these workers to improve and alleviate other symptoms and signs of AVM such as headaches, progressive neurological deficits, and seizures. Betti has now been able to show similar results with the use of photon beam delivered with a linear accelerator (1). A significant modification of the technique, called dynamic stereotactic radiosurgery, has been developed at McGill University (9). This technique utilizes the modern method of imaging done in stereotactic conditions including DSA, MRI, and CT coupled to the simultaneous rota-

tion of the patient and accelerator around a common isocenter. It is felt that the very sharp gradients thus obtained will find numerous applications not only in the treatment of AVMs, but also in the management of deep seated tumours and functional disorders, such as pain and epilepsy. The reversal of symptoms in the case presented is most encouraging.

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## Le Docteur Jean-Lorrain Vézina premier récipiendaire du Prix Albert Jutras



#### SUZANNE FONTAINE **DENIS MELANSON**

Le Docteur Jean-Lorrain Vézina a eu l'honneur d'être le premier récipiendaire du Prix Albert Jutras, le 28 novembre dernier, lors du dernier congrès annuel de la Société Canadienne-Française de Radiologie.

À 57 ans, le docteur Jean-Lorrain Vézina a atteint une renommée internationale dans le domaine radiologique grâce, notamment, à l'une de ses publications qui lui a valu, en 1984, la mention honorifique d'être l'un des auteurs les plus mondialement cités de la littérature médicale. Le titre de cette publication "Prolactin-secreting pituitary microadenomas: roentgenologic diagnosis", parue dans l'American Journal of Roentgenology a été cité à plus de 185 reprises, selon l'Institute for Scientific Information.

En plus d'être auteur ou collaborateur de plusieurs publications scientifiques, le docteur Vézina est un conférencier recherché. C'est à Paris qu'il présente, pour la première fois en 1973, le fruit de ses recherches

sur le microadénome à prolactine qui le rend célèbre. Il a. depuis, présenté de nombreuses conférences de par le monde et dans pratiquement toutes les langues.

Neuro-Image profite de l'occasion pour féliciter le docteur Jean-Lorrain Vézina pour l'obtention de ce prix et pour sa contribution à la neuroradiologie.

PROLACTIN-SECRETING PITUITARY MICROADENOMAS\* ROENTGENOLOGIC DIAGNOSIS

N L. VEZINA, M.D. F.R.C.P.C., and H.DOR J. SUTION, M.D. monteen, c. estrema rthea-galac-g sellar en-with optic mission transsphenoidal open surgery of with optic microscopic explorati out by Dr. J. Hardy.\*

without exception ind. The sella with these patients; for In all cases four of size in 14 of hus genologic, biol bes presented in h 6 patients h findings are



NEURO-IMAGE | 13

## Holding a mirror up to life

**JENNY SANDISON** 





Professor Wheatstone assumes that this phenomenon of threedimension is caused by the actual projection, on similar parts of the retina of the eye, of the two dissimilar perspective pictures of an object as outlined in Fig. 1. The mind utilizes the differences between the two views to create the perception of depth. He notes that normally the converging eyes focus on an object which is seen at the meeting-point of the optic axes (Fig. 2a). He goes on to inquire whether it be possible to actually fool the eyes into seeing 3-D, by presenting them with two dissimilar perspective drawings of an object. These drawings would have to be positioned at similar points along the optic axes, but not at their convergence.



only occurs when an object is close enough to the observer so that his eves must converge in order to focus on the object. In this position each eye actually perceives a slightly different perspective view of the object. This is due, of course, to the fact that the eyes are approximately



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He found that this was indeed possible. If two perspective projections of the same object are placed at a point either before the intersection of the optic axes (Fig. 2b), or after the intersection of the optic axes (Fig. 2c), the observer does indeed

perceive a figure of three dimensions.

However, Professor Wheatstone also found that many people have difficulty adapting their eyes to focus and unite the pictures. Hence, he invented the stereoscope.

NEURO-IMAGE 15

The diagrams are from Wheatstone's original in Fig. 3 paper and a modern reader will readily recognize the principles of the modern stereoscope. Professor Wheatstone explains that the purpose of this apparatus is to enable perspective pictures to be placed at a point which corresponds to the normal convergence of the optic axes, by means of two mirrors placed so as to interrupt the optic axes. With this apparatus he was able to produce an elegant series of experiments that demonstrated different aspects of binocular vision, and shed light on some problems of depth perception that had been noted and puzzled observers.

Soon after Roentgen's discovery of X-Rays in 1895, and its medical value was established, the importance of three-dimensional radiography was appreciated. To Elihu Thompson belongs the credit for the first publication suggesting the application of stereoscopy to radiography. Dr T. Keats admirably expresses the debt of the Radiological community in this way: "Many students will recall their delight with their first exposure to stereoscopic radiographs. The initial experience of exploring the intact human body in three dimensions is an unforgettable one, made possible by an ingenious application of a photographic principle to roentgenography and resting squarely on the work of Sir Charles Wheatstone." (2)

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have diffuse cerebral lesions (consistent with demyelinating disease: MS or post-infectious encephalomyelopathy) (Fig. 5), while others have only a single spinal cord lesion and no cerebral lesions (Fig. 6). The MRI in ATM/CPM can thus be helpful in detecting multifocal lesions in the CNS that avoids the need for myelography and renders an accurate diagnosis earlier than previously possible. In ATM the MRI may be useful in determining more accurately which patients will eventually develop MS.



Figure 5



Figure 6

# Fonds de<br/>recherche McRaeMcRae<br/>ResearchInstitut Neurologique<br/>de MontréalMontreal<br/>Neurologique

Les collègues et amis qui ont connu Donald L. McRae peuvent, en faisant un don, témoigner de leur reconnaissance pour son influence et son enseignement dans le domaine de la Neuroradiologie.

Les sommes recueillies serviront à la promotion de l'enseignement de nouvelles techniques et à l'organisation des conférences McRae consacrées à l'image Neurologique.

Envoyez votre don à l'adresse suivante:

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## McRae Research Fund Montreal Neurological Institute

Friends and colleagues of Donald L. McRae may wish to show their gratitude for his influence and teaching in the field of Neuroradiology.

The proceeds of this fund will be used to promote education in this field, specifically, to develop new techniques in Interventional Radiology and to support the McRae Lecture in Neuro-Imaging.

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