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Focal Heavy Charged Particle Irradiation of the Mammalian Cortex: Temporal Pattern of Changes Followed by Magnetic Resonance Imaging and Positron Emission Tomography

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DISCLAIMER

FOCAL HEAVY CHARGED PARTICLE IRRADIATION OF THE MAMMALIAN CORTEX: TEMPORAL PATTERN OF CHANGES FOLLOWED BY MAGNETIC RESONANCE IMAGING AND POSITRON EMISSION TOMOGRAPHY[1]

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Introduction

Studies in progress examine the radiation response of the normal rabbit brain to accelerated focal charged particle (helium, 230 MeV/u) beams. We have demonstrated that we can produce well-defined focal lesions that are detectable on nuclear magnetic resonance (NMR) and positron emission tomography (PET) imaging procedures in the rabbit brain. These lesions appear to be similar to those observed in humans following stereotactic heavy charged particle radiosurgery [1,2,3]. The rabbit does not deteriorate neurologically with the appearance of these deep white matter lesions thereby permitting the examination of the cerebrovascular and metabolic basis of delayed radiation injury in the brain *in vivo*. The following report describes radiation-induced alterations in the rabbit brain observed with NMR and PET *in vivo* and the corresponding histopathological correlations.

Materials and Methods

The male (6 mo, 2.5 kg) New Zealand White rabbit brain is used as a model for delayed heavy charged particle radiation injury in the human brain. The rabbits were fed Purina rabbit chow and water ad libidum. All animals were anesthesized for about 1-1.5 hr with an intramuscular injection of 32 mg/kg Ketamine, 3 mg/kg Rompun, 0.6 mg/kg Acepromazine for all irradiation procedures and NMR and PET studies.

Partial hemibrain irradiation procedures were used, and the unirradiated hemisphere served as an internal control. A 20 mm x 10 mm hemicircular port was used for beam delivery to restrict the dose to the left hemisphere (Figure 1). The Bragg peak of a 230 Mev/u helium ion beam from the 184 inch Synchrocyclotron at the Lawrence Berkeley Laboratory was directed into the dorsal surface of the animal's head and stopped 13 mm below the skin surface. This ensured that only the telencephalon and the upper portions of the diencephalon are irradiated,

sparing the midbrain and its critical structures and associated nuclei from radiation exposure. The Bragg peak was spread to ensure uniform dose distribution throughout the the irradiated volume. Single doses of 15 Gy and 30 Gy were delivered; these represented the lower and upper dose levels used in the Donner Laboratory program of stereotactic heavy charged particle radiosurgery of intracranial arteriovenous malformations (AVMs) in clinical research patients.

NMR studies were begun 8 mo post-irradiation on a GE Signa 1.5 Tesla machine. Spin echo scan sequences of TR 2500 ms and TE 25 ms with 4 echos were used to produce T2-weighted images where pathological regions of increased T2 results in increased signal. TR 600 ms and TE 25 ms sequences were used for T1-weighted images where pathological increases in T1 results in signal decrease. Sagittal localization scans were performed before every study and coronal images were obtained from the cerebellopontine angle to the olfactory bulbs. All images were obtained with a 256# x 256# matrix and a slice thickness of 5 mm with an interslice spacing of 1.5 mm. Gadolinium diethylaminetriaminepentaacetic acid (GdDTPA) was used for contrast enhanced T1-weighted NMR studies to detect blood-brain barrier (BBB) perturbations. Gadolinium is a paramagnetic ion that enhances spin relaxation resulting in decreased T1 values [4,5]. This paramagnetic tracer does not normally cross the BBB so that regions of BBB disruption will accumulate GdDTPA in the affected parenchyma and produce a region of signal enhancement on T1 weighted NMR scans [6]. GdDTPA was infused through an ear vein through a gauge catheter after the rabbit had been anesthesized; 1 mmol per kg of GdDTPA was administered for each GdDTPA NMR study.

PET studies were performed on the Donner 600 crystal positron emission tomogram with an in-plane resolution of 2 mm and slice thickness of 4 mm [7]. Fluorodeoxyglucose (^{18}FDG) PET studies were performed to examine cellular glucose uptake, a measure of metabolic integrity, in the irradiated hemispheres. ^{18}FDG

freely crosses the BBB and is taken up by actively metabolizing neurons [8]. 7-8 mCi of ^{18}FDG was administered as a bolus dose through an ear vein catheter for each ^{18}FDG PET study. Scans were taken immediately after injection and followed through 60 min post-injection until complete washout of the ^{18}FDG has occurred from the vascular compartment and the remaining radioactivity accurately represents cell metabolic uptake. Rubidium (^{82}Rb) PET studies were conducted in a similar manner with the injection of a bolus dose of 24 mCi per image into an ear vein catheter. Scans were taken through a 5 min post-injection interval since the half-life of ^{82}Rb is 76 sec. ^{82}Rb is rapidly cleared from the brain so the PET image represents the tracer activity that has crossed a disrupted BBB into the brain parenchyma [9]. After each ^{82}Rb scan a follow-up ^{18}FDG PET scan was obtained immediately in order to confirm the positioning of the rabbit brain so that consistent neuroanatomical correlations may be made between the different imaging techniques.

Neurohistological analysis was conducted on excised brains. Hematoxylin-Eosin stains were used for general morphological histology and Luxol Fast Blue stains were used for defining demyelinated areas.

Results

All rabbits irradiated with 30 Gy to the left hemisphere demonstrated alterations in their functional anatomy as defined by various NMR and PET studies between 9 to 11 mo post-irradiation. T2 weighted NMR scans revealed extensive areas of increased signal in the irradiated hemisphere restricted primarily to the white matter regions of the outer corona radiata and the inner tracts of the internal capsule and fimbria and the perithalamic area (Figures 1a-b). T1 weighted scans also demonstrated radiation induced changes in the white matter (Figure 1c) but in general these T1 lesions were not as extensive as the T2 lesions. GdDTPA NMR images revealed disruption of the BBB indicated by accumulation of the paramagnetic

tracer and enhanced signal on the T1 weighted images (Figure 1d). The regions of disrupted BBB were restricted to the deep white matter tracts of the perithalamic area; the BBB of the outer corona radiata was intact. Rapid sequential GdDTPA NMR scans demonstrated that there was some spreading of the tracer from the primary site of injury, although it did not spread to the outer corona radiata (Figure 2). ^{82}Rb PET scans confirmed the presence of the focal BBB disruptions (Figure 3a). The neuroanatomical location of the ^{82}Rb PET lesions correlated well with the GdDTPA NMR images. ^{18}FDG PET studies demonstrated widespread decrease in ^{18}FDG uptake throughout the cortical regions and associated deep nuclei within the irradiated hemisphere indicating marked metabolic depression (Figure 3b).

Neurohistological analysis was conducted on rabbits irradiated with 30 Gy and sacrificed at 12 mo post-irradiation and the findings correlated well with the *in vivo* NMR and PET scans. A focal region of cystic necrosis and vacuolation in the deep white matter and the perithalamic areas was found in the irradiated hemisphere (Figure 4a). There was widespread loss of both neuronal and glial elements and an chaotic abundance of reactive astrocytes and lipid-laden microglia as well as abnormally dilated blood vessels. This central region of injury corresponded with the region of BBB disruption defined by GdDTPA NMR and ^{82}Rb PET scans. The outer white matter tracts of the corona radiata were edematous and demyelinated but non-necrotic and there was no extensive neuronal loss within the cortical layers of the irradiated hemisphere (Figure 4b). This region of injury did not demonstrate any BBB perturbations on the various *in vivo* imaging scans.

Rabbits irradiated with 15 Gy were neurologically normal and did not demonstrate any changes on T1 and T2-weighted NMR scans nor BBB perturbations on GdDTPA NMR scans through 15 mo post-irradiation. It is possible, however, that radiation-induced alterations at this dose may occur after a longer latent period. Rabbits in this dose group will be kept alive for 2 yr or more to to investigate the

possible late effects of delayed radiation injury.

Discussion

We have demonstrated that the rabbit brain proves to be a suitable model for delayed radiation injury in the brain. Well-defined lesions can be observed *in vivo* 9-11 mo post-irradiation (30 Gy helium ions, 230 MeV/u) with various NMR and PET imaging techniques. The rabbit does not deteriorate neurologically with the appearance of the radiation-induced alterations so that long term changes may be followed. Histological findings correlated well with imaging results. It appears that GdDTPA NMR may be able to detect and define the region of BBB disruption more clearly than ^{82}Rb PET although it is possible that ^{82}Rb PET may be more sensitive to small BBB perturbations because the Rb ion is smaller than the GdDTPA molecule. ^{18}FDG PET studies demonstrated the widespread decrease in glucose uptake in the irradiated hemisphere indicating severe metabolic depression. However, histological results did not demonstrate parenchymal necrosis or neuronal loss in the cortical layers of the affected gray matter. This implies that these neurons may be metabolically depressed but not killed. Hence it is possible that some degree of metabolic recovery may occur if the edema and demyelination in the outer white tracts are reversible.

Although repair of frank necrosis is not possible, lesser perturbations of the BBB may result in spreading vasogenic edema without neuronal death and parenchymal necrosis. Such a phenomenon of limited radiation injury may be repairable. About 20 % of patients treated for intracranial AVMs with stereotactic heavy charged particle radiosurgery have developed alterations in deep white matter regions around the previous location of the malformation [1,2,3]. These white matter alterations are detected on follow-up NMR scans a few mo and as late as 1-2 yr after treatment, are usually asymptomatic and resolve in another 1-2 yr. It is unlikely that these changes represent actual cellular necrosis since there is ample

evidence of repair and these widespread changes are usually asymptomatic. It is possible that the narrow focal dose distributions of heavy charged particle radiosurgical beams minimize radiation exposure to the surrounding normal brain thus resulting in BBB perturbations and spreading vasogenic edema in the deep white matter without frank neuronal or glial necrosis. Treatment schemes where larger volumes of normal brain are irradiated may lead to more extensive and severe and irreversible parenchymal necrosis. This may represent the clinical advantages of the unique biophysical characteristics of heavy charged particle beams [10].

Conclusions

Further studies that examine more closely the temporal development of BBB and metabolic perturbations as well as the possibility of repair of radiation injury in the rabbit brain are being conducted. It appears that the rabbit brain serves as a reliable surrogate to evaluate the relative biological effectiveness (RBE) of different radiation types and qualities especially heavy ions. Ongoing investigations are also being carried out to correlate the alterations in regional cerebral blood flow with the development of delayed radiation injury. And finally, studies are in progress to investigate the radiation response of hypoperfused brain tissue as it has been suggested that regions of brain surrounding an AVM may be slightly ischemic due to the steal syndrome [11,12].

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Figure Legends

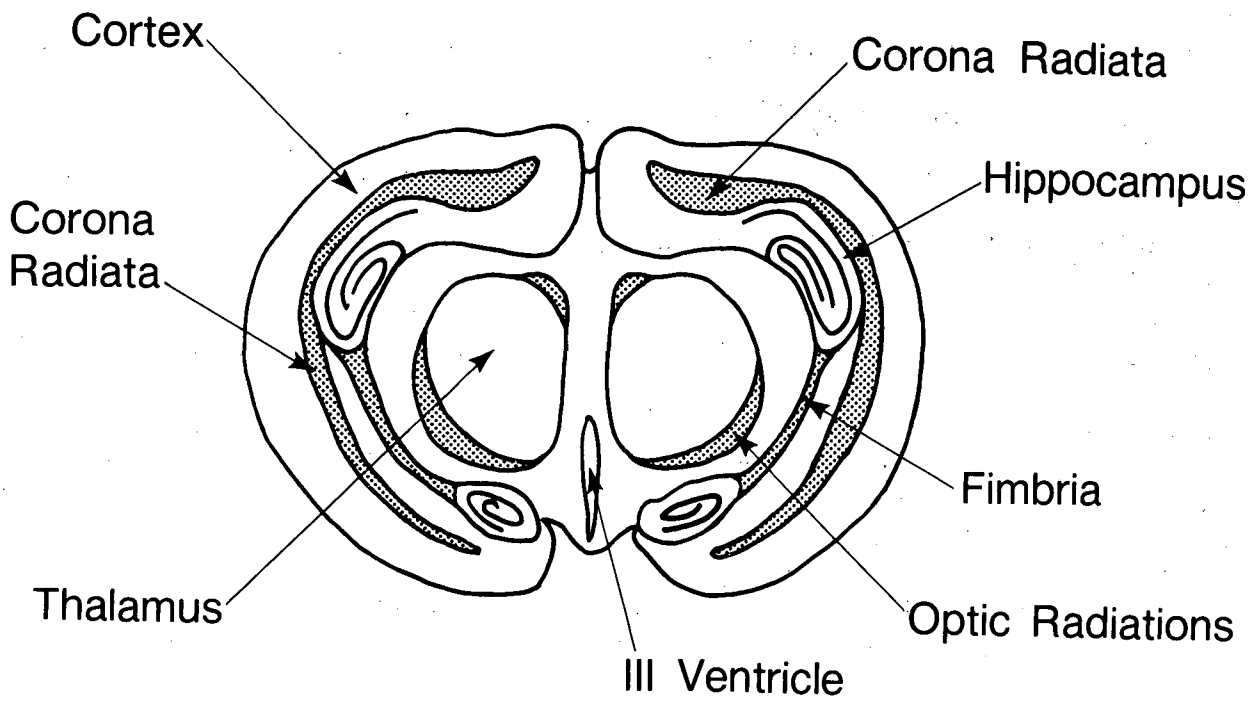
Figure 1a. The location of important neuroanatomical structures within a coronal slice of the rabbit brain corresponding to *in vivo* NMR and PET imaging scans. **1b.** Coronal T2-weighted NMR scans demonstrate increased T2 (signal increase) within the white matter regions of the outer corona radiata and the perithalamic and thalamic area after the rabbit brain was irradiated with 30 Gy of 230 MeV/u helium ions to the left hemisphere. Lesions first appeared 9 mo post-irradiation. **1c.** Coronal T1-weighted scan of the same coronal slice demonstrates the smaller region of increased T1 (signal decrease) in the deep perithalamic area. **1d.** GdDTPA enhanced NMR scan detects focal BBB disruption in the lesion; the size of the BBB disruption is smaller than the region of injury indicated by T2-weighted NMR imaging and does not include the outer corona radiata.

Figure 2 Rapid sequential GdDTPA NMR scans taken after bolus injection of the paramagnetic tracer; 10 min **(upper left)**, 16 min **(upper right)**, 22 min **(lower left)**, 28 min **(lower right)**. Some spreading of the tracer is observed although the GdDTPA is still primarily localized to the focal area of BBB disruption without spreading to the outer white matter tracts of the corona radiata.

Figure 3a. A ^{82}Rb PET scan of the same coronal slice (**Figure 1**) that confirms the presence of BBB disruption in the irradiated hemisphere. **3b.** Corresponding ^{18}FDG PET scan shows the extensive decrease in cerebral glucose uptake in the irradiated hemisphere indicating metabolic depression throughout cortex and deep nuclei of the basal ganglia and thalamus.

Figure 4a. Focal region of cystic necrosis in the perithalamic and thalamic areas of the 30 Gy irradiated hemisphere. There is a disruption of architectural structure, an abundance of reactive astrocytes and lipid-laden glial cells, and some abnormally

dilated cerebral blood vessels (Hematoxylin-Eosin stain, x100). **4b** Outer white matter tracts of the corona radiata in a 30 Gy irradiated hemisphere demonstrates edema and demyelination without cellular necrosis and neuronal loss in the cortical layers (Luxol Fast Blue myelin stain, x40). This region of edema was observed on T2-weighted NMR scans but did not demonstrate any BBB disruptions on either GdDTPA enhanced NMR or ^{82}Rb PET studies.



XBL 893-5047

Fig. 1A

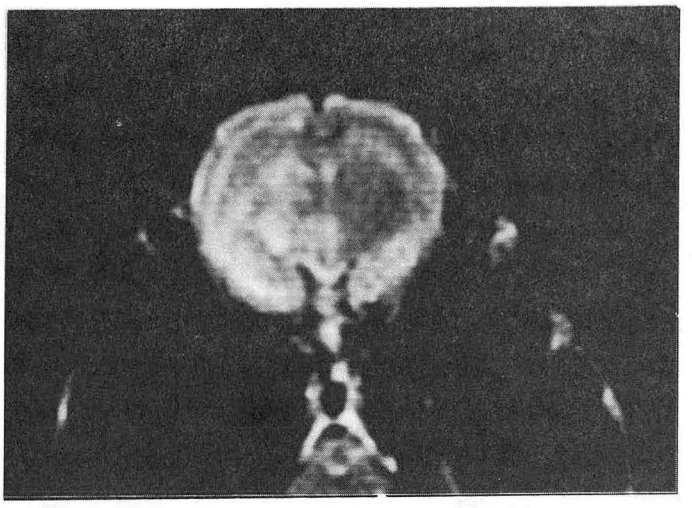


Fig. 1B

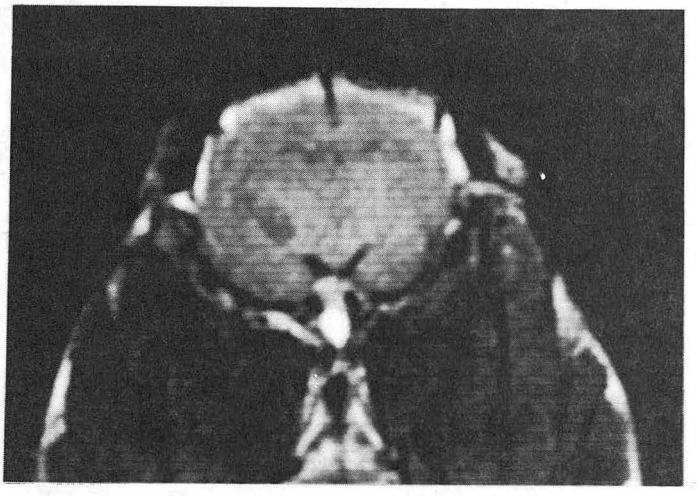


Fig. 1C

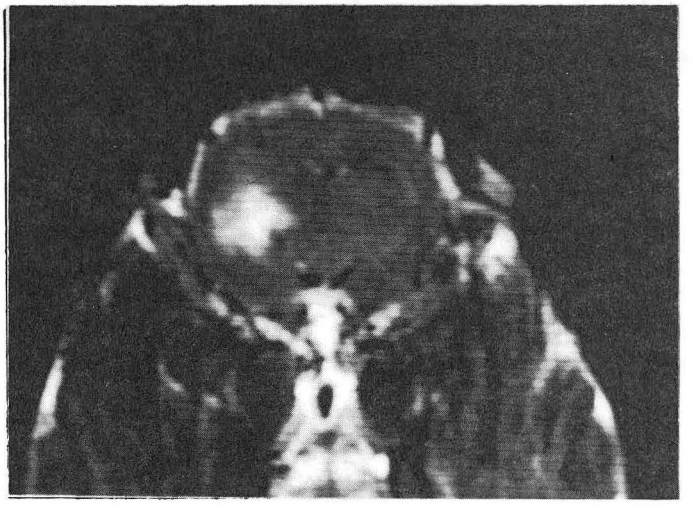
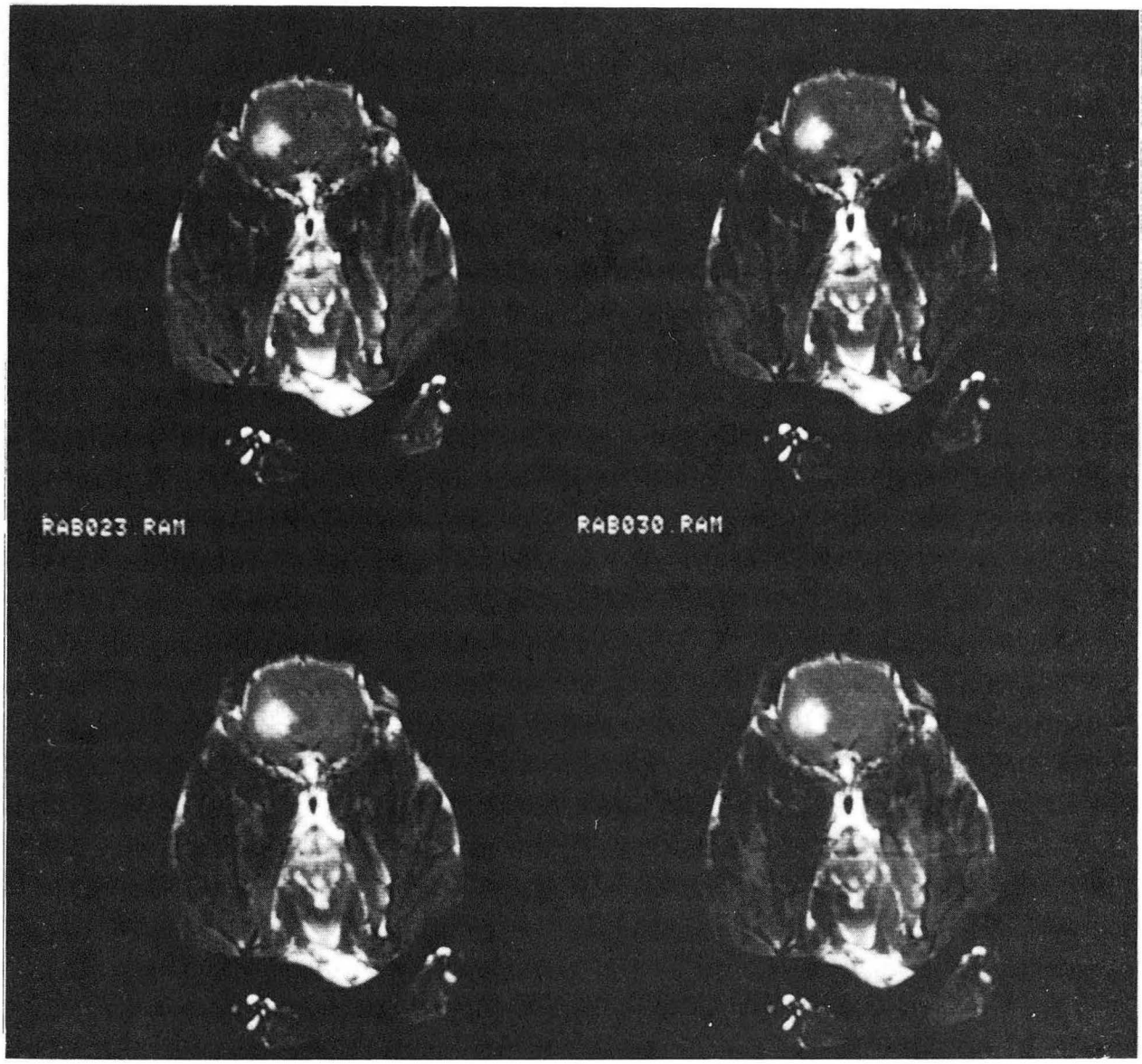
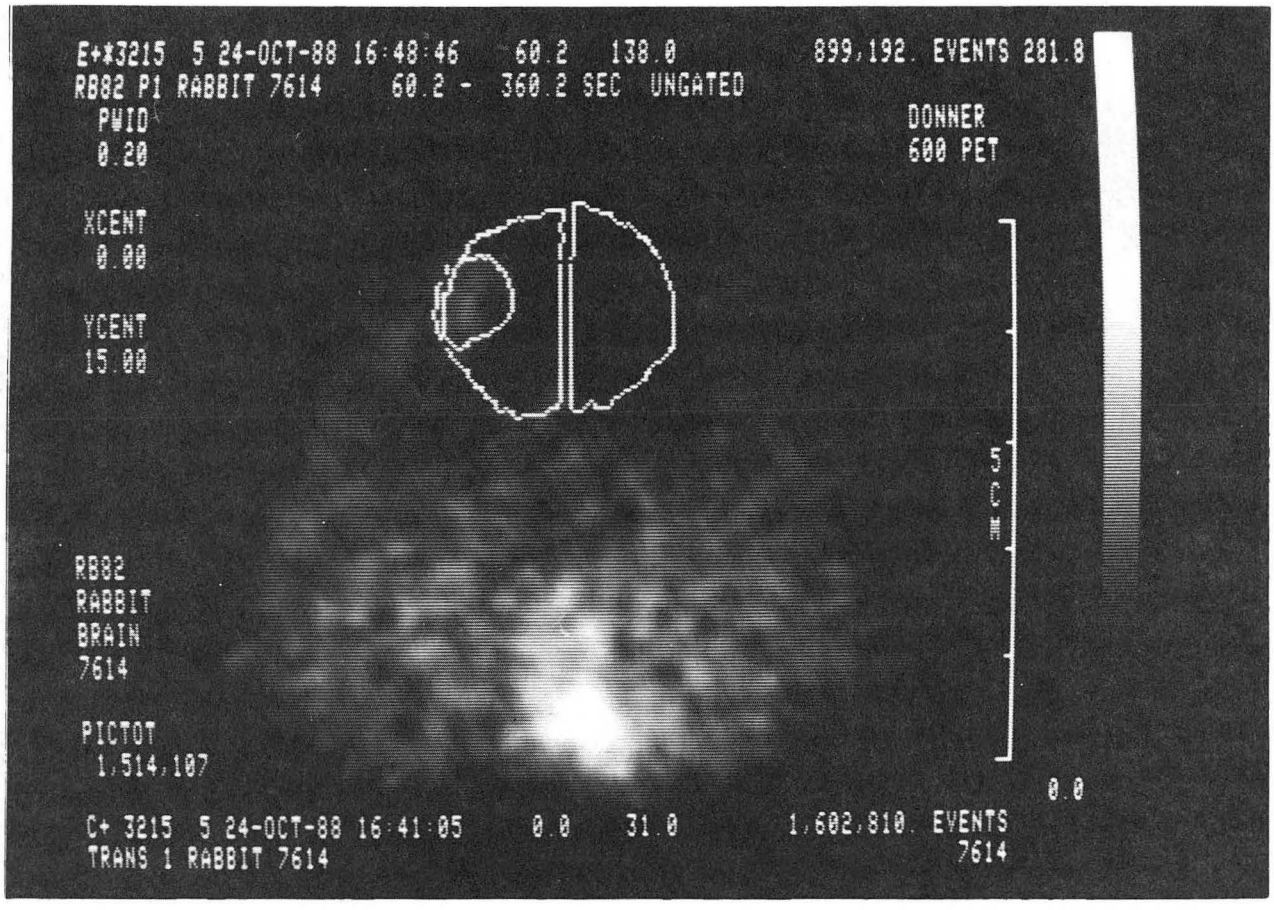


Fig. 1D XBB 8812-11834 A



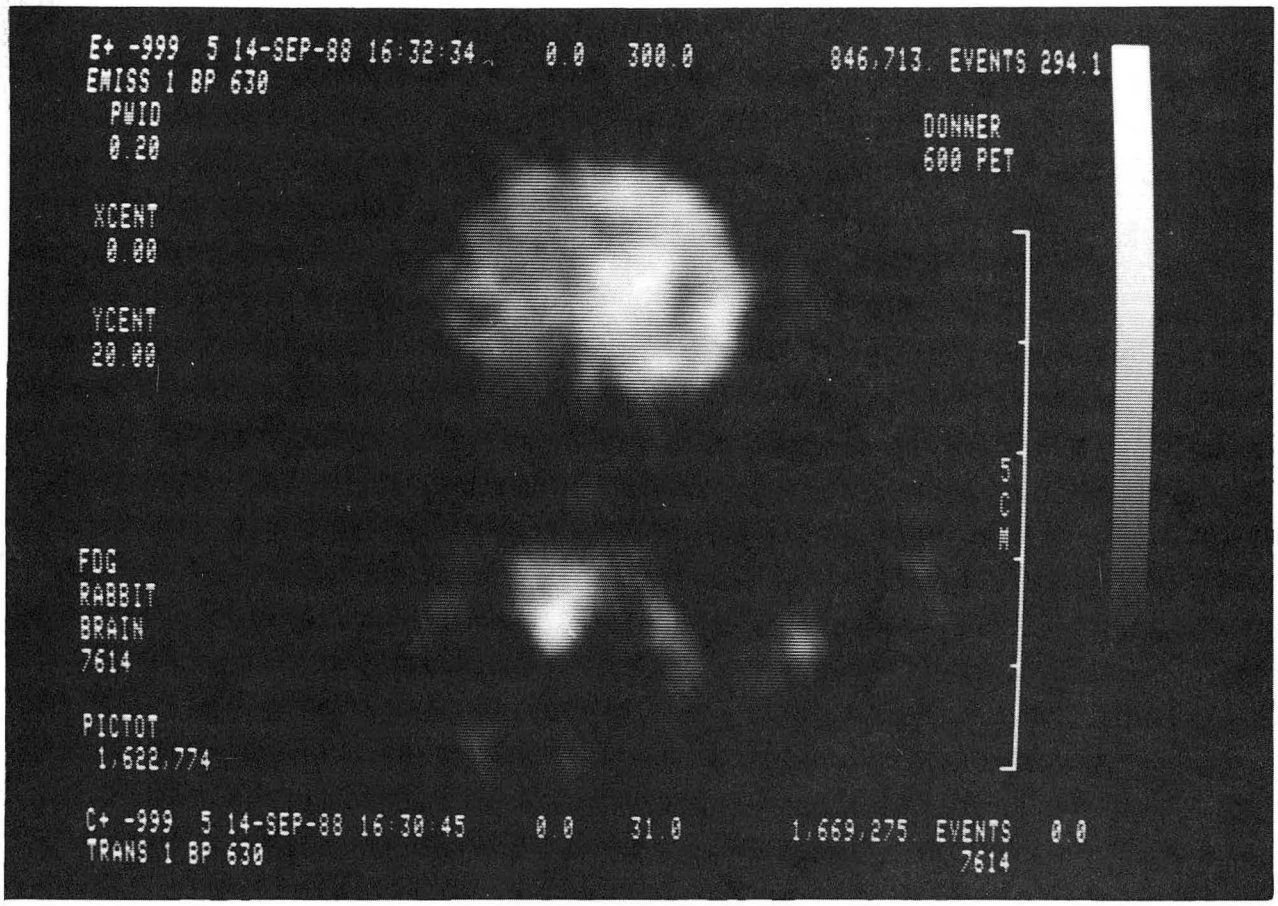
XBB 880-11836

Fig. 2



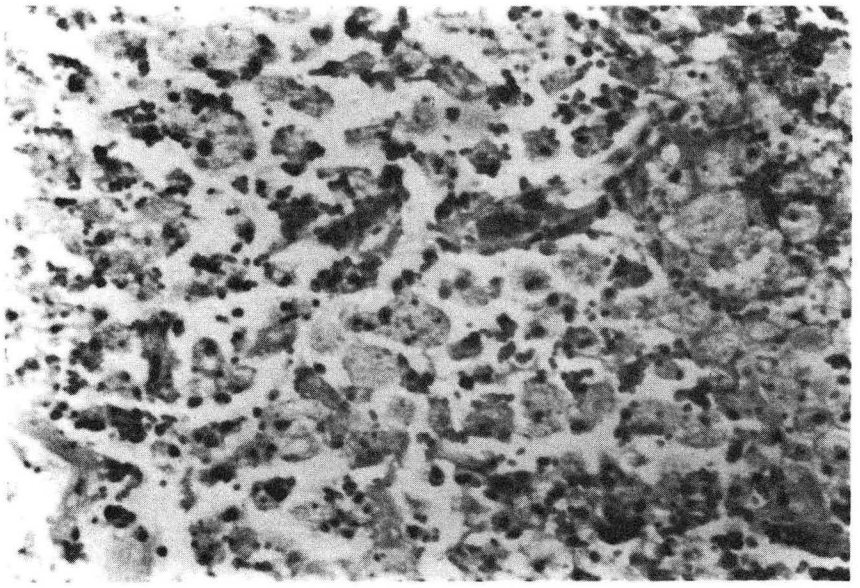
CBB 880-11829

Fig. 3A



CBB 880-11823

Fig. 3B



CBB 895-4222

Fig. 4A

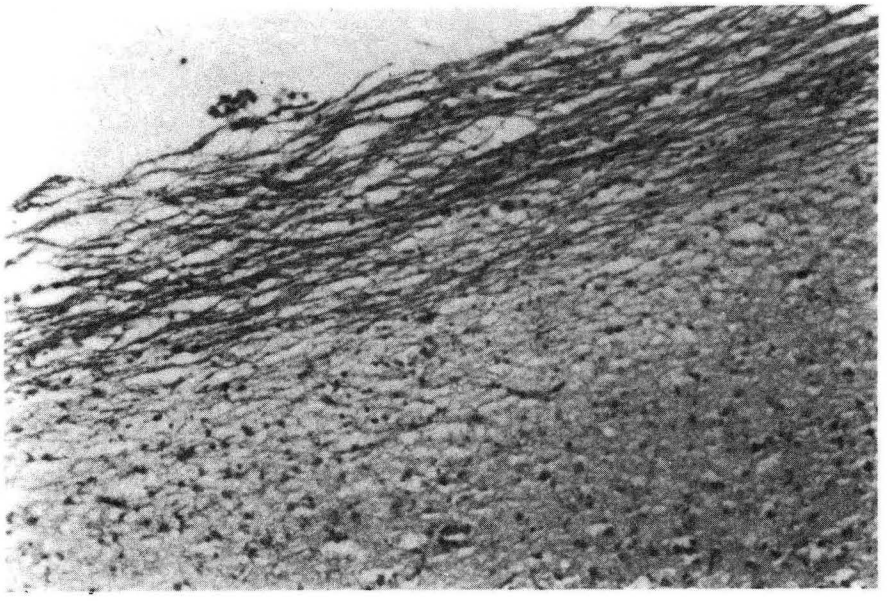


Fig. 4B CBB 895-4220

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