

## NEOPLASTIC ANGIOENDOTHELIOSIS

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(Received 6 July, 1981)

(Accepted 21 July, 1981)

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### SUMMARY

We add two cases of neoplastic angioendothelirosis to the previous 13 with central nervous system manifestations. This unusual neoplastic phenomenon is thought to represent a diffuse malignant proliferation of endothelial cells. A man aged 58 first had transient ischemic attacks followed by a subacute profound dementia with psychomotor retardation. Remission followed steroid therapy. Abulia recurred along with a gradually progressive paraparesis leading to death 16 months after onset of symptoms. Pathologic examination showed tumor masses in the basal ganglia and widespread patchy cerebral infarction. The spinal cord below the mid-thoracic level was destroyed. Microscopically small mononuclear tumor cells were widespread within and largely confined to the lumens of small cerebral blood vessels which showed varying degrees of occlusion and recanalization. Factor 8 antigen, a specific endothelial cell marker, was not present on the surface of the malignant cells.

Another man aged 61 developed subacute dementia with frontal lobe signs, dysphasia and impairment of memory. Computerized tomography showed multiple infarcts. A brief respite followed steroid therapy but progressive deterioration led to death in 15 weeks. Frontal lobe biopsy revealed the same neoplastic vascular process.

The hallmark of the illness is a progressive subacute lobar dementia. Transient spells may occur. Hemiparesis is unusual and seizures do not occur except terminally. Angiography is normal.

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Supported in part by a grant from the Freed Foundation, Washington, DC and the Departments of Neurology and Neuropathology, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114.

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## INTRODUCTION

Neoplastic angioendotheliosis, although well established as a clinicopathologic entity remains relatively unknown. Only 13 cases with predominantly neurologic involvement have been described. The neurologic features in brief consist of transient ischemic attacks, a subacute apathetic dementia and in some cases progressive paraparesis. In the present 2 cases the clinical and pathological findings are available and in addition an attempt was made to identify the nature of the tumor cells using the immunoperoxidase technique to stain for factor VIII antigen.

## CASE REPORTS

*Case 1*

A 58-year-old man experienced a five-minute episode of numbness and weakness of the right hand during which he was unable to pick up a pencil. Three days later while typing he developed numbness and difficulty controlling the fingers of the right hand. The numbness spread to the right forearm and his speech was slurred and contained some wrong words. The episode resolved after one hour. He was admitted to another hospital where he had some fifteen further spells in the next two weeks involving either hand and usually lasting about five minutes. Evaluation with computerized tomography (CT) and bilateral carotid angiography was normal. Cerebrospinal fluid (CSF) showed 10 mononuclear cells/mm<sup>3</sup> and a protein of 102 mg/dl.

During the next 2 weeks he became progressively more confused, disoriented and greatly slowed in movement and speech. On psychometric testing an oral I.Q. was 50-60 and written 40-50 whereas he had previously been a successful executive.

When transferred to the Massachusetts General Hospital 5 weeks after the onset, he was alert and cooperative but slow, quiet, unanimated, uninterested, emotionally flat and devoid of initiative. He disclaimed depression. Normally he was the dominant figure in the family and had a quiet temper. He had absolutely no insight into his illness. Do you feel sick? "No, I feel sick only because of what I have, the hands feel sick and it is transferred to my body". Are you a patient here? "I don't know, ask my wife". He said it was February 18, 1978 rather than March. He thought he was in Worcester. Counting backwards from 30 or 10 was impossible; from 10: 14321473. Proverbs were interpreted concretely and he was unable to write his name or copy line drawings. He ate his meat with his fingers. Memory was surprisingly good in that after 24 hours he spontaneously recalled 9½ points of a simple 10 point story he was given to remember. How long have you been sick? "5 weeks". There was no dysphasia. Brisk tendon reflexes, bilateral grasp reflexes, and slight lip pursing were noted. Rapid alternating movements were impaired in the right hand and forearm. The remainder of the neurologic examination was normal. An electroencephalogram (EEG) revealed diffuse delta slowing. Body-computerized tomography revealed bilaterally enlarged adrenal glands. Percutaneous biopsy of the left adrenal revealed an undifferentiated small cell tumor.

The transient spells of numbness and weakness ceased without specific therapy and the cortical deficits present on admission improved. He began to faint upon arising from bed and when found to be Addisonian was started on replacement therapy. Further studies revealed no other deposits of metastatic disease. He was begun on cytoxan, hydroxyurea, vincristine and prednisone chemotherapy. While on 100 mg of prednisone daily as part of chemotherapy his apathy diminished further and initiative increased. At the time of discharge, 2 months after admission, his wife felt that his reactions and personality were close to normal.

When seen one month later he felt "great" and could rapidly do serial sevens. Three months after discharge slowness, apathy and loss of spontaneity reappeared. His wife reported, "He looks good but he is blank, the look in his eyes is gone." What are you thinking about? "Nothing". Haven't you anything to think about? "No". "All day long he just sits or pitches horseshoes. He walks and talks in slow motion". When his son was accidentally injured he showed no reaction to the news. Memory was relatively preserved. A repeat body-computerized tomography showed resolution of the adrenal enlargement.

Five months after discharge he was either incontinent or urinated in inappropriate places such as a wastebasket. His appetite was excessive. He received chemotherapy monthly for 6 months. Seven

months after discharge lumbar back pain began and over the next 2 months the patient gradually developed a flaccid paraplegia and fecal incontinence. He became somnolent.

On readmission 9 months after discharge he was apathetic but recalled a 6-point verbal test story after 1½ hours and counted backwards from 10 but not from 20. Examination of the cranial nerves and upper extremities was normal except for the presence of marked grasping and sucking reflexes. There was a sensory level to all modalities at the inguinal ligament bilaterally. The only lower extremity movement was slight flexion of the left hip. The tendon reflexes and plantar responses were absent. Three cerebrospinal fluid examinations showed normal pressures, protein levels of 139–240 mg/dl and 6–32 mononuclear cells/mm<sup>3</sup>. Cytologic examinations were negative. Computerized tomography of the head was normal. A myelogram showed questionable widening of the conus medullaris but no block. Biopsy by way of T<sub>11</sub>–L<sub>1</sub> laminectomy revealed necrotic spinal cord tissue but no tumor. The post-operative survival of 2 months was complicated by fever, increasing disorientation, stupor, recurrent seizures and *pseudomonas* bacteremia. A repeat computerized tomography scan revealed non-enhancing symmetrical low density areas in the basal ganglia consistent with tumor masses. Death occurred 16 months after his initial symptoms.

*Pathological examination*

Undifferentiated tumor involved the adrenal glands, kidneys and liver. On microscopic examination small hyperchromatic tumor cells were confined to blood vessel lumens except in the adrenals where there were small perivascular accumulations. In some areas blood vessels showed intimal thickening with occasional thrombosis. In the kidneys tumor cells showed a predilection for small veins adjacent to the glomeruli and in the adrenals they were largely confined to the medullary sinusoids. Sections of spleen, bone marrow and lung were uninvolved. Muscular arteries were spared.

The brain which was grossly swollen weighed 1360 g and showed bilateral uncal herniation, right greater than left. On coronal sectioning widespread extensive patchy areas of bland and hemorrhagic infarction were seen throughout the hemispheres sparing the frontal and occipital poles. On each side a discrete tan-white tumor mass about 3 cm in diameter extended from the globus pallidus into the lateral thalamus (Fig. 1). The mid brain was elongated longitudinally and petechial hemorrhages were seen in the right pontine tegmentum. The spinal cord from the mid-thoracic region caudally was shrunken and soft (Fig. 2).

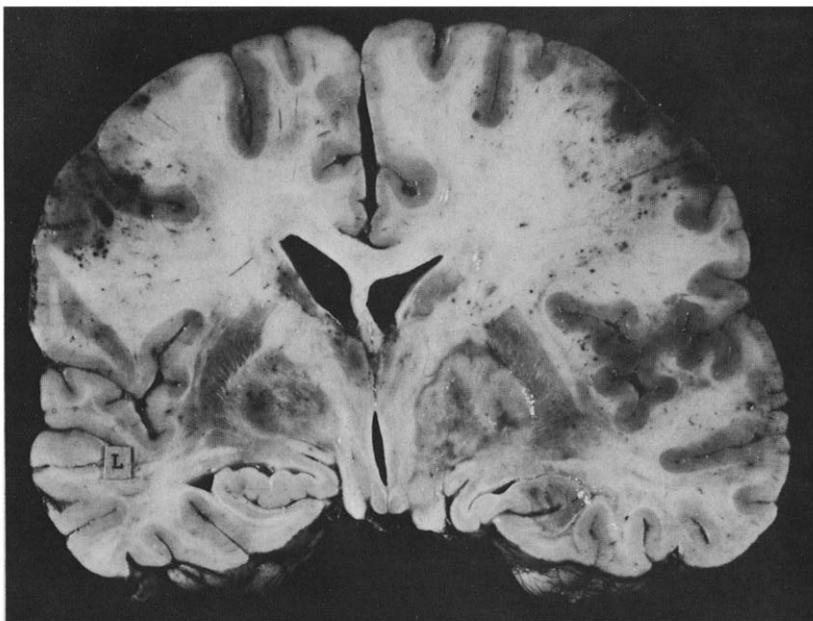


Fig. 1. Coronal section of the brain showing multiple patches of bland and hemorrhagic infarction, bilateral tumor masses in the region of the globus pallidus and bilateral uncal herniation.



Fig. 2. Lower spinal cord and cauda equina showing shrunken and softened cord.

Microscopic sections through multiple areas of cortex revealed areas of bland and hemorrhagic infarction. Numerous small vessels in the subarachnoid space and cortex were filled with hyperchromatic tumor cells. Vessels involved were thin-walled veins and capillaries and small arteries with a tunica media more than 4 cells thick were spared (Figs. 3 and 4). In many areas the vessel walls were necrotic and small extravasations of blood had occurred. The globus pallidus, internal capsule and adjacent lateral thalamus bilaterally were replaced by sheets of small hyperchromatic mononuclear

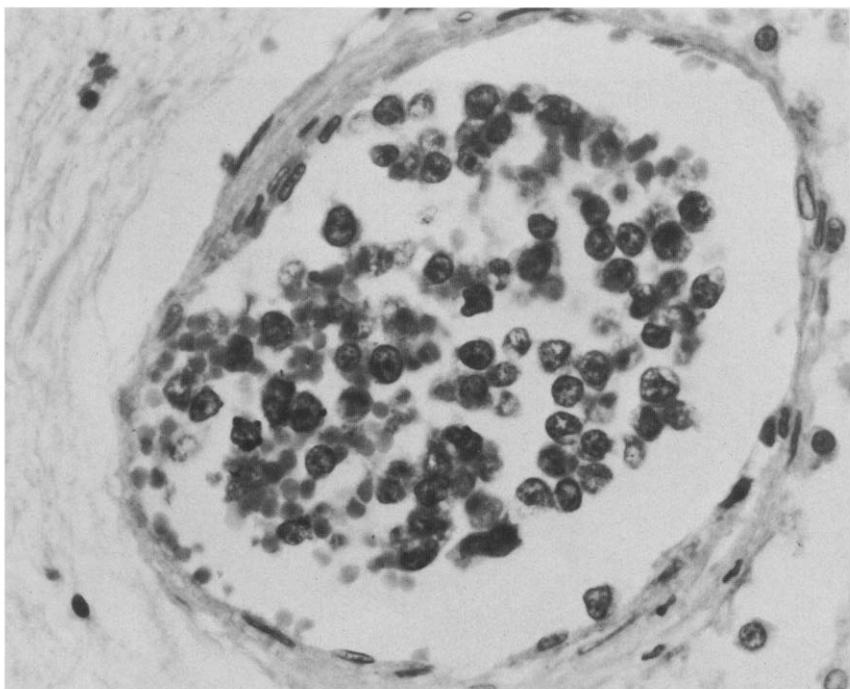


Fig. 3. Cortical arteriole of  $40 \mu\text{m}$  diameter filled with hyperchromatic mononuclear tumor cells showing clumped chromatin. Luxol fast blue, hematoxylin and eosin,  $\times 620$ .

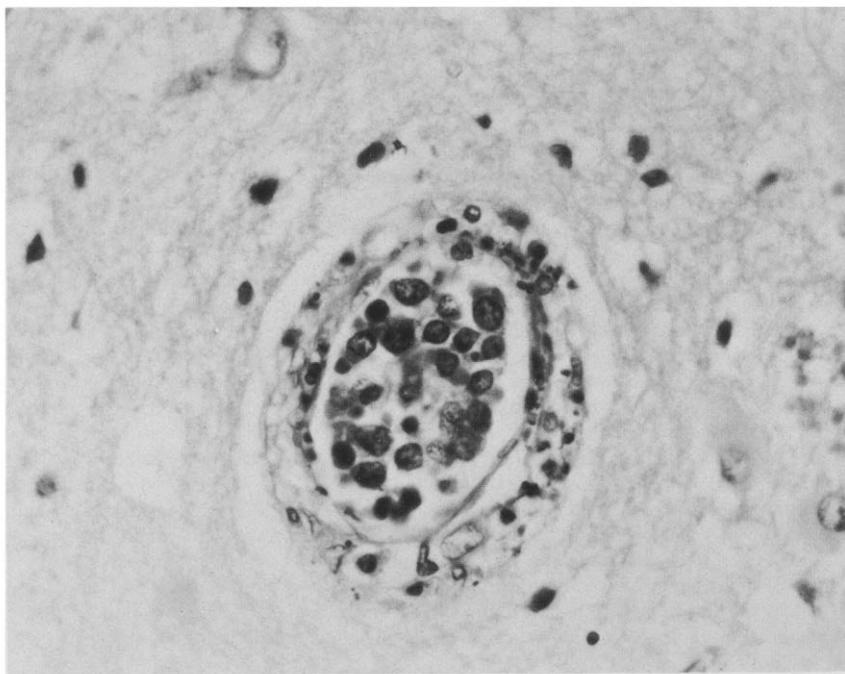


Fig. 4. Small arteriole with mononuclear tumor cells in the lumen and a few in the perivascular space. Luxol fast blue, hematoxylin and eosin,  $\times 320$ .

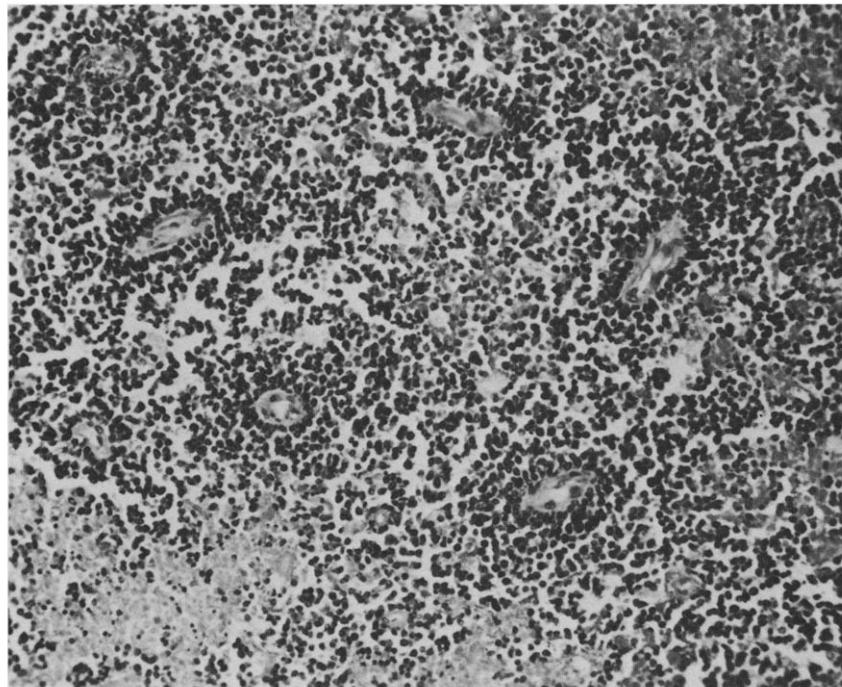


Fig. 5. Section through the globus pallidus showing diffuse infiltration of hyperchromatic mononuclear tumor cells and palisading around small blood vessels. Luxol fast blue, hematoxylin and eosin,  $\times 160$ .

tumor cells with clumped chromatin and scant cytoplasm. The cells were identical with those seen within vessel lumens. They infiltrated diffusely into the surrounding tissue and showed some congregation around vessels (Fig. 5). The pons showed several small hemorrhages in the right lateral pontine tegmentum and numerous small arteries containing tumor cells. The basilar artery was spared.

There was complete necrosis of the spinal cord from the mid-thoracic region caudally. The spinal cord had an extraordinary appearance in that the white matter was trabeculated and the only clearly recognizable structures were the anterior septum and surrounding meninges (Fig. 6). The meninges and anterior septum contained numerous greatly thickened occluded blood vessels in varying stages of organization and recanalization. Fibrinoid necrosis was common. In the anterior septum there was neovascularization (Fig. 7). Many small arteries, capillaries and veins contained tumor cells which were confined to the vessel lumens and in some instances arranged in discontinuous foci (Figs. 8 and 9). In the lumbosacral region the anterior and posterior roots were necrotic. At cervical levels there was secondary demyelination in the fasciculus gracilis.

The peroxidase-antiperoxidase technique (Taylor and Mason 1974; Taylor 1978) was utilized for the detection of factor VIII antigen on the surface of the malignant cells. Unstained sections of cerebral cortex, globus pallidus and spinal cord were deparaffinized with xylene and 100% ethanol. Endogenous peroxidase was blocked with 0.6%  $H_2O_2$  followed by 10 min incubation in 1:2 swine serum. The slides were then incubated in 1:10 rabbit anti-human factor VIII for 45 minutes, washed with buffer, then incubated with 1:20 swine anti-rabbit IgG for 30 min. They were washed and incubated for 30 min with 1:40 rabbit peroxidase-anti-peroxidase and stained with diaminobenzidine for 5 min followed by hematoxylin counter stain. The procedure was also performed with rabbit anti-kappa, anti-lambda, anti-IgA, anti-IgG and anti-IgM in place of anti-human factor VIII.

Positive staining for factor VIII antigen on the endothelial cells of both controls and the patient was demonstrated by the presence of a red-brown precipitate. Malignant cells both in the globus pallidus and in vessel lumens showed no factor VIII staining. The malignant cells showed no staining for light chains or immunoglobulins IgA, IgG and IgM.

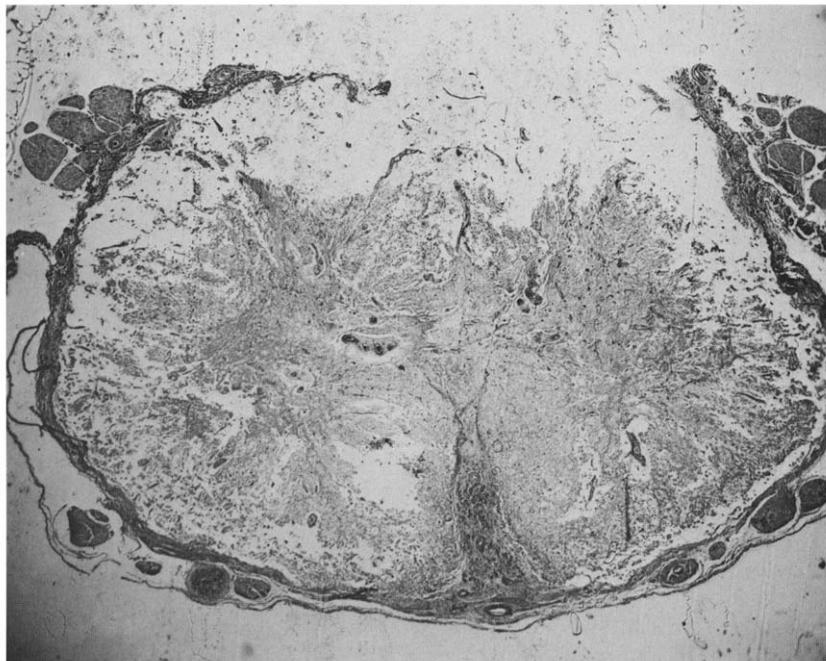


Fig. 6. Lumbar spinal cord showing destruction all cord elements except the anterior septum and surrounding meninges. The white matter has a loose trabeculated appearance. Luxol fast blue, hematoxylin and eosin,  $\times 4$ .

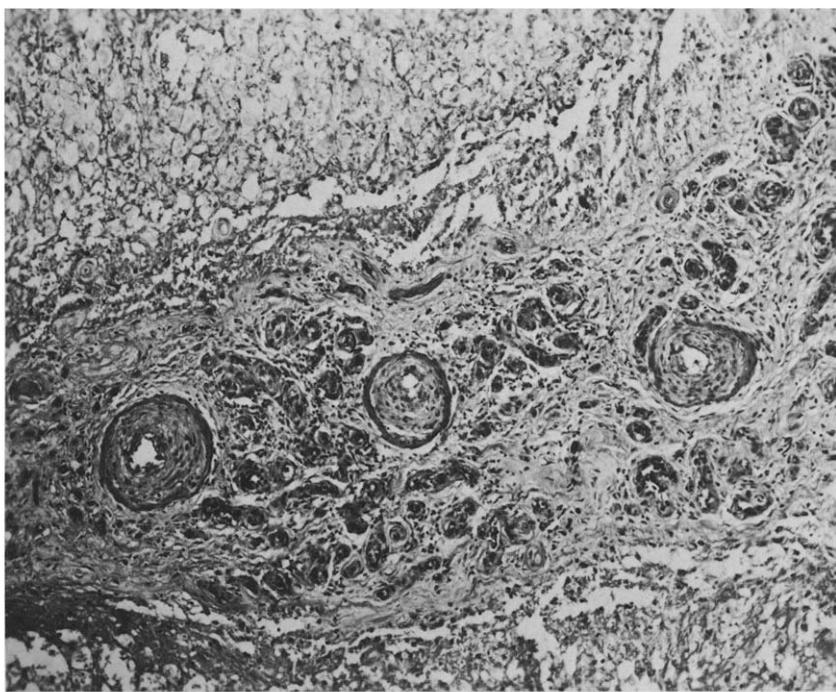


Fig. 7. Higher power view of the anterior septum of the spinal cord from Fig. 6 showing marked intimal proliferation, fibrinoid necrosis of vessel walls and neovascularization. Luxol fast blue, hematoxylin and eosin,  $\times 100$ .

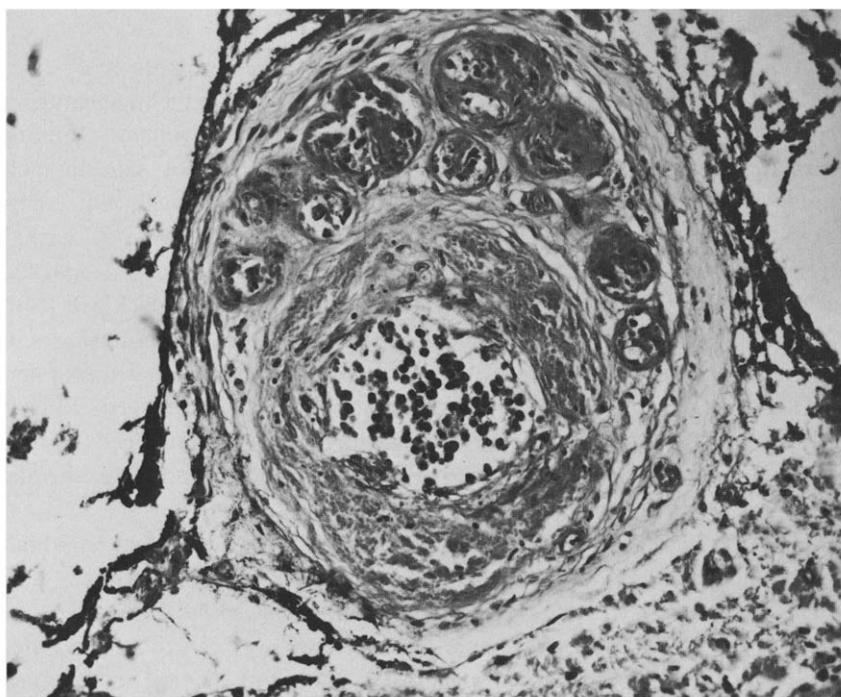


Fig. 8. Spinal meningeal artery containing hyperchromatic mononuclear tumor cells and showing fibrinoid necrosis of the vessel wall. Luxol fast blue, hematoxylin and eosin,  $\times 256$ .

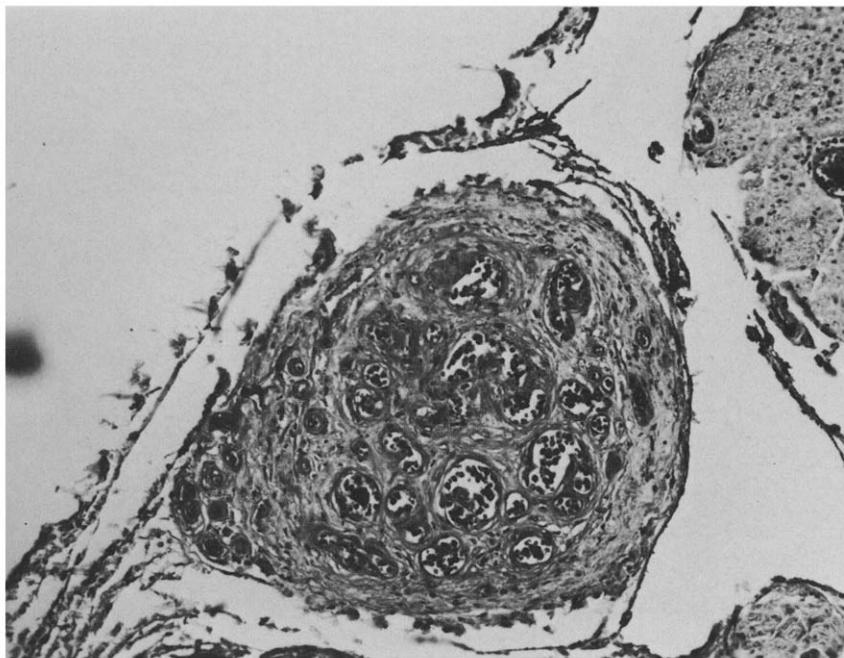


Fig. 9. Recanalized small spinal cord artery containing numerous discontinuous foci of tumor cells within the recanalized lumens. Luxol fast blue, hematoxylin and eosin,  $\times 160$

#### *Comment on Case 1*

After initially presenting with transient ischemic attacks, apparently of cerebrovascular origin, the patient developed a subacute profound dementia featuring mainly a frontal lobe psychomotor retardation with relative sparing of memory function. Investigation revealed an undifferentiated small cell tumor mass in each adrenal. Improvement in the above symptoms occurred spontaneously but particularly after chemotherapy when the patient's mentality returned almost to normal and the adrenal masses disappeared. Respite was brief and in a few months marked abulia returned. After 7 months a gradually progressive paraplegia developed from which the patient died. Pathological examination showed discrete tumor masses in the basal ganglia and widespread patchy infarction of the cerebral hemispheres and brainstem. The spinal cord below the mid-thoracic level was destroyed. Microscopically the special finding was the widespread presence of tumor cells within and largely restricted to the lumens of small blood vessels producing various degrees of occlusion and recanalization.

The clinical presentation was puzzling in particular the mechanism by which an undifferentiated small cell tumor gave rise to transient ischemic attacks and dementia. The computerized tomography scan and cerebrospinal fluid cytology were both negative. The early spontaneous improvement was unexplained. Later the pathological basis for the progressive paraplegia was not evident in life even with the help of surgical biopsy.

*Case 2*

The patient, a 61-year-old man was well until 2 months before admission to the Massachusetts General Hospital. The first symptoms were fatigue and aching in the legs. At about the same time, he was no longer interested in the news and his wife would find him lying on his bed in the dark with his clothes on. He fell asleep after meals. On a Sunday, about 10 days later, he drove away in his car, returning 10 minutes later. He said he thought the day was Sunday. When told it really was Sunday he replied, "I thought today was Sunday." When asked what month it was he said "It's the fourth month of the year, April". (It was July). The year? '74 or '75". (1979). The next day he was disoriented and did not go to work. He put pipe tobacco in the palm of his hand and asked for a match as if he were going to light it. He could not manage to fill his pipe. "His hand wouldn't do what he wanted it to". He was taken to his physician the next day and did not dress properly. "He looked a mess" whereas he normally was vain about his appearance. After the examination he put his pants on inside out and back to front. When the error was pointed out he was hostile and asked to be left alone. Two weeks from the onset he was admitted to his local hospital where he gave answers that made no sense. He asked for a cigarette although he had not smoked them for 10 years. His language was borrowed from earlier years of his life and when asking for a cigarette he would say "Do you have a butt?" He had to be restrained because of instability of gait and failure to stay in bed. A CT scan showed two non-enhancing low density lesions in the left cerebral hemisphere. Angiography and echocardiography were normal. The sedimentation rate was 45 mm.h. The cerebrospinal fluid was normal except for a protein of 70 mg/dl. Decadron 8 mg daily was begun and in 48 h he began to improve and in 1 week had returned to about "85%" of normal. He spent the third and fourth weeks of his illness in hospital and after discharge on Decadron therapy continued to improve. Ten days later he was readmitted for hemorhoidectomy. Postoperatively he again became confused and his gait was more shuffling despite increased steroid dosage. He hung up the telephone on his wife and explained that he didn't know that he had to dial 9 and insisted "yes you have to dial 9 to get Buffalo". This made no sense.

He was at home from the fifth to the eighth week where mental decline continued. At the table eating he was unable to decide if he should use a knife or a fork. He used a fork to butter his roll. He put vegetables in a glass. He reached out too far in picking things up. He was restless and paced around the house unsteady on his feet. He attempted to urinate in the corner of the living room. He became incontinent of bladder and bowel and was unaware of the impact. When visitors were present he attempted to sit in the yard in his pajamas. He became progressively less spontaneous and when told to say something he said "nothing". His signature became terrible. His comments often were wholly out of context. "How long did it take to come here from England by boat?". At times he thought he was in London, England. After smoking a cigarette he put it out by shredding it as he had during his Army days in World War II. In the 9th week he was readmitted to his local hospital where a computerized tomography now showed two lesions in the left cerebral hemisphere, one frontal, the other lateral occipital, and two in the right hemisphere, one frontal, the other posterior parietal. An EEG showed bilateral 4-5 Hertz activity with superimposed sharp waves. He needed help in walking although there was no paralysis. He once said "I have no feeling in my arm (right)" and another time "my hand (left) tingles". Finally, he asked for nothing and wanted nothing.

On admission to the Massachusetts General Hospital 10 weeks from the initial symptoms he lay quietly for the most part but occasionally laughed aloud for a few seconds when he was alone. At times he spoke aloud, mostly jargon, as if talking to an imaginary person. He could give no history. He answered simple questions, for example, Have you a headache?. Are you hungry? He carried out simple commands such as Show your teeth, Put out your tongue, Touch your nose with your finger but after three commands he began to make errors and perseverated touching his nose in response to further commands. When addressed from the right he looked to the left to see who was speaking. When nudged on the right side he quickly looked to the right. The arms and legs moved with good power. He responded correctly to joint position testing in all limbs. The reaction to pinprick was unusual. When pricked 10 or 12 times on a finger it might not move at all or only a few mm. When asked if he felt it he said "yes" and when asked if it was a pin he said "slight". Also, very firm pinprick to the feet elicited no reaction. Pinprick to the upper lip, around the nostril and on the chin produced no turning of the head and only a faint grimace or a nod of the head as if indicating he felt it. During the examination he once said out of context, "It'll go in" and another time he said "I think I'll go". Also, in no particular context he said "I'll put it there". Once he said "no doiz". When asked "Can you look over here?" he said "Oh, yeah", and did so. When asked "Can you hear me?" he said "yes" and after 3 or 4 seconds he changed it to "no" and shook his head. He answered in this way on several occasions. He named a key and a dollar but then called a ring and a tie, a dollar.

When shown a 10 dollar bill he said "a dollar". He counted from 1 to 10, then 10 to 20 and finally to 29. On counting backwards from 10 to 0 he said, "9, 8, 6, 6, 5, 5th". When asked to do this test again a few minutes later he said "9, 8, 6, 5th, 4, 5th, 4, 4, 5, 5th". He gave his age as 40 (61). Are you married? "Oh, yeah". How many children? "Four" (two). Are they all girls? "Yes" (true).

The accuracy of his responses fluctuated. At his best he gave the year (1979) and the city (Boston). When asked what he wanted he said "I need sex, that's all". When asked to write his name the thumb of the left hand became caught on a bar of the siderail of the bed and at first he was unable to extricate it. With the right hand holding the pen he reached 5 or 6 inches past the top of the sheet he was to write on and when the left hand became free he crushed the paper. With the right hand he made a few writing movements in the air. When given a drink he turned his head away and when a cup was placed in his hand he did not carry it to his mouth. When the glass was placed at his lips he drank normally. He sat up in the bed by himself. The tendon reflexes were normal throughout and the plantar responses were flexor. There was a prominent grasping and sucking response bilaterally. There was no toe grasp. He could stand momentarily and when asked to walk he shuffled his feet without moving forward. There was no startle reaction.

A CT scan showed 5 non-enhancing low-density lesions all in the white matter of the hemispheres except one which may have involved the cortex as well (Fig. 10). There was extensive involvement of the right frontal centrum semiovale. Laboratory data were normal except for a sedimentation rate of 55 mm/h. A chest X-ray and studies for collagen vascular disease were normal. An electrocardiogram showed a left anterior hemiblock. Three days after admission the patient underwent a right frontal lobe biopsy. Quick frozen examination revealed 2 small vessels in the white matter ringed with a layer of monocytes, 4 cells thick. Gray matter showed no abnormality. Because of the preliminary impression of a process involving mainly white matter, 2 courses of plasmapheresis were undertaken without benefit. Further pathological sections showed that the two small vessels in the white matter were filled with small round tumor cells with a loose chromatin pattern (Fig. 11). Electron microscopy revealed one vessel in the cortex in which there was an abnormal accumulation of mononuclear cells between the endothelium and the basement membrane. The nuclei of the cells were irregular, pleomorphic and extensively infolded. No cytoplasmic feature of the apparently neoplastic cells indicated the cell type of origin. There was no associated lesion in the surrounding white matter.

In a search for a source of malignant cells an abdominal ultrasound examination revealed a

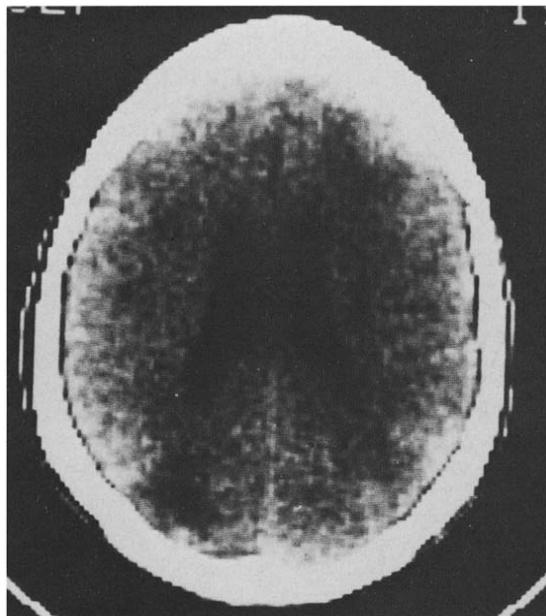


Fig. 10. CT scan of Case 2 showing patchy areas of low density in the left occipital and right frontal lobes as well as diffuse low density throughout the right centrum ovale.

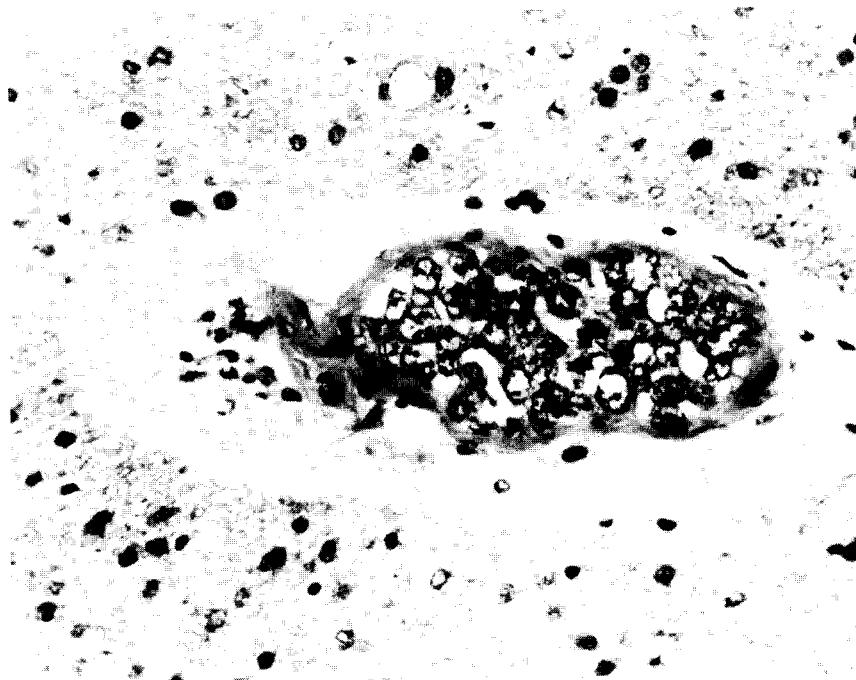


Fig. 11. Frontal lobe biopsy showing small arteriole filled with hyperchromatic tumor cells in the white matter. Hematoxylin and eosin,  $\times 330$ .

3 cm mass in the right lower abdomen. Needle biopsy under ultrasound direction produced 2 specimens without malignant cells.

After admission an increase in steroid dosage produced temporary improvement but relapse soon followed. He seemed not to look directly at objects. He was unanimated and paused for up to 30 seconds before answering. When asked to name a key he said "it radiates money". Two weeks after admission he whispered the year correctly. He gradually became less alert and less responsive and died 4 weeks after admission, 14 weeks from the onset of his illness. Within 1 week of death he still moved all four limbs, grinned a little and waved. Reflex extraocular movements were full horizontally and vertically. A lumbar puncture 4 days after the brain biopsy yielded cerebrospinal fluid containing 87 mg/dl of protein, 78 mg/dl of glucose and 16 WBC's/mm<sup>3</sup> (3 polymorphs and 13 lymphocytes).

#### *Comment on Case 2*

Since an autopsy was not performed, this study remains incomplete. However, the vascular abnormality revealed in the frontal lobe biopsy was identical with that of the first case. Small blood vessels were filled with mononuclear neoplastic cells and in one vessel they infiltrated the media. The findings probably justify the diagnosis of neoplastic angioendotheliosis.

The clinical picture was in accord with this diagnosis. The patient became obviously demented within 2 weeks of onset and except for a period of temporary improvement as a result of steroid therapy, his condition deteriorated to a severely reduced state in about 15 weeks. Frontal lobe signs, dysphasia and impairment of memory were prominent. Transient sensory phenomena may have occurred. Hemiparesis was absent. A CT scan within 3 weeks of onset revealed 2 low density lesions in the hemispherical white matter.

## DISCUSSION

The hallmark of neoplastic angioendotheliosis is the presence usually in many organs of small hyperchromatic tumor cells largely confined to small vessel lumens. In 1959 Pfleger and Tappeiner found intraluminal tumor cells in the biopsy from slightly raised erythematous skin lesions from which the patient eventually recovered on steroid therapy. Subsequently, a number of other cases with predominantly skin involvement were reported, several of which remitted with chemotherapy (Haber et al. 1964; Okagaki and Richard 1971; Rosai and Ackerman 1974; Kurrein 1975; Madura et al. 1975; Scott et al. 1975). There have been 13 cases in which the central nervous system was involved (Shtern and Likhachev 1963; Strouth et al. 1965; Bots 1974; Crosby et al. 1976; Reinglass et al. 1977; Petito et al. 1978; Dolman et al. 1979; Ansbacher et al. 1981) and in 2 of these the skin as well (Braverman and Lerner 1961; Fievez et al. 1971). Other organs for the most part remain asymptomatic despite their involvement at autopsy. The condition has proved to be more serious than in the original case and almost always runs a subacute fatal course. In the central nervous system cases the widespread occlusion of small arterioles and veins results in multiple small pale infarcts in the brain and spinal cord. Multiple small cerebral hemorrhages similar to those in our first patient were described in 2 previous cases (Shtern and Likhachev 1963; Crosby et al. 1976). Extravascular masses of tumor cells as in our case were reported by Crosby et al. (1976) who found symmetrical deposits of tumor in the occipital white matter similar to the globus pallidus masses in our patient. The vascular findings in the spinal cord of our Case 1 were notable in the presence of marked intimal thickening, necrosis of vessel wall and neovascularization. Similar but less extensive changes have been reported in previous cases. Prominent involvement of the adrenal glands with extravascular tumor masses as in our first patient was noted in 2 cases (Strouth et al. 1965; Petito et al. 1978).

*Clinical features of the neurological cases*

One case from the literature was excluded from analysis due to scant clinical details (Shtern and Likhachev 1963). Analysis of the other 14 cases (12 previous cases and the present 2) confirms the impression of others that the main clinical feature of the illness is a *gradually progressive dementia*. This was present in 12 cases (Braverman and Lerner 1961; Shtern and Likhachev 1963; Strouth et al. 1965; Fievez et al. 1971; Bots 1974; Crosby et al. 1976; Reinglass et al. 1977; Petito et al. 1978; Dolman et al. 1979; Ansbacher et al. 1981). Of the 2 exceptions one patient had a spinal cord deficit without cerebral involvement (Dolman et al. 1979, case 2) while the other had blindness and deafness in addition to cutaneous lesions (Braverman and Lerner 1961). The dementia consists of a combination of higher cortical deficits, some localizable, others not, including: aphasia, apractagnosia, impaired memory, abulia (psychomotor retardation) and confusion. Four patients were referred to as demented without further details. The other 8 all showed a frontal lobe deficit with apathy, lethargy and inattention. Four of these also had aphasia.

Two patients had a slowly progressive hemiparesis (Strouth et al. 1965; Reinglass et al. 1977), in another a hemiparesis was found on examination without further details (Fievez et al. 1971) and a fourth patient developed a right hemiparesis, right homonymous hemianopia and expressive aphasia 4 days after hospital admission (Petito et al. 1978). For the most part the onset of neurologic impairment was insidious and sudden stroke-like deficits were uncommon. Seizures were not reported except terminally in our first patient.

In 5 cases the illness was ushered in by transient episodes of numbness, weakness or aphasia suggesting TIA's of cerebrovascular origin (Strouth et al. 1965; Reinglass et al. 1977; Petito et al. 1978; Ansbacher et al. 1981). One patient experienced several episodes of incoherent speech, another reported several bouts of right-sided numbness lasting five minutes, a third patient noted intermittent numbness of the right upper extremity of unspecified duration, and a fourth was noted to have several episodes of numbness of the right arm. Our first patient presented with episodes of numbness and weakness of the right hand, followed by similar episodes involving the left hand. Most of these episodes lasted less than five minutes but once numbness of the right forearm and garbled dysarthric speech persisted for one hour.

A major spinal cord paralysis developed in 5 cases. In 3 patients, including our Case 1, a slowly progressive paralysis of the legs developed over 4-8 weeks leading to areflexic paraplegia (Petito et al. 1978; Dolman et al. 1979). One patient showed hyperreflexia with a left extensor plantar response and weakness of all muscles below the psoas (Strouth et al. 1965), while another developed a "total transverse lesion" at T<sub>1</sub> (Bots 1974).

The onset of persistent symptoms in the cases for which details were provided was as follows: subacute aphasia (Reinglass et al. 1977), poor memory, dysphasia and somnolence (Strouth et al. 1965), paraparesis and lethargy (Strouth et al. 1965), apathy, diminished concentration, dysphasia and confusion (Dolman et al. 1979), paraparesis (Dolman et al. 1979), dementia, lower extremity weakness and numbness (Petito et al. 1978), headache with slight blurred vision and back pain (Ansbacher et al. 1981), severe abulia (present Case 1) and confusion, dysphasia, and shuffling gait (present Case 2). Thus, a somewhat uniform general pattern exists but the neurological details vary greatly.

There were 7 females, 5 males and 2 patients in which gender was not mentioned. The respective ages were 42, 42, 58, 59, 60, 61, 63, 64, 65, 66, 66, 66, 73, and 79 years. The temperature was normal until a late stage of the illness. The sedimentation rate (6 cases) was 42, 45, 50, 60, 63, and 105 mm. An EEG (7 cases) showed a localized slow wave abnormality. Angiograms (7 cases) were normal. CT scan in 2 cases was normal at a well advanced stage of the illness while in a third there were several areas of low attenuation with rim enhancement. CT scan in our second patient showed multiple non-enhancing patchy areas of low density localized mostly in the white matter. Nucleide brain scan (5 cases) was abnormal in 2 cases. The CSF protein (9 cases) was 53, 54, 61, 62, 70, 90, 95, 105 and 108 mg/dl. The CSF sugar was normal. The CSF initial pressure (4 cases) was "normal", 100 and

230 mm of water. Cytological examination of the CSF (3 cases) failed to disclose tumor cells.

In Strouth et al.'s (1965) first case a brain biopsy performed 16 months before death and interpreted initially as normal showed in retrospect the intravascular lesion. In 2 other patients, as in our Case 2, a frontal lobe biopsy was diagnostic (Dolman et al. 1979; Ansbacher et al. 1981). Biopsy of the meningeal vessels should provide the diagnosis since they show widespread involvement.

The general medical examination provides few clues. As already mentioned, there were adrenal masses in 3 cases. The clinical presentation of neoplastic angioendotheliosis may be perplexing but recognition is aided by the fact that most other subacute dementing processes exhibit characteristic features which enable differentiation. The absence of myoclonus, seizures and periodic discharges in the EEG help to exclude Creutzfeldt-Jakob disease (Roos et al. 1973). Progressive multifocal leukoencephalopathy is delineated by its occurrence in an immunocompromised host and the finding of a normal CSF protein (Richardson 1961). Multiple cerebral emboli may result in dementia but the history will usually disclose abrupt episodes of neurologic deterioration (Fisher 1968). In neoplastic angioendotheliosis most deficits evolve insidiously and a paucity of sudden stroke-like deficits is a notable feature. With multiple small cerebral emboli, typified by cerebral cholesterol embolism, there usually will be evidence of embolic damage to other organs.

Steroid therapy has been beneficial in some cases but the effect is only temporary. The patient of Braverman and Lerner (1961) showed an initial response to 60 mg of prednisone. One patient of Dolman et al. (1979) and the patient of Reinglass et al. (1977) showed a remarkable improvement on steroid therapy followed by deterioration upon withdrawal and a return of improvement when it was reinstated. In the patient of Ansbacher et al. (1981) steroid therapy resulted in both subjective and radiologic improvement. Two patients showed no response to steroid (Fievez et al. 1971; Petito et al. 1978). Our first patient initially showed a dramatic response to steroid and chemotherapy lasting 3 months but then relapsed. Our second patient also exhibited striking temporary improvement lasting 3 weeks while on steroid therapy.

#### *Etiologic considerations*

The nature of neoplastic angioendotheliosis is not fully clarified. Pfleger and Tappeiner (1959, 1963) originally proposed that the disease process was a diffuse malignant proliferation of endothelial cells and most subsequent authors have concurred. Evidence in support of this theory was the finding of Weibel-Palade bodies, a specific ultrastructural endothelial cell marker, within the malignant cells of one patient (Petito et al. 1978) and "tubular bodies closely resembling Weibel-Palade bodies" in another (Ansbacher et al. 1981). Dolman et al. (1979) did not confirm this finding in one of their patients. They proposed that the disease was a diffuse intravascular spread of tumor cells from an unrecognized primary source. Meticulous necropsy in their two patients revealed small neoplastic foci in the

thyroid and pancreas, respectively. It is unusual, however, to find diffuse intra-vascular tumor in the absence of extravascular metastases.

We attempted to further elucidate the source of the malignant cells by staining their surfaces for factor VIII antigen, a specific antigenic marker of endothelial cells (Jaffe et al. 1973). Using the immunoperoxidase technique, factor VIII antigen could be demonstrated on the surface of normal endothelial cells but not on the malignant cells. We were likewise unable to demonstrate monoclonal immunoglobulins on the malignant cells, an argument against a lymphocytic origin. The lack of factor VIII antigen on the surface of the malignant cells does not exclude an endothelial origin since dedifferentiation could have resulted in failure to produce the antigen. The proliferation of endothelial cells simultaneously throughout the body is a unique concept with little or no precedent. Reversible endothelial proliferation has been reported with several soluble factors including one associated with experimental carcinomas (Folkman et al. 1971) and another isolated from cultured neuronal and glial cell tumors (Suddith et al. 1975). In any case, in our first patient malignant cells were localized within the lumens of arterioles, small veins and capillaries and were not seen in adjacent muscular arteries or the large arteries of the remainder of the body. Other authors have also noted predominant involvement of thin walled vessels (Strouth et al. 1965; Reinglass et al. 1977; Dolman et al. 1979). This pattern of selective distribution of neoplastic cells is difficult to reconcile with a diffuse proliferation of endothelial cells and is more in keeping with metastasis.

The striking predilection of neoplastic angioendotheliosis for the central nervous system has a counterpart in the experimental studies of metastasis by Nicolson and collaborators (Brunson et al. 1978; Nicolson et al. 1978). They demonstrated that the distribution of metastases was not random nor dependent on the initial vascular bed encountered. Tumor cells which metastasized to specific organs could be cloned in vitro and then selected in vivo until a line of cells was produced which preferentially metastasized to a single organ. Tumor cells could be selected which colonized lung, ovary or brain and differences in the cells surface proteins were demonstrated. The unusual localization of neoplastic cells in neoplastic angioendotheliosis may therefore be a particularly striking example of a clone line adapted to the environment of the lumen of particular small vessels.

At present the origin and true nature of these neoplastic cells must be considered as incompletely resolved problems. The mechanism by which steroid therapy achieves striking benefit is of interest and judging from the promising results of chemotherapy in our first patient it should be possible to devise a more effective therapeutic regimen. Finally it is conceivable that the early recognition of cases of neoplastic angioendotheliosis will permit fruitful investigations concerning the operation of humoral agents and neoplastic factors, the presence of circulating tumor cells and the isolation of highly specialized abnormal cells in tissue culture.

## ACKNOWLEDGEMENTS

We are indebted to Dr. George Kleinman for assistance in performing the immunoperoxidase stains and to Dr. Amy Pruitt for her translation of the reference of Shtern and Likhachev from the Russian. Dr. Dennis Landis performed electron microscopy on the cortical biopsy from our second patient.

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