Brain Tumors with Tuberous Sclerosis*

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In contrast to the high incidence of brain tumors in patients with von Recklinghausen's disease, intracranial tumors are seldom seen in patients with tuberous sclerosis. The present confusion regarding the pathology and preferred therapy for these lesions can perhaps be attributed to the limited number of cases that a single neurosurgeon or pathologist is likely to encounter, and the fact that the related literature is composed mainly of single case reports.

The term "brain tumor," when applied to a lesion in tuberous sclerosis, must be carefully defined, for strictly speaking, each of the multiple intraventricular nodules that characteristically occur in this disease could be considered a tumor. In this report, therefore, the word "tumor" will be reserved for those lesions associated with increased intracranial pressure.

In a recent review of patients at Duke University Medical Center and the mental hospitals serving Eastern North Carolina, 48 cases of tuberous sclerosis were found. Of these 48 cases, seven had intracranial tumors. Five of these were verified at operation, one at autopsy, and one by ventriculography. The clinical and pathological findings, and our experience in treating these seven patients, are summarized in this report. The reader is referred to discussions of the cutaneous,2 retinal,14 cardiac,1 pulmonary,5 renal,8 and bone6 lesions of tuberous sclerosis.

Case Reports

Case 1. This 11-year-old Negro boy was admitted to the hospital because of headaches, vomiting, and coma. His parents considered him moderately retarded. He had had poor vision for 4 years, and had had bilateral occipital headaches for 3 months. Nausea and vomiting had occurred for 1 month prior to admission. For an unknown period of time he had had episodes of transient "drawing of his mouth" to the left. He had gradually developed weakness in his legs, but had had no difficulty with his hands. A congenital strabismus appeared to grow worse. About 5 days before admission he developed hyperextension of the neck and became semicomatose.

Examination. The patient responded only to pain. Bilateral papilledema was noted but no localizing neurological signs were detected. Adenoma sebaceum were noted over the malar areas of the face. Roentgenograms revealed calcifications above the sella. He developed apnea shortly after admission and was immediately taken to the operating room.

Operation. Following bilateral ventricular taps, spontaneous respiration returned. Craniotomy revealed unusually firm frontal gyri. The medial portion of the wall of the anterior horn of the left lateral ventricle, anterior to the foramen of Monro, bulged into the ventricle. When the medial wall of the ventricle was incised, a firm pinkish neoplasm was encountered and easily removed.

Postoperative Course. The resection was felt to be subtotal, and the patient received x-ray therapy. Intracranial calcifications were still present on follow-up x-ray. The patient continues physically well 13 years after surgery. He is institutionalized with the classical stigmata of tuberous sclerosis, but he has no signs of increased intracranial pressure or of focal neurological deficit.

Case 2. An 8-year-old white girl was admitted to the neurosurgical service from another hospital, where nuchal rigidity and papilledema had been noted and a tentative diagnosis of meningitis had been made after a lumbar puncture showed a total protein of 321 mg%. She had been considered mentally retarded since the age of 8 months, when

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she first began having generalized tonic-clonic convulsions. These seizures became well-controlled on anticonvulsants after the age of 5. She never developed the ability to say more than a few words. During the several months preceding admission she had developed a right hemiparesis, and 2 weeks before admission she began bumping into objects and became lethargic. One week before admission she developed fever, anorexia, and increased lethargy.

**Examination.** The vital signs were normal except for a temperature of 38.5°C and Cheyne-Stokes respirations. She had a high-pitched cry in response to painful stimuli, but did not speak. There was bilateral papilledema. She could move her arms and legs, but less well on the right side of the body, and she had bilateral ankle clonus. Her neck was stiff, and MacEwen’s sign was present. Adenoma sebaceum were noted over the malar areas of the face. Routine laboratory studies were unremarkable except for 4+ proteinuria. Roentgenograms of the skull revealed separation of the sutures. Ventriculography showed increased cerebrospinal fluid pressure and a large mass in the right lateral ventricle.

**Operation.** A craniotomy was carried out. The exposed cortex was firm and rubbery. The pink tumor was found to be attached to the ventricular wall along the anterior portion of the septum pellucidum and the anterior wall of the right lateral ventricle. Part of it extended through the foramen of Monro into the third ventricle. It was granular, well-encapsulated, and friable, with several light-yellow areas on its surface. A subtotal resection of the tumor was carried out.

**Postoperative Course.** Twenty months after operation the patient is living, with no evidence of recurrent tumor. Seizures are controlled with mesantoin. She is still mentally retarded.

**Case 3.** A 9-year-old white boy was admitted with a high fever of several weeks’ duration. He had developed seizures at the age of 6 months and had been observed to be retarded. Bilateral subdural taps at the age of 1 year had not revealed any abnormality. He never developed the ability to speak, and had remained helpless and bedridden throughout his life.

At age 6 he had been admitted to a mental hospital for routine physical examination. He was found to have a fibrous thickening in the lumbo-sacral region, convergent strabismus with some nystagmoid movements on looking to the right, and warty brownish red nodules 1 to 2 mm in diameter distributed across the malar area of the face. There was no sign of increased intracranial pressure. The child could sit but otherwise was not able to support himself and was considered extremely retarded. The family history was unremarkable except that one paternal aunt was reported to be mentally retarded.

Two years later he developed intermittent fever as high as 104°F to 106°F for several weeks. The fever did not respond to antibiotics and its cause was undiagnosed by numerous cultures. His pupils were dilated and poorly reactive, and there was papilledema in the right eye. Clusters of phakomatous nodules were noted in the left fundus. His neck was stiff and MacEwen’s sign was noted. He responded only to severe pain. The fever continued unabated and he died at age 9.

**Autopsy.** At autopsy, the kidneys contained many pale, firm nodules measuring up to 1 inch in diameter. Many of these extended through the cortex into the superficial portion of the medulla. There was a rhabdomyoma of the heart. The brain weighed 1250 gm and its surface showed many irregularly arranged gyri, some quite pale and firm, and one over 2 cm wide. Eighty per cent of the brain’s surface was so involved.

The lateral ventricles were markedly dilated and contained a clear straw-colored fluid. Attached to the walls of the lateral ventricles were a number of irregular, pale, firm nodules. The anterior horn of the right ventricle contained a nodule 5 cm in diameter composed of a yellowish-green soft substance suggestive of extensive degenerative change.

**Case 4.** This 7-year-old white boy was admitted to the hospital with bifrontal headaches of 4 months’ duration. The headaches were dull, intermittent, and were relieved by vomiting. For several days before admission the patient had an unsteady gait and had developed weakness in the right side of his body. He had no seizures. He was described as a “nervous” child but apparently his development had been normal and his family
did not consider him retarded. He had been a premature baby with a birth weight of 4 lb 13 oz. The family history was noncontributory.

Examination. The patient was thin and appeared chronically ill. Adenoma sebaceum were noted over the face. A MacEwen's sign was present. Cranial nerves were intact except for right central facial weakness and bilateral papilledema. The right side of the body was mildly weak. No sensory deficit was present. A Babinski response was present on the right side, but otherwise the reflexes were normal.

X-rays of the skull demonstrated separation of the sutures, decreased density of the sella, and scattered areas of intracranial calcification. A brain scan revealed concentration in the left frontoparietal area. The electroencephalogram showed high voltage slowing in the left hemisphere with dysrhythmic background activity over the left hemisphere. Cerebrospinal fluid obtained from the left lateral ventricle had a total protein of 1070, 5 white cells, and a negative STS.

Operation. The ventriculogram showed subependymal nodules, hydrocephalus, and a mass in the left lateral ventricle which had occluded the foramen of Monro. A Torkildsen procedure was performed, shunting spinal fluid from the left lateral ventricle into the cerebral subarachnoid space. Postoperatively, the patient received a course of Cobalt-60 radiation therapy, with an estimated tumor dosage of 4000 r.

Postoperative Course. Following discharge the patient resumed normal activities and, returned to school. He did well for 9 months, the only neurological abnormality being optic atrophy and minimal ataxia. He then developed headaches, which increased in severity and frequency and were associated with vomiting and increased ataxia. The patient was readmitted to the hospital where examination revealed the optic discs to be elevated, with blurred margins bilaterally. Motor function and coordination in the upper extremities were normal, but the gait was broad-based. A Babinski response was noted on the right. Brain scan showed an area of abnormal concentration in the region of the tumor, but it was smaller and better defined than the comparable area seen on the earlier scan. At lumbar puncture the opening pressure was 300; the clear fluid contained 240 mg% protein. Repeat pneumoencephalograms and ventriculograms showed little change in the size of the ventricles or tumor. The Torkildsen tube was patent. During this hospitalization, the patient became more alert and free of headaches and vomiting. He was discharged without surgery.

Case 5. A 5-year-old white boy was admitted for evaluation of seizures and a behavior disorder. He was the product of a full-term pregnancy complicated by toxemia and “flu” during the fourth and fifth months, but delivery was normal. He was well until age 2 when he began to have episodes of “weakness” characterized by falling to the left, but he could immediately right himself. At age 4 he developed left-sided seizures which were preceded by an abdominal aura and a cry. After a tonic-clonic phase lasting about 1 minute, the patient usually went to sleep for 10 to 15 minutes. The family stated that the child had had a severe behavior problem since birth. The family history was negative.

Examination. The boy was unusually active, and cursed, spat, and attempted to bite. General physical and neurological examinations were entirely normal. There were no skin lesions. The electroencephalogram revealed multiple spikes followed by slow waves over all regions of the head. Skull roentgenograms showed a circumscribed area of calcification in the right frontal region and near the midline. The cerebrospinal fluid pressure was 180 mm saline with a protein content of 44 mg%. The pneumoencephalogram was normal. Psychometric tests revealed retardation in both social and intellectual areas, but the patient was considered capable of at least a dull-normal performance. The patient was discharged on anticonvulsant medication and the seizures were well controlled.

Second Examination. The patient apparently did well until age 11 when he complained of poor vision and headaches which were sometimes associated with nausea and vomiting. At this time vision was reduced to light perception in the right eye and counting of fingers at 10 feet in the left. The pupils were equal, and reactive to light. He had extreme papilledema bilaterally. There was questionable left-facial weakness and some weakness in the left arm and leg, but sensory
examination was negative. The reflexes were normal. Coordination was generally poor. The physical examination was otherwise normal.

Skull films showed accentuation of the convolutional markings of the inner table in the frontal region. The cerebrospinal fluid pressure was 250 mm saline and the fluid was yellow. The electroencephalogram showed a right frontal focus of spike activity. A ventriculogram, done through the sutures, revealed clear fluid in the right ventricle and yellow fluid in the left. The protein content in the latter was 930 mg%. Roentgenograms showed dilated left and right lateral ventricles and mural nodules. There was a mass in the region of the foramen of Monro which pushed the third ventricle downward.

Operation. A bilateral Torkildsen procedure was done. Following this, the intracranial pressure was found to be elevated on eight subsequent lumbar punctures. Six weeks after the Torkildsen procedure, a lumbar spinal subarachnoid-peritoneal shunt was performed. The patient was then given a course of Cobalt-60 x-ray therapy with an estimated tumor dosage of 4,500 r. At the time of discharge he was blind, but there seemed to be general improvement.

Fourth Examination. Seven months later he was re-admitted with a 3-week history of increasing lethargy, anorexia, and headaches. Examination at this time revealed adenoma sebaceum over the face in a butterfly distribution. There was bilateral optic atrophy. He had minimal left-central facial palsy and moderate weakness in the left arm and leg. There was still no sensory defect, and the reflexes were normal. His neck was stiff. The night of admission the patient suddenly became apneic and required endotracheal intubation for respiration. At this time the right lateral ventricle was tapped and a pressure of 180 was found. The left lateral ventricle was then tapped; the pressure here was 110. However, even before the taps, the child began breathing on his own. The next day he was well-oriented and in no distress. The apneic episodes were attributed to seizure phenomena. A ventriculogram via the right posterior trephine revealed a tumor involving the anterior third ventricle and the anterior portion of the right lateral ventricle. A second tumor was identified encroaching on the medial side of the left lateral ventricle. The protein content of fluid from the left lateral ventricle was 1,200 mg% and that from the right lateral ventricle, 1,340 mg%.

Operation. Most of the tumor mass from the right lateral ventricle was removed via a right frontal craniotomy.

Postoperative Course. The patient continued to have episodes of apnea, and on the second postoperative day his blood pressure increased and the left pupil dilated. The left lateral ventricle was tapped and a pressure greater than 600 was found. A constant ventricular drainage catheter was inserted, and he was started on Doxapram to stimulate respirations. The patient remained unresponsive, developed pneumonia, and died on the ninth postoperative day.

Autopsy. Autopsy was restricted to the brain. A small epidural hemorrhage was found overlying the right hemisphere. The entire brain appeared somewhat edematous. Dark clotted blood protruded from the transcortical incision. There was contiguous hemorrhage into the right basal ganglia, and the lateral ventricles and third ventricle were filled with blood. The cerebellar tonsils had herniated through the foramen magnum. There were numerous small wart-like excrescences in the floor of the lateral ventricle, and many firm grayish nodules 2 to 5 mm in diameter were scattered over the gyri. All tumor had been resected.

Case 6. This 11-year-old white boy was admitted in 1950 because of headaches, vomiting, and blindness. From infancy he had had generalized tonic states with some clonic movements which occurred as often as two to three times a day, associated with occasional episodes suggestive of status epilepticus. He did not talk or walk until he was 3 years old. One month prior to admission he had developed difficulty with walking, and his previous mental deficiency seemed worse. He complained of diffuse headaches and manifested dysconjugate deviation of the eyes, vomiting, and a stiff neck. Two days prior to admission the child became blind.

Examination. He was well-nourished, but lethargic and irritable. He was blind in both eyes, with bilateral papilledema of 2 dipoters. The right eye was deviated downward and outward, and the left eye was upward and outward. Some suggestion of left facial weakness was noted, but he moved all ex-
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tremities well and had no decrease in his response to pin-prick. He had truncal ataxia. Ventriculography revealed an interventricular neoplasm in the right lateral ventricle, occluding the foramen of Monro.

Operation. Surgery revealed a tumor which had protruded into the right lateral ventricle and through its medial wall to penetrate the septum pellucidum. The tumor was encapsulated, pink, friable, and vascular; although it had occluded the foramen of Monro on both sides, it could be completely removed. A second abnormality found at surgery consisted of an area in the left frontal lobe which felt rubbery and was grayish-white in color.

Postoperative Course. Fifteen years after the removal of the tumor, the patient is institutionalized because of mental deficiency and seizures. He is totally blind, has bilateral optic atrophy and a mild right hemiparesis. He continues physically well with no signs of increased intracranial pressure. Except for a subungual wart he does not have the physical stigmata of tuberous sclerosis.

Case 7. A 10-year-old Negro girl was admitted with a 3-day history of stupor and fever. She had been well until 3 months before admission when she had a generalized convulsion, preceded by a bifrontal headache. A second seizure occurred 1 month before admission when, while lying in bed, she became rigid, her eyes deviated upward, and she urinated, but did not have clonic movements. This seizure was also preceded by a headache; after that time, the headaches increased. Four days before admission she had a third seizure, following which she was stuporous and confused. She was unable to walk or perform coordinated movements with her hands. She had continued to eat and had no vomiting.

Gestation and delivery had been normal. The parents felt that she had always been somewhat retarded; she failed the first grade and had been a consistently poor student. Her grades had been even worse the year before admission. The father, mother, and seven siblings were in good health. A paternal grandmother had epilepsy and heart disease, and several cousins were known to be epileptic.

She was poorly nourished, febrile, and stuporous, but conscious and could respond to pain. The head circumference was 56 cm. There was no MacEwen's sign. The eyes deviated to the right and nystagmus was noted. Her neck was moderately stiff. Some rigidity of the right arm and leg was noted. She moved the right side more than the left, and was incoordinate in all her movements. The tendon reflexes were symmetrical, with normal plantar responses. No skin lesions were noted.

The electroencephalogram revealed suppression of background rhythms and high-voltage slow waves over the right side. Roentgenograms of the skull showed separation of the sutures and intracranial calcification to the left of the sella, which was itself enlarged. Ventriculography demonstrated a lesion mass in the right lateral ventricle. Fluid from the left lateral ventricle had 195 mg% protein and from the right lateral ventricle had 2,890 mg%.

Operation. The right lateral ventricle was dilated and almost occluded by a grayish tumor mass. Subtotal resection of the tumor was done; it could then be seen that the tumor arose from the floor of the right lateral ventricle and extended deep medially into the region of the septum pellucidum and into the third ventricle.

Postoperative Course. Following surgery the patient had fever, persistent hypo-natremia, leukocytosis, and pleocytosis. She was started on intravenous antibiotics for a possible meningitis. X-ray therapy was begun 2 weeks after operation, and a Torkildsen procedure was done 1 month after operation. She died 1 week following the Torkildsen procedure.

Autopsy. At autopsy a rhabdomyoma of the heart and a hamartoma of the kidney were found. The brain revealed markedly flattened gyri with the right cerebral hemisphere larger than the left. There were isolated pearly white gyri in all parts of the cerebral cortex; these were much firmer to palpation than the adjacent normal gyri and in the right frontal cortex became confluent over an area of 10 cm. Marked enlargement and increased firmness of the optic chiasm were noted. The cerebellum appeared smaller than normal, and the diameter of the medulla at the level of the inferior olives was much greater than normal. Both lateral ventricles were dilated; the right was larger than the left and filled with thick, yellow, gelatinous
material and a soft, brownish-yellow tumor 5 cm in diameter, which compressed the surrounding brain and displaced the septum pellucidum to the left. The ependymal surface was nodular; the cut surface was cystic, focally necrotic, and showed some brownish color without hemorrhage. There were numerous projections from both lateral ventricular walls; these varied from clusters of small velvety nodules to single masses 1 to 2 cm in diameter. The ependyma throughout the dilated region was leathery and granular. There was marked right-to-left herniation of the cingulate gyrus beneath the falx. The vessels at the base of the brain were normal.

**Discussion: Clinical Aspects**

The clinical histories of these seven patients are summarized in Table 1. All patients were children ranging from 7 to 11 years of age; five were boys and two were girls. Seizures were the first sign of nervous system disease in all but one patient. None showed a clear-cut family history of tuberous sclerosis, and only two had a family history of epilepsy or mental retardation.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age Tumor Found (yrs)</th>
<th>Race</th>
<th>Sex</th>
<th>Initial Symptom</th>
<th>Family History of Tuberous Sclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>W</td>
<td>M</td>
<td>Headache</td>
<td>Negative</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>W</td>
<td>F</td>
<td>Generalized Seizures</td>
<td>Negative</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>W</td>
<td>M</td>
<td>Generalized Seizures</td>
<td>Paternal aunt retarded.</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>N</td>
<td>F</td>
<td>Generalized Seizures</td>
<td>Mother epileptic.</td>
</tr>
<tr>
<td>5</td>
<td>11</td>
<td>W</td>
<td>M</td>
<td>Generalized Seizures</td>
<td>Paternal grandmother and several cousins epileptic.</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>W</td>
<td>M</td>
<td>Left Focal Seizures</td>
<td>Negative</td>
</tr>
<tr>
<td>7</td>
<td>11</td>
<td>N</td>
<td>M</td>
<td>Left Focal Seizures</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Table 2 summarizes the major physical findings of these 7 patients at the time their brain tumors were diagnosed. Mental retardation was present in 6 patients, adenoma sebaceum in 4, and a so-called "shagreen" patch in the lumbosacral area in one. Except for papilledema, retinal lesions were conspicuously absent. One striking finding was the marked elevation in ventricular fluid protein in some of these patients, which ranged from 60 to 2,890 mg%, averaging over 1000 mg%. Ventriculography was used to locate 6 of the 7 tumors. In each case, the tumors were in the region of the foramen of Monro and were associated with ventricular dilatation (Fig. 1).

Four patients in this series underwent craniotomy with resection of the tumor as the initial operative procedure. One resection was considered complete and the other 3 were subtotal (Fig. 2).

The patient whose tumor was totally resected is alive but institutionalized 15 years postoperatively. One patient who had subtotal resection is alive but institutionalized 13 years postoperatively; another is alive.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Mental Status</th>
<th>Skin Lesions</th>
<th>Retinal Lesions</th>
<th>Intracranial Calcification</th>
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<tr>
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<td>Normal</td>
<td>Adenoma Sebaceum</td>
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</tr>
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<td>2</td>
<td>Severely Retarded</td>
<td>Adenoma Sebaceum</td>
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<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Severely Retarded</td>
<td>Adenoma Sebaceum</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>Mildly Retarded</td>
<td>Adenoma Sebaceum, &quot;Shagreen&quot; patches in lumbosacral area.</td>
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<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>Severely Retarded</td>
<td>Adenoma Sebaceum</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>I.Q. 69</td>
<td>Adenoma Sebaceum</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>Moderately Retarded</td>
<td>Adenoma Sebaceum</td>
<td>None</td>
<td>Yes</td>
</tr>
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</table>
FIG. 1. Ventriculogram showing tumor in its characteristic location, arising in the region of the foramen of Monro. Other smaller nodules can be seen projecting into the lateral ventricles. This patient had previously had a bilateral Torkildsen procedure.

FIG. 2. Tumor in the region of the foramen of Monro as it appeared at surgery. It was exposed through a transcortical incision and presented as a pinkish, friable, encapsulated mass within the lateral ventricle.
but retarded 2 years postoperatively; the third had persistent increased intracranial pressure following operation and died 1 week following a subsequent Torkildsen's procedure.

The Torkildsen's procedure was done initially in two patients, one of whom had a lumbar subarachnoid-peritoneal shunt done 6 weeks later because of persistent hydrocephalus. This patient did well initially but returned 6 months later with episodes of apnea which were considered to be diencephalic seizures. He underwent craniotomy at this time with resection of the tumor and died postoperatively. The second patient with an initial Torkildsen's procedure returned 10 months later with headaches and papilledema. Ventriculogram revealed no increase in ventricular size, but no air in the subarachnoid space. His headaches subsided during the hospitalization, and he was discharged to be followed as an outpatient.

The similarity in the clinical aspects of these cases is notable. All tumors occurred in children. Most patients were mentally retarded and epileptic. All tumors occurred in the region of the foramen of Monro. This combination of findings has generally been present in the published reports although exceptions can be found.

It is also important to note that the classical cutaneous and retinal lesions of tuberous sclerosis were often absent in these children, each of whom had signs of increased intracranial pressure. In such cases, the diagnosis of tuberous sclerosis should still be suggested by any of the following: 1) a history of mental retardation and seizures in a child; 2) the demonstration of small periventricular calcification by plain skull x-rays; 3) the ventriculographic demonstration of an intraventricular tumor at the foramen of Monro or of small nodules projecting into the ventricular system, giving the picture of candle drippings; and 4) the operative finding of pale firm nodules scattered over the cortical surface.

In our experience, the best results were obtained by resection of the tumor. The Torkildsen's procedure was of little benefit in the two cases where it was used as the initial operative procedure. Radiation therapy was used in three cases, but in view of the long survival in patients who did not receive x-ray therapy, we are unable to draw conclusions regarding its usefulness as an adjunctive measure.

Although the mortality rate for resection of the intraventricular neoplasm is acceptable, the prognosis for functional usefulness in these patients is poor. Of the four surviving patients in this series, three are institutionalized with mental deficiency. This is to be expected as one of the several manifestations of this disease, and not as a result of surgical intervention. The fourth patient appears to be of average intelligence and is doing well in school.

Discussion: Pathology

The characteristic central-nervous-system lesions of tuberous sclerosis are the "tubers" of the cortex, and the subependymal nodules which project into the ventricles; the latter give the "candle dripping" appearance typical of the pneumoencephalogram in this disease (Fig. 1).

Tubers. The cortical tubers have been described in detail by Critchley and Earl. They appear as whitish or pale nodules which are usually seen at the summit of the gyrus (Fig. 3). They range from 0.5 to 3 cm in size and have a firm rubbery consistency. There is no apparent predilection as to site. Larger lesions may occupy adjacent gyri or may be elongated along a single gyrus. Although tubers appear sharply demarcated to the naked eye, histologically there is usually gradual merging of abnormal tissue into the more normal areas.

Within the tubers the usual neuronal lamination is disturbed (Fig. 4). Pyramidal cells are sometimes seen in superficial layers and may be disoriented with the apexes no longer directed upward. Scattered neurons can be seen in the white matter. Many pathological changes are observed in the neurons, including chromatolysis, nuclear degeneration, cellular sclerosis, and ghost cells. Large abnormal cells which resemble neurons are often present. There is an increase in the total number of astrocytes. Gemistocytic astrocytes can usually be found, and in the superficial zones there are tufts of glial fibers with so-called ruffled hair appearance (Fig. 5).

The subependymal lesions have a different microscopic appearance (Fig. 6). These lesions are usually covered by a layer of intact ependyma and are well circumscribed.
They are composed predominantly of two cell types: elongated spindle cells which resemble spongioblasts, and plump eosinophilic cells which appear to be gemistocytic astrocytes.

The plump cells have a homogenous eosinophilic cytoplasm, eccentric nuclei, and sometimes contain nucleoli. Neurons were not seen in our sections of the subependymal lesions but other authors have reported neurons in these lesions.

Tumors. Although there is no definite site of predilection for the interventricular nodules, the brain tumors of tuberous sclerosis are almost always situated near the foramen of Monro, either in the lateral ventricles or in the anterior third ventricle (Fig. 7).

There is disagreement regarding the morphology of these tumors. They have been variously classified as astrocytomas,11,17 embryonal gliomas,4 spongioblastomas,10 neurinomas,16 ependymomas,12 and spongioneuroblastomas.7 The disagreement in classification most likely represents different interpretations of the same lesion by different pathologists. As pointed out by Russell,17 most reports concern individual cases and authors who have reported several tumor cases agree that the lesions are similar, although they may not agree on the classification.

The striking finding in our six cases from which tissue was obtained is the microscopic similarity of the lesions.

In some tumors the predominant cell is a large polyhedral cell with distinct cosinophilic homogenous cytoplasm and an eccentric pale nucleus which contains stippled

**Fig. 3.** Cross section of a cortical tuber in an autopsy specimen.

**Fig. 4.** Low-power photomicrograph of cortical tuber. There is loss of normal cortical architecture with pyramidal cells in superficial layers, and loss of normal orientation of pyramidal cells. Scattered neurons can be seen in the white matter. (H & E., X256).
Fig. 5. Photomicrograph showing numerous astrocytes and ruffled hair appearance of glial fibers in cortical tuber. (H. & E., X320).

Fig. 6. Photomicrograph showing histologic appearance of subependymal nodule. (H. & E., X320).

Fig. 7. Gross appearance of typical tumor in transverse section of the brain. Subependymal nodules can be seen projecting into the left lateral ventricle.
FIG. 8. Photomicrograph showing pavement-type arrangement of large polyhedral cells in tumor. (H. & E., ×800).


FIG. 10. Photomicrograph showing transition forms between elongated bipolar cells (spongioblast) and large polyhedral cell (gemistocytic astrocyte) (H. & E., ×800).
chromatin and a definite nucleolus. No tigroid substance was seen within these cells on Nissl stain. In areas which contain this type of cell exclusively, the cells are compactly arranged in a pavement-type pattern (Fig. 8).

In other areas the cells are more loosely arranged and are intermingled with smaller and elongated unipolar or bipolar cells which have hyperchromatic nuclei. These cells are often arranged in whorls (Fig. 9). In other areas, similar cells are arranged in a loose reticular network or around blood vessels to give the appearance of perivascular halos of cytoplasm without nuclei. In areas where spindle-shaped cells are intermingled with the larger cells, apparent transition forms between the two cell types can be seen (Fig. 10).

In some tumors the predominant cell is a large cell which we consider to be a gemistocytic astrocyte, in agreement with Russell.\(^7\) In other tumors, the predominant cell is a smaller, elongated cell which appears to be a spongioblast. In every tumor both cell types could be found. We feel that these tumors can best be classified as astrocytomas, although it must be emphasized that they are all composed of mixtures of two cell types.

**Summary**

We have reviewed seven cases of brain tumor associated with tuberous sclerosis. The typical patient was a mentally retarded child with epilepsy and signs of increased intracranial pressure. Adenoma sebaceum was usually, but not always, present at the time the tumor became apparent. Other skin or retinal lesions were unusual in our experience. The presence of intracranial calcification was helpful in diagnosis, but was seen in only five of our cases. A family history of tuberous sclerosis was rare.

From a pathological standpoint, the tumors were histologically similar and were composed of mixtures of spongioblasts and gemistocytic astrocytes. The tumors were located in the region of the foramen of Monro and resulted in noncommunicating hydrocephalus.

In our hands, best results were obtained by resection of the tumor rather than by shunt procedures. However, most patients will remain mentally retarded because of the basic nature of the disease process.

**References**