The Neuropathology of Temporal Lobe Epilepsy

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INTRODUCTION

One hundred years ago, Jackson made an association between the “dreamy state” form of epilepsy and localized temporal lobe lesions (1), and Horsely removed a temporal lobe tumor curing his patient's seizure disorders (2). This therapeutic triumph was mysterious, for at that time there was no organized classification of the epilepsies, no EEG, no system of pathology for brain lesions, and no brain imaging. With the discovery of the EEG, a measurable definition of the relationship between clinical seizures and altered electrical activity of the brain was possible. In the 1930s Penfield, Jasper and Cone formed the first team to study the seizing brain. With them, in the 1950s Earle (3) considered pathogenic mechanisms in Ammon’s horn sclerosis and Olzewski (4) described Rasmussen’s encephalitis. Elsewhere, the pathology of temporal lobe epilepsy (TLE) was being described: in Germany by Stauder (5); in England by Meyers, Falconer, Beck and Cavanagh (6, 7); in England by Meyer, Falconer, Beck and Cavanagh (8, 9); and in Belgium by Morel and Wildi (10). Within the next decade Margerison and Corsellis (11) wrote their important paper on the “clinical, electroencephalographic and neuropathologic study of the brain in epilepsy,” and Freytag and Lindenberg described the pathology of epilepsy in medical legal autopsies (12). Recently, centers for the surgical treatment of epilepsy have developed and neuroscientists have explored the neurophysiology, neuropathology and genetics of epilepsy in hippocampal slice preparations, lesioned animals, and epileptic mutant animals (13). In all of this work tissue pathology has remained a focal point, and there is an increasing acceptance of the idea that there is an altered morphology in the epileptic brain (14-16). It is still necessary to clarify the relationship between this altered morphology and both the cause and the result of the seizure disorder. An understanding of the pathophysiology of epilepsy requires a knowledge of neuroanatomy and physiology which encompasses concepts of integrated neurologic systems, molecular biology of individual neurons, and the effects of lesions on both of these. This paper will review some features of temporal lobe neuroanatomy and the common lesions which have been defined in the resected temporal lobes of patients with intractable complex partial seizures (TLE) (Table 1).

ANATOMY (17-21)

The temporal lobe is an association area for all the primary sensory modalities: auditory, visual, somesthetic, olfactory and gustatory. There does not seem to be a precise site-specific definition of its complex activities, and there is still much to be learned about temporal lobe connections in man. In temporal lobe surgery each neurosurgeon has a unique procedure, but the neuropathologist will usually receive for examination parts of the hippocampus, parahippocampal gyrus (or entorhinal cortex), the fusiform, inferior and middle temporal gyri, and sometimes the amygdala (15).

The Hippocampal Formation

The hippocampal formation, at the center of the temporal lobe, is in synaptic continuity with subcortical areas, particularly the septal region, the supramammury hypothalamus, the amygdala and the claustrum. From these zones, and also directly, the hippocampus receives input from the anterior and midline thalamus, the locus ceruleus, the raphe nuclei, the ventral tegmental area and the cerebral cortex (orbitofrontal, superior temporal gyrus, insula, piriform, cingulate, perirhinal and parahippocampal). The hippocampus sends efferents to the olfactory regions, claustrum, amygdala, septal nuclei, nucleus accumbens, caudate, putamen, hypothalamus, anterior thalamus, and mammillary nuclei. It serves a complex function which “modulates the control of motor systems, and of non-motor behavioral or psychological processes” (memory may be one of these). Such activity involves the cooperation of many areas of the brain. This must be considered in the evaluation of patients before and after temporal lobe surgery.

Hippocampal Circuitry

Glutamate impulses from the entorhinal cortex constitute the major input into the hippocampus. The entrance is via the perforant pathway whose axons synapse with neurons in the dentate gyrus, Cornu Ammonis (CA) 1, 2, and 3 and the subiculum. Afferent fibers also come via the supracallosal striae to the hippocampal formation.
Granule cells of the dentate gyrus synapse with CA4 and CA3 pyramidal cells via their "mossy fibers" (zinc-containing and demonstrable by Timm's staining) (22). Some pyramidal neurons of CA3 send axons to the subiculum and their Schaffer collaterals to CA1 pyramids. Non-Schaffer CA3 pyramids send a collateral process to CA2 which join with axons of the pyramids there to form the longitudinal axis association path of the hippocampal formation located in the striatum radiatum of CA2 and CA1. Axons of CA1 go to the subiculum. The subiculum sends axons via the alveus-fimbria-fornix system to below the corpus callosum, giving off hippocampal commissural fibers to the other side of the brain or extending anterior to the preoptic area or the mammillary bodies. Thus, the hippocampus, which is considered by some to be the source of seizures, is a unidirectional system of synapses with extensive input and output.

The Cytoarchitecture of the Hippocampus

The cytoarchitecture of the hippocampus is not completely visible in routine stains. Golgi preparations and immunocytochemical preparations are necessary to see many of the special cell types. These are now being characterized functionally by neurophysiologists. Two nomenclatures are applied to the hippocampal formation. One refers to the vertical organization of the cortical layers, and one to the horizontal zones in the various parts of the formation. The vertical layers in Ammon's horn and the dentate gyrus are illustrated in Figure 1. Ammon's Horn (Cornu Ammonis): The Ammon's horn forms the eminentia in the wall of the lateral ventricle between the dentate gyrus and the subiculum. Its relationship to the ventricle changes so that coronal sections may reveal duplication or discontinuities depending upon the level of sectioning. The horizontal zones of Ammon's horn as defined by Lorente de Nó, on the basis of Nissl, Golgi and fiber stains are called CA1-4 and have the following characteristics: CA4: also called the end folium or hilum, contains the polymorphic cell layer of the dentate gyrus and large pyramidal cells which synapse with mossy fibers—these pyramidal neurons are considered by some to be extensions of CA3 pyramids; CA3: contains the largest pyramidal neurons; CA2: contains a thin layer of large pyramidal cells; CA1: appears multilaminated (10–30 cells thick) and contains two layers of pyramidal neurons—the junctions with CA2 and the subiculum are difficult to define. Other neurons are present in all layers of the hippocampal formation. These have been best characterized in animals, e.g. Amarell has described 20 neuronal types in CA4 of the rat (23). Immunocytochemistry has identified additional neurons in the dentate gyrus, e.g. gabacreric basket cells and somatostatin and neuropeptide Y neurons (24–26).

Cytoarchitecture of the Subiculum, Presubiculum and Parasubiculum: Within the molecular layer of the subiculum the perforant pathway courses to the hippocampus from the entorhinal areas. The subiculum has pyramidal neurons in two layers which merge into the pyramidal layers of CA1. Authorities have eliminated the zone which was called the prosubiculum (situated between CA1 and the subiculum) (17). The presubiculum and parasubiculum are poorly defined layers which merge with the entorhinal and subicular areas.

Cytoarchitecture of the Entorhinal and Temporal Cortex: The entorhinal cortex extends from anterior to the amygdala to the level of the lateral geniculate body. It has a unique cellular layer (layer two) composed of stellate and small pyramidal neurons which form characteristic islands of neurons. The third layer contains medium-sized pyramidal cells. Layer four, the lamina desiccans, is agranular. Layer five has large pyramidal cells. The underlying white matter is called the angular bundle. It forms the perforant pathway composed of axons from layers two and three. Details of the cellular architecture of the lateral and medial temporal cortical areas are discussed in references 17 and 18.

Neuropharmacology of the Temporal Lobe (17): The
hippocampal formation receives a cholinergic input from the septal area, a gabaergic input from the septal area, serotonin from the raphe nuclei, noradrenalin from the locus ceruleus, and dopamine from the ventral tegmental area. The transmitter from the perforant and mossy fiber systems is glutamate. Subsystems in the hippocampus are being defined by immunocytochemical methods, e.g. a somatostatin network has been identified to be a neuromodulator in the dentate gyrus.

AMMON’S HORN SCLEROSIS

History: In 1825, Bouchet and Cazauviciel observed sclerotic atrophy of the medial temporal lobes in the brains of patients with epilepsy (of a nonspecified type) (27). Sommer recorded the first microscopic examinations of this atrophy (28). Temporal lobe sclerosis in epilepsy has been confirmed and redefined by many pathologists. Margerison and Corsellis, in an autopsy study of temporal lobe epilepsy, observed two types of hippocampal sclerosis, “classic Ammon’s horn sclerosis” (referred to as AHS in this paper) and “end folium sclerosis” (11). Unfortunately their clearly defined entities, which consisted of decreased numbers of neurons and gliosis in specific areas of the hippocampal formation, have been clustered into lesions bearing names which have enlarged the literature and the confusion about them. The additional diagnoses, which involve neuronal loss and gliosis in the hippocampus but which may also include the amygdala, uncus and fusiform gyrus, are “medial temporal sclerosis” of Falconer (29), “incisural sclerosis of Earle” (3), “parahippocampal sclerosis” of Gastaut (6) and “sclerotic temporal atrophy” of Mathieson (30). Current interest in this lesion has fostered additional terms which refer to the origin of seizure discharges, for example, “primary hippocampal epilepsy” and “extrahippocampal epilepsy” (31).

Classical AHS

Clinical Correlates (2, 13, 15): Ammon’s horn sclerosis is the most frequent lesion associated with intractable TLE. It accounts for 47–70% of the surgical cases at various centers (15) and is associated with an excellent outcome following surgery. Patients with AHS usually have no family history of epilepsy. Their birth history is usually normal, but febrile seizures in infancy or early childhood occur in 75% of patients. There may be a history of prolonged seizures before 3 years of age (32). Complex partial seizures develop in childhood and increase in frequency during adolescence, becoming increasingly refractory to medical treatment. Some patients have learning, emotional or personality disorders. The seizures are described as being “limbic” in character with unusual feelings or sensations heralding the onset of automatisms of which the patient is unaware. The MRI may be normal or may reveal hippocampal atrophy or altered signal (33). The

EEG will usually localize epileptic discharges to one or both hippocampal regions and scalp, sphenoidal, depth or grid electrodes define the precise localizations of the seizure onset. Neuropsychological testing reveals impairment in verbal or general performance, and often patients will have a profound deficit in spatial memory. Electroctroencephalography defines spiking areas. Following surgery patients have a reduction of seizure frequency, require less anticonvulsant medications and show an improvement in performance on testing.

Pathology of Classic AHS (Fig. 2): Ammon’s horn sclerosis, as defined by Margerison and Corsellis, consists of atrophy of the hippocampal formation associated with loss of neurons and gliosis in CA1, CA4 and the dentate gyrus (11). This has become known as the classic lesion and has a characteristic clinical phenotype, as described above. For the purpose of clarity in communication it has been suggested (15) that these definitions be utilized (i.e. classic AHS, end folium sclerosis or another lesion). The original description of the classic lesion has been augmented by recent studies and these are described below.

In the dentate gyrus, the granule cell loss can be exten-
valbumin binding proteins (40), and chromogranin A immunoreactivity (43); a preservation of acetylcholine polymorphic cells (37); the presence of aberrant tyrosine hydroxylase-immunoreactive neurons in CA4 in classic AHS (44); and a loss of kainic acid (KA) and N-Methyl d-Aspartate (NMDA) binding in CA4 (45).

The CA3 usually shows some loss of neurons. Babb reported a 50% loss of GAD inhibitory interneurons in CA3, but no loss of GABA terminals (46). Geddes showed a loss of KA and NMDA binding in CA3 (45), but Represa showed an increase in KA binding sites in CA3 (47).

The CA2 may appear normal or show neuronal loss. The CA1 always shows neuronal loss. The loss may be almost complete, with only isolated neurons surviving within the stratum oriens, or there may be zones of neuronal loss along the stratum pyramidale. There is sometimes a sclerosis of vessels accompanying the neuronal loss, which some researchers consider to be an important aspect of the lesion (48). The gliosis in CA1 is variable. Immunocytochemical and chemical changes have revealed a loss of KA and NMDA binding in CA1 (45), a loss of acetylcholine-rich fibers in Ammon’s horn associated with the neuronal loss (37), a loss of somatostatin receptor binding in CA1 (39), and a survival of neurons with calbindin or parvalbumin binding proteins (40).

Most authors agree that there is no obvious neuronal loss in the subiculum, compared with the loss seen at this site in hypoxic-ischemic injury. However, CA1 and the subiculum overlap, causing some problem with localization. Zhu reported aberrant tyrosine hydroxylase-immunoreactive pyramidal neurons in the subiculum in TLE associated with either AHS or mass lesions (44).

Margerison and Corsellis’ autopsy series revealed neuronal loss and gliosis in the amygdala in 15 of 55 cases of TLE (11). There was associated hippocampal sclerosis in all of these. The complete amygdala is rarely part of the surgical resection, usually being removed by suction. In Bruton’s study of 249 cases there were 18 patients who had two pathologies and in 14 of these the amygdala was gliotic (2). Some authors consider the amygdala to be critical in seizurogenesis in TLE (1).

The Significance of Neuronal Loss in AHS: Long before the pathology of TLE was characterized, Vogt, Spielmeyer and Scholtes were contemplating the significance of AHS in epilepsy of all kinds. They had concluded that sclerosis was the result of the seizures (1). However, when AHS was localized by EEG to a site near the origin of the epileptic discharges, the cause/effect relationship of sclerosis was reexamined (49). Corsellis and Margerison, having defined in some cases of AHS an associated atrophy in the amygdala, thalamus, and cerebellum, doubted the role of an atrophic hippocampus in the pathogenesis of epilepsy (11). Morel and Wildi supported this position because they observed, along with Spielmeyer and Vogt, the presence of AHS without epilepsy (1, 10). However,
Gastaut concluded from his autopsy study that AHS was the cause of the epilepsy (6), as Bratz had previously (50). Earle and Penfield agreed with this interpretation (3) and Bruton's study supports this view (2). In 249 cases he found AHS to be a single lesion in 107 cases, and it was present as a dual pathology in only 15 of the remaining cases, suggesting that seizures arising from other pathologies did not produce AHS. Kim's conclusions are similar (51). The presence of AHS without epilepsy and bilateral AHS in autopsy material are discussed by Meenke and Veith (52).

There have been several theories pertaining to the pathogenesis of AHS. Hypoxic-ischemic damage was suggested as the mechanism associated with seizure injury, birth injury, postnatal injury, and trauma (3, 11, 53). Corsellis recommended that the scarred hippocampus should not be isolated from the rest of the brain, and so other generalised processes have been suggested in relationship to the pathogenesis of AHS. The Vogts considered patholysis to be the mechanism (1), and the Scheibels suggested that there was an ongoing process responsible for the loss of the hippocampal neurons (54). Brown supported this interpretation with electron microscopy (EM) studies (55). However, studies of hippocampal slice preparations have demonstrated that the loss of dendritic spines in epilepsy can be caused by the seizures (56). Excitatory amino acids, such as glutamate, have been suggested as being responsible for the regional neuronal loss in epilepsy (1, 57). None of these theories explains the initiation of the original seizure, except for a malformative theory of AHS which has been proposed. This suggests that injury to the developing nervous system might interfere with the normal circuity of the hippocampal formation, allowing it to assume a greater capacity for spontaneous "bursting" and epileptogenesis than normally exists. With such a "malformation," the brain may be readily stimulated to seizurogenesis with a stimulus, such as fever. This could set into motion the excitotoxins or vascular mechanisms that could further disrupt the circuitry. This theory would explain the observations that AHS only leads to epilepsy if it develops during 3 months to 7 years of age (1).

Quantitation in AHS: Dam quantitated the neuronal loss in the hippocampus in TLE and concluded that neuronal loss in CA4 increased if there were associated generalized seizures and that neuronal loss in CA3 was related to duration of seizures (42). This is refuted by Levesque (58). Babb used quantitation to relate patterns of neuronal loss to clinical outcome after surgery (31).

End Folium Sclerosis

End folium sclerosis was defined by Margerison and Corsellis as neuronal loss and gliosis confined to the end folium or CA4 (11). Patients with end folium sclerosis have a later onset of seizures than patients with AHS (16 years as compared with 6 years). There is no large series to assess the result of surgery on this lesion. Bruton had only four cases (2), and it is possible that end folium sclerosis has been previously interpreted to be a nonspecific change.

Animal Models of Hippocampal Sclerosis

There are several animal models which include stimulation of the perforant pathway (59), selective intoxication of CA3 neurons using KA (60), ischemia, and a combination of these insults (61). Not all of these models replicate all of the changes described in classic AHS.

NEOPLASTIC LESIONS

The naming of mass lesions in TLE has a history of confusing terminology. Brown used "hamartoma" (which included tuberous sclerosis and vascular anomalies) (62) and "glioma" (which included the gangliogliomas). Bruton introduced the term "alien tissue lesion" to signify neoplasms, hamartomas, "certain small tumors of the temporal lobe" and cortical dysplasia (15). The classification used in this paper is that devised by neuropathologists at the Second International Meeting for the Surgical Treatment of Epilepsy in 1992 (16). It is based, but not without assumptions, upon pathologic process. The difficulty in defining the nature of the pathologic process was illustrated above in the discussions about AHS. There are problems, too, in defining several mass lesions as being "neoplastic." Most lesions encountered in the temporal lobe in TLE have a limited growth potential. But occasionally their histology and/or their behavior suggest rapid growth. Studies of natural history and correlations with serial images, DNA analysis, and assays of proliferation markers may better characterize these lesions in the future.

Mixed Tumors

Ganglioglioma: The diagnosis of ganglioglioma in TLE is reported with varying frequencies and has been hidden in nonspecific terminology such as hamartoma, tumor, neoplasm, etc. Recently, the lesion called dysembryoplastic neuroepithelial tumor (DNT) (63) has been identified as a common lesion in temporal resections for TLE. These lesions behave in the same way as gangliogliomas and may represent part of a spectrum of the same lesion. In the Baylor series of 120 cases of TLE, 20% are interpreted to be gangliogliomas and are the second most common lesion (64). The clinical phenotype resembles that of patients with AHS with several exceptions. The ganglioglioma patients usually do not have a history of febrile convulsions. Imaging studies of their temporal lobes usually reveal a mass lesion in the medial part of the temporal lobe involving one or more of the hippocampus, subiculum or entorhinal cortex. During surgery, stimulation of the hippocampal pathways will reveal a complex signal...
as compared with the simplified one observed in AHS (65). Seizure control following lobectomy is usually excellent. The histology of gangliogliomas is variable and, as suggested above, their differentiation from DNT is problematic. In the typical ganglioglioma there are ganglion cells, glial cells, and delicate vessels. The ganglion cells are usually round cells with large nuclei and prominent nucleoli. Occasionally, neurons with two nuclei or a bizarre shape will be present. The number of neurons range from few to many, so that sampling can be a problem. Immature neurons may be present but are difficult to define without EM. Mature neuronal cells may be characterized with antibodies against neurofilament polypeptides, synaptophysin and chromogranin A (16). Neurotransmitter immunoreactivity in these neurons is inconsistent (64). The glial component is usually astrocytic, although oligodendrogial cells may be present. The glial cells display various growth patterns, sometimes spilling into the subarachnoid space. Some contain regular astrocytes surrounding delicate vessels which may show lymphocytic cuffing. Some tumors show cystic degeneration (Fig. 4). Some astrocytes are spindle-shaped or pilocytic. Some astrocytes appear primitive and perivascular (Fig. 5). In some tumors the astrocytes are bizarre, huge "ballooned" cells (resembling the cytology of astrocytes in pleomorphic xanthoastrocytoma or tuberous sclerosis). The possible relationship of gangliogliomas to malformations and microdysgenesis in epilepsy is referred to below. The prognosis for these tumors is generally good but there are reports of aggressive spread (66), so that the growth potential of the tumor is an important consideration in defining follow up and in embarking on additional therapies if excision of the tumor is not possible.

Dysembryoplastic Neuroepithelial Tumor (DNT) (63): Dysembryoplastic neuroepithelial tumor is associated with intractable complex partial epilepsy, and in 62% of the original 39 cases it was located in the temporal lobe. Seizures begin in early childhood. There is no neurologic deficit in patients in the interictal period and they do not have a phacomatosis. The lesion is identified grossly to be intracortical, with a multinodular architecture. It is composed of astrocytes, oligodendrocytes and neurons. Cortical dysplasia may also be present in the resected tissue. The authors of this diagnostic term consider the tumor to be different from a ganglioglioma based on differences in the amounts of the various components, the
strictly cortical location and absence of lymphocytes in DNT. They suggest that the lesions arise in the cortex from subpial secondary germinal layers. The prognosis after surgical removal is excellent.

**Mixed Glial Tumors:** Jensen (67) and Brown (55, 62) have recorded their observations about the small mixed oligoastrocytomas found in temporal lobectomy specimens, and Bruton has considered them to be identical in their behavior to gangliogliomas (2). They are associated with an early onset of intractable epilepsy and a good outcome after surgery.

**Gliomas**

Primary glial tumors of one cell type do occur in the temporal lobe. Bruton has reported glial lesions among his alien tissue lesion group (2). Most of the patients had late onset seizures. Nine lesions were astrocytic tumors; six patients had improved outcome, one developed depression and two died of recurrences. Six patients had oligodendrogliomas; three had a good outcome, one was worse and two died of recurrences. From these few reports, it is suggested that temporal lobe tumors composed of single cell types behave in a more aggressive manner and require complete removal and careful follow up.

**FAMILIAL AND METABOLIC DISEASES**

The category of familial and metabolic diseases is included in the classification of the pathology of TLE because of a suggested association of gangliogliomas and cortical dysplasias with tuberous sclerosis. This is an important consideration for the patient in terms of further treatment, investigation and counseling. Hopefully, genetic markers for tuberous sclerosis will provide a way of verifying or denying this association. Occasionally the initial course of some of the storage or mitochondrial disorders may present as complex partial seizures involving the temporal lobe, but the more generalized aspect of the disease will become apparent, excluding these patients from focal surgical therapy.

**MALFORMATIVE LESIONS**

Malformative lesions in TLE present conceptual problems referred to in the discussion of AHS and neoplasms. The definition of malformations could include cellular, chemical, morphologic or functional criteria. For example, the altered circuitry in the dentate gyrus observed in AHS, as defined by immunocytochemical methods, could be considered a malformation of the hippocampus. Similarly, the behavior and appearance of some mass lesions in the temporal lobe resemble those of a static malformation. Perhaps a study of the lesions in TLE with molecular techniques will enable us to clarify these definitions. In the meantime, the use of standardized diagnostic terminology should allow us to accumulate informative data about the lesions. Toward this purpose we have considered as malformative lesions those in which there is an apparent disorganization of the cytoarchitecture of the brain or its vessels. There are two kinds of dysmorphic lesions recognized in the brains in TLE. The first, focal cortical dysplasia, is a gross lesion which can be identified in the specimen on imaging studies as an alteration in the shape or thickness of the cortex or the gyril. There is no mass effect, enhancement or associated edema. The cortex usually looks and feels normal. The second lesion, microdysgenesis, is a microscopic malformation which is not visible by routine imaging studies. The natural history of these malformative lesions requires study. It is not known when or why they become epileptogenic or whether some of them will transform into a neoplasm. It is not known what cause/effect relationship some of these “malformative” lesions have to the seizures.

**Focal Cortical Dysplasia (Dysgenesis):** This abnormality was recorded in 1971 by Taylor et al (68). The lesion usually cannot be seen or palpated but involves a major part of a lobe (temporal, frontal, occipital and parietal). The microscopic reveals “conglomerations of large bizarre neurons,... littering the cortex... and grotesque cells, probably of glial origin in the subjacent white matter.” Surgery provides considerable relief from seizures. Bruton reported eight cases which presented with seizures at ages 3–35 years (2). Jensen and Marchal have experience with cortical dysplasia (67, 69). (It should be noted that the use of the term dysplasia in this context does not necessarily imply, as it does in the rest of the body, a pre-neoplastic growth.)

**Microdysgenesis:** In the literature about TLE there are references to lesions which satisfy our definitions of microscopic malformations (15, 30, 36, 70–72). Meneke was one of the first to use the term microdysgenesis (20). He observed these abnormalities of cytoarchitecture in the brains of patients with generalized epilepsy and included the following as examples of microdysgenesis: uni- and bipolar neurons under the pia, increased neurons in the first layer of the cortex, indistinct boundary between first and second layers of cortex, neuronal–glial heterotopias into the pia, persistence of a columnar architecture of the cortex, increased numbers of neurons in the white matter, disturbed architecture of the hippocampus, and ectopic Purkinje cells in the cerebellum. In the temporal lobe other types of microdysgenesis have been defined: gray matter heterotopias, dentate dispersion or duplication, increased cellularity of the white matter and neuronal clustering, satellitosis, and rows of perivascular glia (Fig. 6). These are observed in association with AHS and ganglioglioma (15). Reports of microdysgenesis have been viewed with some skepticism (14). Nevertheless, they cannot be ignored and their role in epilepsy requires definition. These microscopic alterations have been classified as being malformative lesions. However, some of them have been seen in situations which suggest that they
may develop as a result of epilepsy. For example, Meenke reported increased numbers of neurons in the white matter of patients who had both generalized primary epilepsy and post-traumatic epilepsy (73). We reported increased glial cell nuclear size in the white matter of patients with temporal lobe seizures who had AHS, ganglioglioma and nonspecific changes (74). Experimental epilepsy induces changes in astrocytes (74).

Vascular Malformations

Vascular lesions may present as longstanding seizure disorders of temporal lobe type and are now readily identified on imaging studies. They accounted for 11% of Edgar and Baldwin’s temporal lobectomy specimens (75). In them seizure onset was 18 years, and males and females were equally affected. Some patients had mental retardation and hemiplegia. The lesions were intracerebral or meningeocortical. They were arteriovenous malformations and cavernous angiomas associated with stained sclerotic brains, some with calcifications. Bruttom reported four cases of which three improved following surgery (2). A lesion called “hemangioma calcificans” was reported in the temporal lobes of patients with TLE. It consists of foci of intensive calcification with calcospherites, increased delicate vascularity and gliosis of brain, with microcystic change (76).

CEREBROVASCULAR DISEASE AND TRAUMA

Intractable seizures occasionally occur in patients who have suffered cerebral infarction in infancy or following head trauma. Bruttom had ten patients with head injury, two related to birth injury. Following surgery, six had improvement in their seizure disorder, three were unchanged and one was worse (2). The history, imaging studies and gross pathology differentiate these cases from most of the lesions discussed above.

INFLAMMATORY/INFECTIOUS

Occasionally intractable epilepsy will arise in the temporal lobe following an identified infection (53). Bruttom reported 11 patients, five with meningitis, four with cerebral abscesses and two with encephalitis. The seizure disorder was improved following surgery in eight patients but six had no change in their social adjustment to their condition (2). Sometimes Rasmussen’s encephalitis is diagnosed in the temporal lobe (4).

NONSPECIFIC LESIONS

“Nonspecific changes, equivocal lesions, no apparent pathology, negative pathology, no specific pathology” have accounted for a considerable proportion (20–33%) of the reported cases of pathology of TLE (15). There may be an explanation for absence of a diagnosis, such as the extent of the resection does not include hippocampus or the tissue can not be removed en bloc. There are also, undoubtedly, cases in which our methods of examination do not reveal the abnormality.
TABLE I
Classification of the Lesions of the Temporal Lobe in Intractable Complex Partial Seizures (modified from the temporal lobe from Table 1 reference 16)

1. Ammon's Horn Sclerosis
   a. Classical
   b. Endfolium
2. Neoplastic Lesions
   a. Mixed tumors
      1. Ganglioglioma
      2. Dysembryoplastic neuroepithelial tumor
      3. Mixed glial tumors
   b. Gliomas
3. Familial and Metabolic Diseases
   a. With focal lesions; pheochromatosis
4. Malformative Lesions
   a. Cortical dysplasias
      1. Focal cortical dysplasia
      2. Microdysgenesis
   b. Vascular malformations
      1. Arteriovenous malformations
      2. Cavernous malformations
5. Cerebrovascular Disease and Trauma
6. Inflammatory/Infectious
   a. Fulminant encephalitis, meningitis
   b. Chronic encephalitis, meningitis
   c. Rasmussen's encephalitis
7. Nonspecific Lesions


DUAL LESIONS

Brunton analyzed the pathology of 249 patients who had similar investigations, surgery and pathological examinations (2) and found 18 cases with two pathologies. Fifteen of these had AHS and some other mass, inflammatory or malformative lesion. Patients with two pathologies did not respond to surgery as well as those with single pathologies. Recently, Levesque reported 178 patients with en bloc resections for limbic epilepsy, 30% of whom had dual pathology. These authors advise that a precise definition of the epileptogenic area should be made so that the correct resection can be planned (58). It was suggested above that microdysgenesis has been observed in association with most pathologies, so that the definition of dual pathologies requires clarification.

SUMMARY

Complex partial epilepsy arising in the temporal lobe has been associated with several types of pathologic lesions including Ammon's horn sclerosis, malformations, neoplasms, and inflammatory scars from infarcts or infection. These lesions are usually situated at various sites in the medial temporal lobe, so that one of the enigmas of attempting to understand the pathogenesis of TLE pertains to the clinical manifestation of a single epileptic disorder which is associated with dissimilar lesions at dissimilar sites. Recent demonstrations of an alteration in temporal lobe anatomy, i.e. malformations of the normal circuitry of the temporal lobe and foci of microdysgenesis, have given rise to the hypothesis that insults which occur during a critical period of brain development could alter the connections within the hippocampus and predispose it to increased excitability and seizurogenesis. Such a hypothesis forces us to reconsider TLE in reference to risk factors which may act as "teratogens" and produce these malformations. These malformations may range from a subtle alteration in the neurotransmitters of the dentate gyrus to large areas of cortical dysplasia or the hamartomatous neoplasms seen in TLE. A reevaluation of the neurometabolite disruptions created by the various lesions may allow us to define a minimal optimal surgical resection for each lesion, or, the definitions of neurotransmitter deficits may lead to alternative pharmacologic therapies. As neuropathologists we have the exciting opportunity to participate in the definition of the neuropathology of temporal lobe epilepsy.

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