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Clinical Research

Subacute Electrical Stimulation of the Hippocampus Blocks Intractable Temporal Lobe Seizures and Paroxysmal EEG Activities

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Summary: *Purpose:* To investigate the clinical, electroencephalographic (EEG), and histopathologic effects of subacute electrical stimulation of the hippocampal formation or gyrus (SAHCS) on 10 patients with intractable temporal lobe seizures.

Methods: Bilateral, depth, hippocampal or unilateral, subdural, basotemporal electrodes were implanted in all 10 patients for a topographic diagnosis of the site and extent of the epileptic focus before a temporal lobectomy. In all patients, antiepileptic drugs (AEDs) were discontinued from 48 to 72 h before a program of continuous SAHCS, which was performed for 2–3 weeks. Stimulation parameters were biphasic Lilly wave pulses, 130/s in frequency, 450 μs in duration, and 200–400 μA in amplitude. The stimuli were delivered 23 of every 24 h for the 2–3-week SAHCS period. The effects of SAHCS on the number of clinical seizures per day and the percentage of interictal EEG spikes per 10-second samples of maximal paroxysmal activity at the epileptic focus were determined daily during the 16 days of SAHCS. At the completion of this program, patients underwent an en bloc temporal lobectomy, and the histopathologic effects of SAHCS on the stimulated tissue were analyzed by means of light-microscopy studies.

Results: In seven patients whose stimulation electrode contacts were placed within the hippocampal formation or gyrus and who experienced no interruption in the stimulation program, SAHCS abolished clinical seizures and significantly decreased the number of interictal EEG spikes at the focus after 5–6 days. The most evident and fast responses were found by stimulating either the anterior pes hippocampus close to the amygdala or the anterior parahippocampal gyrus close to the entorhinal cortex. Other surface, hippocampal, and basotemporal EEG signs predicted and accompanied this antiepileptic response. These included an electropositive DC shift and monomorphic delta activity at the medial hippocampal and parahippocampal regions, and a normalization of the background EEG activity and signs of slow-wave sleep in surface, depth, and subdural regions. In contrast, no evident antiepileptic responses or no responses at all were found in three patients when stimulation was either interrupted or when it was administered outside the hippocampus.

Light microscopy analysis of the stimulated hippocampal tissue showed histopathological abnormalities attributable to the depth-electrode penetration damage or to the pial surface reaction to the subdural, Silastic electrode plate. However, no evident histopathological differences were found between the stimulated and nonstimulated hippocampal tissue.

Conclusions: SAHCS appears to be a safe procedure that can suppress temporal lobe epileptogenesis with no additional damage to the stimulated tissue. **Key Words:** Temporal lobe seizures—Pes hippocampus–amygdala—Parahippocampal–entorhinal cortices—Electrical stimulation—Histopathologic confirmation—Neurosurgery—Electroencephalography.

In recent studies, Velasco et al. (1–5) have shown that bilateral, prolonged electrical stimulation of the centromedian thalamic nucleus (ESCM) is a safe and efficient procedure for the control of severe generalized seizures that are otherwise untreatable by conventional antiepileptic drugs (AEDs). This procedure significantly decreased the number of generalized tonic–clonic seizures in adults, atypical absence seizures in children with Lennox–Gastaut syndrome, and interictal paroxysmal electroencephalogram (EEG) activities in both. In addition, ESCM improved the psychological performance of patients and normalized background EEG activity. ESCM

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has been recently proposed as an alternative neuroaugmentive procedure for the surgical treatment of certain forms of epilepsy (6,7). It is believed that the beneficial effect of ESCM on generalized epilepsy is due to its desynchronizing and hyperpolarizing effects on the reticulo-thalamic cortical neurons that participate in the initiation and/or propagation of tonic–clonic seizures (8–10). Other possible mechanisms include regulation of the oscillatory thalamocortical rhythms, low threshold Ca^{2+} currents, and γ-aminobutyric acid (GABA) activity, among others (17). On the other hand, the efficiency of ESCM in controlling temporal lobe seizures is very low or nonexistent.

Enough evidence exists to suggest that temporal lobe seizures are initiated from and/or propagated through the hippocampal formation. Clinical experience shows that ictal and interictal epileptiform EEG activity occurs first in the hippocampus (12), and that basal and anterior temporal lobectomies involving the hippocampus are associated with a substantial reduction in the number of seizures (13). Furthermore, temporal lobectomies that involve the hippocampus reduce siezures more than those in which the hippocampus is preserved or is only partially resected; in many cases, surgical reintervention to eliminate remaining hippocampal tissue is necessary to suppress seizures completely (14). On the other hand, recent experiments in animals by Weiss et al. (15–18) showed that the application of an electrical stimulus to the amygdala after a kindling stimulus produces a marked and long-lasting suppressive effect known as "quenching" on experimental models of epilepsy. Kindling and quenching are also produced by hippocampal stimulation (Weiss, personal communication).

In our experience (19), temporal lobectomies that include the hippocampus but spare the amygdala and a good portion of the temporal cortex have been very successful in eliminating or reducing the number of temporal lobe seizures. However, the general consensus (14) is that temporal lobectomies are not advisable for patients with bilateral temporal foci or a unilateral focus spreading to surrounding cerebral regions of the dominant hemisphere because both bilateral conventional and unilateral extensive temporal lobectomies produce devastating effects on brain functions, particularly on language and memory. Therefore new alternative procedures are required for the treatment of these patients.

This study represents an initial stage in the development of an alternative, surgical, neuroaugmentive procedure for the control of intractable temporal lobe seizures in the previously mentioned type of patients. Subacute electrical stimulation of the hippocampal formation or gyrus (SAHCS) for 2–3 weeks can suppress temporal lobe epileptogenesis with no additional damage to the stimulated tissue.

In subsequent studies, we will attempt to demonstrate that the suppressive effect of SAHCS can persist for years without undesirable effects on language and memory.

METHODS

This study was done with 10 patients with intractable temporal lobe seizures who had depth and subdural electrodes implanted to determine the location and extent of the epileptic focus before a temporal lobectomy. They were four men and six women, with an average age of 23.8 years. Three of the patients had complex partial seizures alone; seven had them combined with secondarily generalized tonic–clonic seizures. They had an average of 11.3 seizures per month in spite of treatment with high dosages of AEDs.

In two patients with surface EEG spikes localized to the right and left anterior temporal regions, bipolar, depth, multicontact, platinum–iridium electrodes (model SD 8P, AD-TECH, Racine, WI, U.S.A.) (tip diameter, 1 mm; separation, 2.4 mm; impedance, 10 k ohms) were stereotaxically and bilaterally implanted within the hippocampal axis through occipital burr holes to determine the side of the epileptic focus (20). In the other eight patients with surface EEG spikes localized to either the right (n = 2) or the left (n = 6) temporal regions, multicontact electrode grids (model TWS 20P, AD-TECH) (contact diameter, 4 mm; center-to-center separation, 10 mm; impedance, 10 K ohms) were visually and unilaterally implanted at the pial surface of the basotemporal cortex through a wide temporal craniotomy to determine the precise site and extent of the focus (21). The definitive positions of both depth and subdural electrodes were determined by magnetic resonance imaging (MRI) studies (Fig. 1).

All patients underwent standard temporal lobectomies on the basis of a unilateral focus at the anterior hippocampal formation or gyrus determined by the initiation of ictal EEG activity at the seizure onset in video-EEG studies, and of surrounding cerebrum eloquent areas determined by electrical stimulation studies (22). Further demographic details of the patient group are shown in Table 1; further details of the criteria for patient selection for electrode implantation and temporal lobectomy are reported elsewhere (19).

SAHCS procedure and evaluation of the antiepileptic response

In all patients, AEDs were discontinued 48 to 74 hours prior to SAHCS initiation, after which SAHCS was applied from 2 to 3 weeks (minimum, 16 days). SAHCS was bipolar and between contiguous electrode contacts, with the cathode of the first biphasic, Lilly wave pulse attached to the most anterior electrode of the contact pairs. In eight patients with focal and regional initiation of ictal EEG activities, SAHCS was applied within or

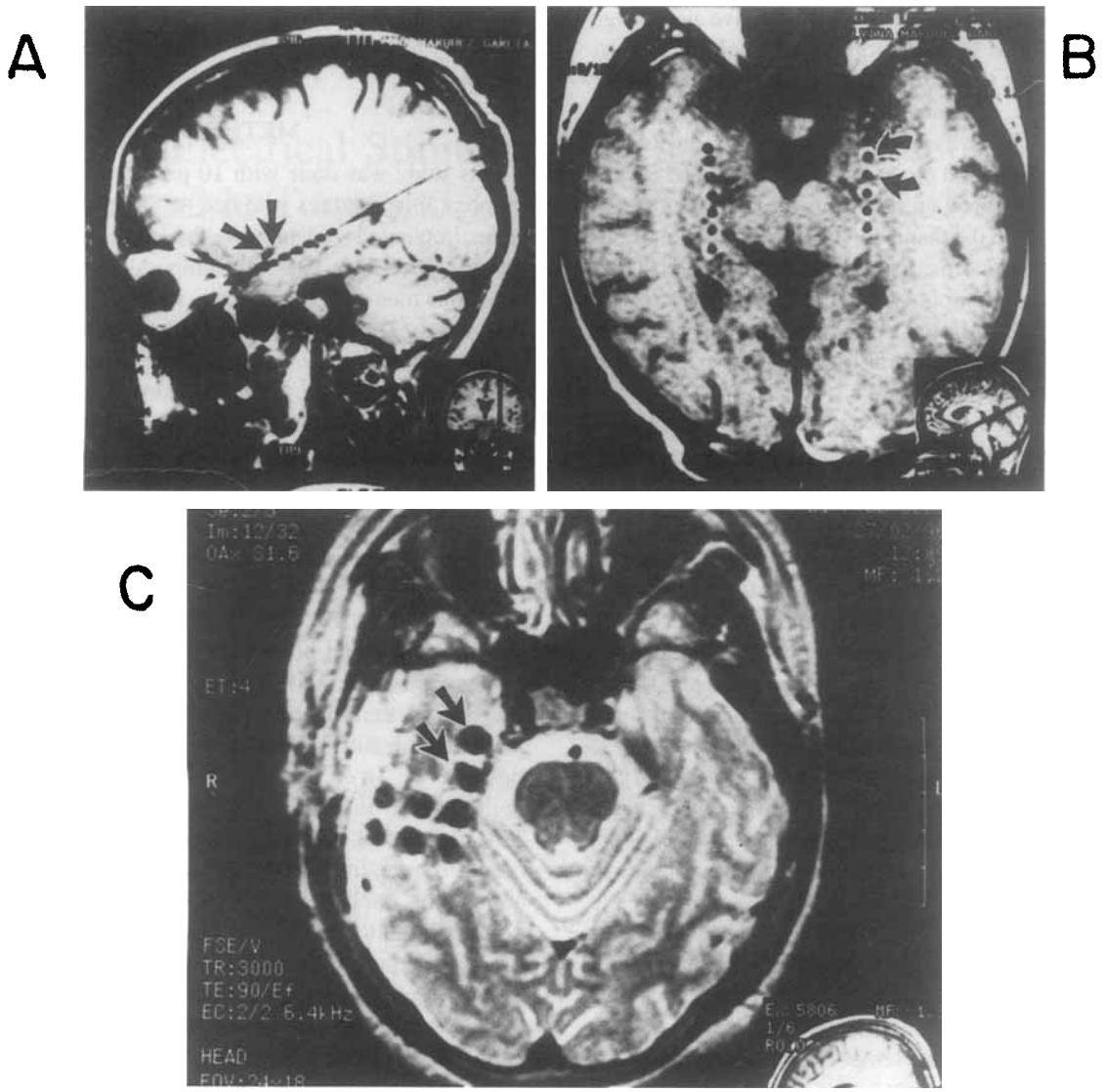

FIG. 1. Position of the depth and subdural electrodes **A, B:** Parasagittal and axial magnetic resonance imaging (MRI) sections showing the position of bilateral depth electrodes stereotaxically placed within the hippocampal axis inserted through occipital burr holes in two patients. **C:** Axial MRI section showing the position of unilateral electrode placed on the pial surface of the right basotemporal cortex through a wide craniotomy of another patient.

close to the epileptic focus, which was usually located at the anterior hippocampal and parahippocampal regions. In the other two patients with generalized, basotemporal ictal activities, SAHCS was applied at the most anterior and mesial electrode contact pairs (Fig. 1).

SAHCS always consisted of continuous stimulation with rectangular pulses interrupted only 1 h/day while EEG recordings were taken. Individual pulses consisted of biphasic, Lilly wave pulses 130 per second in frequency, 450 μs in duration, 200–400 μA in amplitude. Amplitude was adjusted for threshold or slightly suprathreshold levels in the eliciting of electropositive DC shifts just posterior to the stimulation sites. In one patient with stimulation electrodes out of the hippocampus, the electropositive DC shift was absent, and the intensity of stimulation was arbitrarily adjusted to 200 μA for the first 7 days and increased to 400 μA on subsequent days.

SAHCS was performed by a pulse generator (model DBS, Medtronic, Minneapolis, MN, U.S.A.) attached to the AD-TECH externalized connectors. Because SAHCS did not produce any subjective or objective behavioral responses at these stimulation parameters, the reliability of SAHCS was determined by daily measurements of the voltage, impedance, and current flow at the intracerebral electrode contacts as recorded by an electronic monitoring system that was used by Velasco et al. (2) in their ESCM studies, and by the surface and depth electrocortical responses elicited by acute, unilateral, hippocampal stimulation. The latter included responses elicited by 1, 3, 6, and 60 per second stimulation frequencies (23).

TABLE 1. *Demographic features, localizing studies, and SAHCS results*

Patient no.	Age (yr)	Sex	Seizures: Age at onset (yr)	Seizures: Duration (yrs)	Seizures: Frequency (no./mo)	Seizures: Types: Most frequent	Seizures: Types: Less frequent	AED (mg/d)	MRI: Ipsilateral	MRI: Contralateral
1	25	F	11	14	3	CP		CBZ (600) + PRM (750)	N	N
2	11	F	5	6	4	CP		OXC (4,800)	SCL	N
3	11	M	7	4	12	CP	SGTC	CBZ (300) + VPA (1,000)	N	N
4	30	F	13	17	18	CP	SGTC	CBZ (1,000) + GBP (600)	N	N
5	29	M	20	9	13	CP	SGTC	CBZ (600) + PRM (250)	SCL	SCL
6	24	M	15	9	10	CP	SGTC	OXC (600) + PRM (250)	N	N
7	25	F	17	8	15	CP	SGTC	CBZ (600) + VPA (600)	N	N
8	23	F	6	17	11	CP	SGTC	CBZ (600) + PHT (300)	SCL	N
9	35	M	12	23	20	CP	SGTC	PHT (300) + GBP (1,200)	SCL	N
10	25	F	13	7	7	CP		CBZ (800) + GBP (600)	N	N

Patient no.	EEG: Ipsilateral	EEG: Contralateral	Hippocampal depth electrodes: R	Hippocampal depth electrodes: L	Ictal discharges at seizure onset[a]: FOC	Ictal discharges at seizure onset[a]: REG	Ictal discharges at seizure onset[a]: GEN	SAHCS results
1	FS	N	–	+	+	–	–	EF
2	FS	FS	+	+	–	+	–	NE
3	FS	FS	+	+	–	–	+	EF
4	FS	N	+	–	+	–	–	ES
5	FS	N	–	+	+	–	–	EF
6	FS	N	+	–	+	–	–	NE
7	FS	N	–	+	–	–	+	ES
8	FS	N	–	+	+	–	–	ES
9	FS	N	–	+	–	+	–	NE
10	FS	N	–	+	+	–	–	EF

SAHCS, subacute electrical stimulation of the hippocampal formation or gyrus; AED, antiepileptic drug; MRI, magnetic resonance imaging; EEG, electroencephalogram; FOC, focal; REG, regional; GEN, generalized; F, female; M, male; CP, complex partial; SGTC, secondary generalized tonic-clonic; CBZ, carbamazepine; PRM, primidone; OXC, oxcarbazepine; VPA, valproic acid; PHT, phenytoin; GBP, gabapentin; N, normal; SCL, medial temporal sclerosis; FS, focal spikes; FOC, focal; REG, regional; GEN, generalized; EF, evident and fast response; NE, no evident response; ES, evident and slow response.

[a] Focal refers to the anterior hippocampal or parahippocampal region; regional to the anterior and middle hippocampal or the parahippocampal and fusiform regions; and generalized to all basotemporal regions.

The effect of SAHCS on temporal lobe epileptogenesis was quantitatively evaluated by determining the number and type of clinical seizures per day and the number of interictal, negative EEG spikes at the epileptic focus per 10-s samples of maximal paroxysmal activities appearing during the 1 h of referential EEG recording performed daily during the SAHCS weeks. EEG sample selections were chosen by visually inspecting one or several samples showing the maximal amount of EEG spikes at the focus. Then one of these samples was randomly selected. Other details on the quantitative evaluation of epileptogenesis were reported in a previous work (2).

Histopathological evaluation of the stimulated hippocampal tissue

At the completion of the clinical and EEG studies, SAHCS was discontinued, the electrodes were removed, and a conventional en bloc temporal lobectomy ipsilateral to the epileptic focus was performed. The resected block, which had a length of ~3 cm, involved the portion of the temporal lobe located 2 cm posterior to the temporal pole and immediately anterior to the Labbé's vein. It was formed by two biopsies individually excised: one mesial biopsy containing the stimulated hippocampal formation and gyrus and one lateral biopsy containing the nonstimulated fusiform and inferior temporal gyri. Afterwards, the mesial and lateral biopsies were fixed in a 10% formaldehyde buffer solution and embedded in paraffin. Serial coronal sections of 10-μm thickness perpendicular to the fascia dentata were taken every 1,000 μm and stained with hematoxylin–eosin and silver Gomori's staining for the perikaryon and the collagen, respectively.

Histopathologic analysis of the temporal lobe tissue was performed under a light microscope by comparing the hippocampal tissue contiguous with the stimulated contacts (usually within the mesial biopsies) with tissue contiguous with the nonstimulated contacts (usually within the lateral biopsies). Other details of the histopathologic evaluation of cortical tissue were reported elsewhere (24,25).

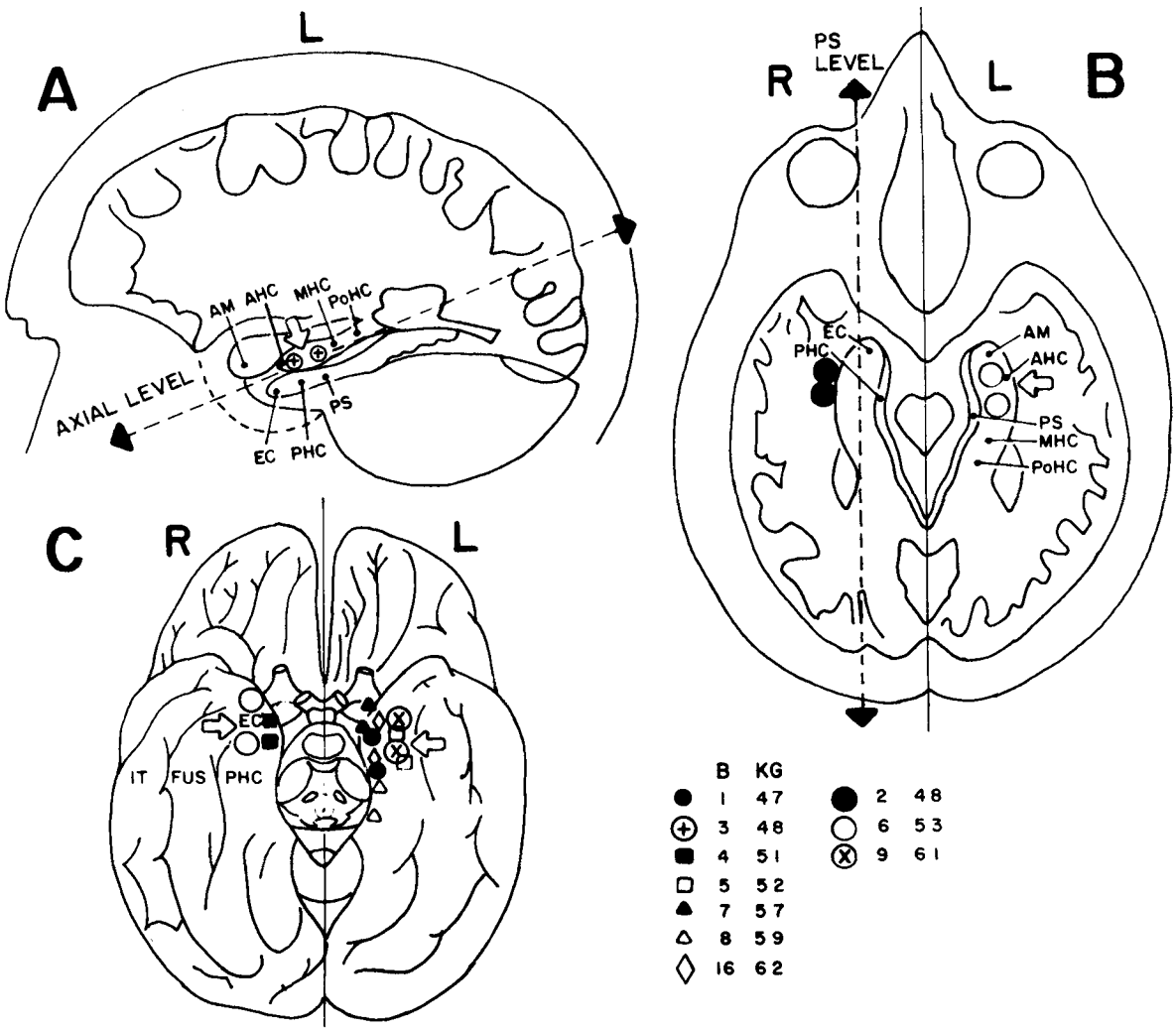

FIG. 2. Position of the depth and subdural stimulation contacts. **A, B:** Diagrams of parasagittal and axial magnetic resonance (MRI) sections. **C:** Diagram of the basotemporal cortex showing the position of the stimulation contact pairs in different patients (indicated by different symbols at the right bottom corner). Arrows indicate the sites where subacute electrical stimulation of the hippocampal formation or gyrus (SAHCS) produced evident and fast antiepileptic responses. AHC, anterior hippocampus; MHC, medial hippocampus; PoHC, posterior hippocampus (Amon's horn); AM, amygdala; PS, presubiculum; PHC, parahippocampal gyrus; EC, entorhinal cortex; FUS, fusiform gyrus; IT, inferior temporal gyrus.

RESULTS

Effect of SAHCS on seizures and interictal EEG activities

All patients showed clinical seizures and EEG interictal spikes at the hippocampal and parahippocampal focus during the first 6 days of SAHCS. The maximal number of seizures (five per day) and interictal spikes at the epileptic focus (33 per 10-s samples) were found during the first and second days of SAHCS.

In seven patients whose stimulation contacts were located within the hippocampal formation and the gyrus and who received continuous stimulation (except for the 1 h/day EEG recordings), an evident and progressive antiepileptic response was observed (Fig. 3). Both complex partial and secondarily generalized tonic–clonic seizures were abolished after day 6 of SAHCS (Figs. 4A and 5A), and interictal spikes were either blocked completely or significantly reduced from days 4 to 11 (Figs. 4B and 5B). The most evident and fast antiepileptic responses were found in five patients whose stimulation contacts were located at either the anterior pes hippocampus close to the amygdaloid nuclei or at the anterior parahippocampal gyrus close to the entorhinal cortex (Figs. 2, white arrows, and 4A and B). Evident slower responses were also found in two other patients whose stimulation contacts were located either at the medial parahippocampal gyrus or the anterior perforate space (Figs. 2 and 4, solid and open triangles). In two other patients with anterior parahippocampal stimulation, the antiepileptic responses were not so evident and were delayed when SAHCS was accidentally or intentionally

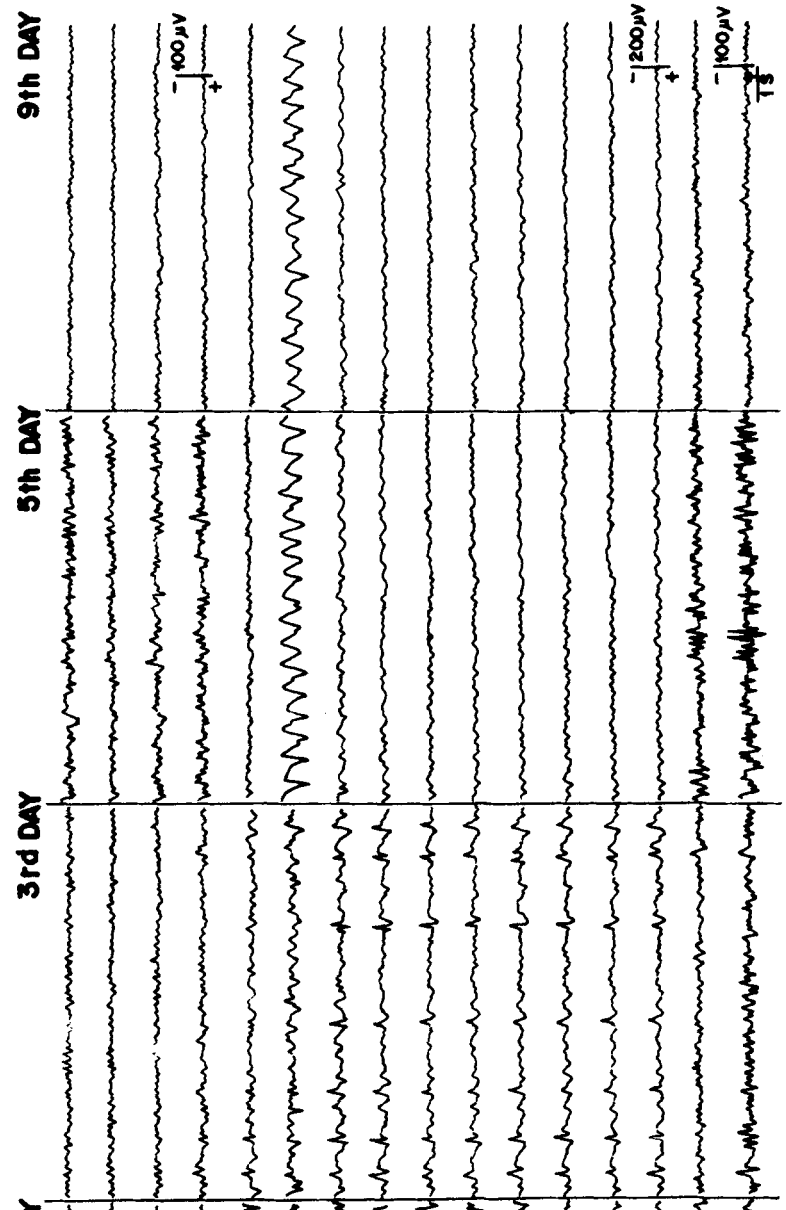

FIG. 3. Effect of subacute electrical stimulation of the hippocampal formation or gyrus (SAHCS) on interictal paroxysmal and background (EEG) activities. Ten-second samples of maximal paroxysmal EEG activities from four consecutive records performed on day 1, 3, 5, and 9 of SAHCS applied to the parahippocampal-entorhinal junction (indicated by filled circles in Fig. 2). Recordings were made from surface right and left frontotemporal (FP2, F8, FP1, F7), central (C4, C3), and left subdural anterior (ANT), medial (MED), and posterior (POST) parahippocampal (PHC), fusiform (FUS), and inferior temporal (IT) gyri. All EEG recordings were referred to ipsilateral ear lobe electrodes (A2 and A1). Note that during day 1 of SAHCS and 48 hours after antiepileptic drug (AED) withdrawal there was a large number of interictal spikes and slow waves in all subdural recordings, particularly at the anterior parahippocampal gyrus where the epileptic focus was previously localized by the initiation of ictal activity at the seizure onset. After day 3 of SAHCS, both spikes and slow waves were evidently reduced, and they were completely blocked after day 5 and 9 of SAHCS. In addition, a prominent monomorphic (1.0–1.5/s) delta activity appeared at the medial parahippocampal region (just posterior to the stimulated region) after day 5 of SAHCS (3).

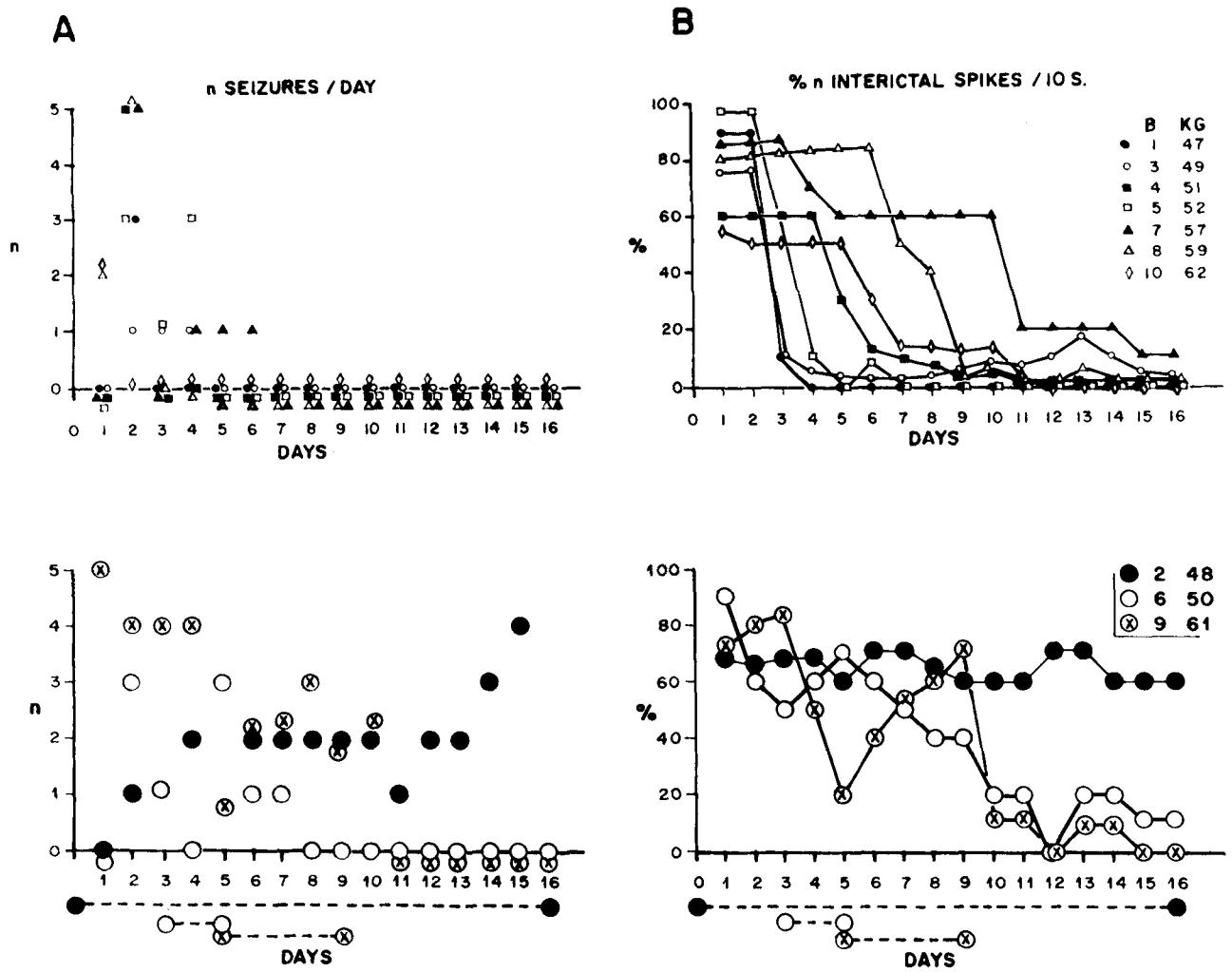

FIG. 4. Effect of subacute electrical stimulation of the hippocampal formation or gyrus (SAHCS) on seizures and interictal spikes in individual patients. **A:** Number of seizures/day. **B:** Percent of interictal spikes/10s at the epileptic focus recorded daily during 16 days of SAHCS. Data from different patients are indicated by different symbols listed at the right. Data from patients with fast and slow antiepileptic responses (n = 7) are grouped at the top, and those with no evident responses (n = 3) are shown in the bottom graphs. Fast responses (n = 5) were produced by continuous stimulation of either the anterior pes hippocampus close to the amygdaloid nucleus or anterior parahippocampal gyrus close to the entorhinal cortex. Slow responses (n = 2) were produced by continuous stimulation of either the medial hippocampus or the anterior perforate space. No responses (n = 2) were produced following interruption of stimulation applied to the anterior parahippocampal gyrus, and no response at all was observed (n = 1) with continuous stimulation out of the hippocampus. Note that the periods when SAHCS was interrupted or stimulation was applied out of the hippocampus are indicated by discontinuous horizontal lines and corresponding symbols (empty circles and crosses within circles or filled circles).

interrupted (Figs. 2 and 4, open circles and crosses within circles); in another patient whose stimulation contacts were located at the white matter lateral to the hippocampus, the SAHCS responses were absent (Figs. 2 and 4, solid circles).

Other EEG signs predicting and accompanying the SAHCS antiepileptic response

In all patients stimulated within the hippocampal formation or gyrus, a low-threshold (200 μA) electropositive DC shift was observed at the hippocampal regions just posterior to the stimulated site (usually at the medial parahippocampal region) (Fig. 6A). In the patients with continuous SAHCS and evident antiepileptic responses, this positive DC shift was present from the first stimulation trial and persisted through all subsequent trials. The positive DC shift was absent whenever the SAHCS was interrupted or applied out of the hippocampus.

Prominent and organized monomorphic (1–1.5/s) delta activity was present at the same middle parahippocampal region where the DC shift was observed, and it persisted during the on and off SAHCS stimulation periods in all patients with evident and fast response (Fig 3). In other patients with slow responses, this monomorphic delta activity was found only during some stimulation sessions, intermixed with 1–1.5 per second isolated spikes

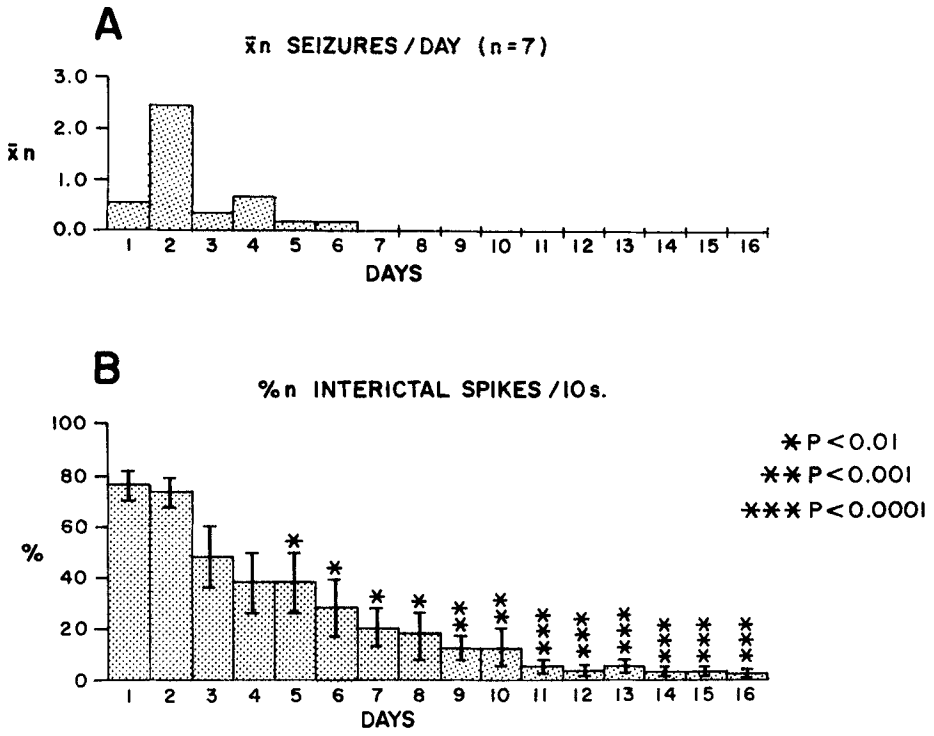

FIG. 5. Effects of subacute electrical stimulation of the hippocampal formation or gyrus (SAHCS) on seizures and interictal spikes in the group of patients with evident fast and slow antiepileptic responses. **A:** Average number of seizures/day. **B:** Average (±SEM) number of interictal spikes/10s at the epileptic focus recorded daily during 16 days of SAHCS in patients with fast and slow antiepileptic responses. Note that clinical seizures were abolished after day 6 of SAHCS, and the number of interictal spikes were progressively and significantly decreased from 80 to 40% after 5 days ($p < 0.01$), from 40 to 18% after 9 days ($p < 0.001$), and from 18 to 8% after 11 days ($p < 0.0001$).

or spike bursts that spread to other regions of the basotemporal cortex (Fig. 6B and C, asterisks).

Other EEG signs accompanying the SAHCS antiepileptic response included progressive normalization of surface, hippocampal, and basotemporal background EEG activities, occurrence of K-complexes; and other signs of slow-wave sleep not usually observed during morning recording sessions of patients with intractable seizures and medication discontinuation (Fig. 6B and C, arrows). Further details on surface, hippocampal, and basotemporal EEG changes by SAHCS during wakefulness and sleep will be reported in a subsequent article.

Histopathologic analysis of the stimulated hippocampal tissue

Histopathologic interpretation of the findings in the stimulated and nonstimulated hippocampal sites was sometimes difficult because of the underlying pathology (atrophy and sclerosis) of the epileptic hippocampus. Nevertheless, histopathological abnormalities were found that may be attributable to either lesions of the hippocampal axis produced by depth electrode penetration or to the foreign-body reaction of the pia and cortex to the presence of the Silastic sheet of the subdural electrodes (i.e., cell loss and lymphocytic and astrocytic reactions around the electrode's trajectory). These abnormalities include diffuse, moderate gliosis and cell loss of cortical layers I and II, increase in mononuclear inflammatory cells in the subarachnoid space, and meningeal thickening of the cerebral tissue attached to the electrode's sheet. Neither gross pathology of tissue (vacuolation, chromatolysis, and neuronophagia) nor signs of scar formation were found. In addition, no histopathologic differences were found between the stimulated and nonstimulated hippocampal tissue (Fig. 7).

DISCUSSION

These results indicate that in humans, SAHCS blocks temporal lobe epileptogenesis with no obvious, light-microscopic, pathologic, hippocampal damage attributable to the electrical stimulation.

SAHCS on epileptogenesis

Recent studies in rats by Weiss et al. (15–18) have shown that low-frequency stimulation (1 per second stimulation for 15 min) applied immediately after high-frequency kindling stimulation (60 per second for 1 s) of the amygdala inhibited the development of amygdala-kindled seizures and afterdischarges (AD); this effect was termed "quenching". Quenching was associated with a long-lasting increase in the AD threshold. Moreover, in fully kindled animals, quenching once daily for 7 days (without concurrent kindling stimulus) similarly produced an increase in the seizure threshold, which resulted in an inhibition of seizures. Subsequent experiments showed that similar quenching effects were produced by either low-level DC leakage of some stimulators (i.e., when the rat was connected but the stimulation program was off) or by the delivery of a positive DC stimulus of very low intensity (1–15 μA for 15 min) following the kindling stimulation. Daily application of this DC stimu-

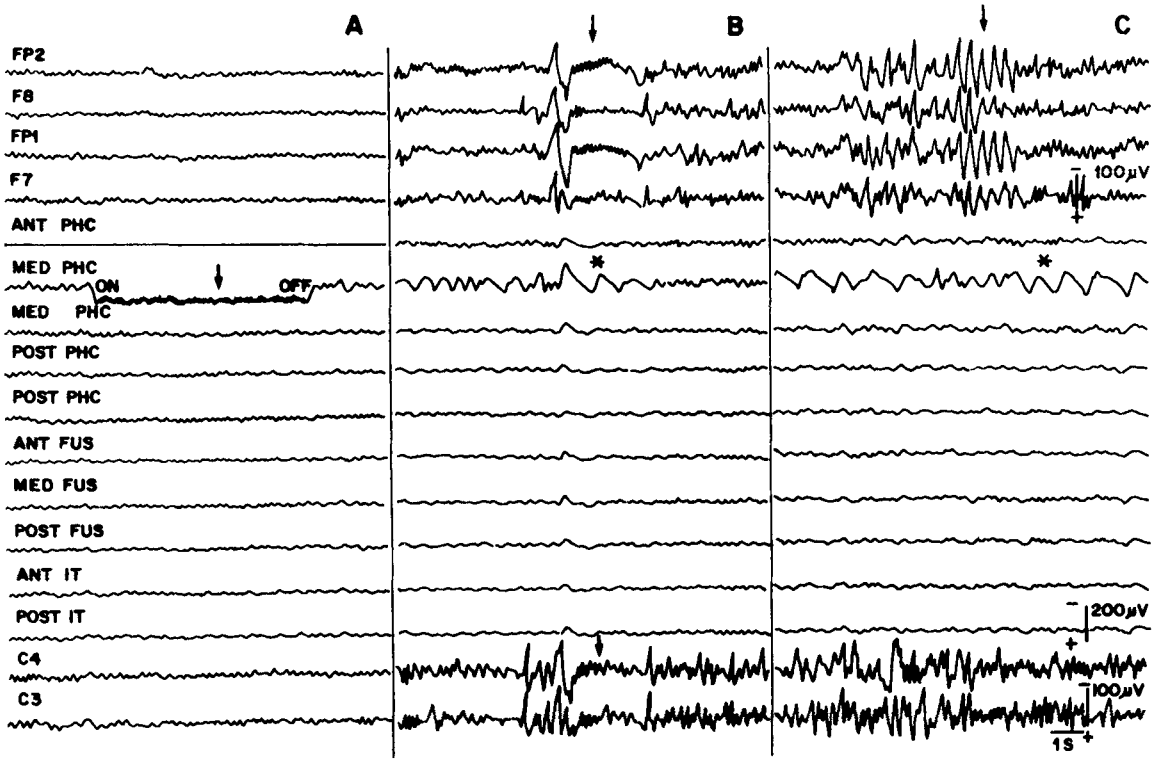

FIG. 6. Other electroencephalogram (EEG) signs predicting and accompanying the subacute electrical stimulation of the hippocampal formation or gyrus (SAHCS) antiepileptic responses. All EEG recordings from same surface and subdural regions as in Fig. 3. **A:** Electropositive DC shift recorded at the medial parahippocampal gyrus by threshold (200 μA) stimulation of the anterior parahippocampal gyrus. ON and OFF indicate the duration of the stimulation trial. The isoelectric record at the anterior parahippocampal (ANT PHC) region was due to the fact that contacts were disconnected from the recording and attached to the stimulating equipment. **B, C:** K complexes and burst of frontal vertex-like waves appearing after day 7 of SAHCS usually at the surface leads that were not observed during morning EEG records of patients with intractable seizures and antiepileptic drug (AED) withdrawal. Note also the development of the monomorphic delta activity at the middle parahippocampal region (indicated by asterisks). Abbreviations as in Fig. 3.

lus over 7–14 days increased the AD threshold from 280 to ⩾800 μA and produced a sustained period of seizure inhibition for >30 days. According to Weiss et al. (18), pathologic studies still under way showed no obvious lesions in the amygdaloid tissue due to quenching, although a localized increase in silver staining in fibers or dendritic processes appears around the electrode tip. Therefore, at present, the mechanism of quenching is not clear. But because low-frequency stimulation was not critical for quenching, such stimulation is unlikely to be related to the long-term depression or depotentiation reported by others working with in vitro experiments (26,27). Quenching in the amygdala may involve GABA systems because the process is accompanied by increased levels of [^{3}H]flunitrazepam binding to benzodiazepine receptors in the entorhinal and perirhinal cortices. According to Weiss (personal communication) kindling and quenching can also be produced by hippocampal stimulation.

These results in humans show that continuous high-frequency, 130 per second and low-intensity, 200- to 400-μA stimulation of the hippocampus (which is 10 to 20 times smaller than the AD threshold) produced a focal, hippocampal, electropositive DC shift and a complete blockage of clinical seizures (both complex partial alone and complex partial associated with tonic–clonic generalized seizures) and significantly decreased epileptiform EEG activity at the epileptic focus. The apparent increase in the number of seizures and focal EEG spikes during the first 1–3 days of SAHCS may be attributable to AED discontinuation rather than SAHCS, because this increase was observed in another 48 patients who had implanted electrodes but received no stimulation (19). In these patients, AEDs were discontinued as a conventional procedure to activate and localize the epileptic focus (14). The general consensus (28–31) is that abrupt discontinuation of AEDs progressively increases both the number of seizures and interictal EEG spikes. In all of our nonstimulated patients, seizures appeared from 24 to 72 h after AED withdrawal, and their number increased with time until the temporal lobectomy was performed (usually 12–17 days after AED discontinuation). A maximal number of three to seven seizures a day was attained after 10 days of AED discontinuation in spite of the administration of diazepam (10 mg intramuscularly), which was frequently given at night and on weekends for

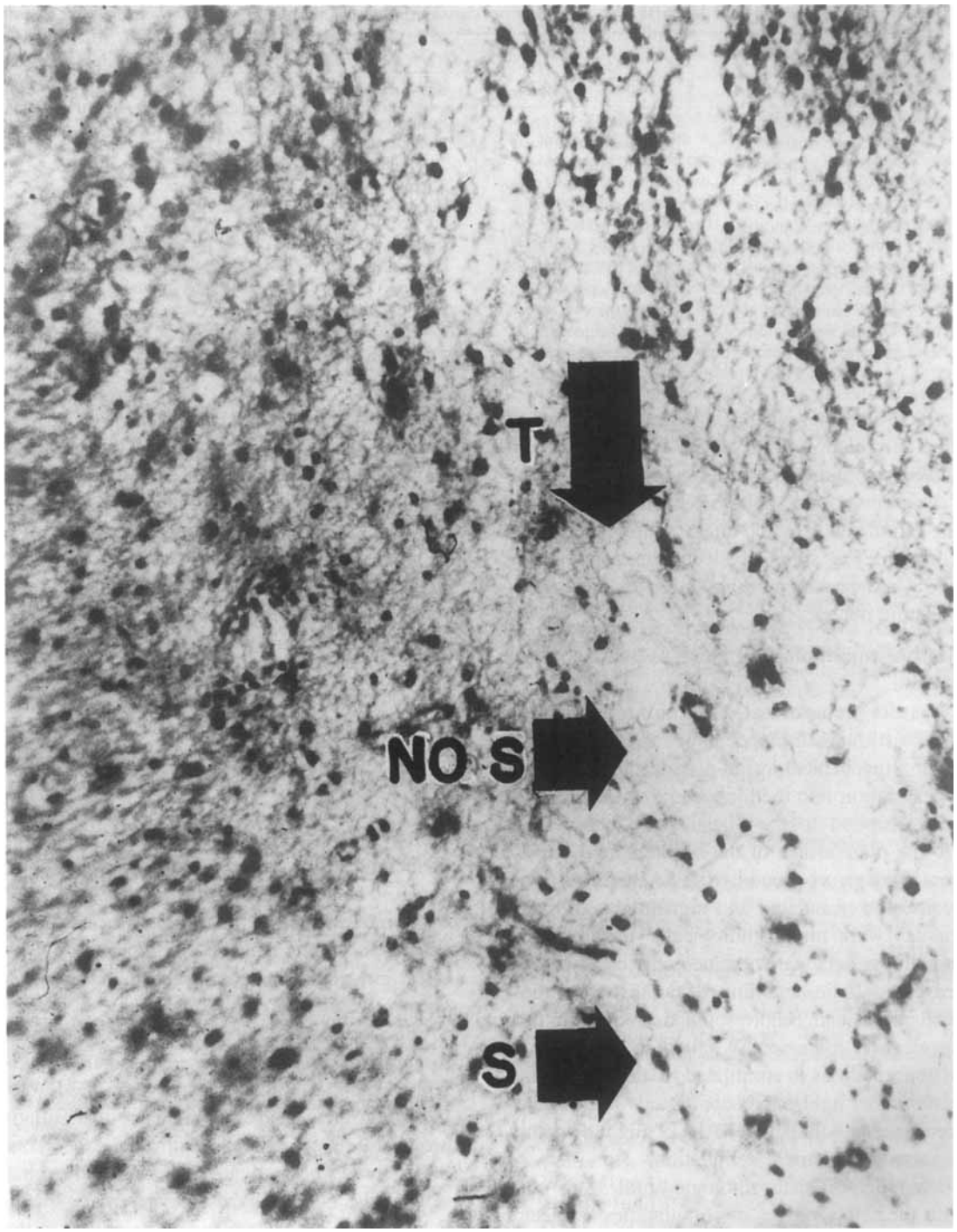

FIG. 7. Histopathological confirmation of the stimulated hippocampal tissue. Microphotography (Hematoxiline-Eosine X20) showing the hippocampal tissue damage caused by the depth electrode trajectory (T arrow) as well as the cell loss and lymphocytic and astrocytic reactions of the adjacent tissue. No evident histopathological differences were found between the stimulated (S arrow) and nonstimulated tissue (NS arrow).

the patients' protection when video-EEG monitoring was discontinued. The SAHCS effect was not long lasting because both clinical seizures and paroxysmal EEG activity returned when SAHCS was interrupted 3–5 days after initiation (Fig. 4). In other experiments, however, we have shown that prolonged electrical stimulation of the thalamic centromedian nucleus (with similar parameters to those of SAHCS) during ≥3 months also produced a surface, electronegative DC shift at the frontal and central cortical regions and a decrease of generalized epileptogenesis that lasted from 1 to 2 months after stimulation was discontinued (2,4). Longer lasting

TABLE 2. *Safety procedures in man and monkey*

Stimulation paradigm	Monkey Babb et al. 1987	Human Gordon et al. 1990	Human Velasco et al. 1998
Stimulation site	Cerebellar cortex	Basotemporal cortex	Basotemporal cortex
Electrode material	Platinum iridium	Platinum iridium	Platinum iridium
Electrode impedance	10 K ohms	20 K ohms	10 K ohms
Electrode size	3,4–6,8 mm	3.1 mm	4.0 mm
Type of stimulation	Referential	Referential	Bipolar
Stimulation duration	102.0 hs	0.5 hs	368.0 hs
Type of pulse	Biphasic	Biphasic	Biphasic
Pulse frequency	10/s	30/s	130/s
Pulse duration	1,000 μs	300 μs	450 μs
Pulse intensity	1,000 μA	12,800–15,000 μA	200–400 μA
Charge density	7.4 $\mu A/cm^2/h$	52–57 $\mu C/cm^2/h$	1.15 $\mu C/cm^2/h$

SAHCS effects may be evident with longer periods of hippocampal stimulation than we are currently investigating. Further experiments also have to be done on the nature of the monomorphic delta EEG activity appearing close to the stimulated sites and on the significance of the surface cortical EEG signs of sleep appearing during both SAHCS and prolonged stimulation of the centromedian thalamic nucleus (9).

SAHCS and histopathological changes at the stimulated site

These results demonstrate that histopathologic changes of the stimulated hippocampus may be attributable to either a mechanical lesion produced by the depth electrode penetration into the hippocampal tissue or to a foreign-body reaction to the Silastic electrode's sheet attached to the pial surface of the basotemporal cortex. No apparent damage produced by the SAHCS itself was found because the stimulated and nonstimulated hippocampal tissues were histopathologically indistinguishable. Although our data were obtained only by the use of light microscopic studies and limited staining techniques, other investigations using more sophisticated techniques (including electron microscopy) failed to demonstrate additional abnormalities in stimulated tissue that was not also observed under light-microscopic study (32). Therefore it is reasonable to think that SAHCS might be within the safety range of electrical stimulation.

A good number of histopathologic studies are concerned with the safety ranges of stimulation parameters on different cerebral structures in various animal species and humans (33–35). They have shown that short-, medium-, and long-term electrical stimulation of the brain may be completely innocuous, and they have recommended safety limits for stimulation studies in humans. Data provided by different studies, however, are controversial, with the controversy dependent mainly on the size of the stimulated brain studied and the specific stimulation paradigm used. Our safety SAHCS studies were performed with methodologic procedures comparable to those used by Babb et al. (36) on the cerebellar cortex of monkeys and by Gordon et al. (37) on the human basotemporal cortex. The latter study also showed an absence of cerebral lesions attributable to the brain stimulation (Table 2). In spite of minor differences between studies, we consider that safe stimulation procedures are those that use strong but brief stimulation parameters (52–57; $\mu C/cm^2/h$ during 0.5 h), such as those used by Gordon; mild and prolonged stimulation (7.4 $\mu C/cm^2/h$ during 102 h), as used by Babb; or those used here (1.15 $\mu C/cm^2/h$ during 360 h).

Assuming that SAHCS may be a safe procedure, we conclude that its effect on temporal lobe epileptogenesis may be explained by physiologic rather than pathologic (ie, lesion) factors. A number of physiologic mechanisms may participate in the SAHCS effect, such as those previously mentioned for amygdaloid and hippocampal quenching in the rat. In the present work, the more evident and fast antiepileptic responses to SAHCS occurred by stimulation of a critical region located at the anterior pes hippocampus and the parahippocampal gyrus close to the amygdaloid nucleus and the entorhinal cortex, respectively; therefore, it is reasonable to assume that the SAHCS responses are due to the activation of the perforant pathways running close to the amygdala that exert a polysynaptic inhibitory drive upon the CA1–CA4 epileptogenic neurons responsible for the initiation and/or propagation of intractable temporal lobe seizures. Why SAHCS does not activate the associated excitatory pathway to the dentate gyrus, however, remains unknown. Other possible mechanisms participating in the SAHCS antiepileptic effect are currently being investigated on tissue from our hippocampal biopsies. These include changes in benzodiazepine and opioid receptors produced by SAHCS by means of autoradiographic techniques and changes in the reorganization of the epileptic hippocampus produced by immunohistochemical techniques.

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