GABAergic Disinhibition and Reversible Secondary Epileptogenesis in Man

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Hughlings Jackson rightly proposed that seizures result from “excessive neuronal discharge”. A growing body of evidence suggests that disinhibition may be necessary but not sufficient for initiating excessive neuronal discharge (2). From a study of penicillin-induced generalized epilepsy in the cat, Gloor (14) has argued that:

“... bilaterally synchronous spike-and-wave discharge represents an abnormal response pattern of cortical neurons to afferent thalamocortical volleys normally involved in the elicitation of spindles. Such a response occurs under conditions of diffuse mild cortical hyperexcitability that causes cortical neurons to generate an increased number of action potentials per afferent volley. This secondarily leads to powerful activation of the intracortical recurrent inhibitory pathway. The result is an alternation of short periods of increased cortical excitation corresponding to the EEG spike with longer-lasting periods of intense cortical inhibition corresponding to the wave component of the spike-and-wave complex. This pattern of widespread synchronous oscillation between increased excitation and increased inhibition profoundly disrupts the normal pattern of cortical neuronal activity necessary for sustaining higher nervous functions....”

Evidence also exists that when focal application of penicillin induces seizures, an area of inhibition surrounds the epileptic focus (20). “Surround inhibition” is not unique to the penicillin model, but occurs also in iron- or cobalt-induced focal epilepsy (21,28). Schroeder and Celesia (26) have studied the effects of penicillin applied to primary auditory cortex of cats. The initial effect was attenuation of auditory-evoked responses to clicks at the focus, and also in the homotopic area

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of contralateral hemisphere. Shortly thereafter, interictal spikes appeared; later, clicks evoked responses indistinguishable from interictal spikes ("reflex spikes"). Finally, spontaneous seizures occurred in the primary focus; at this stage, clicks evoked "reflex spikes" in the contralateral "mirror" focus. Evolution of a secondary focus depends on callosal mechanisms and is preceded by inhibition in the homotopic site (3).

Gamma-aminobutyric acid (GABA) is generally accepted as the principal inhibitory transmitter in cerebral cortex (4). Administering the alkaloid bicuculline, a competitive antagonist of GABA, induces generalized seizures (17). Conversely, inhibition of the high-affinity GABA uptake, elevating GABA concentrations in synaptic clefts, raises the threshold for inducing convulsions by electroshock of pentetrazole (11). Furthermore, Gale and Iadarola (12) have shown that after inhibiting GABA transaminase "the onset and peak of anticonvulsant activity against maximal electroshock seizures directly parallel the time course for the increase in GABA in nerve terminals" and that, although total GABA reached a maximum level within 12 hr, the GABA pool associated with nerve terminals did not increase until 36 hr, and reached a maximum at 60 hr. Ribak et al. (23) have shown a deficiency of terminals containing glutamic acid decarboxylase, the synthesizing enzyme of GABA, in epileptogenic foci created in the sensorimotor cortex of monkeys by applying alumina gel.

Such studies provide no evidence concerning behavioral effects of seizures upon processing in sensory cortex. It is clear that in koniocortex short axon, local-circuit neurons (Golgi Type II or stellate cells) inhibit cortical pyramidal cells (18, 31) via GABA (4, 22, 24). Sillito (29) has studied effects on single cells in visual cortex of disinhibition induced by microiontophoresis of bicuculline. In receptive fields of both simple and complex cells, he found decreased specificity for visual parameters of axis orientation and direction of movement. These defects were reversible. Tsumoto et al. (33) combined systemic administration of an inhibitor of GABA synthesis with iontophoretic application of bicuculline and found summating effects which almost completely abolished orientation and direction sensitivity. During disinhibition, excitatory receptive fields of these cells increased slightly in size and became virtually round; they concluded "that intra-cortical inhibition plays a major if not an exclusive role for the orientation and direction sensitivity of cortical cells." In somatosensory cortex, the same mechanism appears to underlie directional sensitivity in neurons responsive to moving stimuli (13). For the counterpart, we are unaware of studies that explore what changes, if any, occur in receptive fields during enhanced GABA-mediated inhibition.

In light of these experimental data, we consider the case of a 12-year-old boy who suffered from focal seizures arising in left auditory cortex. For almost 3 years, we have used proprietary auditory testing to study his seizures. We use computer-synthesized sparse acoustic stimuli (SAS) containing some acoustic features of speech sounds to assess processing in auditory cortex (7). If one acoustic parameter is varied systematically, certain minor alterations in acoustic composition of SAS produce profound changes in perception (Fig. 1). For example, with SAS having two formants,
FIG. 1. **Top:** Diagrammatic acoustic spectrogram of SAS. *Ordinate:* frequency in kHz. *Abscissa:* time in msec. F1 F2, F3: frequency of first three formants.

**Bottom:** Ideal classifications of SAS illustrated in upper section. *Left ordinate:* percent SAS identified as /ge/. *Right ordinate:* percent SAS identified as /ye/. *Abscissa:* stimulus value, representing duration of F to change from value 1 (20 msec) to value 12 (130 msec). Diagonals at top of graph indicate duration of F2 change for appropriate stimulus value. Note that for all stimulus values up to 5, subject classifies sound as /ge/, and for all stimulus values 8 and greater, subject classifies SAS as /ye/. For stimulus values 6 and 7, subject classifies less consistently.

Shorter durations of rising second formants are perceived as /be/ and longer durations as /we/. With falling second formants, shorter durations are perceived as /ge/ and longer durations as /ye/. If duration of formant change is held constant, with direction and extent as the significant parameters, SAS are perceived as the stop consonants /b/-/d/-/g/, which differ in place-of-articulation. If a brief
resonance precedes second formant change, such SAS are perceived as the nasal counterparts /m/-/n/-/ŋ/. Patients and subjects classify sets of SAS and indicate classification by a motor act, e.g., pointing. Responses are arranged in multidimensional contingency tables and tested for divergence from homogeneity (8). The results of analysis with likelihood ratio $X^2 (G^2)$ can be expressed with traditional probability values. Classification can also be compared with ideal values, to determine departure from "normality."

A 12-year-old boy had developed seizures at age 6. Seizures first occurred in church during hymn-singing; his parents observed him to stare, pale, gulp, and not respond. Later, spontaneous seizures occurred, often preceded by crude auditory hallucinations described as buzzing, humming sounds, or repetitive sounds in the right ear which he described as "clicking" or a sound like drums. His family physician referred him to a neurologist. EEG showed a focus of spikes in left midtemporal region. He was given phenytoin (PHT) with a reduction in number of seizures. As time passed, seizures recurred despite addition of phenobarbital (PB). He said that at times during seizures he heard sounds like voices; sometimes he heard a single voice, at other times voices of two or more persons including men, women, and children. He said the voices sometimes seemed to mumble; at other times he reported intelligible words such as "boy, boy, boy" or "don't, don't." Initially, music appeared to precipitate seizures; later, sounds with quasirhythmic features also precipitated attacks. His parents observed attacks when he heard a pennant fluttering, tires thumping on pavement, or water gurgling while the bathtub was filling. Because seizures continued for 18 months, his physician sought a second neurological opinion. At that time, EEG revealed more complex abnormalities. The focus of spikes in left midtemporal region discharged relatively infrequently; however, frequent spike discharges appeared in right hemisphere. These arose independently from two sources with surface-negative orientations. One had large surface distribution with maximum voltage in the midtemporal region; the other appeared in the centroparietal parasagittal region. The latter focus fired less frequently than did the midtemporal focus. Primidon (PRM) was substituted for PB; this altered regimen reduced seizures. About 6 months before our initial examination, his parents had noted an increase in brief attacks consisting of impaired perception of speech or auditory hallucinations often succeeded by momentary unresponsiveness. As these attacks increased in frequency, he experienced difficulty comprehending speech. His parents noticed that he refused to talk on the telephone to his friends, saying that he could not understand mem. Later he had trouble understanding speech if more than one person spoke or if music was in the background. Finally, he had difficulty understanding his parents although he obviously heard environmental sounds clearly.

At our initial examination he could not comprehend speech, although he localized sounds and appeared to distinguish between environmental and speech sounds. He understood and responded appropriately to written questions and requests, speaking or writing his responses. His oral replies were appropriate and without aphasic defect, although in succeeding days he showed some oral apraxia. Pure-tone audiometry and brainstem-evoked responses gave normal findings.
A radioisotope study revealed markedly increased blood flow in left temporal region, consonant with increased metabolic activity in the area of auditory cortex due to frequent seizures (19, 25). Another EEG again showed independent foci of spikes in each hemisphere, identical with those seen previously. In addition, hyperventilation induced an electrographic seizure lasting 4 min; this arose in left midtemporal (T3) region and eventually spread to include anterior and posterior temporal electrodes (F7 and T5). Because of his auditory problems, the technologist had difficulty in communicating with him; however, she observed that he hyperventilated erratically, stared briefly, and yawned. The upper panel of Fig. 2 shows the results of our first examination: he classified randomly SAS presented monaurally to each ear.

Antiepileptic drug (AED) levels showed PHT = 3 µg/ml and metabolically derived PB = 21 µg/ml. His attending physicians increased total daily dose of PHT and started carbamazepine (CBZ) as an "add-on" drug. In ensuing weeks, the number of brief seizures steadily declined, and his comprehension slowly but def-

**FIG. 2.** Classifications of SAS by patient on four separate occasions. *Abscissa and ordinates* as in Fig. 1. AS, left ear presentations; AD, right ear presentations; $P(X^2 > G^2)$, probability that $X^2$ is greater than $G^2$. Numerical values below AED, concentration in µg/ml).
initely improved. Within 8 weeks he comprehended speech in most circumstances, although he still had difficulty when listening on the telephone, when more than one person spoke, and in understanding teachers in the classroom. After 5 months, AED levels were PHT = 8 µg/ml, PB = 26 µg/ml, and CBZ = 1 µg/ml. Because the CBZ level was inadequate and auditory problems continued, the daily dose of CBZ was increased. During the next 2 to 3 weeks, his parents observed no brief attacks. Over the subsequent 6 to 8 weeks, comprehension improved, and his parents believed that he understood speech normally. The second panel of Fig. 2 shows the results of testing 8 months after initial examination; AED levels were within "desirable therapeutic range." He had remained well for about 4 months when he began to grow rapidly. His parents noted recurrent brief seizures and deteriorating comprehension of speech. AED determinations revealed PHT had dropped to 6 (µg/ml with PB and CBZ levels unchanged. His physicians increased total daily dose of PHT; within 3 weeks, patient was clinically intoxicated with PHT = 24 µg/ml, PB = 26 µg/ml, and CBZ = 8.5 µg/ml. The third panel of Fig. 2 shows the results of testing at this time. Reducing PHT dosage abolished intoxication; however, compensatory increase in CBZ dosage produced no obvious improvement. At school, his teachers observed that in mid to late afternoon he had increasing difficulty in understanding speech. With concurrence of school authorities, his parents brought him from school in early afternoon for repeated testing. The fourth panel of Fig. 2 shows the results of testing in early afternoon. At that time, PHT = 7 µg/ml, PB = 13 µg/ml, and CBZ = 5 µg/ml—values not strikingly different from those times when seizures were controlled.

To evaluate stability of each auditory cortex, we used sets of SAS with acoustic features such that, if presented monaurally, only contralateral auditory cortex processes them appropriately (7). Figure 3 shows the results of such testing later in the afternoon. The top panel demonstrates normal processing in right auditory cortex. The second panel shows results 5 min later with slight but significant deterioration in left auditory cortex. The third panel shows alterations in the right auditory cortex. The final panel, 15 min after beginning testing, shows significant impairment in the left auditory cortex. During this run, an 85-sec period of fixed responses to randomized stimuli occurred. Shortly thereafter he reported changes in SAS, which he described as "r's" and "l's" intermixed with "g" sounds. Perceptual alterations also occurred with SAS of set BDG. Initially, with left monaural presentations, his classifications were appropriate. However, during subsequent right monaural presentations, he reported episodes in which he heard "m" and "n" sounds for SAS which he had previously classified appropriately as /b/ and /d/. In normal subjects, perceptual differences between stop consonants and nasals reflect differences in basilar membrane movements caused by these SAS. /b/ differs from its nasal cognate /m/ in abrupt onset of its second formant and, thus, in "crispness" of initial movements of basilar membrane; /d/ and /n/ are comparable.

We concluded that, were his seizures not intractable, these perceptual alterations must reflect significant fluctuation in AED levels over relatively short periods. We proposed to patient and his parents that we carry out prolonged auditory testing
while obtaining periodic blood samples for AED determinations. After careful consideration, the patient and his parents gave informed consent. On the day of study, at 8 a.m. he received PRM (125 mg), PHT (75 mg), and CBZ (200 mg); at 1:20 p.m. he received CBZ (200 mg). Testing began at 1:45 p.m. As shown in Fig. 4, AED levels during testing fluctuated widely and rapidly. PB was metabolically derived from PRM. Note CBZ followed a temporal pattern separate from other AED. Monaural performances over this same time also fluctuated widely, and sometimes apparently independently (6). Figure 5 shows fluctuations in the left auditory cortex (right monaural presentations) during this first study.

Our various studies had demonstrated that CBZ was the most-efficacious drug, and during the kinetic study, best performance occurred at CBZ levels of at least 9 µg/ml. We also noted transient somnolence coinciding with peaks in PB levels. Accordingly, we eliminated PRM and increased the total daily dose of CBZ to 1.0 g. His parents noted increased alertness as PB was eliminated. We next discontinued PHT but buttressed CBZ with small amounts of sodium valproate (VPA) because of its known action as a GABA agonist. His final regimen was: 4 a.m. CBZ (200 mg); 8 a.m. CBZ (300 mg) and VPA (250 mg);
FIG. 4. Serum levels during initial continuous testing period. *Ordinate*: serum levels in µg/ml. *Abscissa*: clock time on 24-hr cycle.

FIG. 5. Results of serial testing in patient. *Ordinate*: for right ear, probability that $X^2 > G^2$. *Abscissa*: clock time on 24-hr cycle. *Filled circles*: patient reported subjective difficulty in comprehension and clicks in right ear.
12 p.m. CBZ (200 mg) and VPA (250 mg); 4 p.m. CBZ (200 mg); 8:30 p.m. CBZ (100 mg) and VPA (250 mg). During the next 2 weeks, his parents observed steady improvement in speech comprehension, and after 3 weeks, the patient said he understood speech at all times. During the ensuing year, he had no seizure and maintained a school record of A- grades. Somnolence associated with elevated PB levels directed our attention to his ability to remain vigilant. Further inquiry disclosed that his father had suffered from life-long inability to sustain vigilance which interfered with his work as an engineering draftsman and, at times, culminated in falling asleep at table or while watching television. We treated this genetic disorder of vigilance with methylphenidate (MPD) (5).

During the latter half of the school year, the patient again began to grow. His teachers reported occasional brief episodes of either incomprehension or inattention. The patient said that these episodes were not intervals of altered auditory perception, but difficulty in remaining alert. Concerned that the growth spurt foreshadowed relapse, his parents requested that we repeat a kinetic study. The patient and his parents again gave informed consent. So that the study would encompass hours of the school day, the patient was admitted to General Clinical Research Center, Parkland Memorial Hospital, whose staff and facilities made it possible to obtain blood specimens every 20 min without disrupting ongoing testing. Figure 6 shows results of AED determinations during this 9-hr period. The study revealed highly stable levels of CBZ above the level we had demonstrated necessary to control seizures. VPA levels were also relatively stable.

![Graph showing serum levels during second monitoring session.](image)

**FIG. 6.** Serum levels during second monitoring session. *Ordinate:* serum levels in µg/ml for VPA and CBZ. *Abscissa:* clock time on 24-hr cycle. Patient received CBZ (200 mg) and VPA (250 mg) at 12 p.m., CBZ (200 mg) at 4:20 p.m.
Figure 7 shows cortisol levels during each kinetic study. Initial marked but transient elevations appeared both times. These probably reflect stress effects from intravenous catheterization. However, this stress appears not to disrupt significantly circadian cortisol cycles. During the first study, there appears to be interaction between cortisol and AED. In the second study, no such interaction can be detected.

Figure 8 shows results of behavioral testing on each occasion. In the second study, two episodes of altered performance occurred during the morning. The first was mild and appeared about 11 a.m.; the patient reported no alteration in quality of SAS but complained of being "a little sleepy." About 1 hr later, marked deterioration in performance occurred. Again, he reported that SAS sounded unchanged but that he was sleepy. He was given MPD (Ritalin, 20 mg sublingually); within 20 min, performance improved abruptly. Two mild intervals occurred during the afternoon, each alleviated by MPD. Effects of steady-state emerge in behavioral testing. During the initial study, fluctuating performance paralleled fluctuating AED levels. In the second study, AED levels remained stable; performance was stable, significantly improved (100-fold), and he was without seizures. Episodes of impaired vigilance continued unrelated to peaks in AED.

DISCUSSION

Observations in this patient permit several conclusions about treatment of patients with seemingly intractable seizures:

1. With appropriate doses and times between doses, pharmacologic steady-state can be achieved.

![FIG.7. Plasma cortisol concentrations during first and second studies. Ordinate: plasma cortisol concentration in µg/dl. Abscissa: clock time on 24-hr cycle. T1: first test (Fig. 4), T2: second test (Fig. 6).](image)
2. Steady-state at effective AED levels can eliminate even the briefest focal seizures.

3. After control of seizures, interictal defects resolve rapidly.

4. Combined therapy makes achieving steady-state difficult or impossible because of differing half-lives of AED, drug interactions, enzyme induction (10), and, possibly, interactions with endogenous substances such as cortisol.

5. With many AED, dose-related somnolence impairs cognitive performance (16). Somnolence, fluctuating with peak levels of AED, may produce varying impairments in performance throughout the day. Furthermore, in patients with genetic disorders of vigilance, peaks may cause even more intense disruptions in performance. Eliminating peaks can diminish interaction between somnolence and impaired vigilance.

The evolution and resolution of this patient's disease can be considered in light of various experimental models of epilepsy. Initially, his seizures began in left
auditory cortex, as manifested by repetitive sounds in right ear. At this time, EEG showed interictal spikes only in left temporal region. As his seizures increased, he developed increasingly severe interictal defects which eventually involved both auditory cortices. EEG revealed independent foci of interictal spikes in right hemisphere, the sites of which reflect orientation of primary auditory cortex and planum temporale orthogonal to the convexity of the hemisphere. Clinically, and in the one EEG-recorded seizure, left hemisphere appeared to generate most seizures.

In the experimental penicillin focus, Schwartzkroin and Prince (27) have argued that disappearance of IPSPs (disinhibition) eliminates the control mechanism which prevents repetitive orthodromic axonal spikes (burst firing) by shunting calcium-mediated dendritic spikes. These IPSPs are GABA-mediated; moreover, a deficiency of GABAergic terminals exists, at least in alumina foci. In the penicillin focus, as well as aluminum and iron models, the epileptic region is surrounded by a zone of inhibited cells including a homotopic area in contralateral hemisphere generated by callosal afferents known to arise from pyramidal cells in cortical layers III and IV (15). In cats, Toyama and Matsunami (32) have shown that specific geniculocortical afferents and commissural fibers "share an inhibitory interneuron in the final common pathway to the efferent cells in the visual cortex." Prince and Wilder (20) have argued that these inhibited cells reflect a homeostatic mechanism which prevents repetitive firing in cortical pyramidal cells adjacent to the focus. Emergence of a mirror focus suggests disinhibition of GABAergic cells, possibly from declining transmitter synthesis. If seizures continue unabated, transmission failure or even more severe disruptions of cellular metabolism could follow. Such widespread disinhibition would cause marked alterations of processing in sensory cortex.

In this light, let us consider the nature of this patient's auditory defects. Perhaps even before focal seizures in the left auditory cortex, he perceived /be/ as /me/ and /de/ as /ne/; he was thus unable to distinguish direction at onset of basilar membrane movements though he distinguished appropriately differences in location of movement. Such changes are consonant with effects of GABA disinhibition on receptive fields of visual cortical neurons (29).

Short-term deterioration illustrated in Fig. 3 may illuminate mechanisms of disinhibition. Acoustic features of SAS in this set can be processed appropriately solely in the hemisphere opposite the ear stimulated. At first, performance with left ear presentations was appropriate, indicating normal processing in the right auditory cortex. A few minutes later, left auditory cortex (right ear presentations) showed slight but significant alterations. Over the next few minutes, portions of the right auditory cortex evidenced altered processing with prolonged transitions. Over the time shown in the final panel, processing in the left auditory cortex was severely altered. The patient first reported experiencing a prolonged episode during which all SAS were clear, but "sounded like the same 'geh'" regardless of the stimulus value; this episode, which lasted for 85 sec, suggests prolonged and excessive inhibition. Abruptly he again distinguished SAS, although increasingly he reported
hearing "gr" or "gl" sounds instead of /g/; this may reflect partial and augmenting disinhibition.

Early in patient's illness, various types of repetitive sounds consistently triggered seizures. This is analogous to development of "reflex spikes" and is supported by observations during evolving epileptogenesis in visual cortex. Ebersole (9) found that preferred stimuli in receptive fields resulted in abnormal burst firing while nonpreferred stimuli elicited no unit responses. In our studies, we observed no instance in which SAS triggered seizures; this would be expected if only because stimuli were presented at low rates.

A final aspect in the evolution of this patient's epilepsy involves the frequent periods of unresponsiveness at the height of his illness. Unresponsiveness (automatism) results when epileptic discharges in temporal neocortex propagate via temporo-amygdalar bundle to ipsilateral amygdala (1) and subsequently to contralateral amygdala, perhaps via anterior commissure. This provides an anatomic system through which kindling might influence a preexistent epileptic focus.

A convincing body of evidence, summarized by Sironi et al. (30), demonstrates significant correlation between concentrations of AED in plasma and both neocortex and limbic structures. Therefore, if seizures persist in patients known to be in steady-state with effective levels of free (unbound) AED, such patients may be termed "medically intractable." Our observations bear on the role of surgery in patients with medically intractable seizures. In some patients, reversal of secondary epileptogenesis may identify a primary focus amenable to standard regional resection. In other patients with bihemispheric foci, limited commissurotomy may isolate reciprocally exciting foci, reducing them to critical masses amenable to AED therapy.

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REFERENCES


MODERATOR

Dr. Wada: Thank you, Michael. I think this is an important paper demonstrating the reversibility of epileptogenic cortical functional disturbance which can occur across the midline. This has a significant implication when we try to understand the kindling phenomenon across species. I am sure there will be comments posed to this study. However, since we are running a bit late, let us now break for lunch.

This afternoon we are going to present some recent findings from our laboratory. I will lead off with some observations on AM kindling in forebrain bisected monkeys, then Dr. Kaneko will pose the question - "Is the Amygdaloid Neuron Necessary for Kindling?". Dr. Kimura will follow with his findings on histochemical neuroanatomy. Since the topics of all three papers are closely related, I would like to suggest that you save your comments and questions until the end of Dr. Kimura's talk, when we will have our discussion period.


“... Not to be missed, is one of the most fascinating and elegant studies of the nociferous influence of epileptic discharge in auditory cortex of man. Daly et al. confirm that such discharge interrupts normal acoustical discrimination but they, in addition, demonstrate that such interference can be correlated with hour by hour shifts in anticonvulsant blood levels. This finding may explain much of the variation in performance of epileptic patients. Hopefully, it may also alert physicians and educators involved in these issues to take a closer look at the pharmaco-kinetics of drug action and to explore the possibility that differing metabolic degradation of drugs is simply another reflection of biochemical individuality; each patient deals differently, not only with his or her epilepsy, but also with every therapeutic agent.

I would like to discuss many other issues raised by each of the papers. I wish I had been able to participate in the symposium itself. With neither option now available, all that I do is to recommend this volume as one of seminal importance and one which offers significant insights into the process scientific endeavor. Neurologists, epileptologists, electroen-lhalographers, as well as all those interested in the mechanism(s) of neural plasticity, will want to read and own this book.”

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