



Special Communication

Epilepsy and sudden death: Personal reflections and call for global action [☆]Claire M. Lathers ^{*}

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ABSTRACT

To solve the mystery of sudden unexpected death in persons with epilepsy (SUDEP), a global focus is needed to identify persons at risk, develop treatment regimens, and prevent its occurrence. A world wide network of professionals must focus on basic scientific research programs and clinical and epidemiology studies. Team work among different multidisciplinary professionals in clinical settings and within and among laboratories should address the global issues of SUDEP. If the correct term 'SUDEP' is used on autopsy reports and if verbal autopsies postmortem are conducted when needed, the true incidence of SUDEP may be found to be much higher than previously thought and the market for new antiepileptics and other drugs to prevent SUDEP will be larger. Symposia should discuss new data and lessons learned from the last 20 to 30 years to be applied by scientists and clinicians worldwide to gain a better understanding of SUDEP. 'Think out of the box' when evaluating an established animal model with potential for modification(s) to study mechanism(s) of SUDEP. Multiple relevant animal models are needed to understand the pathophysiology of SUDEP, hypothesize about effective treatments, develop small pilot studies in persons with epilepsy, and conduct confirmatory large-scale clinical trials. The fields of pharmacology, clinical pharmacology, and cardiology have much to offer as we work to improve compliance, develop new antiepileptic drugs, and apply different categories of drugs to resolve the mystery of SUDEP. Ambulatory simultaneous EKG and EEG telemetry monitoring of patients at risk for sudden death will help identify cardiac vs. brain epileptogenic triggers for treatment to decrease risk of SUDEP. Respiratory function monitoring is also needed. Academic fellowships and competitions for medical students, postdoctoral fellows, residents and faculty will attract medical and graduate trainees to work on SUDEP. Grant funding is essential to move the SUDEP knowledge base forward. Leaders must solve the global mystery of SUDEP using a leadership philosophy foundation that provides innovative vision and approaches for SUDEP research and teaching programs. The interaction of teaching and research is essential: while a student is learning how to conduct research he must simultaneously learn to become a teacher. Medical and graduate leaders must provide vision and a fertile environment to teach students of today to become the self learners and leaders of tomorrow to find solutions for SUDEP.

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1. Personal reflections and lessons learned

In 1773 George Washington reported the sudden death, during a seizure, of his stepdaughter, a person with epilepsy [1,2]. Additional sudden deaths have been reported, but surprisingly, little progress has been made in solving the mystery of sudden death [3–6] over the ensuing 236 years.¹ Today, *at least* the existence of the clinical problem of sudden unexplained death in persons with

epilepsy (SUDEP) is recognized and acknowledged.² However, we still must identify the incidence and cause(s) of death, mechanistic risk factors, and preventive measures. A global focus is needed to accelerate understanding of how to identify persons with epilepsy at risk and to then prevent occurrence of sudden death.

² Dr. Lathers presented SUDEP Grand Rounds at the FDA on November 11, 1989 [11]. Extensive discussion of the definition and occurrence of the clinical problem transpired. Discussions continued long after the seminar with leaders of the FDA, as all discussed questions of what role, if any, did drugs, compliance, and generics play as risk factors and how to label "risk" for relevant drugs. Eventually an FDA task group was assembled to address SUDEP labeling issues and the results were published [12]. It is of interest to note that this 1997 article of Leestma et al. was published 14 years after the September 26, 1983 International Symposium on SUDEP at which Dr. Lathers [13] discussed her research in the animal model and its relevance for SUDEP, and Dr. Lathers' FDA seminar was presented six years after the 1983 International Symposium. Research into the pathophysiology, risk factors, and prevention of SUDEP has progressed too slowly. It is time for a global effort focused on solving the mystery of SUDEP [3–6,74].

[☆] Opinions expressed are solely those of the author.

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¹ Earlier reports of sudden death and epilepsy exist (Bacon, 1868 [7], Geysen, 1895 [8], and Spratling, 1902 [9]) and have been summarized by Terrance [10].

Exciting, heated discussions during national scientific meetings attracted Dr. Lathers to accept a National Institutes of Health (NIH)-funded postdoctoral fellowship with Jay Roberts, Professor and Chair at the Medical College of Pennsylvania. Original laboratory polygraph records were carried to the microphone and pounded on while a scientific point was made. Scientific controversy focused on a question that has contributed to our knowledge today of risks for and mechanisms of SUDEP: “Was digitalis glycoside cardiac toxicity and death primarily due to a peripheral or a central or a direct action on the heart or to a combination of action sites?” (See reviews [14–16].) Multiple-year, continuous grants³ provided by NIH and the American Heart Association funded Dr. Lathers’ laboratory at the Medical College of Pennsylvania, where studies were conducted to develop a ouabain toxicity model. Electrophysiological recordings of peripheral discharge from cardiac postganglionic nerves were obtained before and after cardiac arrhythmias elicited by ouabain toxicity [17–19]. Simultaneous electrophysiological recordings obtained from two or three cardiac peripheral nerve branches revealed that neural discharge just prior to initiation of arrhythmia was nonuniform, exhibiting various combinations of increases, decreases, and no change. This nonuniform cardiac nerve discharge was hypothesized to be manifest in the heart as inhomogeneity of myocardial electrical excitability and conduction patterns, as demonstrated by Han and Moe [20]. They found that myocardial nonuniformity could cause ventricular arrhythmias, including ventricular fibrillation. Direct stimulation of the sympathetic ventrolateral cardiac nerve produces a shift in the origin of the pacemaker and tachyarrhythmias, because the nerve is not uniformly distributed to the various regions of the heart, but is localized to the atrioventricular junctional and ventricular regions [21–23]. Such nonuniform distribution of sympathetic nerves also contributes to initiation of arrhythmia as a nonuniform neural discharge occurred. The technique of simultaneous electrophysiological recordings from two or three cardiac peripheral nerve branches was then applied to a different cardiac sudden death animal model. Postganglionic cardiac nerve recordings were done before and after abrupt occlusion of the left anterior descending coronary artery to mimic sudden cardiac death in humans [17–19,24–26]. Postmortem cardiac pathology was done to establish the location of the coronary arteries and the location and size of the ischemic areas in each animal. Sympathetic innervation and its role in initiation of abnormal cardiac function, that is, arrhythmias and/or sudden death, are now recognized. Use of this animal model has allowed several questions to be raised: “Do disease states alter the function of the sympathetic postganglionic neural discharge and is this one site of action for pharmacological agents to act by altering or preventing the nonuniform neural discharge” [17–19,24–26]? Additional scientific excitement and interest occurred when the American College of Cardiology awarded Dr. Lathers the third of five competitive positions for their Young Investigator Prize for development of the basic cardiac neural discharge model comparing digitalis toxicity and coronary occlusion. The Pharma Foundation awarded two research grants and a Faculty Development Award to Dr. Lathers.

The Epilepsy Foundation then funded modest research proposals to allow Dr. Lathers and Dr. Schraeder to modify the original sudden death model first developed by Lathers and published with her colleagues [17–19,24–26]. A new animal model to study the clinical problem of sudden death in persons with epilepsy was developed. We published our first papers [27–30] on potential pathophysiological mechanisms for SUDEP. Continued teamwork with students (some funded by the Epilepsy Foundation) studying in my laboratory (Gerard-Ciminera [31–33], Carnel M.D./M.S.)

[34,35], Suter [36,37], Lerner [37], Klions [15,16], Lipka (M.D./Ph.D.) [15,16,38–42], Flax [39], Kraras (M.D./M.S.) [43–45], Goldman [45], and Tyau, Spino, and Agarwal [46,47]); with postdoctoral fellows Dr. Tumer [37,43–45,48–53], Dr. Frame [48], and Dr. Jim [54–58]; and with Residents Spivey [49,50,52,4–67], Malone [50], Unger [50,61,62,64], Bhat [50], McNamara [50,61–64], Schoffstall [50,51,67], Bonner [63], Aaron [63], LaManna [64], and Ho [64] allowed us to conduct studies to provide additional information about the central and peripheral neural autonomic aspects, direct cardiac actions, and role of adrenal catecholamines in the clinical problem of sudden death associated with both interictal and ictal epileptogenic activity [3–6]. Medical students Weiner [68], Stauffer [69,70], Dodd-o [69–71], and O’Rourke [72] worked with us to characterize the phenomenon observed while conducting the cardiac neural studies. The firing pattern of cardiac sympathetic and parasympathetic neurons during both interictal and ictal epileptogenic activity has been shown to change and was termed the *lock-step phenomenon*. This is some of the evidence that epileptogenic activation of the cardiac sympathetic nerves, resulting in ventricular fibrillation and death, may be another contributing cause of SUDEP. Likewise, epileptogenic activation of the cardiac parasympathetic nerves, revealed by ictal bradyarrhythmias or cardiac asystole, may be one contributing cause of sudden death of patients with epilepsy. Both ventricular fibrillation and asystolic events were observed in series of animals studied. In addition, an imbalance between the two systems, that is, the cardiac parasympathetic and the cardiac sympathetic neural discharge patterns, may contribute to SUDEP [27–30,73,74]. Wang et al. [75] provided supporting data for the lock-step phenomenon finding of Lathers and colleagues. Blockade of GABAergic and glycinergic receptors in medulla slices of newborn rats evoked intermittent seizure-like firing of cardiac parasympathetic neurons, suggesting the seizure-like pattern of firing during an epileptic attack may cause neurogenic ictal bradyarrhythmias, cardiac asystole, or even sudden death in persons with epilepsy.

Carnel, an M.S./M.D. student, was selected to compete in the Eastern Student Research Forum, University of Miami School of Medicine [76]. Dr. Ajmone Marsaille was present and quizzed her extensively. One very important question was: “What is the current incidence of sudden death in epileptics?” She responded that SUDEP accounts for 5–17% of mortality in persons with epilepsy. The relative frequency of the sudden unexplained death syndrome in people with epilepsy has remained unchanged since the early 1900s, despite advances in therapy and management of epileptic seizures. Approximately 3000 to 10,000 deaths per year, which occur in a relatively young population of people with epilepsy, are attributed to this syndrome [9,77–84]. Today, newer data indicate the incidence of SUDEP may be much higher than previously thought [85]. Medical examiners and coroners often fail to report the classification of SUDEP on the death certificate [86,87]. Physical autopsy data are needed worldwide to understand the incidence and cause of death. Verbal autopsies are needed to supplement autopsy findings and/or to provide information when no autopsies are available [88].

Lathers et al. conducted experiments to search for the mechanism whereby the nonuniform cardiac postganglionic sympathetic neural discharge produces cardiac arrhythmias and sudden death. In a series of animal experiments designed to explore sympathetic innervation and β receptor density in association with sudden cardiac death, Lathers et al. [37,52,60,66] examined sympathetic β receptor density gradient as a measure of cardiac sympathetic innervation in the cat heart. β receptor density was determined by binding of [³H] dihydroalprenolol [60]. The β receptor density of the right atrium was significantly lower than that of the left atrium; the β receptor density of the right ventricle was significantly lower than the density of the left ventricle. The density of the

³ Original research funded by NIH Grant BRSGRR-4518, HL 13666, the American Heart Association, Pharma Foundation Research Grants and Faculty Development Grant, the Epilepsy Foundation of America, and the Ben Franklin Partnership.

receptors of the ventricles was higher than those of the atria. The β receptor density of the distal distribution of the left anterior descending coronary artery was significantly higher than the proximal distribution. These regional differences in β -adrenoceptor densities are related to cardiac contractile strength of the different areas of the heart. The regional difference in the β -adrenoceptor densities reflects differences in postganglionic cardiac sympathetic innervation of the myocardium [22–24], and these site differences will vary the release of norepinephrine in the various sites of the heart. This modifies cardiac contractile function and may trigger development of cardiac arrhythmias and/or sudden death. Site difference, in part, is one component of mechanism(s) involved in sudden cardiac death. The nonuniform postganglionic cardiac sympathetic cardiac innervation is related to the nonuniform β sympathetic receptor locations in the heart, and these two parameters affect cardiac contractility and development of cardiac arrhythmias and/or death.

The Ben Franklin Partnership Fund awarded a grant to Dr. Lathers for her laboratory to train emergency medicine residents while developing intraosseous needles to establish an intravenous route for seizing children or pediatric cardiac arrest patients in whom an intravenous line cannot be established. Studies in a new animal model, using swine, demonstrated that the intraosseous route via the tibia bone allowed rapid intravenous access [50,51,54–58,61,62,64,67] in pediatric seizing patients or pediatric cardiac arrest patients and that the beta blocker propranolol [3,54,58] exhibited anticonvulsant activity, as did lorazepam and diazepam [56,57,61,62]. Today, the intraosseous technique is routinely employed in all emergency rooms. Persons with epilepsy at risk for SUDEP may benefit from the addition of a beta blocker. In addition to the intraosseous route, another unusual route for antiepileptic drug (AED) administration, the endotracheal route, was also tested in swine [63].

In the discussion of our articles, we listed the mechanisms (see Table 1) thought to be contributing to SUDEP. Most likely, different mechanisms and/or different combinations of mechanisms are responsible for death in different persons with epilepsy. Clearly, mechanisms contributing to SUDEP include actions located in the peripheral and central sites. Peripheral sites include, in part, a direct action on the heart, indirect and/or direct actions on the lungs, and actions on the adrenal glands.

Schraeder and colleagues [96] reported a case of a healthy young male fainting with seizures when listening to a sermon of how martyrs were tortured. Simultaneous recordings of ECG and EEG during repetition of the sermon provided a diagnosis. Implantation of a cardiac pacemaker left the patient symptom free. Dr. Schraeder and Dr. Lathers each delivered many national and international symposiums [International Epilepsy Symposium, Washington, DC, 1983 [13]; Am Coll Clin Pharmacol SUDEP Symposium, Co-Chairs: CM Lathers and PL Schraeder, and Clinical Pharmacology Problem Solving Teaching Clinic 1992, Co-Chairs: CM Lathers and CM Smith [103,104], research seminars, and grand rounds to audiences of cardiologists, neurologists, and clinical pharmacologists, and emphasized the importance of continuous ECG and EEG recordings to identify persons with epilepsy at risk for sudden death. Despite this effort over a 27-year period, discussion at the recent (November 2008) NIH SUDEP Workshop [105] revealed that many physicians still do not think about the necessity of examining both heart and brain electrical activity for clues to the clinical problem when examining persons at risk for sudden death. Clearly, it will take a global effort by many multidisciplinary physicians and scientists to help all understand the reasons to simultaneously monitor ECG and EEG in persons thought to be at risk for sudden death. Neurologists are still focused on the brain, cardiologists on the heart, and clinical pharmacologists on drugs. Integration of their thinking is needed for

the best diagnosis and treatment of persons with epilepsy thought to be at risk for SUDEP.

In 1990, Lathers and Schraeder [73] edited the first book on SUDEP, *Epilepsy and Sudden Death*. The book summarized “state-of-the-art” experimental and clinical information available about sudden death and epilepsy and provided a guide of where researchers and clinicians should look to detect, understand, and prevent the occurrence of SUDEP. J. Thomas Bigger, Jr., M.D., Professor of Medicine and Pharmacology, College of Physicians and Surgeons, Columbia University, succinctly summarized, in the Foreword, eight areas of inquiry that needed to be addressed to answer questions about SUDEP (Table 2).

Some, but not all, of Dr. Bigger’s suggestions have now been addressed.

1. *Additional epidemiology studies have been conducted* [107–111]. Also see reviews by Lathers et al. [3–7,73,74].
2. *Studies of ambulatory recordings to capture recordings before and during sudden death are still needed today.*
3. *EEG, ECG, and respiration must still be recorded.* Simultaneous recordings of these variables, and arterial oxygen saturation, during sudden death would permit us to evaluate the role of apnea or hypoxia. Postictal central apnea does appear to be one potential mechanism for SUDEP. A 55-second convulsive seizure occurred in a 20-year-old woman as she underwent video/EEG monitoring [112]. Persistent apnea then developed. ECG-monitored rhythm was not altered for the first 10 seconds; then it gradually and progressively slowed and stopped 57 seconds later. Cardiorespiratory resuscitation was successful. No evidence of airway obstruction or pulmonary edema was noted. One previous cardiorespiratory arrest after a complex partial seizure without secondary generalization had been reported for this patient. So et al. [112] note that although epileptic seizures may be associated with arrhythmogenic actions at the heart, in this patient the mechanism of marked central suppression of respiratory activity after seizures was clearly involved and almost resulted in sudden death. This case and Dr. Schraeder’s case [96] highlight that both respiratory and cardiac changes do occur in persons with epilepsy. The timing of events such as seizures, respiratory and/or laryngospasm, and cardiac ECG changes does vary in different patients. The physician must consider risk factors for a given patient and protective procedures to prescribe to protect the person from future unwanted events that may result in SUDEP. The question must be asked as to whether a person first experienced seizures and respiratory events and then cardiac events or first experienced seizures and arrhythmia and then respiratory events. There is documented evidence in the literature to support both cardiac and respiratory events as initiating mechanisms of sudden death. Obviously, rapid reversal of these changes is essential, and the “availability of resuscitation methods on the spot where the victim is located” certainly increases the likelihood that SUDEP will be prevented. In a recent study, Bateman et al. [113] examined the incidence and severity of ictal hypoxemia in patients with localization-related epilepsy undergoing video/EEG telemetry. They measured seizure-associated oxygen desaturation and hypoventilation. Pulse oximetry revealed oxygen desaturation below 90% in 33.2% of all 304 seizure events. The degree of desaturation was significantly correlated with seizure duration and with electrographic evidence of seizure spread to the contralateral hemisphere. Central apneas or hypopneas occurred with 50% of all seizures. Ictal hypoxemia occurred often in these patients with localization-related epilepsy, and may be pronounced and prolonged, even if the seizures do not progress to generalized convulsions. End-tidal carbon dioxide

Table 1

Summary: Some mechanisms/sites associated with SUDEP.

1. Autonomic postganglionic cardiac sympathetic neural discharge was nonuniform just prior to development of arrhythmias with interictal and ictal activity [27,28,34,35].
2. Examination of the distribution of cardiac β receptors revealed a correlation with the release of norepinephrine at sympathetic nerve terminals in the heart in a manner to produce arrhythmia. Innervation density is high in the subepicardium and the central conduction system. The nonuniform postganglionic sympathetic cardiac innervation is related to the nonuniform beta sympathetic receptor locations in the heart, and these two parameters affect cardiac contractility and development of cardiac arrhythmias and/or death. In diseased hearts, cardiac innervation density varies and this may lead to sudden cardiac death. After myocardial infarction, sympathetic denervation is followed by reinnervation within the heart, leading to unbalanced neural activation and lethal arrhythmia [37,52,60,66].
3. Autonomic parasympathetic neural discharge was increased or decreased and often accompanied by a respective decrease or increase in sympathetic neural discharge and epileptogenic activity [27,28,34,35].
4. Autonomic imbalance between sympathetic and parasympathetic discharges occurred in association with epileptogenic activity. Variability within each division of the autonomic nervous system, as indicated by the large standard deviations of the mean, occurred in both divisions but the timing differed [27,28,34,35].
5. Autonomic cardiac arrhythmias, with both sympathetic and parasympathetic components, induced ventricular fibrillation or asystole, respectively, via combinations of central and peripheral autonomic mechanisms associated with epileptogenic activity [27,28,34,35].
6. Dysfunction between the autonomic controlled parameters of heart rate and blood pressure occurred prior to development of interictal discharges and continued with ictal discharges [27,28,34,35,68–74].
7. Lock-step phenomenon. Cardiac postganglionic sympathetic and vagal nerve discharges have been demonstrated to be correlated with interictal and ictal discharges [68]. Autonomic cardiac neural discharges were intermittently synchronized 1:1 with the epileptogenic discharge. This observation was designated the *lock-step phenomenon* (LSP). The occurrence of LSP was not observed in the control period [68–74].
8. Epileptogenic activity may alter autonomically-mediated central [89–91] or peripheral release of catecholamines, including those from the adrenal medulla [92–94].
9. Respiratory. Postmortem we observed multiple areas of punctuate hemorrhages and large areas of gross hemorrhage and edema in animals dying after inducing epileptogenic activity, asystole, or ventricular fibrillation [27,28,34].
10. Tissue hypoxia and hypercarbia and alterations in acid–base balance may have contributed to the results in our model of experimental epilepsy. Acid–base balance was maintained within physiological range prior to initiation of epileptogenic activity [27,28,34,35].
11. Changes in cardiac function lead to alterations in cerebral blood flow, which in turn produce central hypoxia resulting in epileptogenic activity. Some patients exhibit changes in cardiovascular status preceding the onset of convulsions [95,96].
12. γ -Aminobutyric acid (GABA). Modulation of presynaptic GABA release by prostaglandin E2: Explanation for epileptogenic activity and dysfunction in autonomic cardiac neural discharge leading to arrhythmias [36,97].
13. GABA, the major inhibitory neurotransmitter in the central nervous system, has a prominent role in maintaining control over neuronal excitability. Compounds that inhibit GABA synthesis (3-mercaptopropionic acid, isoniazid) [98] and receptor antagonists that block GABA_A recognition sites (bicuculline) or the chloride channel directly (picrotoxin, pentylenetetrazol [99]) induce seizures [100]. Mechanisms for interference of GABA neurotransmission may lead to initiation of arrhythmias and/or epileptogenic activity in persons with epilepsy. This chain of events may produce sudden death [36,98].
14. Neuropeptides. Intracerebroventricular D-Ala2-methionine enkephalinamide affects cardiovascular parameters in the cat [44,101]. Origin of arrhythmia and sudden death in the patient with epilepsy [43].
15. Penicillin administered centrally: Another new small animal model to study autonomic dysfunction in association with epileptogenic activity produced by injecting penicillin into the hippocampus of the cat. Epileptogenic activity spread to left and right hippocampi and cerebral cortices and was associated with autonomic dysfunction in the parameters of blood pressure and the ECG [102].
16. Beta blockers exhibited anticonvulsant activity whether administered via the intraosseous route or intravenously [3,54,58].

increase occurred with oxygen desaturation and supports the assumption that ictal oxygen desaturation is a consequence of hypoventilation. Both ictal hypoxemia and hypercapnia may be risk factors contributing to SUDEP.

4. *The role of the sympathetic nervous system could be explored more intensively by functional and biochemical evaluation of cardiac sympathetic nervous activity.* Lathers and Levin have examined the distribution of cardiac β receptors and found a correlation with the release of norepinephrine at sympathetic nerve terminals in the heart in a manner to produce arrhythmia. Innervation density is high in the subepicardium and the central conduction system. In diseased hearts, cardiac innervation density varies. This may lead to sudden cardiac death. After

myocardial infarction, sympathetic denervation is followed by reinnervation within the heart, leading to unbalanced neural activation and lethal arrhythmia [37,52,60,66]. Recently, Ieda et al [114], as in the earlier studies by Lathers et al. [17–19,24–26] and Lathers and Schraeder [27,28], raised the question of whether regulation of cardiac nerves is a “new paradigm” in the management of sudden cardiac death, as the heart is extensively innervated and its performance is regulated by the autonomic nervous system. In the case of diabetic sensory neuropathy, silent myocardial ischemia may occur, associated with loss of pain perception during myocardial ischemia, a major cause of sudden cardiac death in diabetes mellitus [115]. To date, molecular mechanisms underlying

Table 2

Eight areas of inquiry by Dr. Thomas Bigger: Questions about SUDEP, 1990.

Although many pieces of the epilepsy–sudden death puzzle are in place, the total picture is not clear... We seem a long way from understanding and controlling the problem of sudden death in epilepsy. How shall we proceed toward those goals?

1. Additional epidemiologic inquiry should sharpen the focus on the high risk groups and we should study them intensely.
 2. Studies with ambulatory recordings will capture the events before and during sudden death.
 3. To understand this problem, we need recordings not only of the electroencephalogram and electrocardiogram, but also of respiration. Simultaneous recordings of these variables, and arterial oxygen saturation, during sudden death would permit us to evaluate the role of apnea or hypoxia.
 4. The role of the sympathetic nervous system could be explored more intensively with functional and biochemical evaluation of cardiac sympathetic nervous activity.
 5. The anatomic distribution of cardiac sympathetic nerves in epileptics vs. normals could be clarified by imaging with substance taken up by sympathetic nerve terminals in the heart.
 6. Studies in relevant animal models will permit a quantum leap forward in our capability for generating relevant new knowledge and greatly accelerate the rate of progress.
 7. Once the pathophysiology of sudden death in epileptics is clarified, hypotheses about effective treatments will naturally follow and can be pursued using animal models, small pilot studies in epileptic patients, and, finally, large-scale clinical trials.
 8. Studies of the factors that govern compliance in epileptic patients should proceed now because the results can be put to immediate use controlling seizure disorders and will be important in planning effective means of controlling sudden death in this group in the future.
- We are on the threshold of major advances in the problem of sudden death in epilepsy. The tools to advance our knowledge are at hand and we should energetically put them to use for the future benefit of patients with epilepsy. Knowledge gained from studies of sudden death in epileptics will very likely be useful for understanding sudden death in other situations as well.

Source. Reprinted, with permission, from Bigger [106].

innervation density are not well understood. Ieda et al. [115] have demonstrated that cardiac sympathetic innervation is determined by the balance of neural chemoattraction and chemorepulsion, both of which occur in the heart. Nerve growth factor, a potent chemoattractant, is synthesized by cardiomyocytes and is induced by endothelin-1 upregulation in the heart. In contrast, *Sema3a*, a neural chemorepellent, is expressed strongly in the trabecular layer in early-stage embryos and at a lower level after birth, resulting in an epicardial-to-endocardial transmural sympathetic innervation pattern. Cardiac nerve growth factor downregulation is a cause of diabetic neuropathy, and nerve growth factor supplementation rescues silent myocardial ischemia in diabetic neuropathy. Both *Sema3a*-deficient and *Sema3a*-overexpressing mice showed sudden death or lethal arrhythmias due to disruption of innervation patterning [116]. All of these regulatory mechanisms involved in neural development in the heart and their critical roles in cardiac performance need to be examined to determine their relevance to methods to decrease the risk of SUDEP.

5. *The issue of using imaging studies to examine the anatomic distribution of cardiac sympathetic nerves in persons with epilepsy versus normals has been answered recently.* A postmortem imaging study of postganglionic cardiac sympathetic innervation in patients with chronic temporal lobe epilepsy, using meta-^{[123]I} iodobenzylguanidine single-photon-emission computed tomography (SPECT), has been conducted [117]. The authors observed sympathetic dysfunction in the form of altered postganglionic cardiac sympathetic innervation in patients with chronic temporal lobe epilepsy and suggested that altered postganglionic cardiac sympathetic innervation may increase the risk of cardiac abnormalities and/or SUDEP. The exact role of innervation in arrhythmogenesis and developmental and regulatory mechanisms determining density and pattern of cardiac sympathetic innervation are still unclear. This clinical study of Druschky et al. [117], conducted in humans, confirms the results and conclusions of the animal studies conducted by Lathers et al. in which postganglionic cardiac sympathetic neural discharge was associated with arrhythmias and/or sudden death.

Kerling et al. [118] stated that because tachyarrhythmias are common during epileptic seizures while bradyarrhythmias or asystoles occur less frequently, they evaluated cardiac postganglionic denervation in patients with epilepsy to evaluate ictal asystole. They used SPECT to examine meta-^{[123]I} iodobenzylguanidine as a marker of postganglionic cardiac norepinephrine uptake. The pronounced reduction in cardiac SPECT uptake in asystolic patients indicated postganglionic cardiac catecholamine disturbance. Impaired sympathetic cardiac innervation limits adjustment and modulation of heart rate and may increase the risk of asystolic events and, eventually, SUDEP. The data of Kerling et al. [118] support the findings of Lathers et al. [37,52,60,66] and those of Han and Moe [20].

6. *Studies in relevant animal models.* Many different relevant animal models for SUDEP are still needed to understand the pathophysiology of sudden death in persons with epilepsy and to hypothesize about effective treatments [106]. The importance of using many different animal models to study SUDEP to glean insight into the various mechanisms of risks and their contribution to the initiation of the death event is discussed in detail by Lathers [119]. Schwartz et al. [120] concluded that delayed enhancement of GABAergic neurotransmission directly at the site of vulnerability after an ischemic event does protect the neurons from death. This finding should be explored to further study the effect of diazepam on GABA-mediated effects that

may prevent ischemia-induced neuronal death and ultimately prevent the worsening of central neuronal communication due to epileptogenic activity. This may eventually contribute a protective central nervous system effect to make an individual less likely to be at risk for SUDEP. There are many more basic science questions to be raised and answered. The studies by Wang [75] discussed above must be expanded to examine anti-epileptic or other categories of drugs and their effect on the intermittent seizure-like firing of cardiac parasympathetic neurons that may cause neurogenic ictal bradyarrhythmias, cardiac asystole, or sudden death. So [121] emphasized the significance of using audiogenic seizure mice to study postictal respiratory arrest. Postictal respiratory arrest was induced by serotonin receptor inhibition and prevented by selective serotonin reuptake inhibitor drugs. The role of serotonin in SUDEP must be examined in future animal studies [122].

7. *Hypotheses about effective treatments* will naturally follow and can be pursued using animal models, small pilot studies in patients with epilepsy, and, finally, large-scale clinical trials [106]. We have not yet fully addressed this area of inquiry about SUDEP. There are several questions to be asked postmortem [86–88] about the patient who is on an AED but still dies from SUDEP. A very important clinical pharmacology question that must be asked is whether the patient was on the correct AED to control his or her particular type/mixture of seizures. A second question to be asked is whether the correct categories of drugs have been prescribed. There may be a role for using beta blocking agents. When evaluating the role of drugs as protectors of life, clinical pharmacologists [123] caution us to remember that use of all drugs entails a risk/benefit ratio evaluation [124]. Thus, the use of AEDs may not protect the patient 100% against sudden death. Celiker et al. [125] reported clinical experience with patients with catecholaminergic polymorphic ventricular tachycardia and concluded that medical treatment with propranolol and verapamil may decrease the incidence of arrhythmia. If a person is still refractory, implantation of intracardiac defibrillators should be considered. Houle et al. [126] reported enhanced *in vivo* and *in vitro* contractile responses to β_2 -adrenergic receptor stimulation in doses conducive to lethal arrhythmias. Billman et al. [127,128] found that β_2 -adrenergic receptor antagonist protected against ventricular fibrillation, and endurance exercise training attenuates cardiac β_2 -adrenoceptor responsiveness and prevents ventricular fibrillation in animals. There seems to be a direct correlation between a β -adrenergic receptor sensitivity and the level of arrhythmia and mortality following a coronary occlusion. The greater the sensitivity to β -adrenergic agonists, whether from hormones, exercise, or genetics, the greater the level of arrhythmia and mortality [126–129]. Whether we can learn from these data when considering persons with epilepsy at risk for SUDEP remains to be seen. Data suggest beta blockers exert a protective effect against seizure induction and/or the development of cardiac arrhythmias with interictal and ictal activity [3–6,54,58,73,74]. The question must be asked if persons thought to be at risk for SUDEP should be placed on a beta blocker in addition to the prescribed anticonvulsant(s). Beta blockers are also used to reduce stress, and persons with epilepsy generally are stressed by the disease and associated problems [130].
8. *Studies of the factors that govern compliance in patients with epilepsy should proceed now* [106]. To determine whether SUDEP occurred one must inquire as to whether the person was compliant [123]. In 2003, Lathers et al. [131,132] found low or no levels of AEDs postmortem in persons with epilepsy deemed to have died of SUDEP. These data suggested compliance is a problem in some of those who die from SUDEP. In 2009 Hughes [133] deemed the most important SUDEP risk factor to be

noncompliance with antiepileptic medication. Ryvlin et al. [134] found the risk of SUDEP is increased in patients who have poor compliance and exhibit nocturnal seizures and generalized tonic–clonic seizures. However, compliance is not the only question to ask about victims of SUDEP. One must also ask if the correct dose of the AED was being used for a given patient to control his or her seizures. All agree that maintenance of therapeutic drug levels is a crucial factor in lessening the risk of SUDEP.

2. Epilepsy and SUDEP: The need for a global focus

Despite some progress, many of the suggestions for future studies made by Dr. Bigger in 1990 [106] have not yet been addressed today, almost 20 years after they were first written! The total picture of SUDEP is not clear. An understanding of the mechanism(s) of the pathophysiology of SUDEP and all the risk factors for death still has not been obtained. Let all now work to address these questions. However, without funding for basic and clinical studies, the answers to the questions raised by Dr. Bigger and by the authors of the chapters in the book *Epilepsy and Sudden Death* [73] will not be answered. The NIH-sponsored workshop in November 2008 [105] also highlighted the lack of progress made from 1982 to today. It was agreed that many questions must be addressed and monies are needed to fund studies. This workshop was one needed step. However, the momentum gained during the last 20 to 30 years and summarized at the NIH workshop discussions must not be lost. Globally, we, as scientists, clinicians, and granting authorities, must not allow another 20 years to go by with little additional information gleaned. Future needed steps have also been suggested by the American Epilepsy Society and the Epilepsy Foundation Joint Task Force on SUDEP [135]. During the interim, before the aforementioned needs have been fulfilled, it is most important to provide prompt and optimal control of seizures, especially generalized convulsive seizures, to prevent SUDEP. Knowledge of SUDEP has been assessed and the following conclusions have been drawn.

1. A multidisciplinary workshop is needed to refine current lines of investigation and identify additional areas of research into mechanisms underlying SUDEP.
2. Patients and their families and caregivers should be surveyed to identify effective means of education to enhance participation in SUDEP research.
3. A campaign is required to emphasize the need for complete autopsy examinations for patients suspected of dying from SUDEP.
4. Secure infrastructure grants are needed to fund a consortium of centers to conduct prospective clinical and basic research studies to identify preventable risk factors and mechanisms underlying SUDEP.

Dr. Lathers, Dr. Schraeder, Dr. Bungo, and Dr. Leestma are currently working with experts around the world to write/edit a new book to be published in 2010 entitled *Sudden Death in Epilepsy: Forensic and Clinical Issues* [74], to update the 1990 *Epilepsy and Sudden Death* book edited by Lathers and Schraeder [73]. In our new book, we focus on the forensic and clinical information known today about the problem of SUDEP and the issue of where we need to go, using both animal and human studies, to develop preventive methods. Most likely, different mechanisms and/or different combinations of mechanisms are responsible for death in different persons with epilepsy. Many different case histories are needed to provide a composite of the mechanism(s) involved in SUDEP. One SUDEP case history alone will not tell the entire story,

and we are all cautioned to remember this and to focus on review of many cases obtained in many different victims of SUDEP to expand our knowledge of how best to treat persons with epilepsy at risk for sudden death. Unusual factors have been examined by the laboratory of Scorza and colleagues [136] to determine if they are risk factors for SUDEP. Suggested SUDEP factors include: the lunar phase [137], temperature [136], climate fluctuations [138], and seizure activity and neurogenesis [139]. Aberrant dentate granule cell neurogenesis may influence negatively the cardiovascular system of the patient with epilepsy and lead to cardiac abnormalities and then to the unwanted event of SUDEP. Studies are needed to examine the role in SUDEP played by these unusual factors to determine if they are risk factors.

New data and lessons learned from the last 20 to 30 years should be applied by scientists and clinicians worldwide to gain a better understanding of SUDEP. All of us, working in a worldwide network, must focus our efforts in basic scientific research programs and clinical and epidemiology studies to identify risk factors and pathophysiology to develop the best treatment regimens for persons identified to be at risk to prevent the unwanted occurrence of sudden death. Additional symposia focused on SUDEP, such as the International Epilepsy Meeting in 1983 [13], the American College of Clinical Pharmacology SUDEP Symposium and Teaching Clinic in 1994 [103,104], and the recent 2008 NIH Workshop [105], must be held to encourage discussion and “thinking out of the box” to solve the problem. Around the world, all must work to introduce excitement and an intellectual interest in young students, scientists, and clinicians to encourage them to focus on epilepsy and sudden death for future understanding of the problem. The mystery of sudden death [3–6,73,74] can be solved by addressing the clinical question of how to identify persons at risk for sudden death and how to prevent the occurrence of sudden death.

3. Summary

1. Mechanistic risk factors for SUDEP, obtained in animal studies in Dr. Lathers' laboratory, appear to include cardiac arrhythmias and/or death associated with changes in autonomic cardiac postganglionic sympathetic neural discharge, cardiac parasympathetic neural discharge, and respiratory changes including multiple areas of punctuate hemorrhages and large areas of gross pulmonary hemorrhage and pulmonary edema [27,28,34,35]. Both central and peripheral sites are involved in the pathophysiology of SUDEP. (See Table 1.)
2. Many different relevant animal models for SUDEP are still needed [119] to understand the pathophysiology of SUDEP, to hypothesize about effective treatments, to develop small pilot studies in persons with epilepsy, and finally to conduct confirmatory large-scale clinical trials.
3. Researchers should “think outside of the box” when evaluating an established animal model with potential for modification(s) to be used to address questions about the mechanism(s) of SUDEP.
4. The field of pharmacology/clinical pharmacology has much to offer as we work to improve compliance and to develop new AEDs and/or apply new categories of drugs, such as beta blockers and selective serotonin reuptake inhibitors, to prevent and resolve the mystery of SUDEP [3–6,54–58,73,74,123]. Different routes should be considered for AED administration, such as the intraosseous [54–58,61,62] and endotracheal [63] routes, during emergency situations that may evolve into an unwanted SUDEP if not corrected immediately.

5. Teamwork is needed among different multidisciplinary professionals working in clinical settings and/or within a laboratory, among laboratories within the United States, and in laboratories located around the world to solve the global mystery of SUDEP.
6. Ambulatory simultaneous ECG and EEG telemetry monitoring of patients thought to be at risk for sudden death will help to identify cardiac versus brain epileptogenic triggers/causes to be treated/prevented in an attempt to decrease the risk for SUDEP. Respiratory function monitoring is also needed [106].
7. Academic fellowships and competitions for medical students and postdoctoral fellows/residents and faculty will attract medical and graduate students and faculty to work in the field of SUDEP.
8. Grant funding is essential to move the SUDEP knowledge base forward. Academic administrative leaders are not interested in faculty and investigators addressing a problem that is not well funded at the national/international level.
9. Pharmaceutical industry leaders are not interested in addressing a problem if the market for a new product is not large. Incentives must be offered to encourage them to examine the problem of SUDEP and to develop new drugs that may or may not have a large market. If the true incidence of SUDEP is established to be much higher than previously thought by the correct use of the term *SUDEP* on autopsy reports and/or the use of verbal autopsies postmortem, then the market for new antiepileptic and/or other new drugs in different categories to prevent SUDEP will be larger than presently determined. The FDA category of orphan drug development should be considered if necessary.
10. Leadership foundations of vision, knowledge, and courage are essential to address the global mystery of SUDEP. A leadership philosophy foundation should be used that provides strength primarily for research and teaching programs from faculty members and students and, secondarily, for the administration that must provide the innovative vision and approaches, facilities, and monies to support the needs of faculty and students. The interaction of teaching and research is essential. While a student is learning how to conduct research, she or he must simultaneously learn how to become a teacher her- or himself. The components of teaching, including excellent communication and writing skills, coupled with patience, form the foundation for communicating the findings of research to the academic and research communities and to funding agencies. Today's medical and graduate programs will not be able to train *each* student for each and every advance that will develop in his or her selected profession, including a focus on SUDEP. Therefore, the program must help today's student understand the basic approach to survival in a rapidly changing technological, academic, and political environment. The best prepared student for the challenges of tomorrow will be one trained to be flexible, possessing the basic knowledge and tools and courage to adapt to the different career twists and turns encountered as modern technology rushes to the forefront with numerous new techniques, understandings, and thoughts foreign to us at this time in our lives. Today's medical and graduate leadership must have the vision to provide a fertile and proper environment for teachers to work with academic freedom to teach today's students how to become the self-learning student of tomorrow. While addressing issues of SUDEP, teach our students of today to become self-learners and leaders in the field for tomorrow's solutions [140–142].

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