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Evaluation of Sudden Death in Psychiatric Patients with Special Reference to Phenothiazine Therapy: Forensic Pathology

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ABSTRACT: The investigation of sudden unexpected death in psychiatric patients and the ensuing litigation has brought to our attention many unusual features important in the evaluation of such deaths. Certain pathophysiologic mechanisms of death, rarely encountered in routine forensic science practice, may be important in determining the cause of death in psychiatric patients, especially in cases where the autopsy is unrevealing. Of particular concern is a tendency in the current literature to implicate phenothiazines as a cause of death when the death investigation and the autopsies are incomplete. Thus, based on our experience and on a review of the current literature, we have set forth factors that the forensic pathologist should consider when faced with a sudden psychiatric death. A case report illustrates these unique aspects of scene investigation and analysis of terminal events and autopsy findings.

KEYWORDS: pathology and biology, death, mental illness, phenothiazine, sudden death

Medicolegal investigation of sudden death in psychiatric patients forms a special diagnostic subset of cases reported to the medical examiner's office. Since such cases may achieve high visibility within the community, it behooves the medical examiner to establish certain facts at the outset which will allow the greatest chance for just resolution of any subsequent disputes based on objective data, rather than allow for open-ended arguments based on speculation as to what might have happened to the deceased. The greatest difficulties are presented by the sudden death of a psychiatric patient where the autopsy fails to reveal a cause of death. Thus, we address aspects of the scene investigation, postmortem examination, toxicology evaluation, and pathophysiologic mechanisms which will be helpful in correctly assessing the cause of death or factors contributing to it or both in these difficult cases. Since phenothiazines are commonly used in the treatment of psychiatric patients and have been reported to cause sudden cardiac death, particular emphasis is placed on possible phenothiazine associated causes of death.

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Scene Investigation

After a death in a psychiatric ward is reported, it is advisable for the medical examiner to visit the scene, preferably before the body is removed. In addition to routine scene investigation, particular note of the temperature of the room and the postmortem body temperature (preferably core liver temperature) as soon after death as possible is important because phenothiazine medication is known to predispose to fatal hyperthermia [*1*]. In this situation core body temperature is 104°F (40°C) or above. The skin of the deceased may be moist from excessive perspiration, since anhidrosis is not found in phenothiazine associated hyperthermia. The mechanism postulated involves drug induced alteration of the central nervous system thermoregulatory center in addition to anticholinergic effects which inhibit peripheral mechanisms of heat loss. In particular, if the weather is hot and humid or the patient is agitated or exercising, or both, phenothiazine treatment increases the risk of fatal hyperthermia. Since the autopsy findings of hyperthermia are nonspecific, this diagnosis cannot be made if temperature measurements are neglected.

If possible, all hospital records including nurses' notes, doctors' notes, and drug administration check sheets should be obtained for study before the autopsy. For example, correlation of the number and location of injection sites with the treatment record can become an important issue when improper medication is implicated as a cause of death.

The presence of patient restraint apparatus is a significant observation since sudden unexpected deaths have been reported in patients as well as experimental animals who struggle against restraints [*2,3*].

Finally, reliable witnesses, if any, to the terminal event should be found and detailed statements obtained from them. The behavior and complaints of the patient immediately before death is essential to establish a pathophysiologic mechanism of death. Thus, the value of information obtained from reliable witnesses cannot be overemphasized.

Possible Causes of Unexpected Death Related to Phenothiazine Therapy

In addition to drug induced alterations in body temperature, the extrapyramidal, antiadrenergic, and anticholinergic properties of phenothiazines may produce potentially fatal effects and should be considered in the differential diagnosis of autopsy-negative sudden psychiatric death. The extrapyramidal side effects of phenothiazines may present as muscular rigidity associated with altered consciousness, autonomic dysfunction (manifested by tachycardia, labile blood pressure, diaphoresis, and dyspnea), and possible hyperthermia, the symptom complex known as the neuroleptic malignant syndrome (NMS) [*4*]. The potential of the particular phenothiazine to induce the NMS parallels its antidopaminergic potency. Once initiated, NMS can develop rapidly and cause death from respiratory failure or cardiac arrhythmia or both within 24 h. Distinct subgroups of phenothiazine induced acute extrapyramidal reactions are respiratory dyskinesias which may impair muscular coordination of respiratory movement and oxygenation [*5*] and oral-laryngeal-pharyngeal dystonias [*6*] which present as acute airway obstruction with increased oral secretions. Since these extrapyramidal syndromes are unusual and can develop rapidly, they may be undiagnosed or the symptoms judged not to be of particular significance in the psychiatric patient. These reactions may be diagnosed retrospectively by the medical examiner if an adequate clinical data base regarding terminal behavior and medical monitoring exists. For example, Moore et al. [*7*] report a case of sudden psychiatric death where, although they implicate phenothiazine cardiac toxicity, the signs and symptoms given more clearly describe a fatal dyskinetic reaction to fluphenazine consisting of orofacial grimacing and grunting respirations followed by respiratory arrest. Neither the clinician nor the pathologist recognized the significance of these symptoms.

The antiadrenergic properties of the phenothiazines can result in peripheral vasodilation and orthostatic hypotension [*8,9*]. This alpha adrenergic antagonism may produce postural

hypotension, tachycardia, fainting, or dizziness most commonly after the first injection, occasionally after subsequent injections, but rarely after an oral dose. Although recovery usually occurs spontaneously within 1/2 to 2 h, hypotension may be prolonged and lead to cardiovascular collapse. Epinephrine is contraindicated for treatment of hypotension in this situation, since its vasoconstrictive properties are blocked. Thus, only its vasodilatory effect will be apparent and will result in further lowering of blood pressure. A phenothiazine induced acute hypotensive reaction that progresses to shock and death may be suggested by terminal events such as complaints of dizziness with sudden collapse related temporally to drug injection. The anticholinergic properties of phenothiazines predispose to the development of ileus and toxic megacolon [*10*]. Unlike the above-mentioned autopsy-negative deaths, this condition can be diagnosed at autopsy, but may be unsuspected clinically and may cause death from colonic rupture or sepsis. For example, Giles et al. [*11*] and Rosati [*8*] describe two cases where ileus was diagnosed clinically and followed shortly thereafter by cardiovascular collapse. Although presented as case of phenothiazine induced cardiac death, the possibility of cardiovascular collapse from sepsis secondary to the paralytic ileus is a diagnosis which is consistent with the history given.

Phenothiazines have also been reported to lower the seizure threshold [*12*], although some dispute this association [*13*]. In a well-controlled epileptic patient, phenothiazines may be implicated if seizures appear coincident with initiation of phenothiazine treatment. Lastly, allergic reactions to phenothiazine occasionally develop within the first few months after treatment. These reactions are usually innocuous and may include dermatitis, jaundice, and photosensitivity, but they can also be life-threatening, as with agranulocytosis [*12*]. A history of recurrent infections coupled with examination of bone marrow as part of the postmortem examination may be helpful in assigning the correct cause of death. Thus, an awareness of the potential side effects of phenothiazine treatment along with a careful evaluation of the terminal events may in some cases suggest a mechanism and cause of death in an autopsy-negative sudden psychiatric death.

Phenothiazines and Sudden Cardiac Death

There is disagreement in the current medical literature over whether or not phenothiazines can cause sudden cardiac death in an otherwise healthy psychiatric patient. The fact cited most frequently in relating phenothiazines to sudden cardiac death is electrocardiogram (EKG) changes induced by phenothiazines, in particular clinical reports of QT interval changes as well as episodes of congestive heart failure and angina temporally related to phenothiazine administration [*14,15*]. Numerous animal studies both in vivo and in organ and tissue perfusion systems have demonstrated alterations in the electrical events of the myocardium in response to the acute administration of phenothiazine or its numerous metabolites or both [*16*]. Animal experiments to determine the effect of chronic phenothiazine administration are somewhat lacking. Although some investigators feel that the phenothiazine associated EKG changes are benign and have been misinterpreted [*17*], it is recommended that patients with atherosclerotic heart disease or prolonged QT interval syndromes who are receiving phenothiazines be monitored closely for the development of arrhythmias [*18*]. In addition, phenothiazines have been shown to block cardiac catecholamine receptors and alter plasma catecholamine concentrations [*15*], both potentially arrhythmogenic effects. Structural alterations in cardiac muscle, at both the light and electron microscopic level, have been reported in patients receiving phenothiazines [*14,18*]. These include increased glycogen deposition and disordered mitochondria at the ultrastructural level; focal fibrosis, myofibrillary degeneration, and hyperplastic intramyocardial arterioles containing PAS+ material at the light microscopic level. Some of these changes, however, are consistent with cardiomyopathies (for example, alcoholic cardiomyopathy [*14*]) or con-

sidered nonspecific [*11*]. These structural alterations have not been further substantiated as diagnostic of or resulting from phenothiazine administration.

Thus, in certain clinical and experimental situations, the ability of phenothiazines to alter cardiac rhythm in potentially deleterious ways appears clear, and these patients should be monitored closely. It is critical, however, that phenothiazine associated sudden cardiac death not be used indiscriminately as a cause of death in all cases of autopsy-negative sudden death in patients receiving phenothiazine. Only when the medical examiner can document a past history of rhythm disturbances or cardiac symptoms in conjunction with episodes of phenothiazine administration can phenothiazine alone be considered clearly causative. Certification of death as due to phenothiazine strictly from toxicologic analysis of blood and tissue drug levels cannot be advocated at the present time in view of the wide range of therapeutic dosages administered, the wide therapeutic margin of safety, and the multiplicity of active and nonactive metabolites [*16*].

Causes of Unexpected Death Unrelated to Phenothiazine Therapy

Consideration of mechanisms of sudden death unrelated to phenothiazine administration are equally important in the evaluation of an autopsy-negative sudden death in patients receiving phenothiazines. Three such entities are neurally mediated sudden cardiac death related to patient restraint, acute exhaustive psychosis, and inherited sudden death syndromes.

Neurally mediated sudden cardiac arrest has been noted to occur in patients struggling against restraints, the application of which in themselves would not cause death. A situation that the patient perceives as overwhelmingly stressful may cause death by fatal cardiac arrhythmia [*2,3*]. The arrhythmias may be precipitated by increased catecholamines and glucocorticoids or by vagal and adrenergic excess stimulation [*19*]. Animals placed in restraint situations have an increased frequency of cardiac arrhythmias, and some animals die while in the restraints [*3,20,21*]. At autopsy, myofibrillar necrosis is found in the hearts of some of these animals, a lesion associated with high catecholamine levels. Cases in the literature reported by Leeshma et al. [*12*], Hollister et al. [*22*], and Reinert et al. [*23*] cite phenothiazines as the cause of sudden cardiac death where the description of the terminal events included violent struggle against restraints. In such instances it seems erroneous to reach a conclusion as to the cause of death without consideration of the terminal events.

Unexpected sudden death in psychiatric patients is not a newly recognized phenomenon coincident with the advent of the major tranquilizers. In 1849, Dr. Luther Bell of the McLean Asylum in Massachusetts described the occurrence of sudden death in psychiatric patients who pursued a continuous manic and agitated course without rest or food and who unexpectedly collapsed and died during this period of agitation [*24*]. As originally described by Bell, this type of sudden death is variously known as acute exhaustive mania, Bell's mania, lethal catatonia, and acute exhaustive psychosis. As currently postulated by Peele, the situation still exists where despite tranquilization, an acutely agitated, combative, excited patient will suddenly collapse without apparent reason [*25*]. The cause of death in these situations is probably similar to that postulated for sudden death during emotional stress in a nonpsychiatric patient. Such emotional causes of sudden death, a mechanism of death leaving no morphologic alteration distinguished at autopsy, is a well-recognized syndrome familiar to forensic pathologists [*26–28*]. Thus, a death occurring in the setting of acute agitation may be difficult to attribute *solely* to phenothiazines, although their contribution to such deaths, via their cardiac actions, is likely. It should be noted that vigorous exercise has been shown to predispose to the development of exercise induced fatal arrhythmias in patients with prolonged QT intervals [*29*].

Inherited syndromes of sudden death may involve a component of mental handicap, and their initial presentation may be in the psychiatric population, their cardiac abnormalities

potentially unrecognized. Jervel and Lange-Nielson describe a syndrome with autosomal recessive inheritance of severe hearing loss and syncopal attacks associated with a long QT interval [*30*]. The Romano-Ward syndrome, transmitted via an autosomal dominant inheritance, is similar except that the individuals are not congenitally deaf [*31*]. Individuals with these conditions are known to be at risk for sudden death. Thus, study of the medical history of the deceased and his or her family for evidence of hearing loss, EKG abnormalities, and episodes of sudden death in other family members may suggest the possibility of inherited sudden death syndromes not recognized clinically.

Clearly, nonnatural autopsy-negative deaths form a subset of nonphenothiazine-related deaths in psychiatric patients. In particular, in asphyxial deaths, evidence such as bed pillows or plastic bags may be easily removed by other patients or negligent attendants in an effort to cover up the true nature of the death. If the stigmata suggestive of an asphyxial death are not present on the body or not recognized as such, the correct cause of death in these cases cannot be determined.

Comment

As detailed here, many pathophysiologic mechanisms can produce an autopsy-negative sudden death in a psychiatric patient, both related and unrelated to phenothiazine administration. In view of this, of particular concern are case reports citing phenothiazines as the cause of death based only on positive toxicology and without evidence of adequate postmortem examination, scene investigation, or knowledge of terminal events or past medical history. For example, reports of death as a result of phenothiazines which appear in the older literature, still often cited as evidence of phenothiazine associated cardiac death, should be viewed more critically since histopathologic changes of early myocardial ischemia had not been well described and techniques for examination of the conduction system and its role in the evaluation of sudden death were not clearly established [*32,33*]. Similarly, cases where sudden collapse while eating was witnessed and food occluding the oropharynx was found at autopsy [*7,22*] were attributed to phenothiazine induced sudden cardiac death. Currently these would be classified as death as a result of aspiration of food, the so-called "Café Coronary." Many case reports fail to mention the condition of the upper airway passages or extend of dissection of the coronary arteries and cite autopsy findings such as cerebral edema and visceral congestion as compatible with phenothiazine related death [*2,22,34*]. In a report by Smith et al. [*35*], the pathologist who initially offered phenothiazine as a cause of death was asked to reexamine the organs and with further dissection of the coronary arteries disclosed an acute thrombus. The accuracy of the finding "no anatomic cause of death" must be viewed in light of the extent of the examination performed. Thus, without a description of the extent of the autopsy including pertinent positive and negative findings, an accurate conclusion as to the cause of death cannot be reached. Similarly, without complete scene investigation, medical history linking prior ingestion of phenothiazine with adverse reaction, or a reliable witness to the terminal event, the lack of findings after a complete autopsy in a patient taking phenothiazines does not lead to the conclusion that phenothiazine caused the death. It is important to note that all information necessary to evaluate completely a sudden psychiatric death may not be available or may not be possible to obtain within a particular coroner's or medical examiner's jurisdiction. Thus, it is particularly important in these situations, where an adequate data base does not exist, to resist the tendency to assign phenothiazines as the cause of death. This practice is scientifically unsound and will only hinder efforts to identify correctly the cause of death and to delineate clearly the risks of phenothiazine therapy. Factors responsible for autopsy negative sudden death in psychiatric patients, some of which may be erroneously attributed to phenothiazine induced cardiac death, are presented in Table 1. Sudden unexpected deaths of psychiatric patients are relatively rare events. The elucidation of causes will only be clarified with time and the possible advent of new technology to better evaluate the autopsy negative death.

TABLE 1—*Factors responsible for autopsy-negative sudden death in psychiatric patients receiving phenothiazines.*

Diagnosis	Conditions Useful for Diagnosis (After Complete Autopsy, Toxicology and Histologic Examination)
CAUSES OF DEATH UNRELATED TO PHENOTHIAZINES	
Natural	
sudden cardiac death during restraint	witnessed terminal events
sudden cardiac death during agitated or manic behavior	witnessed terminal events
inherited sudden death syndromes (for example, Jervel-Lange-Nielson, Romano-Ward)	h/o EKG changes (prolonged Q-T interval); ± hearing loss; + family history
Nonnatural	
asphyxia (homicidal or suicidal)	witnessed terminal events (information may be withheld by witnesses)
CAUSE OF DEATH POSSIBLY RELATED TO PHENOTHIAZINES	
hyperthermia	elevated core body temperature; + increased physical activity
neuroleptic malignant syndrome	muscular rigidity and incoordination; autonomic dysfunction; ± hyperthermia; witnessed terminal events
respiratory dyskinesias laryngeal-pharyngeal dystonias	muscular incoordination limited to particular muscle groups; witnessed terminal events
hypotension	symptoms of dizziness, hypotension, and tachycardia followed by cardiovascular collapse temporally related to phenothiazine administration
seizure	appearance of fatal seizure in previously well-controlled epileptic coincident with phenothiazine administration
phenothiazine-associated sudden death	prior history of EKG changes, CHF, or angina concomitant with phenothiazine administration and disappearing after drug withdrawal in a witnessed autopsy-negative death

Meanwhile, reporting of such cases in detail is essential to clarify the role of psychiatric medication in sudden death.

Some of the factors important in the evaluation of the sudden death of a psychiatric patient are illustrated by the following case report.

Case Report

A 28-year-old white, single male with a long history of behavior problems was admitted to the psychiatric ward from the emergency room with a 2-week history of agitated behavior, most recently having threatened members of his family. His past medical history, admission physical exam, and laboratory data were recorded as unremarkable in the hospital chart. During his 3-day hospital course he was moderately hyperactive and uncooperative and was begun on chlorpromazine 100 mg three times a day (t.i.d.) and 100 mg at bedtime. As determined from witnesses' statements and the hospital chart, the following events took place on the afternoon of his death:

3:15 p.m.—patient running in the halls looking for an exit; 50 mg chlorpromazine administered intramuscularly (IM).

4:00 to 4:30 p.m.—running shirtless in the halls, agitated, fighting with aides and violently resisting staff efforts to prevent him from hurting himself and others.

4:00 to 5:00 p.m.—maintenance dose of chlorpromazine increased to achieve control of patient before evening shift arrived.

5:05 p.m.—100 mg chlorpromazine IM.

6:00 p.m.—200 mg chlorpromazine concentrate orally; patient was seen to recline on hospital bed.

6:15 p.m.—aides tried to arouse patient and found him unresponsive.

6:18 p.m.—cardiopulmonary resuscitation (CPR) started; oral airway placed, then endotracheal intubation accomplished; heart rate 85; blood pressure 58/60 mm/Hg; respiratory rate 12, idioventricular rhythm with periods of asystole and ventricular fibrillation noted on EKG.

7:20 p.m.—CPR terminated.

A mildly agitated patient and two staff aides were also present in the room, but did not directly observe the deceased. The deceased was never alone with just one person. The room was 70 to 72°F (21.1 to 22.2°C) and the outside temperature was 96.4°F (35.7°C). The patient had been restrained by aides for the IM injections. However, no restraining devices were used.

Postmortem body temperature taken at the scene was 99°F (37.2°C). The autopsy was performed 14 h after death. The body was that of a normally developed white male, 165 lbs (75 kg) and 69½ in. (176.5 cm). Internally, all organs were normally developed and without signs of natural disease. The mouth and upper airways were unobstructed aside from a small amount of vomitus. The heart weighed 400 g and was grossly normal, the coronary arteries were serially sectioned every 2 to 6 mm for their entire lengths. All organs were examined microscopically, including numerous sections of the heart and conduction system, and no significant abnormalities were found. The brain was examined after formalin fixation and revealed no gross or microscopic abnormality aside from slight blunting of the anterior horn of the left lateral ventricle. Examination of the subcutaneous tissues of the buttocks revealed no sites of hemorrhage.

Numerous resuscitation injuries were present: contusions of the chest, fractured sternum and 4th and 5th ribs on the left, pulmonary contusions, gastric mucosal lacerations, laceration of hilum of spleen, contusions of mesentery and diaphragm, vomitus in the trachea, recent abrasions of the lips, hemorrhage at the base of tongue and epiglottis, defibrillator paddle marks on skin of chest, small contusions on right and left parietal scalp and postauricular scalp; discoloration of base of neck with subcutaneous hemorrhage (subclavian lines), puncture wounds in antecubital tissue and groin, bone marrow emboli in lungs (microscopic). These resuscitation injuries were immediately brought forth by particular interest groups as evidence of homicide. In this regard it should be remembered that resuscitation efforts may often be intense in the situation where a young, physically healthy person suffers an unexpected cardiac arrest and may be performed by staff relatively inexperienced at CPR. In a resuscitation effort lasting 30 min, 1800 separate chest compressions may be completed. Hemopneumothorax, ruptured liver, heart, spleen or stomach, flail chest, pulmonary laceration, broken sternum, mesenteric hemorrhages and diaphragmatic contusions have all been reported as injuries produced by resuscitation [*36–38*]. Similarly, neck and jaw manipulation required to place the mouth and pharynx in alignment for intubation may produce contusions about the neck. Fractures of the hyoid bone or thyroid cartilage or both have been reported, which could be misinterpreted as evidence for manual strangulation if the association with vigorous resuscitation efforts is not recognized [*39*].

Toxicological analysis was positive for chlorpromazine (1 μg/mL blood; 15.7 μg/gm liver). Quantitative chlorpromazine determinations were by gas liquid chromatography with a nitrogen detector [*40*].

The thorough investigation of his past medical history revealed no history of deafness or dizzy spells, no EKG abnormalities, no prior reactions to chlorpromazine, and no episodes of sudden death in the family. The chlorpromazine had been given according to guidelines found in the *Physicians Desk Reference.* Although chlorpromazine may have contributed to

the ultimately fatal pathophysiology, it in itself cannot be implicated as the sole factor responsible for death in this case.

Thus, no trauma, toxin, or disease could be clearly implicated as a cause of death. The case was viewed as an autopsy-negative sudden adult death with toxicology positive for chlorpromazine. The death certificate was signed "cause of death unable to be determined after autopsy, toxicologic, and histologic examination." The manner of death was considered undetermined.

Summary

The investigation of the sudden death of a psychiatric patient forms a special subset of medical examiner cases with unique problems related to the frequent lack of autopsy findings and unusual mechanisms of death. Without proper scene investigation, knowledge of past medical history and terminal events, and adequate autopsy, the cause of death may be incorrectly assigned. Unfortunately, in many cases where phenothiazines are cited as the cause of death, other causes have not been ruled out. Further, in view of the reflex mechanisms responsible for sudden death which leave no structural alterations, a positive drug screen for phenothiazines in the face of a negative autopsy does not always implicate the drug as a cause of death.

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References

[1] Zelman, S. and Guillan, R., "Heat Stroke in Phenothiazine Treated Patients: A Report of 3 Fatalities," *American Journal of Psychiatry,* Vol. 126, June 1970, pp. 1787-1790.

[2] Leestma, J. E. and Koenig, K. L., "Sudden Death and Phenothiazine: A Current Controversy," *Archives of General Psychology,* Vol. 18, Feb. 1968, pp. 137-148.

[3] Johansson, G., Jonsson, L., Lannek, N., Bomgren, L., Lindbergh, P., and Poupa, O., "Severe Stress Cardiomyopathy in Pigs," *American Heart Journal,* Vol. 87, April 1974, pp. 451-457.

[4] Caroff, S. N., "The Neuroleptic Malignant Syndrome," *Journal of Clinical Psychiatry,* Vol. 41, March 1980, pp. 79-83.

[5] Weiner, W. J., Goetz, C. G., Nausieda, P. A., et al., "Respiratory Dyskinesias: Extrapyramidal Dysfunction and Dyspnea," *Annals of Internal Medicine,* Vol. 88, March 1978, pp. 327-331.

[6] Modestin, J., Krapf, R., and Boker, W., "A Fatality During Haloperidol Treatment: Mechanism of Sudden Death," *American Journal of Psychiatry,* Vol. 138, Dec. 1981, pp. 1616-1617.

[7] Moore, M. T. and Book, M. H., "Sudden Death in Phenothiazine Therapy," *Psychiatric Quarterly,* Vol. 44, 1970, pp. 389-402.

[8] Rosati, D., "Hypotensive Side Effects of Phenothiazine and Their Management," *Diseases of the Nervous System,* Vol. 25, June 1964, pp. 366-369.

[9] Cancro, R. and Wilder, R., "A Mechanism of Sudden Death in Chlorpromazine Therapy," *American Journal of Psychiatry,* Vol. 127, Sept. 1970, pp. 368-371.

[10] Giordano, J. et al., "Fatal Paralytic Ileus Complicating Phenothiazine Therapy," *Southern Medical Journal,* Vol. 68, March 1975, pp. 351-353.

[11] Giles, T. D. and Modlin, R. K., "Death Associated with Ventricular Arrhythmias and Thioridazine Hydrochloride," *Journal of the American Medical Association,* Vol. 205, 8 July 1968, pp. 108-110.

[12] *Physician's Desk Reference,* 40th ed., Medical Economics Co., Oradell, NJ, 1986, pp. 1728-1730.

[13] Panig, P. M. et al., "Thioridazine Hydrochloride in the Treatment of Behavior Disorders in Epileptics," *American Journal of Psychiatry,* Vol. 117, 1961, pp. 832-833.

[14] Alexander, C. S. and Ninu, A., "Cardiovascular Complications in Young Patients Taking Psychotropic Drugs," *American Heart Journal,* Vol. 78, Dec. 1969, pp. 757-769.

[15] Fowler, N. O., McCall, D., Chou, T., Holmes, J. C., and Hanenson, I. B., "Electrocardiographic Changes and Cardiac Arrhythmias in Patients Receiving Psychotropic Drugs," *American Journal of Cardiology,* Vol. 37, Feb. 1976, pp. 223-230.

[16] Hollister, L. E., "Drug Treatment of Schizophrenia," *Psychiatric Clinics of North America,* Vol. 7, Sept. 1984, pp. 435-452.
[17] Huston, J. R. and Bell, G. E., "The Effect of Thioridazine Hydrochloride and Chlorpromazine in the Electrocardiogram," *Journal of the American Medical Association,* Vol. 198, 3 Oct. 1966, pp. 16-20.
[18] Richardson, H. L., Graupner, K. I., and Richardson, M. E., "Intramyocardial Lesions in Patients Dying Suddenly and Unexpectedly," *Journal of the American Medical Association,* Vol. 195, 24 Jan. 1966, pp. 254-260.
[19] Dimsdale, J. E., "Emotional Causes of Sudden Death," *American Journal of Psychiatry,* Vol. 134, Dec. 1977, pp. 1361-1366.
[20] Gustafson, R. and Petremen, M., "Myocardial Necrosis in the Golden-Mantled Squirrel," *Canadian Medical Association Journal,* Vol. 89, Oct. 1963, pp. 900-901.
[21] Raab, W., Chaplin, J., and Bajusz, E., "Myocardial Necrosis Produced in Domesticated Rats and in Wild Rats by Sensory and Emotional Stress" in *Proceedings of the Society for Experimental Biology and Medicine,* Vol. 116, July 1964, pp. 665-669.
[22] Hollister, L. and Kosek, J. C., "Sudden Death during Treatment with Phenothiazine Derivatives," *Journal of the American Medical Association,* Vol. 192, 21 June 1965, pp. 1035-1038.
[23] Reinert, R. E. and Hermann, C. G., "Unexplained Death during Chlorpromazine Therapy," *Journal of Nervous and Mental Disease,* Vol. 131, 1960, pp. 434-442.
[24] Bell, L. V., "On a Form of Disease Resembling Mania and Fever," *American Journal of Insanity,* Vol. 6, 1849, pp. 97-127.
[25] Peele, R. and Von Loetzen, I., "Phenothiazine Deaths: A Critical Review," *American Journal of Psychiatry,* Vol. 130, March 1973, pp. 306-309.
[26] Davis, J. H. and Wright, R. K., "The Very Sudden Cardiac Death Syndrome—A Conceptual Model for Pathologists," *Human Pathology,* Vol. 11, March 1980, pp. 117-121.
[27] Lown, B., Tempte, J. V., Reich, P., et al., "Basis for Recurring Ventricular Fibrillation in Absence of Coronary Heart Disease and its Management," *New England Journal of Medicine,* Vol. 294, 18 March 1976, pp. 623-629.
[28] Lown, B. and Verrier, R. L., "Neural Activity and Ventricular Fibrillation," *New England Journal of Medicine,* Vol. 294, 20 May 1976, pp. 1165-1170.
[29] Goldschlager, N., Cohn, K., and Goldschlager, A., "Exercise-Related Ventricular Arrhythmias," *Modern Concepts in Cardiovascular Disease,* Vol. 48, Dec. 1979, pp. 67-71.
[30] Jervell, A. and Lange-Nielson, R., "Congenital Deaf-Mutism, Functional Heart Disease with Prolongation of the Q-T Interval and Sudden Death," *American Heart Journal,* Vol. 54, July 1957, pp. 59-68.
[31] Itoh, S., Munemura, S., and Satoh, H., "A Study of the Inheritance Pattern of Romano-Ward Syndrome," *Clinical Pediatrics,* Vol. 21, Jan. 1982, pp. 20-24.
[32] Baroldi, G., "Different Types of Myocardial Necrosis in Coronary Heart Disease: A Pathophysiologic Review of their Significances," *American Heart Journal,* Vol. 89, June 1975, pp. 742-752.
[33] James, N., "Neural Pathology of the Heart in Sudden Death" in *Sudden Death,* H. E. Kulbertus and H. J. J. Wellens, Eds., Nighoff, Boston, 1980, pp. 49-65.
[34] Whyman, A., "Phenothiazine Death: an Unusual Case Report," *Journal of Nervous and Mental Disease,* Vol. 163, Sept. 1976, pp. 214-217.
[35] Smith, R. E., Lowe, N. N., and Nasrallah, H. A., "Haloperidol and Unrelated Sudden Death," *American Journal of Psychiatry,* Vol. 137, July 1980, pp. 843-844.
[36] Paaske, F., Hansen, J. P. H., Koudahl, G., and Olson, J., "Complications of Closed Chest Manage in Forensic Autopsy Material," *Danish Medical Bulletin,* Vol. 15, Oct. 1968, pp. 225-230.
[37] Nagel, E. L., Fine, E. G., Krischer, J. P., and Davis, J. H., "Complications of CPR," *Critical Care Medicine,* Vol. 9, May 1981, p. 424.
[38] Enarson, D. A. and Gracey, D. B., "Complications of Cardiopulmonary Resuscitation," *Heart and Lung,* Vol. 5, Sept.-Oct. 1976, pp. 805-807.
[39] Gregerson, M. and Vesterby, A., "Iatrogenic Fractures of the Hyoid Bone and the Thyroid Cartiolage. A Case Report," *Forensic Science International,* Vol. 17, 1981, pp. 41-43.
[40] Bailey, D. N. and Guba, J. J., "Gas Chromatographic Analysis for Chlorpromazine and Some of its Metabolites in Human Serum, with a Nitrogen Detector," *Clinical Chemistry,* Vol. 25, No. 7, July 1979, pp. 1211-1215.

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