
HISTORICAL NOTES

Digitalis Poisoning: Historical and Forensic Aspects

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Since the introduction of digitalis into therapy approximately 200 years ago, there have been continuing admonitions concerning its toxicity. Over 400 years ago, herbalists listed the plant as being poisonous. In fiction, the homicidal use of digitalis has appeared in the writings of Mary Webb, Dorothy Sayers and Agatha Christie. Ten instances in real life of alleged homicide by digitalis and trials of the accused are listed. The drug has been used with suicidal intent rather infrequently, compared with other medications. Possibly, it is more commonly used for such a purpose in France than in England or the United States.

The fraudulent use of digitalis in the support of claims for disability because of heart disease has occurred, and one large conspiracy of physicians and lawyers in the swindle of insurance companies during the 1930s is a

shameful episode in the record of these professions. Although innocent, one professor of medicine who was involved committed suicide.

Two pharmaceutical (manufacturing) blunders that occurred in Belgium and Holland with mislabeling are mentioned. These resulted in numerous deaths and the profession seemed rather slow to recognize the nature of these small epidemics of poisoning.

Instances of psychiatric illness with digitalis seem well documented. The story of digitalis toxicity continues into the present and physicians should be vigilant regarding the drug's potential for poisoning that can result from prescribing digitalis with ignorance of proper dosage, pharmacodynamics or drug interactions, as well as from accidental overdose as in children and use with self-destructive or homicidal intent.

Digitalis toxicity, often candidly indexed as poisoning, has plagued the medical profession for 200 years. The situation qualifies as a professional disgrace on the basis of three items: the situation persists, physicians are often slow to recognize it and, over the decades, writers have been harsh in their denunciation of fellow physicians when toxicity has occurred. The *Index Medicus*, in the codes "Digitalis Toxicity" and "Digitalis Poisoning," listed 5 to 10 papers yearly from 1925 to 1955, then with change in the system has listed about 20 papers yearly. The incidence of toxicity may be decreased by educational efforts within an institution, and the availability of radioimmunologic determinations of blood and tissue levels has been of great help in identifying the poisoned patient (1,2).

Early History and Controversies

In any drug effect, the ratios of therapeutic/toxic or lethal doses are of paramount importance; for digitalis compounds,

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the ratios are 1:2, with variations depending on the mode and rate of administration. Although some physicians lament the smallness of this ratio, I have been relatively comfortable with it because it is generally dependable; however, the lethal potential of overdose has not been forgotten. The dose constitutes the threat to life; "Dosis facit venenum" or, as some colleagues sensitive to biorhythm effect in theory would prefer, "Tempus non solum Dosis facit venenum." Germane to this appreciation of the dose hazard is Withering's account (3) of a near lethal poisoning in which a wife stewed a large handful of foxglove leaves in a half pint of water and gave the liquor to her husband for his asthma. "This good woman knew the medicine of her country, but not the dose of it, for the husband narrowly escaped with his life." Human behavior is repetitive and the revival in the use of homemade herbal teas has brought new reports of death from teas inadvertently made with foxglove.

Withering's treatise on the foxglove (1785) was the first organized collection of reports indicating its value in dropsy. The plant was not indigenous to the Americas but was cultivated here shortly after the appearance of his monograph (4,5). As early as 1800, John Moore (6) presented his inaugural dissertation in Philadelphia on "Digitalis purpurea or the Foxglove," describing not only its clinical use, but

also its toxic effects when taken by himself and his classmates. Acrimonious debate promptly ensued after Withering's report concerning the efficacy of digitalis in treating persons suffering from swollen legs and bellies. Those practitioners who, I believe, followed Withering's directions regarding selection of cases were lavish in their praise; those who inappropriately treated patients with abdominal swelling due to liver disease, often with less attention to the dosage, were strident in their denunciation. The journals in the first quarter of the 19th century contain, in tedious repetition, papers that emphasize the toxic symptoms, particularly vomiting, headache, visual disturbances and sometimes dementia and death. The early 19th century volumes of *Lancet*, *British Medical Journal* and *Edinburgh Journal of Medicine and Surgery* contain recurring accounts of digitalis toxicity. The centenary of digitalis therapy was noted in 1885 by articles in the *Lancet*, and one letter (7) to the editor states that a relative's "mother's mother was killed by an overdose of digitalis administered by a medical man." Possibly pertinent to the death was the mention that the woman had protruberant eyes, suggesting to me Graves disease. Relative to my theme of jurisprudence, I quote Oliver Wendell Holmes (8), "Presumptions are of vast importance to medicine as in law. A man is *presumed* innocent until proved guilty. A medicine . . . should always be *presumed* hurtful." In early herbals (9-11) illustrating the foxglove, the plant is classified outright as a poison, and Christison's opus (12) on medical jurisprudence in 1845 describes its lethal potential.

The decrease in use of digitalis during the 19th century was as much related to its inefficacy in the treatment of pulmonary tuberculosis, as from its use and misuse in edematous patients. The detractors of the drug were blunt in their accusations, stating that they suspected more persons with consumption were being harmed or killed than improved by the digitalis.

Sir John Kirk, physician to the Livingstone expedition, sent a poison used on arrows to England nearly a century after the digitalis had been first used. This lethal material was identified as an active cardiac glycoside, having actions on the frog heart like those of digitalis (13). There is an interesting tale that in Africa, Kirk had put an arrowhead with its poison in his shirt pocket where he also kept his toothbrush. Later, after brushing his teeth, he developed slowing of the heart and symptoms akin to those of digitalis toxicity. Livingstone's account (14) also included a statement that the strophanthin arrow poison was used by the natives in the hunting of animals, but generally not in tribal wars; other more rapidly acting poisons were preferred for human beings. In the hunting of game, the strophanthin poison inflicted by the silent arrow would gradually disable the affected animal, causing it to drop out of the herd so that its butchering would be easy and safe.

Fox and VanGogh Allegations

It has been inferred that the terminal illness of the English statesman Charles James Fox was shortened by digitalis (15), and that his London consultant was Lettsom. Some accounts (16) indicate that Fox had suffered from liver disease, that is, portal cirrhosis. The new medicine he took, mentioned in his biographical history, was undoubtedly digitalis, but it does not seem to have been responsible for his death. Withering (17) was probably referring to this patient when he wrote, "Indeed, the controversy, not long ago resulting from the case of a celebrated statesman, would justify the supposition that some of the faculty were again experimenting, *de novo*."

It has been suggested that digitalis played a role in the illness of Vincent VanGogh and that his use of yellow and color swirls was generated by his memory of toxic visual symptoms. Lee (18) gives reserved support for this hypothesis. As evidence for the indictment are two paintings of VanGogh's doctor, who sits near a table with flowers on it that appear to be foxglove flowers though the shape of the leaves is not correct. Although the possibility that digitalis might have contributed to VanGogh's depression and caused visual hallucinations cannot be denied, his mental disturbance and color usages predate the period when he was most likely to have been exposed. This was my conclusion after studying his paintings over the years in the VanGogh Museum in Amsterdam.

Condemnation of Physicians—Ancient and Modern

Think of the field day that a plaintiff's counsel of today might have if a judge were lax and allowed him to quote ancient and recent authorities to the jury or to interrogate a physician witness on whether he was familiar with all the derogatory statements concerning the use of the digitalis by the medical profession. Just a few examples of the many available are:

Withering (19), 1787, England: "He [Lettsom] would hardly have thought it necessary to have published more instances of what I had stigmatized as bad practice . . . or further proofs how it might be employed as a deleterious poison."

Rush (20), 1797, America: "Foxglove . . . I suspect the cases in which they were useful to have been either so few or doubtful and that the cases they had done harm were so much more numerous and unequivocal as justly to banish them from the *Materia Medica*."

Beddoes (21), 1799: "The strictest caution is necessary to prevent the alarming, and even fatal, consequences. I mean not to conceal that the foxglove is a dangerous, which means only that it is a powerful medicine."

Sanders (22), 1808, Edinburgh: "I fear, not rarely death itself has been the consequence of the unguarded or indiscriminate administration of digitalis"

Lettsom (23), 1812, London: Pulmonary consumption: "I believe it never cured any and that its indiscriminate use has killed many"

Blackall (24), 1818, London: "In phthisis pulmonalis . . . I am persuaded [it] has sometimes been attended with effects more immediately fatal than the disease itself."

And from contemporary cardiologists:

Master (25), 1945: "I believe that digitoxin poisoning has now become as frequent an occurrence that it presents a real hazard." (He translates the Von Jasch, 1910, textbook; "Digitalis and digitoxin, as frightful poisons.")

Plummer (26), 1925, Mayo Clinic: "The reduction in mortality from hyperfunctioning adenomatous goitre is attributed to the stopping the use of digitalis in those cases with auricular fibrillation, broken compensation and so forth."

Lown (27), 1957, Boston: "Young and enthusiastic physicians at times like to expedite the process of digitalis by giving intravenous medication; there is expedition, the patient is expedited out of this world."

Enselberg et al. (28) reviewed cases of fatal ventricular fibrillation from digitalis and strophanthin documenting how they have occurred.

Batterman (29), 1957, New York: ". . . I would say, many deaths using, for example, cedilanid in patients with advanced heart disease, just by a single injection of 0.25 mg intravenously." (52)

Selzer (30), 1981, San Francisco: "That digitalis is a highly toxic drug has never been disputed. It is generally acknowledged that digitalis toxic effect . . . may be the cause of death in some patients." In this short communication Selzer points out a past problem related to a change in the bioavailability of digoxin, without the profession being well informed of it.

Moss et al. (31), 1981, Rochester, New York: "Digitalis-associated mortality after myocardial infarction." This title of a paper invites accusatory inferences regarding the profession.

The American Medical Official Handbook "Useful Drugs," 15th ed. (32), 1952, Chicago: "Caution: Digoxin is extremely poisonous."

Homicidal Use of Digitalis in Fiction

There is one novel, set in the English midlands of Shropshire, that is a favorite of mine and in which the foxglove is mentioned. Written by Mary Webb in the 19th century, *Precious Bane* gives a touching account of a girl with a harelip, living with an embittered brother and an aged mother on a small farm that grudgingly gave them a living in return for their incessant toil. In a preliminary event, Gideon, the harsh, callous brother, in a discussion of giving foxglove to one of the cows, reflects a folklore knowledge that tol-

erance to digitalis decreased with increasing age. Here is the conversation between the "doctor's man" and Gideon:

Gideon said he was going to stock afore turning it
"The brindling longhorn's very middling," he said
"Heart's like to burst sometimes. I suppose a dose of foxglove ud put her right, maybe." "Ah. Foxglove'll lower the pulse as quick as anything." "But you mund be careful When things get old and worn out, they canna stand much of it." (The cow died.)

Gideon particularly resented the food that his invalid mother ate and the doctor's bills. His selfish harsh approach, seemingly to justify euthanasia, was embodied in his repetitious remark to her, "You'd be leif be dead as quick," and she seemed to capitulate, wondering whether it would not be so. It is clear that he prepared a potion of a bitter tea from foxglove that hurried his mother's demise. The doctor comes and his interesting conversation with Prudence has ethical implications.

Prudence: "I sent for the doctor to see what mother died of, and he said, were we in the habit of giving her digitalis, a strange word I dinna know . . . but he spelled it out for me, and I wrote it down. So I said no, I'd never heard of it. So he says, Foxglove! Foxglove! "Foxglove?" I says, "No, whatever should I give her that for?" "What, indeed?" he says, looking at me very sharp. "What do puzzle me, sir," I said, "is what mother died of." "That's what I want to know, too," he says. "May be we'd ought to have a Crouner's Quest, sir," I says. "Oh, you'd be willing to have an inquest on the body?" "Why, yes indeed, if it was right and proper." "Well, if you're willing to have it, there's no need to have it."

Mary Webb, the author, was a granddaughter of an Edinburgh physician, grew up in the Shropshire area and was knowledgeable of the local beliefs and customs of the land. It seems that she assigned the doctor the prerogative of making a moral judgment, which was that an inquest would not contribute to goodness in the community.

Another novel, *Silas Marner*, has frequently been required reading in American schools. It was written by George Eliot, who also lived in the English midlands. Silas was a social outcast who was finally rescued from a life of a bitter miserly recluse by the love of a child who wandered to his doorstep after the death of her broken-hearted unmarried mother. Early in the story, Silas had used an infusion of foxglove to cure a chronically ill woman, swollen with fluid, whom the doctor failed to help. The woman, Sally Oates, gets well, but Silas suffers from further community alienation because the people regard the event as akin to witchcraft. He had learned the foxglove remedy from his mother. Because of the community's reaction and the legal implications, he was afraid to repeat any therapeutic ventures,

although many people came to ask for his help after Sally Oates's cure.

From this century's plethora of murder mysteries, there are several in which digitalis is utilized for the murder. The stories bear witness that the authors had carried out considerable study of the drug's actions and lethal dosage. The victim was usually aged and had been under treatment with digitalis and, incidentally, there was a greater credit given to the medical examiner as being able to quantitate digitalis in a corpse than could possibly be true at the time.

Agatha Christie frequently utilized poisons in her stories (33). In 83 poisonings, digitalis was used six times. In *Appointment with Death*, published in 1937, the lethal dose of digitalis was given by hypodermic injection; the method of its accomplishment is somewhat implausible and the speed of death without environmental disturbances seems hardly credible. Notwithstanding these medical shortcomings, the plot of the story is entrancing. It has a psychological setting; among the group in which her great detective Hercule Poirot exposes human frailties with his analytic logic are: 1) a nurse who is also the unhappy wife of the victim's demoralized son, 2) a newly graduated, idealist woman physician, and 3) a world-renowned psychiatrist.

A short story, the plot of which I enjoyed even more because of Dame Agatha's manifest familiarity with lethal doses of digitalis, is entitled "The Herb of Death," written in 1932. What a field day this writer might have now with other plots involving enhanced toxicity of digitalis because of electrolyte aberrations (for example, low potassium), drug interaction (for example, quinidine) or environmental change (such as altitude hypoxia).

Another mystery, to which I was introduced by its dramatization on television's Masterpiece Theater, was Dorothy Sayers' *The Unpleasantness at the Bellona Club*. An aged general had been poisoned by an extra large dose of digitalis and the mechanism of death was consistent with the sequence that the events unfolded in the story. It was Peter Wimsey's perspicacity which, of course, generated the exhumation and examination. The fictional climax was the examiner's report that gave the amount of the digitalis that must have been taken. It is evident that Dorothy Sayers did her homework on the pharmacology of digitalis. The victim was supposed to have died about an hour after a large oral dose. As an update on medical jurisprudence, if Peter Wimsey had had data from present immunoassay methods, it could be confabulated that he might have obtained a better estimate of the time of the old general's death (which was critical in the legal determination of the heir to the bulk of the inheritance). If the examiner had determined the digitalis levels of blood samples from the corpse's heart, a peripheral vein, vitreous humor and the medulla of the brain, some approximation of the sequence of the lethal dose, the time of death and the time of the postmortem might have been

mentioned (34). However, such conclusions for an exhumed body fit fantasy or fiction rather than science.

One can give no credence to a far-fetched suggestion that Ophelia in Shakespeare's tragedy *Hamlet* might have been depressed and died of eating foxglove leaves, the thought being generated by the note describing her garland of flowers as including the foxglove. "Here with fantastic garlands did she come . . . and long purples that likened shepherds give a grosser name, but our cold maids do dead men's fingers call them." (Act IV, Scene VII).

In the fantasy of planning a novel, fill-ins of conversations for one's astute hero detective may be required. Listed below are items (Exotica, Curiosa et Trivia) that could be introduced for his patter to simulate great erudition: "Did you know, madam or sir, that . . .

1. The lethal dose of digitalis is 30 to 50 times greater for toad than frog (35).
2. The accumulation rate of digoxin is lower in rat heart than in guinea pig heart (36).
3. Monarch butterflies concentrate glycoside in some geographic areas. Blue jays avoid eating them (37).
4. What is "nobbling" of race horses? Horses have been doped with drug combinations including digitalis, causing loss of the race."

Homicides (Table 1)

Although homicides from digitalis have been rare events over the decades, their dramatic and tragic quality match any I know of in the world of fiction in respect to the intricacies of the plot and depth of pathos associated with the evil deed. The reports (38-45) that I have found are outlined in Table 1. Each has some unique features.

The recent tragic deaths from digoxin in a large prestigious children's hospital have yet to be reported in a scientific journal. The lay press (46) gave the appellation of murder and as many as 43 deaths were to be investigated. The patients had died rather unexpectedly and, contrary to the generalization in my introductory paragraph, the nature of the death was promptly recognized. Despite the identification of toxic levels of digoxin in the blood of an early victim, further homicidal events could not be prevented. Newspaper reports with glaring headlines seem to go beyond good taste in journalism. The complexities of the events, including the fact that at least one of the victims had Down's syndrome, will be most difficult to unravel.

Dr. Coutis de Pommerais in Paris was a notorious murderer who poisoned by digitalis, and his trial is mentioned prominently in texts of jurisprudence. The case was recently reviewed in detail by Parson (40). The story is basically that of a pompous French physician in the last century, who

Table 1. Reported Homicidal Uses of Digitalis

Years and Country	The Accused	Victim(s)	Circumstances	Outcome
1826 (38), England	Herbalist	Apprentice; death 22 hrs after dose	Help sought by mother of victim, suffering a trivial complaint	Tried for manslaughter, prisoner acquitted "The act did not come under statute regarding manslaughter.
1851 (39)	Fairy doctress	Paralytic child "suppositious"	"Real child stolen by fairies," large doses d purpurae	Tried and convicted
1863 (40), France	Coutis de La Pommerais	Widow and mistress	Inconvenience, insurance, biologic tests; Claude Bernard's evidence	Guillotined
1876 (41), Germany	"Freimacher" (literally "liberator")	Two recruits, death of one	Scheme for rejection for military service by digitalis	Surviving recruit prison term, "Freimacher" convicted of second degree murder; 5 years in prison "Videant consules. . . ."
1930(?) (42), Belgium	Doctor	Husband of mistress	Dinner for the married couple, oysters at each place	Indicted—verdict?
1934 (42)*, Germany	Doctor (otorhinologist)	Girl friend	Offered physical exam, (rectal exam) strophanthin on finger of rubber glove	Indicted—verdict?
1935 (43), Belgium	Widow "notorious nurse Becker"	26 persons dead	Widow volunteered to help elderly lonely persons with housework	Condemned to life sentence
1962 (44), Israel	"A friend"	Woman- vomiting, heart block, death	A glass of fruit juice, digitoxin identified	Author: "I am sorry but I must omit fascinating details of the romantic background." Verdict?
1972 (45), United States	Chinese chemist as a student, gold medal for digitalis research	Foster daughter and mistress; foster son	Surgical defense, "wished to punish, not kill." Digoxin in analgesics, bonbons on birthday	Result of trial? 8 years imprisonment?

*This reported death from rectal absorption of strophanthin has strained the credulity of my pharmacologic acquaintances. The drug is absorbed by this route but quantitatively unpredictable

wished to live beyond his means and who was convicted of poisoning two former patients to whom he had once professed his love. He was the only suspect who could seemingly have administered the lethal doses of digitalis. Before the second death, that of his former mistress, he had taken out large insurance policies on her life. She had been coaxed into participating in a different conspiracy from that which de Pommerais actually had in mind. She understood the plan to be that after some time passed, she would fake a life-threatening disease with his help so that the insurance company would be pleased to cancel the contracts having the provision of a life annuity of 6,000 francs.

The 1873 to 1874 trial attracted much publicity and many "expert" witnesses, including the famed Claude Bernard. A novel aspect of court procedure was the admission as

evidence of biologic tests, which showed that the vomitus scraped from the floor had digitalis-like effects when given to laboratory animals. During the trial, de Pommerais did not lose his self-confidence or the support of his wife. He was found guilty and lost his head by guillotine. It seems to have been the circumstantial evidence, not the medical testimony, that convinced the jury of the doctor's guilt.

Another case in the last century listed in Table 1 (41) on which I shall briefly comment is that of the two young recruits given digitalis by an irregular practitioner ("Freimacher") in order to escape military service (41). One died; the other, who did not, received a prison term, as did the conspirator who supplied the medicine. This article ends with the phrase, "Videant consules." For completion of the quotation, one adds, "ve quid res publica detromenti

capiat." Cicero's admonition "that the consuls see to it that the republic suffers no harm."

Each of the cases mentioned in Table 1 has interesting human interest details. The case of the physician who allegedly poisoned the husband of his paramour by putting digitoxin in an oyster is interesting. After collapse of his victim, he was reported to have injected intracardiac digitoxin to render any analysis of the corpse more difficult.

The last listed case (45) is a relatively contemporary one in which the physician, an acquaintance of mine, was confident from the electrocardiogram that the patient's illness was due to digitalis and I was in agreement with him. The victim had been operated on for an abdominal emergency and had undoubtedly been close to death. She denied taking digitalis, despite the electrocardiographic evidence, but a blood level of digoxin of 12.6 ng/ml was a convincing basis for calling the police. An older family member was indicted. The defense submitted the plea of not guilty of homicidal intent; the indicted foster father, a senior member in a Chinese family, claimed the right to punish a junior member. In addition, as a chemist and having received a prize in college for his digitalis research, he would have known the true lethal doses of digitalis, thereby supporting his claim that he wished only to punish and not kill her.

Suicides

Considering the availability and toxicity of digitalis, it has been used relatively little in self-destructive attempts. Suicides by digoxin may have been more frequent in continental Europe, but they also occurred in America and England. Of the reported 3,000 or so yearly poisonings in the United Kingdom, only 5 were caused by digitalis (47). More cases may be expected to be reported because of the increased interest in pharmacokinetics which can now clearly define the poison immunoassay methods, the introduction of new treatments including the administration of antibody fragments that can fix (or "neutralize") digoxin and then be excreted (48) and the investigations on removal of the drug early in the poisoned state by hemoperfusion. Bismuth et al. (49), specifically reporting on the value of electrical pacing of the heart, based their opinions on the surprising number of 133 patients referred to their center with massive poisoning within the 8 year period from 1967 to 1975.

I noted one published report (50) of a pregnant woman who attempted suicide with a massive dose of digitoxin. She recovered after severe vomiting and arrhythmias. However, a living premature infant was born who succumbed, apparently from digitalis intoxication. The medical report did not mention whether the death of the infant resulted in any legal action. The situation does pose some problems for jurisprudence and ethics. In blunt terms, the infant was poisoned, but I hope the mother was referred for psychiatric care and not to the state prosecutor.

Fraud Through Simulated Heart Disease (Table 2)

This section in the saga of deflowering the foxglove relates mainly to courts of law, and focuses on the use of digitalis to mimic serious heart disease for fraudulent purposes (that is, to collect insurance). This has occurred in both single cases and conspiratorial large groups of cases (51,52). In New York during the 1930s, the legal and medical professional societies must have been distressed to learn that there had existed in their midst an organized group of lawyers and doctors who had sought out clients whom they instructed in the symptoms of heart disease and administered large doses of digitalis to produce electrocardiographic abnormalities. The exposure of the fraud and the trial had numerous tangential aspects showing human weaknesses and legal conniving. The susceptibility of numerous policy holders to the suggestion that they participate in the swindle and the later motivation of some of these people to help expose the ring because the lawyers had taken a very large slice of the ill-gotten gains are discomfiting reminders of human avarice and duplicity. One lawyer was further indicted for attempts to bribe a witness to change his testimony.

A professor of medicine who was peripherally involved by his interpretations of some of these electrocardiograms committed suicide. I have had some long discussions with Charles Kossmann, a junior physician at the time at Bellevue Hospital, concerning the professor's death. What precipitated his self-destruction? Was it the shock of learning that

Table 2. History of the Heart Disease Racket: Fraud Through Simulated Heart Disease

1920s	Relaxation requirements for issuance of disability clause of life policies.
1929	"Financial crash," the Great Depression.
1930	Ring of <i>physicians</i> coaching persons on heart disability and digitalis to produce abnormal electrocardiogram. <i>Lawyers</i> with runners
1935	Insurance companies suspected they were being victimized, sought additional legal counsel.
1937	Confessions of certain participants after hearing recorded conversation. Ground for indictment of 75.
1939 (April)	<i>Circuit Court of Appeals</i> (2nd Circuit) U.S. vs. Weiss et al. Convictions affirmed.
1940 (October term)	<i>Supreme Court</i> ? admissibility of recorded telephone conversations. Judgments reversed. Remanded to District Court.
1941 (June)	<i>Circuit Court of Appeals</i> . ? wire-tapping influence on confessions ? were confessions needed as evidence. Convictions affirmed.

Prof. W. in whose cardiac clinic the cardiologists had worked, committed suicide
No defense of insanity due to digitalis in claimants Two wives pushed husbands
to confess

some of his previous students were involved in the ring and the feeling that they had double-crossed him? Was it his pride in not recognizing or having greater conviction of the cause of the electrocardiographic picture, as he was an expert in this area (despite having been assured that no digitalis had been taken)? Or, did he feel such deep shame for being even peripherally involved that he felt compelled to remove himself literally from the professor's chair? Indeed, how chagrined he must have felt remembering that a few years previously, he had published a paper with Gold (53) entitled, "A Dangerous Preparation of Digitalis" (a product, incidentally, manufactured in Minnesota). He had been born in India of missionary parents, and the final event had some symbolic modeling of hara-kiri philosophy with a self-injection in the anatomy laboratory. Kossmann has given me permission to quote from a recent letter.

"When all of the dirty business came to a head in 1937 I was a clinical assistant visiting physician at Bellevue. . . . Wyckoff was a strict disciplinarian with himself and with others. One evening, I believe in February or March, 1937, I was called by Wyckoff to come to his private patient office. I think on East 37th Street. When I arrived he handed me two electrocardiograms and asked me what I thought of them. Each showed abnormalities of the T wave. I gave my standard correlative interpretation of them, namely, that 'they displayed abnormalities of the T wave ascribable to myocardial disease, digitalis or both.' The light in the waiting room, now devoid of patients, was dim but I thought I perceived a further tightening of his usually tightly compressed lips. He thanked me, turned to enter his consulting room, and left me to find my way out, a brusqueness I had come to expect from him. I thought no more of the episode . . . until after the holiday week-end of 1937. On returning by train, I was shocked to read . . . that John Wyckoff had been found in coma in the anatomy laboratory of the Medical School. This straight-laced, rigidly honest, puritanically ethical man just could not cope with the disgrace that might be heaped upon him by colleagues and the public who would never believe that he had been duped by dishonest and avaricious doctors and lawyers. . . ."

In his autobiographically oriented history of the cardiology subspeciality, Louis Bishop (54) indicates how he was temporarily misled by the conspirators and how astonished he was to learn that his telephone had been tapped.

Another tangential development during the trials was the development of considerable feelings against big corporations among the general population. A medical director of a large insurance company, a classmate of mine, told me that it was the unfavorable body of public opinion which developed during the trials, particularly after the suicide, that dissuaded his company from pushing for further prosecutions, such action being considered bad for their business image. I have requested medical acquaintances with the insurance companies to find some of the electrocardiograms for my review but was informed that they had either been

discarded or retrieval would be next to "impossible in the acres of files."

In the archives of law, wherein are stored the legal developments in the prosecution of the swindlers, *I understand* that many of the arguments presented in the courts (55-58) are still studied by law students. The case was taken to the Supreme Court and the initial lower court's conviction was set aside, being referred back to the lower court for clarification on whether the tapping of the telephone lines had been instrumental in the court's decisions. The arguments make interesting reading and are entrees for conversation with legal friends who have, on occasion, attempted to give me some elemental instruction in due process.

Pharmaceutical Mistakes

Another category of digitalis misuse has been related to errors in dispensing, more understandable in the distant past when the pharmacist mixed his crude extracts of plants, animals and minerals than now when standardized preparations are routine. Historically, for example (59) during 1886 in England, two children died with symptoms suggesting digitalis poisoning after taking a cough medicine. On analysis of the medicine, the miscreant was syrup of squills, a plant that contains a cardiac glycoside.

A continued contribution to error persists in that physicians' prescriptions would hardly ever take prizes for legibility. To quote Oliver Wendell Holmes (60) addressing graduating medical students on the importance of a physician rechecking a prescription, "You will very probably find yourself the author of a homicidal document which, but for this precaution, might have carried out its intentions." Even when an error occurs in the pharmacy, the physician may not escape censure.

It is extremely difficult to understand some recent human errors related to the dispensing of mislabeled drugs. There are two outstanding blunders that have been exposed in the past decade. In Belgium (42), where digitoxin, 10 mg, was labeled estradiol benzoate, a substance then prescribed for advanced cancer of the prostate, as many as 40 patients may have died from digitalis poisoning. Some medically pertinent aspects of this disaster were the delay in recognizing the nature of the tragedy and the exhumation of bodies to aid in the identification of digitoxin. Additionally, the exoneration by their peers of the physicians who had not promptly recognized the toxicity of the medication which had been dispensed is quasi-acceptable as ethical.

The second publicized pharmaceutical error of major magnitude occurred in Holland (61,62) when digitoxin was used in part, instead of digoxin, in the manufacture of nearly half a million tablets, erroneously labeled as digoxin. Approximately 200,000 of the faulty tablets were used by patients with the result that they received two to four times

more medication than prescribed. Of the approximately 250 patients identified as at risk and having symptoms suggesting toxicity, Lely (62) in his doctoral thesis concluded that the tablets contributed to the death of 19 patients. Because of peculiarities in the distribution of the drug, one small city, Veenendaal, had a concentration of the cases, and epidemiologic techniques were applicable to the investigation of the illnesses and deaths. Commentators remarked on the slowness of the medical profession in recognizing the evidence of toxicity, but there was no attempt made to fix blame on a medical professional situation approaching equivalence to the Belgian tragedy.

Role in malpractice suits. In English law, the responsibility of the manufacturer and vendor of drugs has been strictly spelled out for many years (63): "As applicable to persons vending drugs and medicines by retail, the legal maxim should be reversed. Instead of *caveat emptor*, it should be *caveat vendor*."

Despite the loose accusations of physicians over two centuries that the injudicious use of digitalis by other physicians had been responsible for deaths, I know of no publicized instance where an alleged misuse of digitalis was the main issue in malpractice suits. I think the physician now, as in past centuries in England, has enjoyed some protection against criminal indictment, but not to the extent embodied in these opinions of the last century (64):

"If one that is of the mystery of a physician take upon the cure of a man and giveth him such physic so as he dieth thereof, without any felonious intent and against his will, it is no homicide," so saith my Lord Coke.

Blackstone says, "This is neither murder or manslaughter, but misadventure, and he shall not be punished criminally."

The physician today is unlikely to encounter such benevolence, legal partiality or possibly even civility from judges. With the extent of intraprofessional argument, it is perhaps surprising that there have not been more lawsuits.

Others have posed this question: If digitalis were to be manufactured today as a new drug, how would it fare with the Food and Drug Administration? Under the original Food and Drug Act, could it be considered "safe?" From the opinions given and the anecdotal deaths, this could be debatable. Under the 1962 amendment (Public Law 87.871), would the drug be certified as "efficacious?" One would have to be circumspect in answering this with an emphatic "yes" if the recommendations for its specific uses were not spelled out.

Irregular Prescribing

A combination of prescribing and heinous pharmaceutical practice is exemplified in some weight-reducing pills in which digitalis was one ingredient. The medication induced spurious heart disease (65), and the digitalis ingre-

redient was incriminated as probably at least a contributory cause of the death in one subject (66). Pertinent to the problem of digitalis toxicity and the diagnostic challenge it has posed, there is the rare instance of neurotic self-medication for the mimicry of heart disease (67). In the category of accidental poisonings, a curiosity is the Yugoslav farmer who had indigestion and nearly died from taking capsules of digitalis medication prescribed for his horse, thinking they were bicarbonate of soda (68).

The instruction for prescribing digitalis given by Withering in his 1785 monograph, suggesting that it be continued until either a favorable diuresis or toxicity occurred, is often quoted. I offer a better quotation from a letter (69) he wrote in 1786 to Hall Jackson in America:

"Digitalis under a judicious management is one of the mildest medicines . . . as well as one of the most efficacious. It is, I believe, *never* necessary to create nausea or any other disturbance in the system."

Digitalis Toxicity as a Cause of Temporary Insanity

Another category in which digitalis toxicity might concern a court of law is as a defense in homicide, the accused being alleged to have committed the crime while suffering a toxic psychosis from the drug. Arthur Hirschfelder, the first cardiologist of Johns Hopkins Medical School, later Professor of Pharmacology at the University of Minnesota, apparently believed that digitalis could have been responsible for such an altered state of intellect and mood in a person that he or she could not be held responsible for a homicidal act (70). I have been unable to find the details of the trial. Reference to such a case is also made in the third edition of Hirschfelder's *Textbook on the Heart* (1918) but not in the second edition. Possibly this could be the same case that he mentioned in his letter to Macht and Bloom. Although initially skeptical of the validity of Hirschfelder's opinion, my skepticism did not exclude the possibility of admitting that digitalis could have been an instrument in the murder acting in the body of the assailant, and that the death of the victim was then attributable to misuse of digitalis. Allowing such a tenuous train of logic, the murderer's physician could become responsible for the crime. After studying the case reports of digitalis delirium and digitalis depression, including that reported by H.L. Smith of the Mayo Clinic (71) and the reports of the laboratory investigations of William Dearing (72), showing histologic changes in the brains of cats given toxic doses of digitalis and the slowness with which digoxin is lost from the brain (73), one cannot summarily dismiss the contention that transient insanity might be induced by digitalis.

In another example, a 68 year old man was admitted for evaluation of repetitive formed visual hallucination ". . .

intermittent and sudden appearance of butterflies, bird-houses and Confederate soldiers, all in appropriate size and color . . . some born objects had an unusual yellow hue. . . ." A report by Volpe and Soave (74) suggests that such a condition could also instigate violence.

The students of Arlie Barnes of the Mayo Clinic will also remember his label of "digitalis blues" for some depressed cardiac patients. That "digitalis delirium" is not a disease of the past, is evidenced by two cases reported quite recently (1978) in the *American Journal of Psychiatry* (75).

Summary

In preparing this essay, my two original motivations were to entertain myself and possibly others through simple storytelling *and*, by subterfuge, to advance graduate education using the stories as parables to introduce relatively new knowledge of drug kinetics. The study has reminded me of involved ethical and moral questions of our times. It was only after mulling over my first draft of the essay that I was struck by the fact that the works of fiction that I quoted had strong morality inferences; the authors, presumably desirous of having both a happy ending and appropriate retribution of the guilty, avoided bringing the crimes to trial in the (English) law courts. The implication is baldly made in Sayers' story that in the public court, the private lives of innocent, but possibly indiscreet, people would be exposed on the witness stand and that they would be irretrievably hurt without benefit to society. Even though clearly involved in the quest for truth and justice, novelist Sayers has Lord Wimsey say, "What the deuce did it matter if old Fentiman was pushed painlessly off a bit before his time? He was indecently ancient." Also, after the guilty party had written his confession, absolving others of the crime, and had conveniently committed suicide, the conversation in the club includes the comment: "Just as well it never came to trial; with juries you never know." In fiction, the solutions given to problems were anathematous to one's ideals. By coincidence, in the real life situation of the insurance racket trials outlined here, a great loss occurred from the suicide of an innocent person; one that I think was a numbing loss to society. In contrast to fiction, if a Peter Wimsey was commenting on the events in the insurance racket, he might have quipped: "The wrong persons committed suicide."

Another new twist in the complex problem of crime, digitalis and suicide has recently surfaced in the popular press. A banker convicted of fraud took what would be predictably a fatal dose of a digitalis preparation and, from the report, his life apparently was saved (so that he could appear for sentencing) by the new method of giving antibody fragments (76).

I shall pose another question: If postmortem examinations are still to be requested or required, toxicology screens including digoxin serum levels are done and a value for

blood from various parts of the body and the vitreous humor are reported three or more times greater than any expected therapeutic level, what does the Medical Examiner do? If the technique is impeccable and the interpretation of results stands up on challenge, then the patient was poisoned, through accident, homicidal or suicidal intent or inept prescribing. The immediate cause of death on the death certificate should be "digoxin poisoning." This is disquieting to contemplate because death certificates are public documents. On the basis of the circumstances, could the Medical Examiner ethically moderate his actions without concealing the fact, making a moral judgment and listing it as a possible contributing cause?

In conclusion: In its interfaces with the law courts, the evidence is all persuasive that digitalis is a powerful poison. Despite this, its continued use in patients with heart disease attests to its therapeutic usefulness. To borrow language from Mary Webb's novel, digitalis is both the precious bane and the deathly bane. The word "bane" has varied definitions in the dictionary—a poison or a flaw, or a poisoner or person with a flaw. The physician should be ever vigilant of the double role the drug may play and increase his suspicion of digitalis toxicity related to inappropriate dosage, whether through accident, ignorance of pharmacodynamics or murderous intent.

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