Digitalis Delirium
A Report on Three Cases

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ALMOST a century ago Duroziez1 first used delire digitalique to describe mental disturbances that he attributed to digitalis intoxication. Like myxedematous madness, the term digitalis delirium is an alliterative and euphonious "burr that sticks in the memory." The word delirium, literally a wandering from the furrow (L. lira), has become more specific than madness and is properly applied to an agitated form of acute confusional psychosis. Duroziez did not define his use of the term, and King,2,3 in his review of digitalis delirium in 1950, included degrees of mental disturbance varying from calm disorientation to violent psychosis. As the term is euphonious and memorable, its continued use in this wider sense seems justifiable.

Despite its recognition 90 years ago and King's recent thorough review of the subject, and despite the fact that "dementia produced by digitalis" has been upheld in the law courts in defense of homicide,4 the subject has not received much attention. Although reports of intoxication with digitalis preparations have been numerous, instances of toxic psychosis have been few; furthermore, in some of these, the drug has not been clearly incriminated. Recently 3 carefully studied cases of digitalis delirium were seen at the Mercy Hospital.

Case Reports

Case 1

J.M.C., a white man aged 83, had been in excellent health until 2 weeks prior to his admission, when he developed a head cold, chest infection, and subsequently congestive heart failure of moderate degree. There was no history from the patient or his relatives of alcoholism or mental illness. He presented physical signs of aortic insufficiency and examination of his central nervous system was negative. The serologic tests for syphilis were positive. He responded rapidly to therapy with bed rest, low-sodium diet, antibiotics, gitalin, and diuretics. His permission was obtained to keep him in hospital and to include him in a study of digitalis intoxication.

All therapy was withheld except for a 2-Gm. sodium diet and a digitalis preparation. Starting with gitalin, he received 15 mg. over 7½ days. At this point drowsiness, anorexia, nausea, and vomiting appeared and the drug was stopped. His symptoms improved in 48 hours and, after 6 days rest, digoxin was given. He received 2.5 mg. over 36 hours, but then he developed anorexia, nausea, and vomiting. An electrocardiogram showed paroxysmal atrial tachycardia with varying atrioventricular block. Within 24 hours of stopping of digoxin his symptoms had improved and his heart rate was 80 per minute. The electrocardiogram indicated restoration of sinus rhythm. After a 4-day rest period, digitoxin was administered in dosage of 1 mg. in the first 24 hours and then 0.1 mg. at 8-hour intervals. After a total dose of 3.1 mg. over 8 days he became disoriented and wildly excited, stated that he was in a brewery, and repeatedly demanded beer. Restraints and sedation with paraldehyde were necessary, but after 36 hours he became his usual self. There was no alteration in his pulse rate to suggest an arrhythmia and an electrocardiogram taken soon after he had recovered showed sinus rhythm and first degree atrioventricular block. He had apparently complained of slight nausea to a nurse before his last dose, but this had not been reported to the medical staff. Throughout the trial there was no diuresis and no electrolyte abnormality.

He was discharged and followed as an outpatient on digoxin 0.25 mg. twice daily for 9 months. During this time his clinical picture was one of fluctuating congestive heart failure. Eventually he was readmitted with edema and other evidence of congestive heart failure associated with blurring of vision and white spots in his visual fields. He received treatment with a low-sodium diet and diuretics; digitalis was withheld as digoxin intoxication was suspected. After 5 days, im-
proven; there had been no clinical evidence of toxic digitalis poisoning. He was given 0.5 mg. digitoxin in 1 dose and 0.1 mg. 8 hourly thereafter. After 11 days he had received 3.5 mg., when he developed anorexia, nausea, and vomiting. First degree atrioventricular block was noted by electrocardiogram, but no change in electrolytes had occurred. Two to 3 days after stopping the drug, the patient's symptoms disappeared.

Comment. In this case, delirium occurred as the earliest convincing manifestation of intoxication with digitoxin. Previously other digitalis preparations pushed to early toxicity had not produced mental symptoms and subsequently digitoxin itself did not reproduce it.

Case 2

A.R., a Negro aged 57, had been under treatment for 15 years with salt restriction, digitalis preparations, and diuretics for congestive heart failure. His cardiac lesion was aortic insufficiency and he had a positive serologic test for syphilis. He had no signs of neurologic involvement and, although of a rather gloomy nature, the patient had been found cooperative and friendly at out-patient attendance. No history of mental disorder or alcoholism was obtained from him or his friends (he had no relatives). As an out-patient he was being maintained on 1 mg. of digoxin daily, but during the 14 days prior to admission, his condition deteriorated and on admission there was evidence of severe congestive heart failure. He was treated with oxygen, venesection, salt restriction, digoxin (1 mg. daily), meraptomerin and chlorothiazide. He responded rapidly and after 14 days he was free of edema, his liver had decreased in size, and his lung fields were clear.

All therapy other than a 2-Gm. sodium diet was withheld and then digoxin 0.5 mg. 3 times daily was started. After 8 days he developed anorexia, palpitation, dizziness, and blurring of vision, and his pulse, previously regular, developed occasional dropped beats. An electrocardiogram showed sinus rhythm with occasional ventricular premature beats and first degree atrioventricular block. Through a misunderstanding he was given an additional 1.5 mg. of digoxin during the following 24 hours and thereafter he became restless and irritable. He insisted on being isolated with the curtains drawn around his bed as he claimed the other ward patients were making a fool of him. The following day he developed overt paranoia; he complained that the nurses were after him with knives and that the patient in the next bed was about to attack him with his crutch; he would walk warily over his shoulder for an assault from the rear and, suspicious of poisoning, he refused food and drugs.

Restraints became necessary at night when he refused to stay in bed. In conversation he was confused about his home circumstances and in his actions he was hesitant and indecisive. Such behavior patterns continued in varying degree for 14 days; after 9 days he started eating, but as late as the fourteenth day he barracaded himself in a side room to which he had been moved. On this occasion he required restraint and heavy sedation. His pulse became regular 4 days after digoxin was stopped and an electrocardiogram indicated sinus rhythm with no premature beats. After 14 days, improvement set in and at the end of 3 weeks his behavior and train of thought had been normal for 5 days. During the third week after digoxin had been stopped, evidence of heart failure reappeared. This responded to meraptomerin and chlorothiazide. Throughout the period of psychosis, no abnormality in his serum electrolytes occurred and his treatment included sedatives, small doses of insulin to stimulate appetite, meraptomerin, and chlorothiazide.

After discharge he was followed as an out-patient and, when congestive failure recurred, control was at first achieved by diuretics, but after 6 weeks digoxin was restarted in doses of 0.25 mg. twice daily. There was no further occurrence of toxicity or mental disorder during the following 4 months. Finally, when he failed to report for review, it was discovered that he had died suddenly at home.

Comment. The alarming feature of this case was the duration of the delirium which occurred with 1.5 mg. over the minimal intoxicating dose. Manifestations of intoxication with the short-acting glycosides usually disappear within 48 hours, but exceptions do occur and are mentioned later. It is of further interest that delirium persisted long after other signs of intoxication had disappeared.

Case 3

S.A., a white man aged 65, was admitted to the Mercy Hospital with a history of recurrent breathlessness on exertion, palpitation, and ankle swelling of 5 years' duration. He received digitoxin, gitalin, and occasional diuretics. He gave no history of mental illness, but admitted to being a heavy drinker prior to the last 3 or 4 years. On admission he showed obesity, cyanosis, distention of the neck veins, marked pitting edema, and fever of 101 F. The patient was alert, cooperative, and well oriented. The blood pressure was 166/82 mm. Hg, the pulse was 160 per minute and completely irregular, and the heart was enlarged to the left. Crepitations were audible at the lung bases. The liver was palpable 6 cm. below the costal margin and was firm and slightly tender. Examination of
the central nervous system was normal. His prostate was enlarged and the urine contained + albumin, but no cells or casts. The other laboratory data are shown in table 1. The electrocardiogram showed atrial fibrillation and nonspecific ST-T changes. An x-ray of the chest showed considerable left ventricular enlargement and passive congestion of the lung fields.

A diagnosis was made of coronary artery disease with heart failure precipitated by an infection of undetermined site. It was also thought probable that the patient had cirrhosis of the liver and prostatic hypertrophy. Recent myocardial infarction was considered unlikely. The patient was treated with a low-sodium diet, mercaptopurine, chlorothiazide, and penicillin. After initial digitalization with lanatoside-C, 1.2 mg., followed by gitalin, 7 mg. over 3 days, the patient was maintained on gitalin 0.5 mg. daily. A diuresis occurred with improvement in the signs of failure including loss of edema and loss of 20 pounds in weight, but a retinmittent pyrexia up to 101 F. continued.

On the eighth hospital day he developed a chill and a temperature of 106 F. was recorded. His urinary output fell to 80 ml. in 24 hours; then a diuresis followed, but on the sixteenth day the output again decreased to a daily total of between 300 and 900 ml. A urinary tract infection, complicated by bacteremia, peripheral circulatory failure and a low-grade pyrexia, was responsible.

The patient became somewhat lethargic with short spells of confusion during the 8 days following his hyperpyrexia and, parallel with the decline in his urinary output, he became more persistently confused and disoriented with periods of aggressive behavior. No improvement was noted upon use of an oxygen tent. Later he developed visual hallucinations. His appetite, poor since admission, became worse and vomiting started on the seventeenth day gradually increasing in frequency over the next 5 days. On the twenty-first day he was incontinent of urine, hallucinating, and vomiting frequently. Intravenous fluids were commenced. On the twenty-second day a bigeminal pulse was noted and the electrocardiogram showed ventricular bigeminy. This focused attention to gitalin which had been given continually since admission; when it was withheld, improvement occurred dramatically within 48 hours. The patient became alert and cooperative, his appetite returned, and nausea, vomiting, and bigeminal rhythm were no longer noted. No further disturbance of mental behavior occurred. His cardiac status remained fairly well compensated on digoxin 0.25 mg. daily, which was instituted 1 week after omission of gitalin.

Comment. In this case, delirium occurred in the presence of other possible etiologic agents besides digitalis. Severe infection, hepatic failure, uremia secondary to renal failure, and electrolyte imbalance could have been responsible. As the delirium became worse, however, tests of hepatic function improved and the blood urea fell; moreover, little or no increase in his urinary output coincided with the dramatic improvement in his symptoms. The evidences of severe infection developed and disappeared before his delirium reached its peak, and the low-grade pyrexia, which developed later, persisted after improvement had occurred. Electrolyte imbalance was possibly present but, considering the progression, the associated gastrointestinal disturbances and the bigeminy, the weight of evidence appears to inerminate the drug.
DISCUSSION

Following Duroziez' initial report, the role of digitalis in the production of delirium became the subject of controversy, but in 1950 King presented convincing evidence that digitalis itself can indeed induce it. Since this time, although reports of digitalis intoxication have been numerous, little mention has been made of delirium. One unusual case was recently described in which intoxication with digitalis leaf led to prolonged anorexia, nausea, and vomiting which in turn produced vitamin B1 deficiency; delirium was part of the picture of the resulting Wernicke's encephalopathy. There has been mention of acute psychosis and disorientation in other reports of digitalis intoxication, but details of their occurrence are not given and the possible role of other factors is not clearly defined.

Our cases illustrate several clinical points previously noted by other observers, namely, the frequent association of the delirium with aortic valve lesions, the commoner occurrence in older age groups, variation in the type of psychosis with the personality of the patient, its occasional occurrence as the earliest and possibly the only sign of intoxication and its occurrence in the absence of electrolyte changes, sedatives, Cheyne-Stokes respiration, and anoxia. Case 3 illustrates a point made by Duroziez, that when delirium complicates an already complex syndrome, the drug is not suspected. But for the appearance of bigeminy in this patient, the outcome would almost certainly have been fatal.

There are other features of the present series that are unusual and have not previously received emphasis. Case 1 is of interest because the pattern of previous and subsequent intoxications in the same patient were observed and compared. Delirium characterized only the intoxication here reported in detail. This striking variation in the manifestations of toxicity could not be accounted for by variation in the state of heart failure or electrolyte balance, the degree or rate of intoxication, or the preparation used. This patient was intoxicated on 2 previous occasions with-

in 3 weeks of his toxic delirium and subsequently after an interval of 9 months, and on none of these occasions was delirium produced. On the other hand, King was able to reproduce the delirium state after a 2- to 3-day period of mental clarity in one case, and in another delirium reappeared 2 to 3 weeks after resumption of the digitalis preparation on a lower dosage schedule.

Rapidly excreted glycosides owe their reputation partly to the speed with which toxicity disappears; case 2, therefore, is of particular interest, since the psychotic state outlasted the other manifestations of digoxin intoxication and continued for at least 2 weeks. A similar persistence of arrhythmias from digoxin and of blindness from digoxin and lanatoside-C has been reported. Finally, neither digoxin nor gitalin seems to have been clearly incriminated as an agent of delirium in previous reports.

SUMMARY

The use and suitability of the term digitalis delirium are briefly discussed. Attention is drawn to the paucity of detailed reports on this important manifestation of digitalis poisoning.

Three cases of digitalis delirium resulting from toxicity with 3 different preparations—gitalin, digoxin, and digitoxin—are presented. The first case demonstrates how the signs of early intoxication in a single patient may vary with different preparations and indeed with the same glycoside on separate occasions. The second case provides an alarming example of delirium which, although provoked by a short-acting glycoside, nevertheless lasted longer than 2 weeks. The third illustrates how easily the diagnosis of digitalis intoxication can go unrecognized when superimposed on a complex clinical picture.

The clinical features of these cases are discussed in the light of previous reports.

SUMMARIO IN INTERLINGUA

Le uso e le proprietate del termino "delirio per digitalis" es discutite brevemente. Es signalate le paucitate de reportos in detalia
DIGITALIS DELIRIUM

relative a iste importante manifestation de invenenamento per digitalis.

Es presentate tres casos de delirio per digitalis, resultante ab toxicitate inducite per tres diferente preparatos, i.e. gitalina, digoxina, e digitoxina. Le prime caso illustra como le signos de intoxication precoce in un sol patiente pote variar con diferente preparatos e, de facto, con le mesme glycosido administrate a diferente tempores. Le secunde caso representa un alarmante exemplo de delirio que durava plus que duo septimanas ben que illo habeva essite provoke per un glycosido a action non prolongate. Le tertiie caso demonstra quanto facilmente le diagnose de intoxication per digitalis pote escappar al detection quando iste condition se superimpone a un complexe tableau clinic.

Le aspectos clinic de iste casos es discutite in le lumine de previe reportos.

REFERENCES

These things being prov'd, I think it will appear that it doth go round, is returned, thrust forward, and comes back from the heart into the extremities, and from thence into the heart again, and so makes as it were a circular motion.—WILLIAM HARVEY. De Motu Cordis, 1628.
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