OBSERVATIONS ON DIGITALIS INTOXICATION— A PLEA

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I will not give a fatal draught to anyone if I am asked, nor will I suggest any such thing.

From the Hippocratic Oath.

Seldom a day elapses that we do not encounter either minor or major evidence of digitalis over-dosage. Such experience has led a member of the house staff of the Peter Bent Brigham Hospital to remark that nowadays lanatoside is replacing homicide as a leading cause of death.

Bernard Lown, 1957.

In the course of routine reporting on electrocardiograms recorded in a hospital group increasing apprehension was felt about the high incidence of tracings suggesting digitalis intoxication. Two thousand consecutive ECGs, recorded within about six months in 1962 and sent for reporting, were therefore analysed and, as briefly mentioned (Schott, 1964), 597 tracings referred to 348 patients who had digitalis within the fortnight preceding at least one ECG. On a preliminary study, ECGs with arrhythmias highly suggestive of overdigitalization were found in at least 10% of the 348 patients. The present paper reports the more detailed analysis of these records.

The fact that this study was made in a Group electrocardiographic department had the advantage that the recording, carried out by trained technicians, and the reporting, done by one observer, were uniform. Furthermore, the patients whose ECGs were sent represented an unselected cross-section of in- and out-patients, mostly medical, but also including surgical and obstetric cases. They were under the care of different consultants and looked after by various registrars and house physicians, and outside by different general practitioners, with considerable variations in experience in digitalis dosage. The present observations may therefore well be acceptable as an example of conditions prevailing in certain non-teaching hospitals and general practices. This set-up had the disadvantage that only a small minority of the patients was under the care of the reporting physician, who was given the essential clinical data on the request form (reproduced in Schott and Snell, 1963), but was

unable in the majority of cases to correlate the ECGs with all the clinical features or to follow up further developments by personal observation of the patients. The system also accounts for the fact that in some cases the number of ECGs is inadequate as further tracings, which would have been desirable, were not requested.

Results

From Table 1 it will be seen that digitalis over-dosage was suspected on ECG grounds in 42 of the 348 patients, an incidence of 12%. In 2 cases the part played by digitalis was considered doubtful; if these are disregarded (Nos. 37 and 42), the incidence would be 11.5%.

There were 19 males and 23 females. The age distribution is shown in Fig. 1, from which it is seen that the majority of patients were elderly: 33 (78%) were over 61 (16 males (84%) and 17 females (74%)), and 22 (52%) were over 71 (12 males (63%) and 8 females (34%)).

A diagnosis of suspected digitalis intoxication was based on the following arrhythmias:

Ventricular ectopic arrhythmias in the presence of a basic sinus rhythm ...	7 cases
Atrial fibrillation with high-grade partial or complete A-V block or A-V tachycardia, without extrasystoles ...	8 cases
Atrial fibrillation with extrasystoles and high-grade partial or complete A-V block ...	8 cases
Atrial fibrillation with extrasystoles without high-grade partial or complete A-V block ...	6 cases
Paroxysmal atrial tachycardia with A-V block ...	4 cases
Mainly atrial arrhythmias other than paroxysmal atrial tachycardia with A-V block ...	4 cases
Complex arrhythmias (3 with A-V dissociation) ...	4 cases
Second degree A-V block (doubtful regarding digitalis toxicity) ...	1 case

All these arrhythmias have been established as manifestations of digitalis toxicity. It has been stated by several authors that digitalis can cause practically every known arrhythmia (Diefenbach and Meneely, 1948/9; Lown and Levine, 1954; Pick, 1957; Spang, 1957; Fried

FIG. 1.—Percentage age distribution of the 42 patients.

berg and Donoso, 1960; Lown, Wyatt and Levine, 1960; Schwiegk and Jahrmärker, 1960; Schoen and Schröder, 1962). While the incidence of particular arrhythmias as given in various publications differs, an ever increasing number of them has been established as frequently due to, or precipitated by, the drug. Regarding the recent past, this holds good particularly for atrial (Lown and Levine, 1954, 1958; Lown and others, 1960; Oram, Resnekov and Davies, 1960; Harris, Julian and Oliver, 1960; Burton, 1962; Hunziker, Schaub and Holzmann, 1964) and A-V (Pick and Dominguez, 1957) tachycardias, and A-V dissociation (Friedberg and others, 1960; Schott, 1960; Soffer, 1961; Jacobs, Donoso and Friedberg, 1961). Obviously, the converse is also true: practically all abnormal rhythms seen in overdigitalized patients may occur without digitalis or any other drug. However, if such arrhythmias occur in the course of digitalis treatment it is appropriate to consider them as possible, and in many cases probable, manifestations of digitalis toxicity. Those recorded in the present series, with the exception of

Case 42 (second degree A-V block), are known to occur almost exclusively in diseased hearts, digitalis being a precipitating rather than the sole causative, though therefore no less dangerous a factor. In the series under review, 13 patients (31%) died within a short period after the last ECG, at a time when the drug must still have been active, *viz.* 7 of 19 males (37%) and 6 of 23 females (26%). (Nos. *1, 2, 5, 9, 16, 18, 26, 27, 28, 31, 33, 38, 42*). In 9 (21%) death was considered to have been directly due to, or at least accelerated by, digitalis, (numbers of these cases in *italics*), and in one further case (No. 28) this seemed probable.

Discussion

The incidence of about 12% found in this series, while disturbingly high, compares favourably with that reported by others as 15% (Giuffra and Tseng, 1952) and approx. 20% (Rodensky and Wasserman, 1961). There seems little doubt that it is on the increase, paradoxically since the introduction of pure

TABLE 1
CLINICAL DETAILS OF 42 PATIENTS SUSPECTED OF DIGITALIS OVERDOSAGE
AES: Atrial extrasystoles. A.F.: Atrial fibrillation. AR: Atrial rate. C.C.F.: Congestive cardiac failure.
ES: Extrasystoles. VES: Ventricular extrasystoles. VR: Ventricular rate.

Serial No. Sex Age No.	Clinical Diagnosis	Features of Arrhythmia	Dosage	Clinically suspected	Remarks
<i>Ventricular ectopic arrhythmias; basic rhythm sinus rhythm</i>					
F. 1. 30211 67,	Anterior infarct	Multiform VES, at times bigeminy	On adm. was on dig. fol. gr. $\frac{1}{2}$ b.d. + neonaclex. Was put on gr. $\frac{1}{2}$ o.d. despite clinically? coupling. 3 days later dig. stopped in view of ECG. Died 4 days later "in spite of emergency digoxin and hydrocortisone."	Yes, because of coupling on admission	Should not have been put on digitalis without ascertaining previous medication. "Emergency digoxin" suggests unawareness of digitalis intoxication manifesting itself as deterioration of cardiac condition. Overdigitalization assumed to have precipitated death.
M. 2. 30316 61,	Aortic incompetence and stenosis. Angina pectoris. C.C.F.	VES, bigeminy	Digoxin 0.25 mg. b.d. mersalyl, hydrosaluric K. Bigeminy after 10 days. Dig. stopped for 48 hours, resumed o.d., also hydrosaluric K 3 days a week. After 10 days sinus tachycardia of 100.	Yes, because of nausea and coupling.	Overdigitalization obvious since bigeminy appeared only after digitalization. Digitalis toxicity increased by diuretics. Drug stopped for far too short a time. Patient died weeks after admission from pulmonary embolism.
M. 3. 30523 69,	Acute exacerbation of chronic bronchitis	Multiform VES in series. Fig. 2a.	Digoxin 1.25 mg. in 18 hours, then stopped. 5 days later only single uniform VES after every 3 or more sinus beats.	No	Stated on request form that patient never had digitalis. Questioning revealed the large dose.
M. 4. 30142 77,	Ischaemic heart disease. Old infarcts. C.C.F.	VES, bigeminy	On adm. Digoxin 0.5 mg. six-hourly x 3, then 0.25 mg. t.d.s. for 2 days; 3.0 mg. in 3 days (minimum).	No	Dose too high, particularly in view of patient's age.
M. 5. 30819 75,	C.C.F. Broncho-pneumonia. Anterior infarct.	Ectopic ventricular tachycardia. Then A.F. with ES + + + and periods of bigeminy in 2 ECGs.	1.5 mg. Digoxin i.m. in 24 hours (i.e. 0.5 mg. stat, then six-hourly). Then stopped. Procaine amide oral 500 mg., repeated after 3 hours, + 250 mg. after 6 hours, then 250 mg. six-hourly for 5 days, then b.d. for 1 week, then stopped. Digoxin restarted after 4 days, i.e. 0.25 mg. t.d.s. for 3 days, b.d. for next 9 days, o.d. following day. Also hydrosaluric, mersalyl, potassium supplement.	No	Overdigitalization both initially and subsequently. Digitalis toxicity increased by diuretics, procaine amide and infarct. Died 8 days after last dose of digoxin. Digitalis assumed to have precipitated death.
M. 6. 28797 77,	Attacks of nocturnal dyspnoea 6 months. Old post. infarcts.	10 days after admission: Bigeminy in 3 and part of a fourth lead. 1 week before only occasional VES.	On adm.: Digoxin 0.25 mg. t.d.s. for 2 days, then b.d. 7 days. Stopped because of coupling. 5 days later 'pulse regular', digoxin restarted 0.25 mg. b.d. 1 week later 'ES', digoxin stopped 2 days, then restarted; 2 days later coupling, digoxin reduced to $\frac{1}{2}$ tablet b.d. Discharged on 0.25 o.d.	Yes	No information was obtained about digitalis medication before admission. ECG development typical of overdigitalization. Time of stopping too short. Dose on discharge likely to be too high in view of observation in hospital.
M. 7. 30738 78,	Chronic bronchitis, emphysema. Hysterical over-breathing. ? anterior infarct.	Numerous multiform VES, at times two in succession. Also a few AES.	On adm.: Digoxin 0.5 mg. stat, then 0.25 mg. six-hourly till pulse below 75. No record of total amount. Stopped 6 days after admission. Discharged fortnight later without digitalis.	No	Digitalis given without indication. Wrong method to determine digitalis dose.
<i>Atrial fibrillation with high-degree or complete A-V block or A-V tachycardia without extrasystoles</i>					
F. 8. 30579 57,	Mitral stenosis and incompetence. Diabetes.	Complete A-V block, ventricular rate 38.	Had been on digoxin 0.25 mg. t.d.s. for unspecified duration, also on diuretics. Continued on digoxin 0.25 mg. t.d.s.	No	Warning contained in ECG disregarded.

Serial No. Sex Age	Clinical Diagnosis	Features of Arrhythmia	Dosage	Clinically suspected	Remarks
<i>Atrial fibrillation with high-degree or complete A-V block or A-V tachycardia without extrasystoles</i>					
F. 9. 73, 30221	Ischæmic heart disease. C.C.F.	A-V tachycardia of 150, later A.F. Transitional stage of sinus rhythm with many multiform AES.	No record about digitalis before admission. On adm. 0.5 mg. i.m. stat, then 0.25 mg. t.d.s., after 3 days b.d., + mersalyl + hydrosaluric K. A.F. recorded 1 week after stopping digoxin.	No	A-V tachycardia due to overdigitalization, digitalis toxicity increased by concurrent diuretics. A.F. possibly also due to digitalis intoxication. Digitalization started without prior ECG assessment of rhythm and continued despite ECG. Died 11 days after digoxin was stopped and 5 days after A.F. was recorded. Death assumed to have been precipitated by digitalis.
F. 10. 62, 29830	Hypertension 270/130. C.C.F.	Complete A-V block, VR 57, later high-degree but no longer complete A-V block.	Had been on digoxin 0.25 mg. o.d. for 6 months. Changed to fol. gr. $\frac{1}{2}$ o.d. six days after admission, and to gr. $\frac{1}{2}$ on alternate days a fortnight after adm. in view of second ECG still showing signs of overdigitalization.	No	Inadequate supervision outside. Should not have been put on digitalis without prior assessment of rhythm by ECG.
M. 11. 81, 30633	Mitral incompetence. C.C.F.	Complete A-V block. VR. 46-50.	On "long term" digoxin b.d. (probably 0.25 mg.) and navidrex K from G.P. Digoxin reduced to o.d. Navidrex K replaced by mersalyl. Also aminophylline.	No	Inadequate supervision outside. Digitalis medication should not have been continued without prior ECG, assessment of rhythm, particularly in view of low rate.
F. 12. 74, 30675	Acute exacerbation of chronic bronchitis. ? Left lower lobe broncho pneumonia.	Complete A-V block, VR 44.	G.P.'s letter: on dig. fol. gr. 1 b.d. and 2 tablets esidrex K, no duration indicated. On adm. digoxin 0.25 mg. t.d.s. No record whether or when digoxin stopped in view of ECG. About 1 month after ECG indicating overdigitalization put on dig. fol. gr. $\frac{1}{2}$ t.d.s., discharged on that dose.	No	No indication for digitalis. Although patient very ill on admission, retching, vomiting and belching, was put on digoxin 0.25 mg. t.d.s. with a diagnosis of gastritis and digitalis intoxication was not considered.
F. 13. 70, 30705	Mitral and tricuspid incompetence. Gross C.C.F. Ascites.	In parts A-V block, not quite complete. Moderate A-V tachycardia, VR 80-90.	On dig. fol. gr. $\frac{1}{2}$ b.d. "for some time" by G.P. Stopped on adm. because of slow pulse. Serum K 3.4 mEq/l. Digitalis re-instituted about 2 months later. After another 4 months when on digitalis and hydrosaluric ECG showed the same condition.	Yes	Inadequate supervision outside. Dose likely to be too high for maintenance, particularly in view of patient's age, and possibly of increasing severity of condition.
F. 14. 74, 30791	Ischæmic heart disease. ? mitral valvular disease.	A-V tachycardia of 125.	No record of digitalis before admission. On adm. digoxin 0.5 mg. stat, then six-hourly 0.25 mg. till apex rate below 80, then 0.25 mg. b.d. Total dose not ascertainable.	No	Wrong method to determine dose. Dose too large for patient of her age.
M. 15. 59, 30474	Mitral incompetence. C.C.F.	Complete A-V block. VR 55. In Lead aVL one cycle twice the length of preceding and following ones.	On adm. known to have been on "digitalis" tablets 1 b.d. + diuretics. On adm. put on digoxin 0.5 mg. b.d. for the first 6 days; dose not stated for the following 4 days, then on 0.25 mg. b.d. for 1 week, and o.d. for the following 6 days.	No	Should not have been put on digitalis on admission without prior ECG assessment of cardiac condition, least of all on such a high dose.
<i>Atrial fibrillation with extrasystoles and with high-degree partial or complete A-V block</i>					
F. 16. 60, 28508	Cor pulmonale, heart failure.	Extrasystoles as bigeminal and trigeminal rhythm.	Had been on digoxin 0.25 mg. b.d. for 2 months before admission. No digitalis while in hospital. Further ECG 9 days after admission showed sinus rhythm.	Yes	Inadequate supervision outside. Died 10 days after admission. P.M.: Subacute cor pulmonale, organising pulmonary thrombi. Overdigitalization assumed to have precipitated death.

Serial No. Sex Age No.	Clinical Diagnosis	Features of Arrhythmia	Dosage	Clinically suspected	Remarks
<i>Atrial fibrillation with extrasystoles and with high-degree partial or complete A-V block</i>					
17. M. 84, 28853	C.C.F. Chronic bronchitis and em- physema.	On adm. multiform ES. Abolished by procaine amide. 17 days later digoxin re- started, 0.25 mg. b.d. ECG 5 days later: coupled ES and ventricular automatic beats and complete A-V block, VR 88.	Probably on digoxin 0.25 mg. o.d. since last discharge, i.e. at least 6 months. Dig- oxin 0.25 mg. b.d. on adm., stopped 12 days after adm. in view of first ECG. Re- started 0.25 mg. b.d. 5 days later; reduced to o.d. in view of second ECG and discharged on that dose. Had also 'intensive diuretics + supplementary K'.	?	Should not have been put on digitalis on admission with- out prior ECG assessment. Subsequently digitalis was started too soon. Doses too high particularly in view of patient's age. Toxicity en- hanced by diuretics.
18. M. 71, 30701	Mitral incompetence. C.C.F.	Numerous ES. VR variable, with long intervals between some beats, i.e. high- grade partial block at times. Fig. 4a.	No record of previous treat- ment. On adm. digoxin 0.5 mg. stat., repeated once same day, then 0.25 q.i.d. till pulse rate below 80. No record of total dose given.	No	Should not have been put on digitalis without prior ECG assessment of cardiac condi- tion, particularly as pulse admission was below according to chart. Wrong method to determine digitalis dose. Pat. appeared to do well but collapsed and died suddenly 5 days after ECG. No P.M. Death assumed to have been due to, or pre- cipitated by, digoxin causing ventricular fibrillation.
19 M. 73, 30040	Aortic sclerosis, chronic bronchitis, L.L.L. pneumonia, B.P. about 250/105.	ES, at times bige- miny; periods of ectopic ventricular rhythm.	Before admission on tab. dig. b.d., no record for how long. Continued as digoxin, 0.25 mg. b.d. Stopped in view of ECG, restarted after 3 days with half the dose, i.e. once daily. Discharged on that dose. No further ECG.	No	Inadequate supervision out- side. Should not have been put on digitalis without prior ECG assessment of rhythm. Drug stopped for too short a time. Further ECG should have been requested to ter- minate maintenance dose. Particularly in view of doubtful whether any indication for digitalis.
20. M. 72, 30703	Fresh myocardial infarct. R and L ventricular failure.	ES, in one place 3 in succession.	On adm. digoxin 0.5 mg. + 0.25 6 hours later. 0.25 mg. q.i.d. next day; b.d. following day; i.e. 2.25 mg. within 36 hours.	No	Dose too high in view of and cardiac condition.
21. F. 45, 30082	Rheumatic mitral stenosis and incom- petence, aortic stenosis, tricuspid in- competence.	Bigeminy due to ES.	Seen one month before ad- mission as O.P. with bige- miny. No record of dosage at that time. On adm. had not had digitalis for at least a fortnight and ECG showed only 1 ES in whole record. Then put on digoxin 0.25 o.d. which reduced VR to 50-60. Comment by other cardiologist consulted about valvotomy: "Large myocar- dial factor, watch digitalis."	No	A patient particularly sensi- tive to digitalis. Inadequate supervision outside.
22. F. 63, 28954	Mitral stenosis and incompetence.	Bigeminy due to ES. Later complete A-V block, VR 75. Fig. 5.	No record about digitalis before admission. On adm. digoxin 0.5 mg. twice on first day, 0.25 t.d.s. follow- ing day, i.e. 1.75 mg. in 48 hours. Stopped because of 'coupling'. On third day 0.25 o.d., then b.d. for following 6 days.	Yes, because of coupling.	Should not have been put on digitalis without prior ECG assessment of rhythm. In- itial digitalis dose too high in view of possible previous digitalis medication. Drug stopped for too short a time. Case illustrates two different arrhythmias in same patient caused by digitalis intoxica- tion.
23. F. 66, 28456	Hypertension, ar- teriosclerotic heart disease, mental in- stability.	At times bigeminy due to ES, at other times complete A-V block.	Had been on "digitalis" be- fore admission, but dose could not be ascertained. ECG on adm. see preceding column. After 1 week in hospital without digitalis no signs of overdigitalization. Discharged on digoxin 0.25 mg. o.d. Three months later seen as O.P., VR very much lower, suggestive of impend- ing overdigitalization.	—	The patient's mental instabil- ity made it impossible to ascertain how much digitalis she was taking. She seemed to take the drug quite erra- tically. Significant that when under observation in hospital and no digitalis had been taken for 1 week signs of previous overdigitalization had disappeared.

Serial No. Sex Age	Clinical Diagnosis	Features of Arrhythmia	Dosage	Clinically suspected	Remarks
<i>Atrial fibrillation with extrasystoles and with high-degree partial or complete A-V block</i>					
F. 24. 75, 20683	Left ventricular failure.	ES in varying numbers and periods of bigeminy.	Had been on digoxin 0.25 q.i.d. for 2 days before emergency admission. On adm. 0.25 mg. b.d. for 1 day, then o.d. First ECG 1 day after adm.: occasional ES. Second ECG 4 days later: numerous ES with periods of bigeminy.	No	Dosage too high for patient of her age.
F. 25. 63, 28616	Mitral stenosis and incompetence, C.C.F.	Multiform ES, at times bigeminy.	Before admission on digoxin 0.25 mg. b.d. for unspecified period. Overdigitalized on admission. Digitalis withheld for 11 days, then restarted o.d. No further ECG. On adm., according to case note, 'triple rhythm', nausea, vomiting.	—	Inadequate supervision outside. Overdigitalization shown by ECG recorded day after admission.
F. 26. 67, 29899	? Carcinoma of bronchus. ?? Myocardial infarct.	ECG on adm.: A.F., high VR; ECG fortnight after adm.: VR much lower, bigeminy due to multiform ES.	No record of digitalis before adm. in G.P.'s letter. On adm. digoxin 0.5 mg. i.m. repeated six-hourly 3 times, then 0.25 oral t.d.s. till apex rate below 90, then b.d. Had 4.25 mg. in 4 days. Omitted after 4 days, but only for 2 days, then restarted with half the dose, i.e. o.d. Second ECG 6 days after restarting.	No	Doubtful whether any indication for digitalis. No apparent indication for parenteral route. Gross overdosage, particularly in view of age. Wrong method to assess dosage. Stopped for too short a time. Pat. died about 1 month after last ECG with lung abscess; ? carcinoma.
F. 27. 76, 30365	Ischaemic heart disease.	Multiform ES.	G.P.'s letter: C.C.F. for some weeks, on digoxin tab. 1 t.d.s. + saluric tab. 1 t.d.s. on alternate days. On day after adm.: digoxin 0.5 mg. i.m., further 0.5 mg. same day oral, then 0.25 mg. t.d.s. Two days after adm. also 0.25 mg. i.m. "for very fast pulse". Oral medication apparently continued until pat. died 2 days later ("irregular apex beat, rate about 120").	No	Should not have been put on digitalis without prior ECG assessment of rhythm. Gross overdigitalization, particularly in view of age. Wrong method to judge condition and determine dosage by pulse or heart rate. Overdigitalization not recognised as aggravating failure. Death assumed to have been due to digitalis intoxication.
M. 28. 85, 29732	Cerebrovascular accident. Prepare for prostatic surgery.	Low ventricular rate, multiform ES (ECG 1 week after admission).	On adm.: digoxin 0.25 mg. q.i.d. for 3 days, then b.d. for 10 days. Then stopped for 2 days, restarted o.d. Died suddenly 1 month later.	No	Initial dose too high particularly in view of age. ECG requested much later than advisable. Drug stopped for too short a time. Cause of sudden death unknown; digitalis as contributory cause possible.
F. 29. 49, 29212	Mitral stenosis, carcinoma cervix.	Appearance of ES used to determine optimum dose of digitalis as patient very difficult to stabilise.	Digoxin 0.25 mg. o.d. and b.d. on alternate days found to be optimum maintenance dose despite causing 12 ES in 12-lead record. When accidentally without digoxin for 3 days VR 144; when controlled VR about 84.	—	Appearance of ES used to determine optimum maintenance dose.

Paroxysmal atrial tachycardia with A-V block

M. 30. 75, 29509	Cor pulmonale, chronic bronchitis. Old pulmonary T.B.	PAT of 125-150 with varying A-V block, at other times sinus tachycardia with VES and numerous AES.	On adm.: Dig. fol. grs., 3 t.d.s. first day; grs. 2 t.d.s. second day; gr. 1 t.d.s. third day, i.e. grs. 18 = about 3 mg. digoxin within first 3 days. Then gr. 1 b.d. for 3½ weeks, stopped for 6 days, restarted gr. ½ b.d. On oral diuretics throughout.	No	Gross overdosage initially as well as subsequently. Drug stopped for too short a time. Inadequate attention to ECG warning.
F. 31. 72, 29837	Ischaemic heart disease. C.C.F.	PAT, AR 214, 2:1 A-V block.	Had been digitalized by G.P. with digoxin, 0.25 mg. t.d.s. Began to vomit on 4th day, but G.P. reassured her (from G.P.'s letter). Sent to O.P. on (probably) 6th day of digoxin treatment and was admitted. On adm. put on dig. fol. gr. ½ t.d.s. Stopped 2 days later. Patient died 2 days later.	No	Failure to recognise symptom of digitalis intoxication outside. Should not have been put on digitalis on admission. Death assumed due to digitalis intoxication.

Serial No. Sex Age No.	Clinical Diagnosis	Features of Arrhythmia	Dosage	Clinically suspected	Remarks
Paroxysmal atrial tachycardia with A-V block					
32. M. 49, 30317	Septum primum defect; ? common A-V canal.	Right bundle branch block. PAT, AR 250, varying A-V block.	On digoxin 0.25 mg. b.d. and quinidine sulph. grs. 3 t.d.s. for at least a year + most of the time hydrosaluric K 1 tab. 5 days a week. Digoxin 0.25 mg. b.d. continued throughout stay in hospital.	No	Obvious overdigitalization. In case note after last discharge: "In view of his ECG report" (tracing arrived after discharge) "it would be worth while reducing his digoxin to 0.25 mg. o.d. until seen in the O.P. Clinic." But former dose was repeated when he was next seen.
33. F. 63, 29289	Ischæmic heart disease. C.C.F.	Second degree A-V block (3:2). Two days later PAT, AR 300, 2:1 A-V block. Fig. 3.	On adm.: digoxin 0.75 mg. stat., then four-hourly. 0.25 mg. b.d. on following 3 days. Then 0.25 mg. eight-hourly for 1 day, b.d. following day, then stopped. Second degree A-V block recorded 1 week after adm., PAT 2 days later. Patient died the following day.	No	Obvious overdigitalization. 3:2 A-V block considered by H.P. as "pulsus bigeminus", which suggests confusion with ES. Death assumed to have been due to digitalis intoxication.
Mainly or solely atrial arrhythmias other than paroxysmal atrial tachycardia with A-V block					
34. F. 77, 29694	Syphilitic aortic incompetence, C.C.F.	Left bundle branch block. Numerous AES, often occurring in series. Periods of atrial tachycardia without A-V block of about 176, also VES. Later A.F. Fig. 2b.	Had been on digoxin 0.25 mg. o.d. for nearly two years. At the time of ECG was also on hydrosaluric K.	Yes, because of nausea	Very great improvement stopping digitalis. This confirmed the view that the arrhythmia was due to the drug. This observation illustrates the toxic effect of a small dose given over long period in an elderly patient. VR during the later A.F. was controlled by digoxin 0.25 mg. twice weekly.
35. F. 64, 30009	History of attacks of paroxysmal tachycardia. Hysterectomy. Anterior infarct while in hospital.	"Extrasystolie à paroxysmes tachycardiques" (repetitive paroxysmal tachycardia). One day later A-V tachycardia of 150 which changed into sinus rhythm later that day. Fig. 6.	Digoxin 1 mg. stat., then 0.5 mg. q.i.d., then 0.25 mg. q.i.d., i.e. 4 mg. digoxin in 48 hours. Subsequently 0.25 o.d. for (probably) 9 days (no exact record about duration).	No	Gross overdosage resulted first in "Extrasystolie à paroxysmes tachycardiques" and then in A-V tachycardia. Reversion to sinus rhythm on stopping the drug. Signs of infarct with serology developed 8 days after the end of the arrhythmias; ? arrhythmias precipitated infarct.
36. M. 57, 30421	Cor pulmonale, acute exacerbation of chronic bronchitis.	Changes in P waves.	Had been on digoxin 0.25 mg. b.d. since last discharge 7 months and 3 weeks before readmission. Same medication continued. ECG 3 days after readm.: no evidence of digitalis intoxication. 5 days later digoxin reduced to 0.25 mg. o.d. because of nausea. ECG fortnight later showed marked changes in P waves attributed to digitalis. Further changes in ECG 5 days later. Five weeks after reduction of dose P waves had reverted to normal.	Yes	The occurrence of nausea and the changes in P waves indicated that the long continued medication with digoxin 0.25 mg. b.d. had resulted in intoxication. Reduction to half the dose resulted in reversion of waves to normal within 4 weeks. Drug should have been stopped instead reduced at appearance symptoms and signs of intoxication, if there was any indication for it which seems doubtful.
37. F. 79, 30677	Acute exacerbation of chronic bronchitis. C.C.F.	Very numerous AES. Changes in P waves compared with ECG 5 years previously when patient was not on digitalis.	Dig. fol. grs. 2 t.d.s., next day gr. 1 t.d.s. After that gr. 1 b.d. Overdigitalization suggested by ECG when patient had grs. 15=about 2.5 mg. digoxin. Dose subsequently reduced to gr. 1 daily.	No	Overdigitalization suspected by atrial arrhythmia, also in view of large dose for age. This case cannot be considered as more than probable as no further ECGs were taken. Progress appears to have been satisfactory on the smaller dose.
Complex arrhythmias					
38. M. 71, 29162	Chronic bronchitis and emphysema. C.C.F. Old anterior infarct.	Atrial tachycardia of about 300. A-V dissociation. A-V tachycardia of 88. Multiform VES. Fig. 4b.	Had been discharged on digoxin 2 years before readmission; no record about dosage during that time. On adm.: 0.25 mg. b.d. for 4 days, stopped (in view of ECG) for 3 days, then o.d. for 1 week. ECG again multiform VES, fewer next day. Patient died 3 days after last ECG.	No	Inadequate supervision outside of hospital. Should not have been put on digitalis on admission without prior ECG assessment. Drug stopped for too short a time. Death assumed to have been precipitated by digitalis intoxication.

Serial No. Sex Age No.	Clinical Diagnosis	Features of Arrhythmia	Dosage	Clinically suspected	Remarks
Complex arrhythmias					
F. 39, 56, 28723	Acute C.C.F.	Two days after admission and initial digitalization: sinus rhythm with bigeminy due to VES, also periods of ectopic atrial rhythm. ECG 12 days later: much shorter periods of bigeminy, still suggestive of overdigitalization.	Digoxin 0.5 mg. stat., 0.25 mg. six-hourly until apex rate below 80. No record when digitalis was stopped. 10 days after admission 0.25 mg. b.d. for 2 days, then o.d. Second ECG 5 days after start of this treatment. Nine days later digoxin reduced to 0.25 mg. 3 times a week, with note "perfectly well controlled". Patient regarded as "hypersensitive to digitalis".	No	Although the exact dose of digoxin resulting in the arrhythmia is not known it is clear from subsequent development that only much smaller doses were required and the initial doses were too high. Also, wrong method to determine optimum dose from apex rate.
M. 40, 87, 29867	C.C.F.	Before digitalis: sinus rhythm, rate 90, 1 AES and 2 VES in whole ECG. After digitalis and while on mersalyl, 3 days after previous ECG: Sinus tachycardia of 115, more AES. Next day dual tachycardia: atrial of 214, A-V of 136, dissociation with interference, Fig. 7. Next day atrial tachycardia of 176 with 1:1 conduction. Next 3 ECGs on following 4 days: sinus tachycardia with decreasing number of ES consistent with waning digitalis effect.	Not ascertainable as case note misfiled in hospital and temporarily not available.	No	The occurrence of the arrhythmia during digitalis treatment and its waning after reports on overdigitalization cannot leave any reasonable doubt that the arrhythmia indicated digitalis intoxication.
F. 41, 60, 29115	Mitral incompetence, thyrotoxicosis.	During a previous admission, when patient was in hospital for 2 months, difficult to stabilise. Discharged on lanatoside C 0.25 m.g. q.i.d. and neomercazole 10 mg. t.d.s., although ECG 1 week before discharge showed AF with VR of 140 and fairly frequent ES, and caution re digitalis had been recommended. On emergency readmission 2½ months later put on digitoxin 0.1 mg. t.d.s. + quinidine sulph. grs. 3 t.d.s., also hydrosaluric K 100 mg. on alternate days. ECG on day after admission showed in some parts bigeminal rhythm due to VES, in other parts A-V dissociation (Fig. 8). Serum K = 3.3 mEq/l. Extra K given; serum K next day 4.9 mEq/l. Digitoxin and quinidine stopped. 4 days later ECG showed first degree A-V block, P-R 0.24 sec. Quinidine grs. 3 t.d.s. restarted the day before, and digitoxin 0.1 mg. b.d. the day after ECG was recorded. One week later digitoxin reduced to 0.1 mg. o.d.		No	It seems likely though not certain that this patient had been on lanatoside C 0.25 mg. q.i.d. for the 2½ months preceding readmission; in any case, this dose was too high, particularly in view of ECG warning and previous experience of difficulties in stabilising. Digitoxin particularly unsuitable in this patient. The concurrent medication with quinidine and hydrosaluric K increased tendency to arrhythmias due to digitalis toxicity. Quinidine and digitalis restarted too soon. ECG increased tendency to arrhythmias in different parts of the same tracing, and a further ECG a third manifestation (first degree A-V block) during waning digitalis intoxication.
Second degree A-V block					
M. 42, 72, 29060	Chronic bronchitis and emphysema. Status asthmaticus. L. pneumothorax.	First ECG: First and second degree A-V block. Second ECG 8 days later and 1 week after digoxin was stopped: only first degree A-V block.	On "digitalis" b.d. by G.P. for unspecified duration before admission. Also on hydrosaluric K 50 mg. a day 4 days a week for long periods. On adm. put on digoxin 0.25 mg. b.d. continued for 5 months and 8 days, possibly with occasional breaks the duration of which cannot be ascertained from the notes. On the day before stopping digoxin patient had an attack of crushing retrosternal pain and hypotension. ECG showing first and second degree A-V block was taken on the day following this attack and on the first day patient was without digitalis. 11 days later digoxin restarted with 0.25 mg. o.d., increased to b.d. 2 days later. Patient died the following day.	No	Patient died 16 days after the attack. No P.M. The attack was thought to have been myocardial infarction although all tests were negative except S.L.D. 650 units on the day following the attack. In this patient the arrhythmia can only be considered as probably due to, or aggravated by, the long continued exhibition of digoxin 0.25 mg. b.d., particularly in view of patient's age. The occurrence of the arrhythmia and subsequent subsidence would be consistent with a waning digitalis effect, but may also have resulted from an infarct in which case digitalis is likely to have been an aggravating factor.

glycosides from which the reverse was expected (Lown and Levine, 1954; Levine, 1955). The mortality of 21% is higher than that reported as 11% by Rodensky and Wasserman (88 patients), 4% by Von Capeller, Copeland and Stern (148), 6.6% by Flaxman (30), and 4.5% by Moody (44), but lower than the average reported by Dreifus, McKnight, Katz and Likoff in old people where it was 11% in passive nodal rhythm, 35% in paroxysmal atrial tachycardia with block, 42% in active nodal rhythm and 68% in ventricular tachycardia. This comparison emphasizes the importance of age.

Dreifus's statement: "The most significant predisposing factor in the development of digitalis toxicity was inappropriate administration" is unquestionably applicable to the present observations, the following points deserving special consideration as having been largely responsible:

Age

Despite some contrary statements in the literature that the patient's age is of little or no importance (Moody, 1951; Schwiegk and Jahrmärker, 1960; Rodensky and others, 1961), there is no doubt of the overwhelming evidence that old people are more susceptible to the drug than younger ones (Raisbeck, 1952; DeGraff, 1954; Kay, 1955; Wollheim, 1954/55; Crouch, Herrmann and Hejtmancik, 1956; Shrager, 1957; Scherf, 1958; Von Capeller and others, 1959; Lown and others, 1960; Soffer, 1961; Goldberger, 1962; Holzmänn, 1962; Dreifus and others, 1963). Moreover, the more advanced the myocardial changes the narrower the boundary between therapeutic and toxic doses, whereby the considerable variations in the optimum dose between different patients, and in the same patient at different times, increase the difficulties in the management of these cases, necessitating greater individualization of treatment and far closer supervision than is often accorded to them (see below).

A perusal of the dosages and their effect on the ECG, as listed in Table 1, leaves no doubt about their having been excessive in an appreciable proportion of the cases. Furthermore, it should be borne in mind that doses considered as 'average' tend to be too high for patients in these age groups.

Exhibition of Digitalis without Indication

Some patients are given digitalis without indication, common causes being a diagnosis

of 'heart failure' on inadequate grounds, in particular on the strength of some basal rates only, or by mistaking dyspnoea due to pulmonary disease as being cardiac in origin (Levine, 1955). Such considerations seem to apply particularly to Cases 7, 12, 19, 26, 36 and possibly 42 of the present series. Other conditions, cardiac and non-cardiac, where patients were given digitalis without indication, were discussed by Broome and Orgain (1946) and Burwell and Hendrix (1950). In some cases the drug is given parenterally without any apparent reason.

Premature Start of Digitalization in Hospital

In the majority of cases where a diagnosis of congestive heart failure was made, digitalization was started on admission without allowing any time for the effect of rest and nursing to become manifest. Furthermore, diuretics were often given concurrently where perusal of the case notes failed to show any indication for such drastic immediate treatment. The effect on electrolytes of diuretics, mercurial as well as thiazides, in aggravating the toxic action of digitalis is too well known to merit any discussion, except for re-stating that this combination, frequently used in contemporary treatment, is one of the most important factors accounting for the increase in the incidence of digitalis intoxication. In this connexion a normal serum K concentration seems often to be considered an indication that further digitalis medication is safe, although it has been established with certainty that such normal figures do not provide any information about the intracellular K concentration or the intra-extracellular gradient, which in the present context are alone of significance in respect of K depletion.

A further source of error is the initiation of digitalis treatment on admission without ascertaining whether the patient had recently received the drug outside, or how much. Even a patient with obvious symptoms and/or signs of digitalis toxicity may be put on the drug on admission (e.g. Cases 12, 15, 17, 19). To postpone digitalis treatment until an ECG is available, which should be requested as a matter of routine on admission of elderly patients with cardiac disease, is clearly the method of choice in order to avoid this risk of overdosage, with the possible exception of those very few patients in whom immediate digitalization is mandatory and who are known with certainty not to be under the influence of the drug on admission. The importance of ascertaining the cardiac con-

FIG. 2.—(a) Case 3. Lead aVL. After 1.25 mg. digoxin in 18 hours. Numerous multiform ectopic ventricular beats.
(b) Case 34. Lead aVL. After digoxin 0.25 mg. daily for nearly two years. Five atrial extra-systoles in succession followed by three sinus beats the first of which with an abnormal P wave. The last sinus beat is followed by a single atrial extrasystole; the postextrasystolic interval is terminated by a ventricular ectopic beat, followed by two atrial ectopic beats.

dition electrocardiographically before starting digitalization is enhanced by the fact that potentially dangerous arrhythmias due to, or aggravated by, the drug are often present without any of the usual symptoms, such as anorexia, nausea, vomiting or visual disturbances (Herrmann, Decherd and McKinley, 1944; Flaxman, 1948; Master, 1948, 1950; Gootnik, 1949; Moody, 1951; Cohen, 1952; Crouch and others, 1956; Shrager, 1957; Von Capeller and others, 1959; Schwieglk and others, 1960; Soffer, 1961; Goldberger, 1962; Holzmänn, 1962). This is borne out by the present observations which show that overdigitalization was clinically suspected in only a small minority of the patients.

Mistaken Methods for Determining Digitalis Dosage Clinically by the Ventricular Rate; Misinterpretation of Cardiac Rhythms

The mistaken belief that an optimum dose of digitalis must reduce the ventricular rate in every case seems still prevalent. As far as patients with sinus rhythm are concerned this is a misapplication of the condition prevailing in those with atrial fibrillation and a high ventricular rate. In patients with sinus rhythm the drug either does not reduce the rate at all or only slightly, any effect on rate being clinically irrelevant. Overdosage in such patients may result in ectopic ventricular

(Fig. 2a) or less commonly atrial (Fig. 2b) arrhythmias, which may be misdiagnosed as atrial fibrillation; or it may produce paroxysmal atrial tachycardia with A-V block (Fig. 3c), likely to be mistaken for sinus tachycardia if the block is constant (it often is 2:1), or atrial fibrillation if the block is variable. As a result more digitalis is often given. While many physicians are familiar with these arrhythmias as manifestations of digitalis toxicity, it does not seem to be so commonly appreciated that changes in P waves may be the first sign of impending digitalis overdosage, heralding paroxysmal atrial tachycardia with block if medication is continued (Fig. 3c).

In atrial fibrillation a similar mistake is also often made. The aim of digitalization in such cases with a high ventricular rate is, of course, to reduce this rate by increasing A-V block. If the ventricular rate does not drop satisfactorily or even increases in the course of the exhibition of the drug, dosage is increased without considering the possibility that the rapid ventricular action may be due to ventricular ectopic beats due to digitalis intoxication (Fig. 4). A further source of error occurs in patients with atrial fibrillation and irregular ventricular action in whom the ventricular rhythm becomes regular during digitalization as a result of complete A-V block with regular A-V rhythm (Fig. 5b) or non-

FIG. 3.—Case 33. Lead II. (a) After (at least) 5.25 mg. digoxin within 5 days from admission: Sinus rhythm, rate about 82, digitalis effect. (b) One day after (a) during which a further 0.5 mg. had been given: second degree (3:2) A-V block. (c) Two days after (b) during which a further 1.25 mg. had been given, a total of 7 mg. in 8 days. Upper strip Lead II: changes in P waves indicative of an ectopic atrial pacemaker taking over; lower strip Lead V₁ of the same record: Paroxysmal atrial tachycardia with 2:1 A-V block, atrial about 300.

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FIG. 5.—Case 22. Atrial fibrillation. (a) Upper strip V_5 , lower strip V_6 of the same tracing recorded in immediate succession, after 1.75 mg. digoxin in 48 hours.

V_5 : Bigeminal rhythm owing to a ventricular ectopic beat following every conducted one;
 V_6 : A-V tachycardia of about 107.

(b) One week after (a) during which a further 2.25 mg. digoxin had been given.
 Lead III: Regular A-V rhythm, rate about 75.

paroxysmal A-V tachycardia (Fig. 5a), the regular rhythm being clinically misinterpreted as sinus rhythm or sinus tachycardia. Thus, the abnormal rhythm due to digitalis intoxication is not recognised and digitalis medication continued on the erroneous assumption that restoration of sinus rhythm had taken place.

FIG. 4.—(a) Case 18. Lead V_5 . Recorded two days after admission and massive digitalization. Atrial fibrillation, high-grade A-V block, extrasystoles.

(b) Case 38, Lead V_2 . Had been put on digoxin 0.25 mg. b.d. two years before readmission and was still on the drug, possibly same amount though exact dose could not be ascertained. Digoxin 0.25 mg. b.d. started on admission. Atrial tachycardia, A-V dissociation, ventricular ectopic beats.

Not infrequently, one arrhythmia changes into another, sometimes in the same ECG. Fig. 5 provides an example of atrial fibrillation and regular A-V rhythm with and without extrasystoles, Fig. 6 one of two different kinds of supraventricular arrhythmias. Figs. 7 and 8 illustrate various and at times more complex arrhythmias.

Unawareness that Digitalis Toxicity may Manifest itself as Refractory Heart Failure or as Increase in its Severity

Failure to recognise these possibilities is likely to induce the physician to give the overdigitalised patient more digitalis, with the result of further deterioration or even death. Cases 1 and 27 illustrate this sequence. Attention to these manifestations of digitalis intoxica-

FIG. 6.—Case 35. All strips Lead II. (a) The three strips are continuous. After 4 mg. digoxin in 48 hours, followed by 0.25 mg. once daily either for 2 days (total of 4.5 mg. in 4 days) or more likely for 9 days (total of 6.25 mg. in 11 days). Tracing recorded 11 days after initiation of digitalization. 'Extrasystolie à paroxysmes tachycardiques' (repetitive atrial paroxysmal tachycardia). (b) One day after (a): A-V tachycardia of about 150. (c) Later the same day as (b): Sinus rhythm, rate about 83.

FIG. 7.—Case 40. Lead V₁. The two strips are continuous. On digoxin, potassium and mersalyl. Atrial tachycardia of 206, A-V tachycardia of 115; dissociation with interference.

tion was drawn by Batterman and Gutner, (1950); Lown and Levine, (1954); Shrager, (1957); Von Capeller and others, (1959); Friedberg and others, (1960); Soffer, (1961); especially to refractoriness by Kyser, (1955); Rodensky and others, (1961).

Inadequate Action by the Physician in the Presence of Signs of Intoxication

Even if signs highly suggestive of digitalis

overdosage were reported from ECGs, some physicians, disregarding the warning, continued treatment unchanged. Others reduced the dose, others again stopped it for a day or two, that is, for entirely inadequate periods; even a week is too short a time in many cases. The method of choice is to discontinue the drug, which suffices in many cases, re-instituting it in smaller doses at the appropriate time if necessary. In other cases the administration

FIG. 8.—Case 41. (a) Lead aVF; (b) V_1 , recorded in immediate succession. 2½ months before readmission patient was discharged on lanatoside C, 0.25 mg. q.i.d., this dose having possibly been taken throughout the period. On admission put in digitoxin, 0.1 mg. t.d.s. + quinidine sulph. grs. 3 t.d.s. + hydrosaluric K 100 mg. ECG taken on day following admission. aVF: A-V dissociation, atrial rate 88, manifest A-V rate 40, bigeminal ventricular rhythm owing to a ventricular extrasystole following every A-V beat. V_1 : Nearly isorhythmic dissociation, atrial rate 88, A-V rate 83, slow shift of the two rhythms. The P wave last but three is a blocked AES resulting in shift of the atrial rhythm.

of potassium chloride, procaine amide or quinidine is required for the successful treatment of these arrhythmias. How long digitalis should be discontinued varies considerably in different patients and can only be determined by their close supervision.

Another mistake is to continue treatment with the same dose for longer periods without adequate clinical and particularly electrocardiographic controls. This holds good for hospital out-patients as well as those under the care of general practitioners.

Substituting one glycoside for another which had produced digitalis intoxication in the belief that the replacement is less 'toxic', a method adopted by some physicians, has no foundation in fact. It has often been pointed out that every efficacious glycoside, when given in excess of the optimum dose for an individual patient, produces toxicity the signs of which vary and often do so in the same patient at different times. This view has recently been proved to be correct by a study of Church, Schamroth, Schwartz and Marriott, (1962), who deliberately induced digitalis intoxication in 39 patients by three different glycosides: digoxin, gitalin, and digitoxin, and concluded: "When a patient was intoxicated for the second or later time, he was as likely to show different manifestations as he was to show the same; and this was independent of

whether the same or different glycosides were used for the consecutive intoxications."

Conclusions

The main conclusion is to re-emphasize the necessity of regarding the dosage of digitalis as an *individual* problem in *every* case. Doses given in the literature as average ones for initial and maintenance therapy can at best be no more than very approximate guides. It is the writer's firm belief that there is no such thing as generally applicable average doses and in particular that those recommended as such tend to be too high for elderly patients. If every patient's requirements and tolerance of the drug are individually assessed and patients kept under adequate periodical control, smaller doses of digitalis than often prescribed will be found sufficient to achieve the desired effect without producing intoxication. Thus, Szekely and Wynne (1961) wrote: "A number of patients with advanced myocardial disease and atrial fibrillation who developed ventricular rhythms after conventional maintenance doses, have subsequently been maintained in a good state of compensation with satisfactory control of the heart rate on very small doses of digitalis which did not produce toxic arrhythmias." These authors' efforts were so successful that, in a subsequent experimental and clinical study on digitalis-induced arrhythmias, they were only able to muster four patients for their purpose (Szekely and Wynne, 1963).

A Plea

These conclusions lead to a plea, directed to those engaged in the teaching of under- and postgraduates, to emphasize far more strongly than, judging by the results, it has been done in the past, the necessity of individualizing the dosage of digitalis in every patient, especially in elderly people, and of keeping patients under adequate periodical clinical and electrocardiographic control as long as they take the drug. The present observations, particularly when taken in conjunction with the quoted publications of others, leave no doubt that in practice these considerations are not given anything like the attention they deserve.

Summary

Analysis of 2,000 consecutive ECGs recorded in a hospital group revealed 597 tracings referring to 348 patients who had had digitalis within a fortnight preceding at least one ECG. 78% of the patients were over 61 and 52% over 71 years of age. Records highly suggestive of overdigitalization were found in 42

patients, an incidence of 12%. Thirteen patients (31%) died within a short period after the last ECG, at a time when the drug must still have been active. In nine (21%) death was considered to have been directly due to, or at least accelerated by, digitalis. The following points are discussed as having been largely responsible: Disregard of the smaller tolerance and requirements of elderly patients; exhibition of digitalis without indication; premature start of digitalization in hospital; mistaken methods for determining digitalis dosage clinically; unawareness of digitalis toxicity manifesting itself as refractory heart failure or increase in its severity; inadequate action by the physician in the presence of signs of intoxication. As a conclusion it is re-emphasized that the optimum dose of digitalis must be determined individually in every patient, close supervision being necessary throughout the time the drug is taken. A plea is made to those engaged in the teaching of under- and postgraduates to stress these considerations far more strongly than it appears to have been done in the past.

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