Summary

An unselected series of 60 patients with Parkinsonism have been treated by stereotaxic electrocoagulation cerebral lesions. Of these patients 53, or 88%, have had tremor and/or rigidity abolished or significantly reduced without complications in the treated limbs, and have been followed for up to five years. Six patients, despite successful treatment of limb tremor and/or rigidity, have persisting complications of the operations. In only one case have limb tremor and rigidity been unimproved. These results have been achieved by accurate siting of the lesion and by making it as small as would be compatible with maintained improvement. The method used has evolved progressively, and is unique, in allowing the creation of lesions in the globus pallidus, internal capsule, or thalamus with one electrode track at different depths. Such combined lesions are usually necessary to eliminate contralateral limb rigidity and tremor.

As a result of our experience we believe that the selection of patients for operation should be governed by the degree of widespread manifestations of Parkinsonism pre-operatively. Where widespread manifestations are present, surgical lesions to treat limb tremor and rigidity cannot be large or inexact placed, otherwise mental deterioration characterized particularly by akinesia will be accentuated.

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Of the six countries which have the lowest infant mortality in the world, four are European. Statistics for 1958 published by the World Health Organization give the following infant mortality figures per 1,000 live births: Sweden, 16; the Netherlands and Iceland, 17; New Zealand, 19; Australia, 20; Switzerland, 22.

DIGITALIS AS A CAUSE OF PAROXYSMAL ATRIAL TACHYCARDIA WITH ATRIOVENTRICULAR BLOCK

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Digitalis remains probably the most useful single drug in the treatment of all forms of heart failure, though its injudicious use may result in a wide variety of toxic effects on the myocardium. Almost every form of arrhythmia and conduction defect has been attributed to the toxic effects of the drug, most of them arising from the action of digitalis on the ventricles.

The purpose of this paper is to draw attention to an important effect of over-digitalization on the atria—namely, paroxysmal atrial tachycardia with atrioventricular block (P.A.T.B.). The frequency and gravity of this form of digitalis intoxication does not seem to be widely appreciated, yet in certain circumstances very little digitalis can prove fatal. The frequency with which this arrhythmia may result from digitalis is well recognized in the American literature, owing to the work of Lown and Levine (1958), who have summarized their experience in book form. However, it appears to have escaped emphasis in this country, and it does not receive mention in the standard textbooks, where paroxysmal atrial tachycardia is usually dismissed as being of little clinical consequence. This is all the more surprising because it was, in fact, Lewis in 1909 who first described the arrhythmia, and Mackenzie (1911) who attributed it to digitalis.

There is no doubt that digitalis poisoning is occurring with increased frequency, and this is almost certainly due to the greater part played nowadays by therapy which affects the blood electrolytes, particularly the potassium. Among such therapeutic measures may be mentioned the use of salt-reduced diets, potent diuretics both mercurial and of the chlorothiazide type, ammonium chloride, especially if used continuously, cation-exchange resins, and corticosteroids. The importance of the early recognition of this arrhythmia lies in the fact that if it is mistaken for atrial flutter or atrial fibrillation, digitalis may be given, or the dose increased, with fatal results. Similarly, if paroxysmal atrial tachycardia is present but digitalis is not recognized as the cause, the dose may be mistakenly increased, as it is usually regarded as the drug of choice in that condition. In fact, Friedberg (1956) recommends the intravenous route. Provided digitalis is recognized as the cause of the arrhythmia and appropriate treatment given, the prognosis is, in our experience, less serious than has been claimed, and 9 of our 11 patients survived.

Material and Methods

We present the findings in 11 patients, collected over the past two years, in whom P.A.T.B. was present and in all of whom digitalis was believed to have played a major part in precipitating the arrhythmia (Table I).

TABLE I.—Factors Precipitating Paroxysmal Atrial Tachycardia with Atrioventricular Block

Case No.	Age and Sex	Digitalis prior to P.A.T.B.	Other Causative Factors					Serum K (mEq/l.)	Blood Urea (mg./100 ml.)
			Diuretics	Salt Restriction	Steroids	Ischaemia	Others		
1	68 F	Digoxin 0.75 mg./day for 4 months; 1 mg./day for 6 days	Mersalyl	Yes	No	No	Uraemia	3.8	74
2	50 F	Digoxin 0.5 mg. I.M., 0.5 mg. I.V., and 1 mg. orally all during 24 hours	No	No	No	No	—	—	—
3	48 M	Digitalis folia 3 gr. (0.2 g.)/day for 1 year	Chlorothiazide. Mersalyl	Yes	No	No	—	—	—
4	49 F	Digoxin 1.5 mg./day for 2 months; 0.5 mg./day for 11 days	No	No	No	No	—	—	—
5	67 F	Digoxin 1 mg. 1st day; 0.75 mg./day for 5 days	Chlorothiazide	Yes	Dexamethasone	No	—	4.5	24
6	63 M	Digoxin 1 mg./day for 2 days	..	Yes	Prednisone	No	Cholangitis. Uraemia	6.0	89
7	39 F	Digoxin 0.5 mg./day for 130 days	..	Yes	No	No	Childbirth 1 day prior. Carbimazole	—	—
8	51 F	Digoxin 1.25 mg. I.V. over 24 hours	No	No	No	No	Small-bowel obstruction. Gastric aspiration. Intravenous therapy	3.7	44
9	56 M	Digoxin 0.5 mg./day for 30 days	Mersalyl. Acetazolamide. Thiomerin	Yes	No	L.B.B.B.	Renal failure	4.4	50
10	58 M	Digoxin 3.5 mg. over 24 hours	Chlorothiazide	Yes	No	No	—	3.9	41
11	67 F	Digitalis folia 1½ gr. (0.1 g.)/day for 24 days; digoxin 0.5 mg./day for 11 days	Chlorothiazide. Mersalyl	Yes	No	Old cardiac infarct	—	3.8	85

The criteria by which the importance of digitalis as a cause was assessed were as laid down by Lown *et al.* (1959). All but one of the patients had 12-lead electrocardiograms taken before, during, and after the arrhythmia. All were followed until the P.A.T.B. had ceased and had been replaced either by sinus rhythm or by atrial fibrillation. Ten of the patients had heart disease and seven were in congestive heart failure at the time of the arrhythmia (see Table II). In addition, we

TABLE II

Number of cases	11
Heart disease	10
Mitral stenosis	4*
Hypertensive heart disease	2
Chronic cor pulmonale	2
Ischaemic heart disease	2
No heart disease	1
Congestive heart failure	7

* One patient also had thyrotoxicosis.

investigated in some detail a patient suffering from P.A.T.B. and congestive heart failure to whom no digitalis had ever been given, and this is discussed later.

Case Histories

Case 1.—A woman of 68, who had hypertensive heart failure and atrial fibrillation, was treated by sodium restriction and 0.75 mg. of digoxin daily for four months, and after admission to hospital the dose was increased to 1 mg. daily. Mersalyl 2 ml. was given intramuscularly on two occasions and sodium restriction was maintained. No diuresis resulted. Renal function was impaired, as shown by a raised blood urea of 74 mg./100 ml. Six days after admission a regular tachycardia of 140 a minute was noted, and in addition she was nauseated and had xanthopsia. An electrocardiogram showed an atrial tachycardia of 150 a minute with 2:1 block and digitalis effect on the RS-T segment and T wave. The serum potassium at that time was 3.8 mEq/l. Digoxin was stopped and no other therapeutic measures were taken. Within two days atrial fibrillation returned. When seen two years later she was clinically well but the atrial fibrillation persisted.

Case 2.—This patient was a woman of 50 with mitral stenosis and atrial fibrillation. Following on an embolus to the left leg her ventricular rate rose to about 300 a minute. In an effort to control this 2 mg. of digoxin was given over a period of 24 hours, part intravenously, part intramuscularly, and the rest by mouth. In spite of this the ventricular rate did not fall and a further electrocardiogram revealed paroxysmal atrial tachycardia with a 2:1 block and ventricular extrasystoles and S-T segment depression due to digitalis. During the atrial arrhythmia a pulmonary infarct occurred, followed by absorption collapse of the

left lung. Digoxin was stopped and quinidine was given by mouth. After 106 gr. (7 g.) had been given over four days sinus rhythm was established. Six months later mitral valvotomy was performed, and she was well and in sinus rhythm 11 months afterwards.

Case 3.—A man aged 48 with congestive heart failure secondary to bronchitis and emphysema had been treated for one year with digitalis folia 3 gr. (0.2 g.) daily, mersalyl 2 ml. twice weekly intramuscularly, and sodium restriction. Because of an increase in his heart failure he was admitted to hospital, and to the above treatment was added chlorothiazide 1 g. daily for four days a week. Paroxysmal atrial tachycardia with a variable 2:1 and 3:1 block resulted. This responded when digitalis was stopped, the sinus rhythm then returning. He was well nine months later.

Case 4.—A woman of 49 with mitral stenosis and atrial fibrillation was admitted to hospital for consideration of mitral valvotomy. Digoxin 1.5 mg. daily had been given for the preceding two months, but this was reduced to 0.5 mg. a day on admission. After 11 days paroxysmal atrial tachycardia with variable 2:1 and 3:1 block developed. The electrocardiogram also showed ventricular extrasystoles and digitalis effect. On stopping digoxin and giving potassium chloride 3 g. daily, atrial fibrillation returned. Four days later mitral valvotomy was performed, but she died the same day. At necropsy a technically successful mitral valvotomy was found and there was no obvious cause for her sudden death.

Case 5.—A woman of 67 with mitral stenosis, but still in sinus rhythm, also had severe eczema and a hiatus hernia. She developed congestive heart failure as a result of atrial fibrillation with a rapid ventricular rate. Her sodium intake was therefore restricted and 4.75 mg. of digoxin was given over six days together with chlorothiazide 2 g. daily for four days a week. Dexamethasone 1 mg. daily was given because of the severity of her skin condition. Six days after starting digoxin paroxysmal atrial tachycardia with a variable 2:1 block developed. The level of the serum potassium was normal (4.5 mEq/l.) at this point, as was her blood urea (24 mg./100 ml.). Digoxin was stopped and she was given potassium chloride 5 g. daily for two days, at the end of which time sinus rhythm returned. She was alive and well two months later.

Case 6.—A man aged 63 was admitted to hospital with hypertensive heart failure and in sinus rhythm. In the past he had had a pyrexia of unknown origin thought to be due to a systemic collagen disease, and was treated for 18 months with prednisone 12 mg. daily. Over a period of two days 2 mg. of digoxin and 3 g. of chlorothiazide were given and sodium restriction was maintained. Paroxysmal atrial tachycardia with a 2:1 block developed within two days of starting digoxin. The serum potassium level at this point

was 6 mEq/l., while the blood urea was elevated to 89 mg./100 ml. Digoxin was discontinued, and after two days sinus rhythm returned. One month later he was alive and well.

Case 7.—A woman of 39, 32 weeks pregnant, was in sinus rhythm with mitral stenosis and thyrotoxicosis. The thyrotoxicosis was treated with carbimazole 20 mg. daily. Because of a persistent sinus tachycardia and dyspnoea digoxin was used, 0.25 mg. b.d. for 130 days. In addition, for one month, she was given chlorothiazide 2 g. daily for four consecutive days, supplemented with potassium chloride 3 g. daily on the remaining three days of the week. Sodium restriction was also maintained. She had a normal delivery, but next day paroxysmal atrial tachycardia with 2:1 block developed. In order to restore sinus rhythm, which was achieved after 12 hours, it was necessary to stop the digoxin and chlorothiazide, increase the potassium chloride to 6 g. daily, and give quinidine to a total of 50 gr. (3.2 g.). Six months later a successful mitral valvotomy was performed, but the sinus rhythm was replaced by atrial fibrillation, which has since persisted.

Case 8.—A woman aged 51 was admitted to hospital with small-bowel obstruction and no previously known heart disease. Gastric suction and intravenous therapy resulted in hypokalaemia, and an atrial tachycardia without block developed. This was treated with digoxin, 1.25 mg. being given intravenously over 24 hours. Paroxysmal atrial tachycardia with block developed the next day and the serum potassium level was then 3.7 mEq/l. The electrocardiogram showed RS-T segment depression due to digitalis. Digoxin was discontinued and potassium was given slowly intravenously in a strength of 1 g. to the pint (570 ml.). Sinus rhythm returned within three days. When seen three months later she was well and the electrocardiogram was normal.

Case 9.—A man of 56 was admitted to hospital with congestive heart failure. He was in sinus rhythm with left bundle-branch block due to ischaemic heart disease. B.P. 180/120 mm. Hg. During his stay in hospital pulmonary infarction developed. For a month digoxin 0.5 mg. daily was used together with sodium restriction and diuretics. At first mersalyl 2 ml. twice weekly was given, then acetazolamide 250 mg. daily three days a week, and finally "thiomerin" 2 ml. twice weekly. Despite these measures congestive heart failure progressed and paroxysmal atrial tachycardia with a variable 2:1 block developed. The electrocardiogram also showed evidence of digitalis effect. The serum potassium level was normal (4.4 mEq/l.) but the blood urea was 50 mg./100 ml. The tachycardia was treated at first with procainamide 1 g. by mouth over a period of one day while digoxin was continued. On the next day, as no effect had been noted, procainamide was discontinued and the digoxin was increased to 1 mg. over 24 hours, still with no effect. His condition was desperate, and thereafter quinidine was given intravenously to a total of 36 gr. (2.3 g.), but he died the same day. Necropsy was not performed.

Case 10.—A man aged 58 was admitted to hospital in gross congestive heart failure due to cor pulmonale. He was in sinus rhythm. One year prior to this admission he had been admitted in congestive failure and responded to treatment with rest in bed, salt-restriction, and mersalyl injections 2 ml. intramuscularly twice weekly. Digitalis was not used. On his present admission 1.5 mg. of digoxin was given, followed by 1 mg. eight hours later and 0.5 mg. each eight hours thereafter. Chlorothiazide 1 g. was also given on admission and 1 g. b.d. next day. On the second day of his admission an electrocardiogram showed paroxysmal atrial tachycardia with regular 2:1 block, and carotid sinus compression produced a variable block. The serum potassium was 3.9 mEq/l. The arrhythmia was treated by discontinuing digoxin and chlorothiazide and giving potassium chloride by mouth to a total of 6 g. daily, and by the following day sinus rhythm was restored. One day thereafter a regular atrial tachycardia with 2:1 block developed. Digoxin was recommenced with 0.25 mg. t.d.s., and potassium was again given by mouth. Sinus rhythm returned within 24 hours and has remained.

Case 11.—A woman of 67 was admitted to hospital in congestive cardiac failure of six months' duration. In 1955 myxoedema was diagnosed, and since then she had taken 3 gr. (0.2 g.) of thyroid daily. Prior to admission, treatment for her heart failure consisted of digitalis folia 1½ gr. (0.1 g.) daily and chlorothiazide 1 g. with potassium chloride 2 g. for five consecutive days of each week. As no diuresis resulted chlorothiazide was replaced by mersalyl, but in spite of a good diuresis she remained oedematous. When admitted 0.25 mg. of digoxin b.d. and mersalyl 2 ml. intramuscularly on alternate days were given; her intake of fluid and salt were restricted. The serum electrolytes showed moderate reduction of the sodium and chloride with no potassium depletion. The blood urea was elevated to 69 mg./100 ml.; plasma cholesterol 75 mg./100 ml. The electrocardiogram showed sinus rhythm with right bundle-branch block and signs of an old transmural antero-septal infarct. Ten days after admission she felt depressed and complained of nausea and loss of appetite. The pulse was rapid and irregular, and an electrocardiogram showed paroxysmal atrial tachycardia with block, multifocal ventricular extrasystoles, and S-T segment depression and T-wave change due to digitalis. The level of potassium had now fallen to 3.8 mEq/l.; the blood urea had risen to 85 mg./100 ml. Digoxin was discontinued and potassium chloride 3 g. daily was given by mouth. Three days later sinus rhythm returned and has remained.

Discussion

Until recently it was thought that one of the essential differences between paroxysmal atrial tachycardia and atrial flutter was that in the former the ventricles responded to every supraventricular impulse, whereas in the latter some degree of atrioventricular block, constant or variable, was present. Although a few electrocardiograms of P.A.T.B. had been published previously, it was not until 1943 that it was realized that this arrhythmia is by no means rare. In that year Barker *et al.* published details of 17 previously recorded cases and added 18 more of their own, and later Evans (1944) attempted to establish the identity of paroxysmal tachycardia and atrial flutter. In both paroxysmal atrial tachycardia and atrial flutter the ventricular rhythm may be regular or irregular, and the distinction that atrioventricular block is present only in flutter is no longer valid.

Other differences often quoted as evidence of the separate identity of the two arrhythmias are, first, that carotid sinus compression and stimulation of vagal reflexes by other methods may abolish paroxysmal atrial tachycardia but does not have this effect on atrial flutter; secondly, in atrial tachycardia the atrial rate is said rarely to exceed 200 a minute and is often slower, whereas in flutter the atrial rate is faster; finally, the administration of potassium in digitalis-induced P.A.T.B. will almost always stop the arrhythmia, whereas it is ineffectual in atrial flutter. However, it is usually admitted that at times even the electrocardiograph may fail to distinguish the two arrhythmias, and from our studies we are convinced that there is no single criterion, either clinical or electrocardiographic, by which these two arrhythmias can be rigidly separated. All grades exist between classic flutter with "saw teeth" f waves in every lead and classic P.A.T.B. with small upright P waves in the standard leads and separation of the P waves by an isoelectric baseline in all leads. We do not consider that P.A.T.B. is a separate and distinct entity. It often represents a transitional stage between sinus tachycardia and flutter.

Prinzmetal *et al.* (1952) have produced convincing experimental evidence that distinction between P.A.T.B. and flutter is unwarranted. It is not uncommon for an

electrocardiogram to show both flutter and P.A.T.B. (Fig. 1), and in one of our patients carotid sinus pressure changed P waves typical of P.A.T.B. to waves resembling those of flutter. This interchangeability of rhythm was well known to Lewis (1912). We feel that attempts to construct tables purporting to reveal differences of importance between P.A.T.B. and flutter are to a large extent artificial and arbitrary and serve no useful purpose. The only question of real importance when an electrocardiogram is suspected of revealing P.A.T.B. is whether the arrhythmia is due to digitalis, because if it is then the patient is dangerously near the lethal toxic dose. The differences between P.A.T.B. without digitalis and due to that drug are tabulated (Table III), but occasionally it is impossible to be certain on clinical or

TABLE III.—*Differential Diagnosis of Paroxysmal Atrial Tachycardia with Atrioventricular Block*

	Digitalis-induced	Not due to Digitalis
Carotid sinus pressure:		
Atrial rate	Unchanged (i.e., no decrease)	Decreased
Degree of A-V block	Increased	Increased
Effect on P.A.T.B.	Nil	May stop
Atropine:		
Atrial rate	Unchanged (i.e., no increase)	Increased
Degree of A-V block	Decreased	Decreased
Procainamide; quinidine	May be effective	Often effective
Cholinergic drugs	Rarely "	"No effect"
Potassium	Effective	Rare, not multifocal
Electrocardiogram	Ventricular extrasystoles often, occasionally multi-focal Sagging of S-T segment	Absent

FIG. 1.—Leads II, III, and VF show atrial waves of "saw tooth" pattern resembling atrial flutter, yet the chest leads show diminutive, upright, pointed P waves characteristic of paroxysmal atrial tachycardia.

FIG. 2.—Paroxysmal atrial tachycardia with 2:1 block. The atrial rate is 376 a minute.

electrocardiographic grounds whether digitalis has been given, and it has been pointed out elsewhere that in such cases the telephone may prove a more important diagnostic instrument than the electrocardiograph.

Characteristics of Blocked Paroxysmal Atrial Tachycardia

Lown and Levine (1958) have summarized these characteristics as follows:

1. An atrial rate of about 200 a minute. An arbitrary ceiling of 250 a minute has been set by these authors, but in some of their patients this was exceeded and the range was 100-270. In our series the atrial rate exceeded 250 in 3 out of 11 patients. In one patient (Case 7) it was 376 a minute (Fig. 2).
 2. Change in contour of the P waves, which remain upright, though nearly always diminutive, in standard leads II and III.
 3. An isoelectric baseline separates the P waves. This they regard as a *sine qua non*, and if even a single lead, extremity or precordial, showed continuous undulations of the baseline not attributable to T or U waves the patient was arbitrarily excluded as a probable case of atrial flutter. However, Kennamer and Prinzmetal (1954) have denied that the differentiation between flutter and P.A.T.B. may be made by the presence of an isoelectric interval between the P waves, and Simonson and Berman (1951) have stated that some patients may show isoelectric baselines in the chest leads and typical flutter waves in the limb leads (Fig. 1). Lown and Levine (1958) classified such patients as examples of atrial flutter. We consider that, although the most constant electrocardiographic characteristics of P.A.T.B. are the presence of an isoelectric interval between successive P waves and the absence of typical "saw teeth" f waves, occasionally the isoelectric segment may be absent. In some of our patients the atrial rate was so rapid that no intervening flat segment was present—for example, Case 7 (Fig. 2)—yet the P waves were diminutive and not of the typical form seen in flutter.
 4. A variable degree of atrioventricular block. This is, of course, present by definition. Although paroxysmal atrial tachycardia without block may result from digitalis it is invariably short-lived and block soon appears.
 5. Vagal stimulation, such as carotid sinus pressure, tends to augment the atrioventricular block but does not usually influence the atrial rate (Figs. 3 and 4).
- The P wave may be so small that it is barely visible at times, and special leads may be required to reveal any atrial deflection. Evans (1944) favours lead CR₁; at times lead V_{3R} unmasks the P wave, but occasionally an oesophageal or deep epigastric lead is necessary. The P waves differ in contour from patients in sinus rhythm. In the series of Lown and Levine (1958) the mean atrial rate was 182, the range being 150 to 200, and in 76% of episodes the atrial rate was less than 200. The atrial rate in our series varied from 120 to 376. Unlike in flutter or classical atrial tachycardia, the P-P

interval in successive cycles may vary in duration, and at times this can be appreciated without measurement (Fig. 5 A). The degree of block varies from a 1:1 response with an occasional blocked beat associated the Wenckebach phenomenon to complete atrioventricular block, but the atrioventricular response is usually less than 2:1.

Evidence of digitalis intoxication was present in 73% of their cases and one-half showed ventricular premature beats. In contrast, all of our 11 patients showed the effect of digitalis on the electrocardiogram, whereas the incidence of ventricular premature beats was similar to that in their series—namely, 6 out of 11 (Table IV).

Digitalis is undoubtedly the most important single factor in the production of this arrhythmia, and in the series recorded by Lown (1957) 75% of episodes of P.A.T.B. were the result of digitalis intoxication. We wish to draw attention to the fact that the dose of digitalis does not have to be excessive, and it need not be accompanied by other signs of digitalis intoxication

FIG. 3.—Lead III. Paroxysmal atrial tachycardia with block. Carotid sinus compression does not cause slowing of the atrial rate.

FIG. 4.—A, Lead VI. Paroxysmal atrial tachycardia with 2:1 block. Atrial rate 214 a minute. B, Lead VI. On compression of the left carotid sinus the atrial rate remains unaltered but the degree of block increases. Ventricular extrasystoles are present.

FIG. 5.—A, Lead VI. Paroxysmal atrial tachycardia with block. Atrial rate about 150 per minute. No digitalis had been given. B, Lead VI. On carotid sinus compression atrial rate now 100 per minute. C, Lead VI. Three minutes after 0.65 mg. atropine intravenously atrial rate 250 per minute. D, Lead VI. After 400 mg. procainamide intravenously regular sinus rhythm.

TABLE IV.—Analysis of Electrocardiographic Findings

Case No.	Signs of Dig. Toxicity	Original Rhythm	P.A.T.B.				Final Rhythm
			Duration	Atrial Rate	A-V Block	Ventric. Extra-syst.	
1	Yes	A. Fib.	2 days	275	2:1	Absent	A. Fib.
2	"	"	2 "	300	2:1	Present	Sinus, re-verted to P.A.T.B., finally sinus
3	"	Sinus	1 day	250	2:1 and 3:1	Absent	Sinus
4	"	A. Fib.	1 "	214	2:1 and 3:1	Present	A. Fib. Died
5	"	Sinus	2 days	180	Variable 2:1	Absent	Sinus
6	"	"	2 "	150	2:1	"	"
7	"	"	12 hours	376	2:1	Present	"
8	"	"	2 days	120-150	2:1	Absent	"
9	"	Sinus L.B.B.B.	2 "	188	Variable 2:1	Present	P.A.T.B. Died
10	"	Sinus	1 day	214	Variable 2:1	"	Sinus
11	"	"	3 days	115	Variable	"	"

clinically. Digitalis was considered to be the cause in each of the cases we have presented. It is believed that the condition is precipitated by a lowered potassium content of the heart muscle, which may or may not be mirrored in the level of serum potassium. The condition can be induced by extracting potassium by haemodialysis in patients who are receiving digitalis (Lown, 1957), but potassium loss alone without concomitant digitalis never causes the arrhythmia (Lown *et al.*, 1953). It follows, therefore, that any condition leading to loss of potassium from the body, by whatever method, may precipitate P.A.T.B. in any patient being treated with digitalis. In this connexion the effects of diuretics are of great importance, and potassium should always be replaced in a patient who is receiving these drugs, especially those taking chlorothiazide and similar saluretic drugs.

Vomiting, diarrhoea, loss of blood, and renal disease are further states that produce loss of potassium and so may be important in the production of the arrhythmia. Corticosteroids similarly may be an important factor when used in conjunction with digitalis, and were a precipitating cause in two of our patients (Table I).

The exact mechanism by which the loss of myocardial potassium leads to the arrhythmia is not yet known, but it is thought that the loss of potassium preferentially sensitizes the atrium to digitalis. It is known experimentally that when potassium is removed from the perfusing medium bathing the heart there is a gradual loss of atrial responsiveness to the inhibitory action of the vagus (Howell, 1906). This probably arises not by interfering with the production of acetylcholine but by the low potassium interfering with the action of acetylcholine on the sino-atrial node. The vagal effect of digitalis is thought similarly to be interfered with, giving rise to atrial tachycardia, while its direct effect on the atrioventricular node results in atrioventricular block. However, Schnitker and Levine (1937) attribute digitalis toxicity to a cause other than the depletion of the myocardial potassium—namely, to mobilization of digitalis-laden oedema fluid as a result of diuresis. They found up to 0.1 g. of digitalis leaf per litre of oedema fluid. The fact that the atria become relatively insensitive to vagal inhibition when the cardiac potassium is low may be used to differentiate P.A.T.B. due to digitalis from that not so induced. The use of carotid sinus pressure together with atropine and cholinergic drugs such as neostigmine and mechloryl for this purpose is described later (and see Table III).

The frequency of congestive heart failure in patients with P.A.T.B. due to digitalis has been emphasized by Lown (1957), all but 6 of his 64 patients being in congestive heart failure at the time. However, it was absent in 3 of our 11 patients, and in one (Case 8) there was no heart disease whatsoever. Apart from lowering of body potassium by the therapy employed for cardiac patients there is no doubt that heart failure itself may give rise to deficiency in cellular potassium. Biopsy studies of both cardiac and skeletal muscle have confirmed this (Talso *et al.*, 1953). Leakage of cellular potassium is induced in patients suffering from heart failure by anoxia, dehydration, acidosis, oedema, and anorexia, to mention but a few factors.

Differential Diagnosis

The bedside problem is threefold—namely, to suspect the presence of P.A.T.B.; to differentiate it from other arrhythmias; and, most important of all, to determine whether digitalis is the cause of it.

There is no specific syndrome due to the arrhythmia itself, which may last from several minutes to several weeks, and in our experience it is often the electrocardiogram which first reveals the condition, which sometimes has not been previously suspected. However, if careful inspection of the neck veins reveals a jugular a-wave faster than the apical rate the condition is suggested. It should be suspected also in any patient who is receiving digitalis if congestive heart failure suddenly worsens, or reappears, without other obvious cause. A ventricular rate which becomes quicker in spite of digitalis should suggest that an arrhythmia has appeared. A change in rhythm may be the clue—either sinus rhythm changing to an irregular rapid rhythm or atrial fibrillation suddenly giving way to a rapid regular rate. If, while any of these events takes place, the patient is receiving, in addition to digitalis, diuretics, especially chlorothiazide, or cortisone, or vomiting is present, the suspicion is increased. It has been emphasized that most patients are in congestive failure, but in our experience this fact is of little diagnostic help.

The electrocardiographic differential diagnosis of paroxysmal atrial tachycardia, when block is present, is between atrial flutter, atrial fibrillation, and nodal rhythm. If the block remits transiently the condition may be mistaken for sinus tachycardia.

The most common mistake is to confuse P.A.T.B. with atrial flutter, and, as we have emphasized, at times consideration of the electrocardiogram alone may not differentiate them, and indeed the one arrhythmia may merge into the other within the space of a minute or so. It is not the differentiation of flutter from P.A.T.B. which is paramount—the essential problem is to ascertain whether digitalis is the cause of the arrhythmia. The danger lies in mistaking P.A.T.B. for flutter and thereby incorrectly concluding that digitalis should be given.

Atrial fibrillation is also easy to confuse with P.A.T.B., particularly when the P waves in the latter condition are very small, or not visible, and the ventricular response is grossly irregular. At times long-standing atrial fibrillation can suddenly be replaced by P.A.T.B. and only an electrocardiogram reveals that this has taken place. On the other hand, if an increased dose of digitalis is thought to have induced atrial fibrillation, very careful search for P waves should be made, including, if necessary, the use of leads CR1, V3R, VE (ensiform lead), and even oesophageal leads.

If in P.A.T.B. a high degree of atrioventricular block is present and unvarying, and the P waves are not visible, it may be very difficult to differentiate electrocardiographically from nodal rhythm.

If the atrial rate in paroxysmal atrial tachycardia is in the region of only 150 a minute and 1:1 atrioventricular response is present, the disorder may be indistinguishable from sinus tachycardia. However, carotid sinus pressure will usually increase the degree of atrioventricular block in paroxysmal atrial tachycardia, at least for the time being, and this may be recorded simultaneously on a direct-writing electrocardiograph at the bedside. Other points of difference electrocardiographically are that, in sinus tachycardia, as the rate increases the P wave tends to increase in amplitude, whereas this does not occur in P.A.T.B., where the P is usually small in any case. The P-R interval in sinus tachycardia tends to be short, whereas in P.A.T.B. it is variable and may be prolonged.

The problem not infrequently arises in which a patient is admitted with P.A.T.B. and it is not certain whether this, in fact, is the result of digitalis overdosage or whether it constitutes an indication for intensive digitalis therapy. There is no doubt that occasionally P.A.T.B. can persist for long periods without digitalis ever having been given, and Schwartz and Levine (1950) report such a patient in whom the arrhythmia persisted almost continuously for 25 years. If the P.A.T.B. is accompanied by multifocal ventricular extrasystoles and sagging of the S-T segment it can be assumed that digitalis is the cause (Fig. 6).

FIG. 6.—Lead VF. Paroxysmal atrial tachycardia with block, induced by digitalis. Atrial rate 115 a minute. Multifocal ventricular extrasystoles and S-T segment depression due to digitalis are present. Right bundle-branch block.

For patients where doubt exists whether or not digitalis has been responsible for the arrhythmia, Lown (1957) has introduced the intravenous acetyl-strophanthidin test. This is a means of deciding rapidly the degree of digitalization in the patient; but, particularly if the arrhythmia has been brought on by digitalis, the test is not without its dangers (Burgner and David, 1956), and indeed its fatalities, and we have no experience of it. The problem is an important one, and if doubt exists concerning the possibility of P.A.T.B. having been induced by digitalis we believe the following regime to be reasonable, and safer than the acetyl-strophanthidin test. First, carotid sinus stimulation is tried while a continuous direct-writing electrocardiogram is recorded. This simple manoeuvre may stop the P.A.T.B. if it is not due to digitalis but will prove ineffective if digitalis is the cause (see Table III). Whether digitalis is the cause or not, the degree of atrioventricular block will be increased, but if the atrial rate is appreciably slowed the arrhythmia is very unlikely to have been induced by digitalis.

If the result of carotid sinus compression is inconclusive an injection of atropine may be tried. In both P.A.T.B. without digitalis and that induced by digitalis the degree of atrioventricular block usually decreases, but in that not due to digitalis the atrial rate

may quicken (Fig. 5 C), whereas it remains unaffected in the digitalis-induced type.

If doubt still exists procainamide or quinidine should be tried. They are commonly effective in P.A.T.B. without digitalis (Fig. 5 D) but less often if the P.A.T.B. is caused by digitalis. If they prove ineffective then potassium should be given—either by mouth or, if deemed urgent, intravenously in the dosage recommended below.

While these studies were being made we were fortunate to have admitted to our ward a patient who developed both P.A.T.B. and congestive heart failure while under observation but to whom no digitalis or diuretics had been given. We were thus able to observe how carotid sinus pressure, and the administration of atropine, potassium chloride, and procainamide, differed in their effects in this patient compared with those in whom P.A.T.B. had been induced by digitalis.

Case 12.—A woman of 76 was admitted to hospital after an attempted suicide with barbiturates. Three months previously an abdominal-perineal excision had been performed for carcinoma of the rectum. Twenty-four days after admission congestive heart failure developed with a rapid irregular pulse. An electrocardiogram showed an irregular atrial rhythm with at times a 2:1 block, the atrial rate being about 150 a minute (Fig. 5 A). No digoxin or diuretic therapy had been given. An iron-deficient anaemia of 57% was present and occult blood was found in the stools. One injection of mersalyl 2 ml. intramuscularly produced a diuresis of 90 oz. (2,550 ml.), after which the serum electrolytes (mEq/l.) were sodium 126, potassium 3.2, chloride 87, bicarbonate 30. The blood urea was 27 mg./100 ml.

Carotid sinus pressure decreased the atrial rate to 100 a minute and increased the A-V block to 3:1 (Fig. 5). Atropine 0.65 mg. was given intravenously and the atrial and ventricular rates were increased *pari passu* (Fig. 5 C). An infusion of 1 g. of potassium chloride in 540 ml. of normal saline was given over six hours. Serial electrocardiograms during this period showed no significant change. Oral potassium was then given, 9 g. daily over six days. The serum potassium rose to 5.5 mEq/l., but the electrocardiogram remained unchanged. After 400 mg. of procainamide intravenously normal sinus rhythm returned (Fig. 5 D). Although this was followed by 50 mg. of procainamide q.d.s. as a maintenance dose the heart rhythm continued to vary between regular sinus rhythm, sinus rhythm with atrial premature contractions, and atrial tachycardia with block.

Prognosis

Prognosis is said to be grave if P.A.T.B. is induced by digitalis. Of Lown's (1957) 64 patients, 37 (58%) were dead shortly after the onset of the arrhythmia. However, we consider that as many of his patients were already seriously ill with congestive heart failure, and as at times P.A.T.B. can be mistaken for atrial arrhythmias such as fibrillation and flutter where digitalis may be considered the drug of choice and even a small dose thus prove fatal, the mortality is almost certainly less than has been thought. Of our 11 patients only two died, and in one of them death followed suddenly 12 hours after mitral valvotomy (Case 4).

Lown *et al.* (1959) are of the opinion that the state of the myocardium rather than the dose of digitalis is critical for the development of intoxication, and think that severe cardiac disease or acute cardiac infarction lower the threshold to digitalis. While in general this is true, only one of our patients had evidence of cardiac infarction, and this was not recent. Seven were, or had been, in cardiac failure.

Treatment

Treatment should be started without delay, for if the arrhythmia is ignored ventricular tachycardia may supervene at any time and death may result from ventricular fibrillation. As a rule all that is necessary is to stop the digitalis and discontinue diuretics and cation-exchange resins, but if any potassium-losing state is present this must be dealt with as a matter of urgency. The renal mechanism for the conservation of potassium is less efficient than for sodium, and even starvation can cause a low potassium. In practice, however, there are only two causes of severe potassium deficiency—namely, intestinal and renal. Insufficient absorption of potassium from the gut may result from excessive purgation, from chronic diarrhoea, or from loss of intestinal fluid through vomiting or aspiration. We would point out that at times, if the potassium loss is great and digitalis is given, P.A.T.B. may be so induced in the absence of any heart disease, as happened in our patient (Case 8), in whom the serum potassium fell to 3.7 mEq/l. as a result of small-bowel obstruction treated by gastric aspiration and intravenous therapy. Renal loss of potassium occurs in massive diuresis, either therapeutically induced or resulting from uncontrolled diabetes, or from treatment with corticosteroids and A.C.T.H. In the absence of renal disease the acidosis of dehydration can *per se* produce loss of potassium via the kidney.

Unless extreme rapidity of potassium replacement is considered, vital potassium chloride should be given orally. The usual dose to begin with is 2 g. (1 g.=13 mEq), but, provided serious renal disease can be excluded, as much as 5 g. may be given as a starting dose if the serum potassium is greatly diminished. However, as we have said, a normal serum potassium does not imply that the cardiac potassium is also normal, and it is not a contraindication to potassium therapy. It is emphasized that frequent electrocardiographic control is important, and special care is indicated in elderly patients and those with severe congestive heart failure. If after four hours sinus rhythm has not appeared a further dose of 2 g. can be given, and this may be repeated as required. If the need is thought to be most urgent, and provided renal function is adequate, the potassium may be given intravenously. We found a strength of 1 g. to the pint (570 ml.) of 5% glucose in water effective in one of our patients (Case 8).

If serious renal disease is present and oral potassium fails then either procainamide or quinidine should be tried. They may be effective in paroxysmal atrial tachycardia induced by digitalis and that not so induced, but almost certainly more so in the latter. Owing to its tendency to cause a severe fall in blood-pressure, procainamide is probably best given orally in the first place, but if it proves ineffective by this route it can be given intramuscularly with an almost equally rapid effect to that of intravenous injection (Enselsberg and Lipkin, 1952). The oral dose recommended is 1 g. followed by 0.5 g. six-hourly, and the intramuscular dose is 0.5 to 2 g. followed by 0.5 to 1 g. at intervals of several hours, depending upon the response. When quinidine was used we gave it by mouth.

As long ago as 1920 Zondek recognized the close relationship between digitalis, calcium, and potassium, and another treatment suggested for P.A.T.B. is lowering of the serum calcium by chelation. Like digitalis, the calcium ion alters the permeability of the cell membrane to sodium and potassium, and lowering of the serum

calcium may stop P.A.T.B. This can be achieved experimentally by sodium ethylenediamine tetra-acetic acid, which is a chelating agent with the property of binding calcium *in vivo* (Popovici *et al.*, 1950). Treatment of digitalis toxicity by this means has been employed by Gubner and Kallmann (1957). In our experience, however, stopping the digitalis preparation and diuretics, supplementing potassium, and preventing further potassium loss have always proved successful.

Summary

Although digitalis has been in use for over a century and a half and its toxic effects on the ventricles are well documented, its importance in the production of atrial arrhythmias has only recently been stressed. Of these, the commonest atrial disorder is P.A.T.B.

The potential seriousness of this arrhythmia when induced by digitalis is emphasized. Conditions which render the production of the arrhythmia likely, even with doses of digitalis that are small and have been unchanged for long periods, are discussed. The most important of these is a low myocardial potassium, the commonest cause of which is the use of diuretics.

We believe that P.A.T.B. is not a fixed specific entity, and that it merges into atrial flutter, from which at times it may be indistinguishable electrocardiographically or by any other means. Infinitely more important than trying to distinguish atrial flutter from P.A.T.B. is to determine whether digitalis is responsible for the arrhythmia. The problem of distinguishing P.A.T.B. due to digitalis from that arising without digitalis is discussed, and a regime is outlined by means of which it may be possible to differentiate them without submitting the patient to the risks of the acetyl-strophanthidin test.

The differential diagnosis is described in detail. We find the prognosis to be less serious than that usually stated; this is dependent upon the early recognition of the role of digitalis in precipitating the arrhythmia and stopping the drug immediately. Often no other treatment is necessary.

It has been claimed that serious myocardial disease with congestive heart failure is almost invariably present, but this was not so in our series; neither could we confirm the importance of fresh cardiac infarction as a precipitating factor. Details are given of a patient in whom no heart disease was present and yet in whom P.A.T.B. was induced by digitalis in the presence of a lowered serum potassium.

Although depression of the S-T segment was found in all patients, and ventricular premature beats in one-half of them, we wish to emphasize the uncommonness of other symptoms or signs of digitalis toxicity during the arrhythmia. Their absence cannot be taken as evidence that digitalis is not responsible for the P.A.T.B. Estimation of the serum potassium may also be misleading, as it does not necessarily reflect the myocardial potassium, and the administration of potassium, therefore, should not be withheld because the serum estimation is normal.

Addendum.—Since this paper was submitted for publication we have had two further cases, thus emphasizing the increasing frequency of this arrhythmia. (1) A man aged 85 was admitted in congestive heart failure of ischaemic origin and in sinus rhythm. Digoxin, 0.25 mg. b.d., with mersalyl, 2 ml. I.M. twice a week, was given and sodium restriction maintained. One week later P.A.T.B. developed. Digoxin and mersalyl were discontinued and potassium chloride, 8 g. daily, was given by mouth. Four days later sinus rhythm was restored. (2) A woman aged 70 was admitted in gross

congestive heart failure with P.A.T.B. She had received digitalis folia, $\frac{1}{2}$ gr. (32 mg.) t.d.s., for 18 months, with mercaptopimerin, 2 ml. twice weekly, and her sodium intake had been restricted. On her admission the serum potassium was 3.4 mEq/l. and the blood urea 40 mg./100 ml. Digitalis was reduced to $\frac{1}{2}$ gr. (32 mg.) b.d., and she was given potassium chloride, 1 g. t.d.s. by mouth. Atrial fibrillation developed and has remained.

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ATRIAL TACHYCARDIA WITH ATRIOVENTRICULAR BLOCK DUE TO DIGITALIS POISONING

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Digitalis can cause most types of cardiac arrhythmia. Ectopic beats (commonly ventricular), ventricular tachycardia, ventricular fibrillation, and heart-block are well-recognized manifestations of digitalis intoxication. It is not yet widely appreciated that atrial arrhythmias of various kinds may be caused by digitalis, and that one variety, atrial tachycardia with atrioventricular (A.V.) block, is almost always due to digitalis poisoning. This arrhythmia, which was first recognized as a complication of digitalis treatment by Sir James Mackenzie (1910), has received scant attention in this country, although several papers have been published about it in the United States during recent years (Lown and Levine, 1954, 1958; Goldberg, Bristow, Parker, and Ritzmann, 1958; Lown, Wyatt, and Levine, 1960).

The diagnosis of atrial tachycardia with atrioventricular block can be made only from the electrocardiogram. Clinically, its presence may be suspected