1968; Ceremużyński *et al.*, 1969; Kurien *et al.*, 1969), and it is well known that catecholamines can release F.F.A.s from adipose tissue, thus raising their circulatory levels (Carlson, 1968).

The present study has shown that it is possible to predict those patients liable to develop significant arrhythmias following acute myocardial infarction by using a plasma noradrenaline level obtained early in the course of their illness. F.F.A. levels obtained simultaneously were of no value in predicting these vulnerable patients.

It is suggested that plasma noradrenaline estimations could be used to determine those patients who would benefit most from the continuous monitoring facilities of a coronary care unit.

If dysrhythmias following acute myocardial infarction are related to the excess circulating noradrenaline then clearly β-adrenergic blocking agents could be of prophylactic value. Propranolol has undergone several unsuccessful trials in this connexion (Clausen *et al.*, 1966; Balcon *et al.*, 1967; Norris *et al.*, 1968). In these trials the dose administered was limited by the drug's negative inotropic properties. The more recently introduced practolol, which does not possess significant negative inotropic properties, might be of more value as a prophylactic measure in this clinical situation.

This study was suggested by Dr. J. F. Pantridge.

REFERENCES

Balcon, R., Jewitt, D. E., Davies, J. P. H., and Oram, S. (1967). *American Heart Journal*, 74, 582.
Carlson, L. A. (1968). In *Acute Myocardial Infarction*, ed. D. G. Julian and M. F. Oliver, p. 243. Edinburgh, Livingstone.
Ceremużyński, L., Staszewska-Barczak, J., and Herbaczynska-Cedro, K. (1969). *Cardiovascular Research*, 3, 190.
Clausen, J., *et al.* (1966). *Lancet*, 2, 920.
Douglas, A. S. (1962). *Anticoagulant Therapy*, p. 211. Oxford, Blackwell Scientific.
Gazes, P. C., Richardson, J. A., and Woods, E. F. (1959). *Circulation*, 19, 657.
Gupta, D. K., Young, R., Jewitt, D. E., Hartog, M., and Opie, L. H. (1969). *Lancet*, 2, 1209.
Kurien, V. A., and Oliver, M. F. (1966). *Lancet*, 2, 122.
Kurien, V. A., Yates, P. A., and Oliver, M. F. (1969). *Lancet*, 2, 185.
McCullough, H. (1968). *Journal of Clinical Pathology*, 21, 759.
McDonald, L., Baker, C., Bray, C., McDonald, A., and Restieaux, N. (1969). *Lancet*, 2, 1021.
Maurer, B. J. (1970). "The Incidence of Venous Thrombosis following Acute Myocardial Infarction," paper presented to the Association of Physicians of Great Britain and Ireland on 11 April.
Mitchell, J. R. A., and Schwartz, C. J. (1965). *Arterial Disease*, p. 357. Oxford, Blackwell Scientific.
Mosinger, F. (1965). *Journal of Lipid Research*, 6, 157.
Norris, R. M., Caughey, D. E., and Scott, P. J. (1968). *British Medical Journal*, 2, 398.
Oliver, M. F., Kurien, V. A., and Greenwood, T. W. (1968). *Lancet*, 1, 710.
Richardson, J. A. (1963). *Progress in Cardiovascular Disease*, 6, 56.
Rutenburg, H. L., Pamintuan, J. C., and Soloff, L. A. (1969). *Lancet*, 2, 559.
Rutenburg, H. L., and Soloff, L. A. (1970). *Lancet*, 1, 198.
Rutstein, D. D., Castelli, W. P., and Nickerson, R. J. (1969). *Lancet*, 1, 1003.
Staszewska-Barczak, J., and Ceremużyński, L. (1968). *Clinical Science*, 34, 531.
Trout, D. L., Estes, E. H., and Friedberg, S. J. (1960). *Journal of Lipid Research*, 1, 199.
Wright, I. S. (1968). *South African Medical Journal*, 42, 812.

Large-scale Digitoxin Intoxication

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Summary: Because of an error in the manufacture of digoxin tablets a large number of patients took tablets that contained 0·20 mg. of digitoxin and 0·05 mg. of digoxin instead of the prescribed 0·25 mg. of digoxin. The symptoms are described of 179 patients who took these tablets and suffered from digitalis intoxication. Of these patients, 125 had taken the faultily composed tablets for more than three weeks. In 48 patients 105 separate disturbances in rhythm or in atrioventricular conduction were observed on the electrocardiogram. Extreme fatigue and serious eye conditions were observed in 95% of the patients. Twelve patients had a transient psychosis. Extensive ophthalmological observations indicated that the visual complaints were most probably caused by a transient retrobulbar neuritis.

Introduction

At the beginning of February 1969 several patients were admitted to our hospital with symptoms of serious digitalis intoxication. They had all taken tablets containing 0·25 mg. of digoxin in normal daily dosage for months or years without incurring side-effects. This led us to suspect that the composition of the latest tablets supplied was faulty. On 7 February we asked the local pharmaceutical chemist to examine them. On 12 February we were informed that the tablets contained 0·20 mg. of digitoxin and 0·05 mg. of digoxin instead of 0·25 mg. of digoxin.

The chemist, who supplied drugs to the town of Veenendaal (±30,000 inhabitants) as well as to the local hospital had delivered the tablets on 6 December 1968. At the most, therefore, the patients had been taking them for 10 weeks. As we knew the dates of their delivery we could trace the number of days each patient had taken them.

Immediately it became known that digitoxin intoxication had occurred on a large scale many of the patients with serious symptoms were admitted to hospital. We went through the case histories of all those who had been admitted during the previous two months, and it became evident that we had in fact seen even more patients with digitalis intoxication.

In maintenance dosage digitoxin is weight for weight more active than digoxin. This is due to better resorption and slower excretion. Moe and Farah (1965) mentioned a daily maintenance dose of 0·05 to 0·2 mg. for digitoxin and 0·25 to 1 mg. for digoxin. Friedberg (1966) gives 0·05 to 0·2 mg. for digitoxin and 0·125 to 0·75 mg. for digoxin. According to these amounts, our patients had taken a daily dose of cardiac glycosides which was 2·2 to 4·2 times higher than that prescribed. Numerous publications have appeared since Withering's (1785) frequently quoted observations on digitalis intoxication.

Fairly large studies of digitalis intoxication during digitalis therapy among inpatients have been published—by Flaxman (1948) 30 cases, Crouch *et al.* (1956) 100 cases, Shrager (1957) 40 cases, von Capeller *et al.* (1959) 148 cases, Rodensky and Wasserman (1961) 88 cases, Dreifus *et al.* (1963) 161 cases, Schölmerich *et al.* (1964) 143 cases, Dubnow and Burchell (1965) 236 cases, and Chung (1969) 180 cases. With the exception of the reports of Flaxman (1948) and Rodensky and Wasserman (1961) these cases were assembled in retrospect, with all the shortcomings of such situations. In addition, most of these series were based solely on the electrocardiographic evidence of digitalis intoxication. These drawbacks do not apply to the report by Church *et al.* (1962), who, in 41 episodes, deliberately gave excessive amounts of digitalis to 30 patients.

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In France, where frequent attempts at suicide with digitaline (digitoxin) solution have been made in recent years, two large series of intoxication by ingestion of a massive dose of digitoxin have been published by Potter *et al.* (1964), 45 cases, and by Gaultier *et al.* (1968), 70 cases. More than half of these cases were of patients with a previously sound heart. So far as we know an epidemic of digitoxin intoxication among patients on a maintenance dose of digitalis has not yet taken place.

Patients and Materials

In 179 patients (90 females and 89 males) digitalis intoxication was caused by the taking of faultily composed tablets; 68% were 60 years of age or older. Previously all of them had taken digoxin tablets—in a daily maintenance dose—for periods ranging from a few months to several years without showing symptoms of digitalis intoxication. Of these 179 patients 47 were treated in hospital. After the faultily composed tablets had been withdrawn the symptoms of intoxication disappeared in all patients with the exception of those who died.

Ninety-three patients (52%) received a daily maintenance dose of one tablet, 78 (44%) received two tablets, and 8 received three tablets per day. In Table I the time during which the tablets were taken is recorded; on average this was four to five weeks. Twenty-nine patients (17%) took them for more than eight weeks. In 85 patients we could trace the number of weeks during which they had symptoms before use of the tablets was stopped (Table II). Twenty-four patients (28%) had had symptoms for more than three weeks and 7 (8%) for more than five weeks.

The symptoms are recorded in Table III. It was not possible to interview all 179 patients during the period of illness. In 160 we were able to trace the number of weeks which elapsed before they were free from symptoms. In most cases this was from one to four weeks after withdrawal of the tablets (see Table IV). After four weeks 24 patients (15%) were still not free of symptoms. At that time we had assembled the case histories of 111 patients, leaving the remainder to be collected later. Electrocardiograms of 47 patients were taken during intake, or at least within 24 hours after the withdrawal, of the tablets. Changes typical of digitalis intoxication were seen in 38 of these. Between the second and the seventh day after cessation of the tablets, electrocardiograms were taken of another 19 patients, and 11 showed typical changes. When we found disturbances typical of digitalis intoxication, electrocardiograms were taken daily in most patients. Frequently, more than one type of disturbance occurred in the one electrocardiogram, and often during subsequent days still more types were observed. In 48 patients we observed 105 separate disturbances in rhythm or in atrioventricular conduction (Table V).

We may assume that use of the tablets contributed to the death of six of the inpatients. Four of these died before we suspected the faulty composition of the tablets, and we attributed death to their poor myocardial condition. All of the six patients had had an arrhythmia before death. It is known that all the disturbances in cardiac rhythm and conduction caused by digitalis intoxication can also be the result of a poor condition of the heart.

Apart from the 179 patients previously mentioned, we saw 17, of whom 13 had taken the faultily composed tablets for more than two weeks with no or at least only doubtful symptoms of digitalis intoxication. Among these 17 patients there were only a few whose myocardial condition was poor. In a further 17 patients, owing to their poor mental condition, it was not possible to obtain a good history of their symptoms. Information obtained from local general practitioners showed that the faulty tablets had led to fairly serious symptoms of digitalis intoxication in a number of their patients also (not included in this article). It was presumed that the tablets had contributed to the death of some of them.

TABLE I.—*Number of Weeks During which the Faultily Composed Tablets were Taken by the 179 Patients who Developed Digitoxin Intoxication*

No. of weeks	—1	—2	—3	—4	—5	—6	—7	—8	—9	—10	Unknown
No. of patients	8	19	25	24	23	23	15	12	27	2	1

TABLE II.—*Duration of Complaints in 85 Patients Before Withdrawal of the Faultily Composed Tablets*

No. of weeks	—1	—2	—3	—4	—5	—6	—7	—8
No. of patients	9	25	27	10	7	5	1	1

TABLE III.—*Symptoms of 179 Patients with Digitoxin Intoxication*

Symptoms	Percentage	
	Positive	Negative
Fatigue	95	5
Visual complaints	95	5
Muscular weakness	82	18
Nausea	81	19
Anorexia	80	20
Psychic complaints	65	35
Abdominal pains	65	35
Dizziness	59	41
Dreams	54	46
Headache	45	55
Diarrhoea	41	59
Vomiting	40	60
Retrosternal pains	9	91

TABLE IV.—*Duration of the Complaints after Cessation of the Faultily Composed Tablets in 160 Patients*

No. of weeks	—1	—2	—3	—4	—5	—6	—7	—8	—9	—10
No. of patients	22	44	46	24	6	11	4	1	1	1

TABLE V.—*105 Separate Disturbances in Rhythm or in Atrioventricular Conduction Observed on Electrocardiograms of 48 Patients with Digitoxin Intoxication*

Sinus arrhythmia	2
Sino-auricular block	3
Sinus bradycardia	4
Coronary sinus rhythm	1
Supraventricular tachycardia	1
Atrial tachycardia with block	4
Atrial fibrillation	4
Atrial flutter	1
Atrial extrasystoles	5
Atrial bigeminy	1
Nodal rhythm	6
Nodal tachycardia	6
First-degree block	21
Second-degree block	1
Total block	5
Changing A.V. conduction	2
Wenckebach phenomenon	1
Ventricular bradycardia with atrial fibrillation	6
Unifocal ventricular extrasystoles	14
Multifocal ventricular extrasystoles	8
Ventricular bigeminy	7
Ventricular tachycardia	2

Comment

Gastrointestinal Symptoms.—Eighty per cent. of the patients complained of anorexia and nausea (Table III), these often being the first symptoms. In 40% of the patients vomiting occurred, sometimes in combination with stomach pain. For a short time the vomit consisted of mucus. Diarrhoea occurred in 41% of patients, mostly only for a few days, stools resembling a foamy liquid. Abdominal pains occurred in 65%, the patients often complaining of a tight and bloated

feeling. Two were admitted to hospital with an acute abdominal syndrome.

Neuromuscular and Psychiatric Symptoms.—Ninety-five per cent. of the patients complained of acute fatigue. This was often expressed as a "deadly tiredness" and a "most miserable feeling." In 82% muscular strength was diminished, so that there was difficulty in walking and in raising the arms. Ten patients had vague pains in the calves, back, and arms. Psychic disturbances were present in 65% of the patients. These included bad dreams, restlessness, nervousness, agitation, listlessness, drowsiness, and fainting. Pseudohallucinations were observed in 12 patients and delirium in four (Weenink *et al.*, 1969). Two patients had generalized itching.

Visual Symptoms.—Ninety-five per cent. of the patients had visual disturbances, which were often among the initial symptoms. Most of them complained of hazy vision and difficulty in reading. Often the colours of objects seemed altered and indistinct. Some patients had photophobia, and many saw all kinds of glitterings, moving spots, balls, rings, and flames with yellow, red, green, or dark colours. Some distinctly described a dark spot in the centre of their field of vision. Of the 79 patients examined ophthalmologically (Cozijnsen and Pinckers, 1969), 43 were investigated intensively during the first 10 days after withdrawal of the tablets. In eight patients colour vision was studied both at that point and again three months later, with the so-called Farnsworth Munsell Hue 100 test. The clinical picture was that of retrobulbar neuritis. Nearly all patients had a disturbance in red-green perception. More extensive study of the colour vision revealed the presence of a transient acquired disorder of the protan type.

Cardiac Symptoms.—The effects of digitalis, which consist of ST-T wave changes, shortening of Q-T intervals, and pronounced U waves, were observed in 70%. This effect can occur in any patient who takes digitalis, and does not necessarily suggest intoxication. First-degree heart block (PQ time longer than 0·21 second) was observed on 21 occasions and total heart block on five, once accompanied by an idioventricular rhythm and four times by nodal rhythm. Nodal rhythm was seen in six cases, a nodal tachycardia in another six, and one case showed atrial flutter. Atrial tachycardia with block was present in four patients, three of whom were among the six who died. Ventricular tachycardia was observed twice; in one patient it was accompanied by Adams-Stokes attacks and in the other it occurred just before death. Fifteen patients had angina-pectoris-like attacks which disappeared after the tablets were withdrawn. We did not observe any definite aggravation of cardiac insufficiency. Hypopotassaemia was not observed, the lowest level being 3·5 mEq/l.

Therapy

Patients with very serious symptoms were treated with phenytoin (diphenylhydantoin), orally or intravenously. Other patients received oral potassium. Intravenous infusions with lignocaine were given to a few patients with arrhythmia.

Discussion

The symptoms of digitalis intoxication are generally reported to occur in 7 to 20% of adult patients taking digitalis (Rodensky and Wasserman, 1961; Resnick, 1964; Gotsman and Schrire, 1966). Probably the most reliable work in this connexion comprises the recent epidemiological studies of Shapiro *et al.* (1969), who found signs and symptoms of intoxication in 18·3% of 441 patients who took digitalis, and of Hurwitz and Wade (1969), who mention adverse reactions in 19·8% of 192 patients. During the last two decades this percentage has become greater as a result of the use of potent diuretics and the increasing number of elderly patients. Subjects with a poor myocardial condition are more prone to disturbances in heart rhythm and conduction. Among other factors, cor pulmonale, acute myocardial infarction, potassium depletion (whatever the cause), myxoedema, and diminished renal function increase the risk of digitalis intoxication (Cohen, 1952; Chung, 1969; Surawicz and Mortelmans, 1969). Frequently digitalis intoxication is not recognized (Dall, 1965; Sodeman, 1965).

Abdominal pain, as frequently observed by us, is described by some authors as only a symptom of digitalis intoxication (Shrager, 1957; Rosenberg and Graettinger, 1962; Moe and Farah, 1965; Rutledge and Haddad, 1966). Other authors do not mention it (Crouch *et al.*, 1956; von Capeller *et al.*, 1959; Friedberg, 1966).

Less serious psychic conditions such as tiredness, nervousness, restlessness, dreaming, and headache are easily overlooked as symptoms of digitalis intoxication, especially when digitalis is used in a maintenance dose.

Delirium caused by digitalis intoxication was mentioned for the first time by Duroziez (1874). Thereafter it was described on several occasions (King, 1950; Church and Marriott, 1959; Rodová and Hovola, 1959). Gaultier *et al.* (1968) found it in 31% of their cases of digitalis intoxication due to one massive dose of digitoxin.

The frequency of visual complaints in the previously mentioned large series is about 10%. The fact that we found these visual complaints in nearly all our patients is perhaps due to the long duration of intake of the faultily composed tablets.

Angina pectoris has seldom been mentioned as a symptom of digitalis intoxication (Mackenzie, 1908; Fenn and Gilbert, 1932, seven cases). Perhaps it is caused by decreased cardiac output resulting from diminished contractility or arrhythmia due to digitalis overdosage. A relative coronary insufficiency due to the higher oxygen demand of the heart muscle during arrhythmia is also a possible cause. The digitalis effect that, according to Cohen (1952), is present in 30% of cases of digitalis intoxication was observed by us in 70% of our patients. Until 1969 atrial flutter was mentioned only 30 times as a sign of digitalis intoxication; in our series we observed one case. In 75% of the cases of atrial tachycardia with block digitalis the cause of this arrhythmia is intoxication, and is mostly seen when the myocardium is seriously damaged. It has a bad prognosis (Lown *et al.*, 1959). We observed this phenomenon in four patients, three of whom were among the six who died. In the larger series mentioned earlier in this article it was seen in 4 to 10% of the cases.

Nodal escape rhythm and nodal tachycardia are often seen during digitalis intoxication. Shrager (1957), von Capeller *et al.* (1959), and Dubnow and Burchell (1965) observed the condition in 5 to 10% of their patients, and Chung (1969) saw it in 46%. We found this arrhythmia in 25% (12 cases).

Neuralgia and gynaecomastia, occurring as symptoms of digitalis intoxication (Meyler, 1966), were not observed in any of our patients.

Digitoxin, when given in the normal dose, is excreted for the most part in two to three weeks (Friedberg, 1966). In patients who receive an overdosage the period is longer. In our cases 14% still had complaints after four weeks.

We observed 21 patients who resumed digoxin therapy in a normal dose about eight days after they had stopped taking the faultily composed tablets. These patients again incurred all the symptoms of digitalis intoxication. At that point they probably still had a high level of cardiac glycosides in their organs, and thus a normal dose of digoxin could cause a digitalis intoxication.

It is worth noting that this large-scale digitoxin intoxication was recognized only in the town of Veenendaal and not in the rest of the Netherlands, where the cases might have been more scattered. In the country as a whole, out of a total of 470,000 faultily composed tablets, 200,000 were used by patients. The chemist in Veenendaal obtained 47,000 tablets.

When, on 12 February 1969, it became clear that these tablets contained too much active cardiac glycoside 38,000 tablets had already been delivered. Of these, 6,000 could be recovered, so that 32,000 faulty tablets were used. So far as we know, outside Veenendaal, patients with symptoms of digitalis intoxication due to the use of these tablets were discovered only here and there. This could be explained by the fact that the chemist in Veenendaal was the first in the country to be fully supplied with these tablets and also by the fact that this one chemist was responsible for providing drugs to the whole town (about 30,000 inhabitants) and to the hospital. It is possible that many cases went undiscovered. In our material we observed a pattern of complaints different from what is normally described. In particular, the high percentage of extreme fatigue and of visual symptoms (both 95%) is striking. This can probably be explained by the fact that a similar intoxication with an excessive maintenance dose of digitoxin had never before been observed.

We wish to thank Dr. J. Pool, of the department of cardiology, University Hospital, Leiden, for his help in this investigation.

A preliminary report on this large-scale digitoxin intoxication has been published elsewhere (Lely *et al.*, 1969).

REFERENCES

Chung, E. K. (1969). *Digitalis Intoxication.* Amsterdam, Excerpta Medica.
Church, G., and Marriott, H. J. L. (1959). *Circulation,* **20,** 549.
Church, G., Schamroth, L., Schwartz, N. L., and Marriott, H. J. L. (1962). *Annals of Internal Medicine,* **57,** 946.
Cohen, B. M. (1952). *New England Journal of Medicine,* **246,** 225, 254.
Cozijnsen, M., and Pinckers, A. J. L. G. (1969). *Nederlandsch Tijdschrift voor Geneeskunde,* **113,** 1735.
Crouch, R. B., Herrmann, G. R., and Hejtmancik, M. R. (1956). *Texas State Journal of Medicine,* **52,** 714.
Dall, J. L. C. (1965). *American Heart Journal,* **70,** 572.
Dreifus, L. S., McKnight, E. H., Katz, M., and Likoff, W. (1963). *Geriatrics,* **18,** 494.
Dubnow, M. H., and Burchell, H. B. (1965). *Annals of Internal Medicine,* **62,** 956.
Duroziez, P. (1874). *Gazette Hebdomadaire des Sciences Médicales de Bordeaux,* **11,** 780.
Fenn, G. K., and Gilbert, N. C. (1932). *Journal of the American Medical Association,* **98,** 99.
Flaxman, N. (1948). *American Journal of the Medical Sciences,* **216,** 179.
Friedberg, C. K. (1966). *Diseases of the Heart,* 3rd edn., p. 377. Philadelphia, Saunders.
Gaultier, M., *et al.* (1968). *Bulletin et Mémoires de la Société Médicale des Hôpitaux de Paris,* **119,** 247.
Gotsman, M. C., and Schrire, V. (1966). *South African Medical Journal,* **40,** 590.
Hurwitz, N., and Wade, O. L. (1969). *British Medical Journal,* **1,** 531.
King, J. T. (1950). *Annals of Internal Medicine,* **33,** 1360.
Lely, A. H., van Enter, C. H. J., and Pool, J. (1969). *Nederlandsch Tijdschrift voor Geneeskunde,* **113,** 1729.
Lown, B., Marcus, F., and Levine, H. D. (1959). *New England Journal of Medicine,* **260,** 301.
Mackenzie, Sir J. (1908). *Diseases of the Heart.* London, Frowde.
Meyler, L. (editor) (1966). *Side Effects of Drugs.* vol. 5. Amsterdam, Excerpta Medica.
Moe, G. K., and Farah, A. E. (1965). In *The Pharmacological Basis of Therapeutics,* ed. L. S. Goodman and A. Gilman, 3rd edn., p. 691. New York, Macmillan.
Potter, M., Perrot, L., Vendrinne, J., and Restoy, R. (1964). *L'intoxication Digitalique Massive.* Paris, Masson.
Resnick, N. (1964). *Medical Science (Philadelphia),* **4,** 31.
Rodensky, P. L., and Wasserman, F. (1961). *Archives of Internal Medicine,* **108,** 171.
Rodová, A., and Hovola, D. (1959). *Československá Psychiatrie,* **55,** 357.
Rosenberg, M. S., and Graettinger, J. S. (1962). *Disease-a-Month,* November, p. 1.
Rutledge, D. I., and Haddad, R. (1966). *Medical Clinics of North America,* **50,** 501.
Schölmerich, P., Pabst, K., Jahrreiss, O., and Lange, K. P. (1964). *Deutsche Medizinische Wochenschrift,* **89,** 12.
Shapiro, S., Slone, D., Lewis, G. P., and Jick, H. (1969). *Journal of Chronic Diseases,* **22,** 361.
Shrager, M. W. (1957). *Archives of Internal Medicine,* **100,** 881.
Sodeman, W. A. (1965). *New England Journal of Medicine,* **273,** 35, 93.
Surawicz, B., and Mortelmans, S. (1969). In *Digitalis,* ed. Ch. Fisch and B. Surawicz, p. 127. New York, Grune and Stratton.
von Capeller, D., Copeland, G. D., and Stern, T. N. (1959). *Annals of Internal Medicine,* **50,** 869.
Weenink, H. R., Lely, A. H., and van Enter, C. H. J. (1969). *Nederlandsch Tijdschrift voor Geneeskunde,* **113,** 1733.
Withering, W. (1785). *An account of the foxglove and some of its medical uses,* Birmingham, G. G. J. and Robinson, J. (Reprinted in *Medical Classics,* 1937, **2,** 295).

Haemodynamic Studies with Peruvoside in Human Congestive Heart Failure

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Summary: The immediate haemodynamic effects of peruvoside, a cardiac glycoside obtained from the Indian plant *Thevetia neriifolia* Juss, were studied in six patients with congestive heart failure. The drug was found to have an immediate and powerful positive inotropic and negative chronotropic effect, like ouabain, on the failing human heart. Oral peruvoside was also effective in the treatment of congestive heart failure when used on a short-term as well as a long-term basis. It therefore seems that peruvoside is a useful cardiac glycoside in the management of congestive heart failure in man as a quick-acting intravenous preparation. It is equally effective when used orally.

Introduction

Peruvoside, a cardiac glycoside isolated by Rangaswami and Rao (1959) from the kernels of the Indian indigenous plant *Thevetia neriifolia* Juss, is stated to have a positive inotropic effect in the cat papillary muscle (De *et al.*, 1963), guinea-pig heart (Kohli and Vohra, 1960), and the failing heart of mongrel dogs (Arora *et al.*, 1967). Studies in congestive heart failure in man are, however, not available. In this communication we outline the haemodynamic effects of intracardiac peruvoside in six patients with heart failure of varying aetiology. We also report our observations on the clinical response to oral peruvoside in these six and in an additional 22 patients treated for 2 to 54 weeks.

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Patients and Methods

The six patients (two men and four women) with heart failure, physiologically studied, were aged 30 to 60 years. Congestive heart failure was due to coronary heart disease and primary myocardial disease in two patients each and to atrial septal defect and rheumatic mitral incompetence in one patient each. Three patients were in atrial fibrillation at the time of study. Patients were studied within 48 hours of admission. The investigative nature of the treatment was explained to each patient and consent obtained before the study. Any patient who had received a digitalis preparation in the preceding seven days was excluded from the study.

Right heart catheterization was carried out in the post-absorptive resting state in the supine position with standard techniques. The brachial artery was cannulated for continuous monitoring of arterial pressure and as a site for sampling blood-dye mixture for recording indicator dilution curves.