Beta-adrenergic Blockade and Cardiac Arrhythmias*

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The evaluation of beta-adrenergic blockade in cardiac arrhythmias is difficult because of the complex nature of the arrhythmias and the varied modes of action of blocking drugs. Studies have confirmed the therapeutic value of the beta-adrenergic blocking drug pronethalol (Alderlin) (Vaughan Williams, 1963; Stock and Dale, 1963; Payne and Senfield, 1964; Wolfson *et al.*, 1966) and its more potent successor, propranolol (Inderal) in the management of many different atrial and ventricular arrhythmias (Harrison *et al.*, 1965; Sloman *et al.*, 1965; Stock, 1966; Harris, 1966; Szekely *et al.*, 1966; Cherchi *et al.*, 1966; Rochet and Vastesaeger, 1966; Gettes and Surawicz, 1966; Luria *et al.*, 1966; Epstein and Braunwald, 1966).

This study reports our experience in the management of patients with paroxysmal arrhythmias, acute life-threatening arrhythmias, and recurrent arrhythmias associated with prolonged cardiac arrest. An attempt has also been made to assess the prophylactic value of propranolol in reducing the high incidence of arrhythmias associated with acute myocardial infarction.

Materials and Methods

Thirty-one patients presenting with various cardiac arrhythmias were included in this study. Patients in whom full documentation was not available were not included. There were 19 males and 12 females, with an age range from 17 to 78 (mean 50.9 years). In all these patients the arrhythmia had proved disabling; in some it was associated with prolonged cardiac arrest.

Forty-nine patients with acute myocardial infarction were studied to assess the prophylactic value of propranolol in preventing arrhythmias. The patients were divided into four major groups: group A, chronic arrhythmias, recurrent and continuous; group B, acute arrhythmias; group C, arrhythmias associated with prolonged cardiac arrest; and group D, acute myocardial infarction.

Propranolol was given intravenously or orally, depending on the urgency of the clinical situation: the details of drug therapy are discussed under each group.

Results

Group A: Chronic Arrhythmias, Recurrent and Continuous

There were 16 patients in this group (Table I). Four had atrial fibrillation, not adequately controlled by digitalis or other anti-arrhythmic drugs. In three the fibrillation was paroxysmal, frequently causing syncope at its onset. In the fourth fibrillation was continuous, but the rate could not be adequately controlled by digitalis alone. There were five patients with paroxysmal atrial tachycardia, not adequately controlled by digoxin and quinidine sulphate. Four patients had other atrial arrhythmias, while the remaining three were in sinus rhythm with frequent ventricular ectopic beats, but suffered syncopal attacks due to paroxysmal ventricular tachycardia.

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TABLE I.—*Propranolol. Chronic Arrhythmias, Recurrent and Continuous*

Case No.	Age	Sex	Presenting Symptoms	Arrhythmia	Failed Therapy	Propranolol Dose	Results
				Atrial Fibrillation			
1	52	F	Syncope	Paroxysmal	Digitalis	40 mg. 4 × /day	No syncope
2	55	F	„	„	Procainamide	10 mg. 4 × /day plus digoxin	Palpitations only. No syncope
3	56	M	„	Paroxysmal with runs of ventricular tachycardia	Quinidine. Procainamide. Digoxin. Pacemaker + digoxin	20 mg. 3 × /day plus pacemaker	No syncope
4	25	F	Dyspnoea	Continuous atrial fibrillation	Digoxin	10 mg. 4 × /day plus digoxin	Rate slowed
				Paroxysmal Atrial Tachycardia			
5	57	M	Palpitations	Paroxysmal atrial tachycardia	Digoxin. Quinidine	5 mg. 4 × /day inc. to 60 mg. 4 × /day	Control. Occasional palpitations
6	49	F	„	„ „ „	Multiple. Details not known	20 mg. 4 × /day plus digoxin	Control (recent)
7	41	M	Palpitations and faintness	„ „ „	Digoxin. Quinidine	20 mg. 4 × /day plus digoxin	Control
8	69	M	Palpitations	„ „ „	Quinidine. Digoxin	10 mg. 3 × /day plus digoxin	„
9	56	M	Palpitations. Cardiac failure		Digoxin. Procainamide. Quinidine. Phenytoin sodium. D.C. shock	10 mg. 4 × /day plus procainamide	„
				Other Atrial Arrhythmias			
10	20	M	Palpitations 6 years	Atrial tachycardia with A-V dissociation	Digoxin. Quinidine	10 mg. 4 × /day plus digoxin, quinidine, and corticosteroids	Control
11	29	M	Palpitations. Cardiac failure	„ „ „	Digoxin. D.C. shock	10 mg. 4 × /day plus digoxin	Rate slowed. Later reversion to sinus rhythm
12	52	F	Palpitations	Sinus tachycardia	Digoxin	10 mg. 2 × /day	Control
13	42	M	„	Atrial flutter	Digoxin. D.C. shock	3 mg. I.V. then 10 mg. 3 × /day	Slowed
				Ventricular Arrhythmia			
14	58	M	Syncope	Frequent V.E.S. plus ventricular tachycardia	Nil	40 mg. 3 × /day	Control
15	45	M	„	Frequent V.E.S. plus ventricular tachycardia on exercise	Quinidine	10 mg. 3 × /day plus quinidine	„
16	17	F	Palpitations. Syncope	Frequent V.E.S. with coupling on exercise	Quinidine	10 mg. 4 × /day	„

V.E.S. = Ventricular extrasystoles. D.C. = Direct current.

When the arrhythmia could be produced by exercise on the treadmill (Cases 1, 3, 7, 8, 11, 14, and 16) after recording the abnormal rhythm the patient was rested, given an intravenous dose of propranolol (0.1 mg./kg. body weight with 1.2 to 2.4 mg. of atropine sulphate), and after 10 minutes the exercise study was repeated (Fig. 1). Provided the arrhythmia was controlled propranolol was continued in an oral dose, beginning with 10 mg. every six hours. The dose was increased as necessary to a maximum in this study of 60 mg. four times a day.

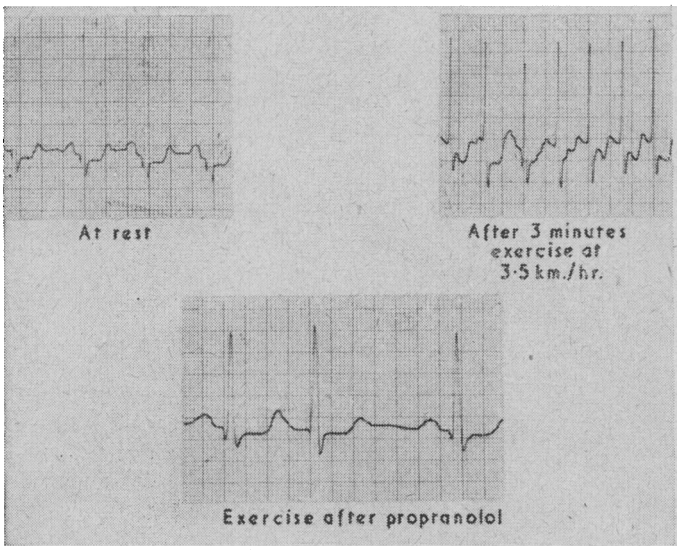

FIG. 1.—Electrocardiograms at rest and during exercise, showing the effect of propranolol in preventing atrial fibrillation.

In the four patients with atrial fibrillation symptoms were controlled in three when propranolol was added to their regimen (Cases 1, 2, and 4). In Cases 1 and 2 the paroxysms continued, but syncope did not occur. In Case 3 syncopal attacks continued to occur with exercise despite full treatment with digitalis, quinidine, and pronethalol. Endocardial pacemaking was then begun; however, the rhythm still alternated between a sinus mechanism and atrial fibrillation. With digitalis and pacing alone syncope continued to occur, but when propranolol was added syncope did not occur.

In the patients with paroxysmal atrial tachycardia the arrhythmia was suppressed provided the dose of propranolol was maintained, except in Case 5, where digoxin was necessary as well as the propanolol. When one patient (Case 7) discontinued treatment after three years he experienced one severe attack before resuming therapy. Two of the four patients with other atrial arrhythmias were suffering from a cardiomyopathy (Cases 10 and 11). Despite a failed direct current reversion in Case 11, both patients reverted to a sinus mechanism while receiving propranolol in addition to other medication. The patient with persistent unexplained sinus tachycardia (Case 12) showed a satisfactory reduction in rate, as did the patient with rapid atrial flutter due to thyrotoxicosis. The arrhythmia in this case reverted to sinus rhythm when the thyrotoxicosis was controlled. In the group with ventricular ectopic beats propranolol reduced the ectopic beats and prevented the syncopal attacks.

Group B: Acute Arrhythmias

The seven patients included in this group had serious arrhythmias of acute onset associated with severe cardiac disease (Table II), and the dose and route of administration of propranolol varied with the type of the arrhythmia and the urgency of the clinical situation. In two patients the arrhythmia was associated with acute myocardial infarction and in three others coronary artery disease was associated with pulmonary embolism, digitalis toxicity, and a past history of paroxysmal atrial tachycardia respectively. Of the remaining two, one developed multifocal ventricular extrasystoles while undergoing surgery for subarachnoid haemorrhage, while the other had rapid atrial fibrillation associated with an alcoholic cardiomyopathy.

There were two patients with acute myocardial infarction. In one atrial flutter occurred (Case 17). After propranolol the ventricular rate slowed initially, and later there was reversion to sinus rhythm. In the other (Case 21) paroxysmal ventricular tachycardia was rapidly suppressed with oral propranolol (Fig. 2). Of the three patients with coronary disease propranolol proved effective in controlling both atrial and ventricular arrhythmias. In Case 18 multiple atrial and ventricular arrhythmias were controlled after quinidine, digoxin, and phenytoin sodium (Dilantin) had proved unsuccessful. In Case 23 an episode of very rapid nodal tachycardia with cardiac

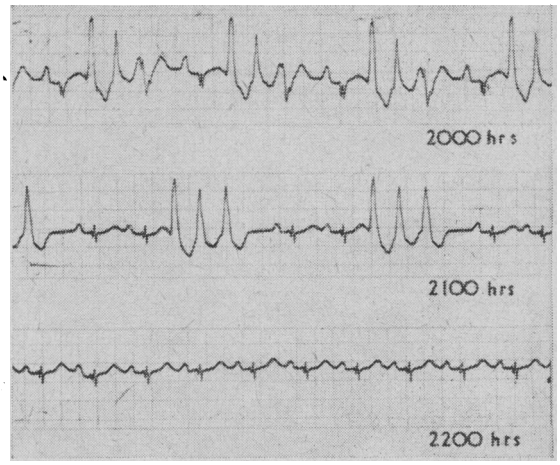

FIG. 2.—Electrocardiogram showing the effect of oral propranolol (20 mg. at 20.15 hours) on runs of ventricular extrasystoles.

TABLE II.—*Propranolol. Acute Arrhythmia*

Case No.	Age	Sex	Aetiology	Arrhythmia	Failed Therapy	Propranolol Dose and Route	Result
17	65	M	Acute infarction	Atrial flutter	Digoxin	10 mg. 4 × /day orally	Initial recurrence, but later controlled
18	66	F	Coronary artery disease. Pulmonary embolism	Atrial flutter. Atrial tachycardia. Ventricular tachycardia	Phenytoin sodium. Quinidine. Digoxin	10 mg. 4 × /day orally plus digoxin	Control
19	40	M	Subarachnoid haemorrhage. Anaesthetic	Multiple ventricular extrasystoles	Nil	2·5 mg. I.M. plus atropine 1·2 mg.	„
20	78	M	Coronary artery disease. Digitalis toxicity	Atrial tachycardia. Atrial fibrillation	Lignocaine I.V.	5 mg. I.V. followed by 10 mg. 3 × /day for 3 days	„
21	57	M	Acute infarction	Runs of ventricular tachycardia	Quinidine	20 mg. statim orally. 10 mg. 6-hourly decreasing doses	Control. Propranolol continued 7 days
22	61	M	Alcoholic cardiomyopathy	Atrial fibrillation	Digoxin	5 mg. I.V.	Control initially, but treatment not continued, and patient died
23	65	F	Coronary artery disease	Nodal tachycardia	„	Pronethalol 60 mg. I.V.	Control

failure was suppressed when intravenous pronethalol was administered to the patient in whom the arrhythmia had not been controlled with full doses of digitalis (Fig. 3). In Case 20 digitalis toxicity was present and atropine premedication produced very rapid atrial tachycardia. This was slowed with 50 mg. of lignocaine intravenously, and reverted to sinus rhythm after propranolol 5 mg. intravenously. In Case 19

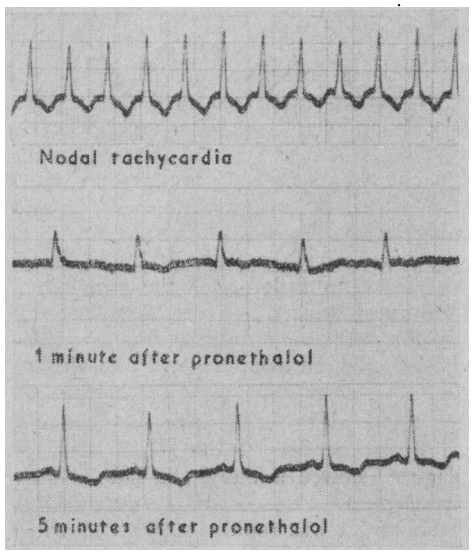

FIG. 3.—Selections from a continuous electrocardiogram taken during the administration of intravenous pronethalol.

the ventricular ectopics were rapidly controlled with intravenous propranolol. In Case 22, a patient with severe alcoholic cardiomyopathy, the ventricular rate was controlled, but the drug was inadvertently discontinued and subsequently the patient died.

Group C : Arrhythmias Associated with Prolonged Cardiac Arrest

There were eight patients in this group (Table III). In one propranolol was used initially, while in the remainder there had been prolonged cardiac arrest associated with resistant or recurrent ventricular fibrillation not responding to usual resuscitation methods, including the correction of acidosis, together with the administration of procainamide (Pronestyl) or lignocaine. In one (Case 25) 250 mg. of phenytoin sodium intravenously had also failed to maintain sinus rhythm.

In these patients the intravenous dose of propanolol ranged from 1 to 15 mg. The drug was always given cautiously in increments of 1 to 2 mg. covered by a single dose of atropine sulphate, 1.2 to 2.4 mg. intravenously. The duration of external cardiac massage varied from 20 to 120 minutes before the administration of propranolol. In one patient (Case 24) propranolol alone was used to terminate ventricular tachycardia. In Case 25 ventricular fibrillation recurred after reversion with direct current counter shock on nine occasions (Fig. 4). Propranolol was administered after further counter shock and the patient then remained in sinus rhythm. In the other six patients (Cases 26 to 31) propranolol was given before direct current counter shock and in all cases satisfactory cardiac function was restored. All survived at least 12 hours, with four long-term survivors. Of the four deaths only one (Case 28) was due to a complication of drug therapy. This case has been previously reported (Sloman *et al.*, 1965). Complete heart block developed while the patient was still receiving propranolol by slow intravenous infusion. The drug was not stopped, and the patient died in ventricular standstill.

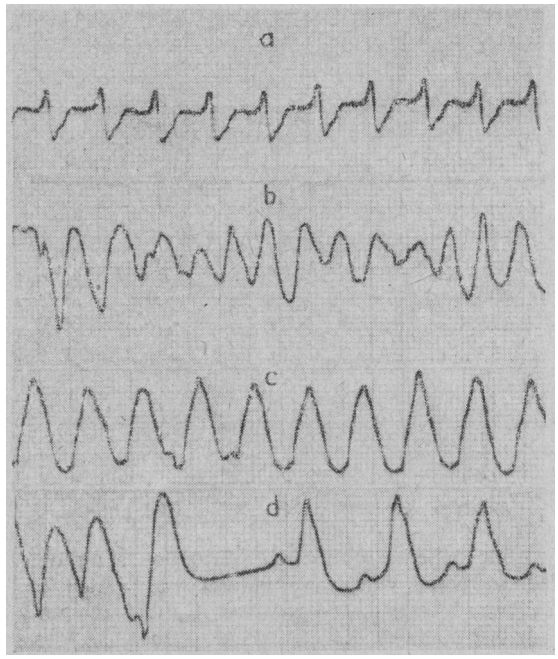

FIG. 4.—Selections from a continuous electrocardiogram taken during recurrent cardiac arrest: (*a*) supraventricular tachycardia; (*b*) ventricular fibrillation; (*c*) ventricular flutter; (*d*) ventricular fibrillation and the effect of direct current shock.

Group D : Acute Myocardial Infarction

Forty-nine patients admitted to the coronary care ward with proved acute myocardial infarction were studied to assess the possible prophylactic value of propranolol in reducing the inci-

TABLE III.—*Cardiac Arrest Group*

Case	Age	Sex	Cause of Arrest	Duration of Cardiac Massage	Failed Treatment	Propranolol Dose and Result*	Follow-up
24	57	F	C.V.A. anoxia	20 min.	Nil	5 mg. I.V. *Sinus rhythm	Died 2 days later—C.V.A.
25	65	M	Coronary artery disease. Digoxin toxicity	Approx. 10 arrests over 2 hours	Procainamide. Phenytoin sodium. D.C. shock	2 mg. I.V. *Sinus rhythm	Survived
26	54	M	Coronary artery disease	60 min.	Lignocaine. Procainamide. D.C. shock	2 mg. I.V. + D.C. shock *Sinus rhythm	Died 2 days later of pulmonary oedema
27	61	M	Acute myocardial infarction	90 ,,	Digoxin. Procainamide. Sodium bicarb. Isoprenaline	5 mg. I.V. × 3 + D.C. shock *Sinus rhythm	Survived. Propranolol continued for six weeks
28	46	F	Digitalis toxicity	35 ,,	Sodium bicarb. Procainamide. Isoprenaline	5 mg. I.V. × 4 + D.C. shock *C.H.B.	Died—complete heart block
29	28	F	Renal failure. Pulm. embolism. Digitalis toxicity	75 ,,	Procainamide. Isoprenaline. Corticosteroids	2 mg. I.V. + 2·5 mg. I.M. *Sinus rhythm	Survived. Drug continued for seven days
30	60	F	Recurrent myocardial infarction	30 ,,	Procainamide. D.C. shock	5 mg. I.V. D.C. shock *Sinus rhythm with ventricular ectopics	Survived. V.F. recurred, but controlled by further 5 mg. I.V.
31	42	M	Aortic stenosis	40 ,,	Procainamide. Sodium bicarb. Isoprenaline	2 mg. I.V. + D.C. shock *Sinus rhythm	Died. Recurrent V.F. 3½ hours later

D.C. = Direct current. C.V.A. = Cerebrovascular accident. V.F. = Ventricular fibrillation. C.H.B. = Complete heart block.

dence of arrhythmias associated with acute infarction. Those with cardiogenic shock, complete heart block, or a past history of asthma were excluded from the trial. Patients were allocated to the treatment or the control group by random numbering. Twenty-six patients received propranolol, initially by the intravenous route in a dose of 0.1 mg./kg. body weight with 1.2 mg. of atropine sulphate followed by oral propranolol 10 mg. every four hours, beginning one hour after the intravenous injection and continuing for up to three weeks. Atropine sulphate 0.6 mg. intramuscularly four-hourly was continued for 12 hours and then propantheline 15 mg. eight-hourly was substituted. The control group comprised 23 patients who received treatment with analgesics, anticoagulants, diuretics, and digitalis as indicated, but no anti-arrhythmic drugs. If a significant arrhythmia developed in either group it was treated on its merits, usually with procainamide 500 mg. intramuscularly, repeated four-to-six-hourly as necessary. The patients remained in the coronary care unit for a minimum of 72 hours with continuous electrocardiographic monitoring throughout their stay. Alterations in rate or rhythm and conduction were documented by a 10-second recording of the electrocardiogram every 30 minutes, together with recordings of any arrhythmia which activated the automatic recorder or which was observed by the nursing staff. All arrhythmias were counted and the treated and control groups compared (Table IV).

TABLE IV.—*Classification, Deaths, and Incidence of Serious Arrhythmias in Propranolol Trial*

	Propranolol	Control
Mild	16	15
Severe	10 (26)	8 (23)
Shock	0	0
Deaths	3	4
No. of patients with serious arrhythmias	3	5
„ „ episodes of serious arrhythmias	4	5

Apart from atrial, nodal, and ventricular ectopic beats, which were common and of similar incidence in both groups, the incidence of serious arrhythmias was slight. In the group receiving propranolol one patient had two episodes of ventricular fibrillation and another two short episodes of ventricular tachycardia. There were three deaths in the treated group, one due to cardiogenic shock, another to brain damage following resuscitation from ventricular fibrillation, and the third due to ventricular fibrillation which occurred after the patient was discharged from the coronary care unit.

The incidence of non-specific side-effects was nil. One patient developed cardiogenic shock and another Wenckebach heart block after the administration of propranolol, but hypotension and cardiac failure were neither severe nor frequent.

In the control group two patients had short episodes of ventricular tachycardia and another prolonged slow ventricular tachycardia, which required treatment with procainamide. One patient developed ventricular fibrillation while in the coronary care unit and died, while another developed ventricular fibrillation in a general ward and was successfully resuscitated. The remaining two deaths in this group occurred in the general ward after discharge from the coronary care unit, and the mode of death is unknown. There was therefore no indication that propranolol reduced the frequency of arrhythmias in patients with acute myocardial infarction, but to reach a valid statistical conclusion much larger numbers would have to be studied.

Discussion

These clinical observations indicate that beta-adrenergic drugs have an important place in the treatment of acute and chronic arrhythmias irrespective of their origin or cause. These results are in agreement with previously published reports.

Propranolol was found to be useful in controlling the rate of ventricular response in patients with paroxysmal atrial fibrillation and flutter. The drug was used with digoxin, and syncope and giddiness no longer occurred. Syncope was also prevented by propranolol and digoxin when combined with endocardial pacing, supporting the work of Harris (1966), who was able to reduce the number of ventricular ectopic beats occurring during cardiac pacing by the use of oral propranolol when large doses of quinidine and procainamide had not been successful.

The efficacy of propranolol in preventing paroxysmal arrhythmias may be reliably assessed by provoking the arrhythmia by exercise on a treadmill and repeating the exercise on a treadmill after the administration of intravenous propranolol.

There appears to be a special place for the use of propranolol in patients with prolonged cardiac arrest associated with resistant, recurrent ventricular fibrillation. Propranolol has been shown to have an anti-fibrillatory effect, and we believe it should be used when standard resuscitation methods and drugs have not produced a satisfactory cardiac rhythm. It was found that a satisfactory anti-arrhythmic effect could be produced with a dose of propranolol much smaller than a recognized beta-blocking dose, supporting the work of Stickney *et al.* (1966) and Howe and Shanks (1966), who showed that the drug has a biphasic mode of action. Propranolol should therefore be given in small intravenous doses of 1–2 mg., repeated as necessary, and covered by a full dose of atropine sulphate to prevent overactivity of the unmasked parasympathetic nervous system. As propranolol appears to have an anti-arrhythmic effect which is not due to its beta-blocking effect it would therefore seem reasonable in certain circumstances to use propranolol in combination with isoprenaline. We have used this combination with success in six patients. In Cases 27, 28, 29, and 31 both drugs were used during resuscitation, and in Cases 25 and 26 isoprenaline was used after successful resuscitation without producing further ventricular fibrillation.

In Case 28 complete heart block developed after successful resuscitation. A slow intravenous infusion was continued, whereas cessation of the drug, followed by the administration of isoprenaline and perhaps endocardial pacing, may have led to a successful outcome.

Trials of the prophylactic value of propranolol in acute myocardial infarction were given impetus by the work of Snow (1965), who reported a mortality of 13% in 52 patients treated with propranolol compared with 29% mortality in a comparable control group of 55 patients. However, in our study of a relatively small group of patients monitored after infarction we found no significant difference in the incidence of arrhythmias. Studies by Clausen (1966), Balcon *et al.* (1966), and Barber *et al.* (1966) have failed to confirm any difference in mortality in patients treated with oral propranolol or to demonstrate a difference in the incidence of arrhythmias. In addition, initial favourable results prompted the arrangement of a multicentre double-blind trial which was reported by Stephen (1966). Ten centres participated, providing data on 195 patients, and no difference in mortality between treated and untreated group was demonstrated. Pentecost (1966) has questioned the amount of absorption of propranolol given orally in the early stages after myocardial infarction, as this was the mode of administration in these trials. However, in our studies the initial dose was always given intravenously, but, even so, no difference in the incidence of arrhythmias was detected.

The whole question of prophylactic treatment of cardiac arrhythmias after acute infarction is now under intense study. We accept the hypothesis of Lown and Killip (personal communications, 1966) that certain arrhythmias, particularly ventricular extrasystoles when they occur frequently, arise from multiple ventricular foci or occur in runs, are forerunners of more serious potentially lethal arrhythmias, and must be treated at once. Procainamide, propranolol, phenytoin sodium,

and lignocaine may be used by the intravenous route to suppress these arrhythmias, but why one morphological type of ventricular ectopic will respond to one of the above anti-arrhythmic drugs and not to another remains to be studied. Currently, lignocaine is the drug of choice because of its high therapeutic effect compared with its relatively slight negative inotropic effect. It is used in incremental doses up to 200 mg.

Summary

Thirty-one patients with cardiac arrhythmias were treated with beta-adrenergic blocking drugs propranolol and pronethalol. Propranolol was found to be particularly useful in the management of rapid arrhythmias when other anti-arrhythmic drugs had not been successful. Beta-adrenergic blockade was of value in reducing the ventricular rate in paroxysmal atrial fibrillation, atrial flutter, and rapid atrial and sinus rhythms. Propranolol also possessed a specific anti-arrhythmic effect not clearly related to its beta-adrenergic blocking effect, and was found to be useful in the treatment of ventricular extrasystoles, paroxysmal ventricular tachycardia, ventricular arrhythmias associated with digitalis intoxication, and recurrent and resistant ventricular fibrillation.

Forty-nine (26 treated, 23 control) patients with acute myocardial infarction were studied to assess the prophylactic value of propranolol in reducing arrhythmias in acute myocardial infarction. The drug was administered intravenously initially in a dose of 0.1 mg./kg./body weight together with atropine sulphate 1.2 mg. followed by 10 mg. of propranolol orally four-hourly for three weeks. There was no difference in the incidence of arrhythmias between the two groups.

Our thanks are due to the medical staff, Royal Melbourne Hospital, who allowed us to treat patients under their care. The propranolol used in this study was made available by Dr. Charles Proctor (Medical Director, I.C.I., Australia), to whom we are grateful. Mr. J. R. Bainbridge, Computer Centre, Monash University, advised on the statistical treatment of the results from the coronary care ward.

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Serum Folate Values in 423 Psychiatric Patients

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With the widespread introduction of efficient ways of estimating serum folate, there have been reports of folate deficiency in malnutrition (Gough *et al.*, 1963), old age (Read *et al.*, 1965), a number of chronic physical illnesses (Batata *et al.*, 1967), neurological disease (Grant *et al.*, 1965), and patients receiving anticonvulsants, barbiturates (Klipstein, 1964 ; Malpas, 1966), antibiotics, and cytotoxic agents (Dr. E. J. Watson-Williams, personal communication). Folate deficiency and psychiatric conditions have also been associated—for example, anxiety/depression (Gough *et al.*, 1963) and dementia (Henderson *et al.*, 1966)—while 12 out of 43 patients with subnormal serum folate were currently attending a psychiatric department (Forshaw, 1965). Reynolds (1966, 1967) has gone so far as to suggest a causal relation between folate deficiency and certain forms of mental illness, especially affective changes and, in long-standing cases, dementia. There seems, however, to have been little systematic investigation of the incidence of folate deficiency in psychiatric populations.

These reports encouraged me to ascertain the incidence of low serum folate levels in a psychiatric population and its relation to a number of variables, including diagnosis, age, nutrition, physical state, drugs, and chronicity of illness. Though this investigation was not specifically designed to answer the question, it was felt that some clues regarding the possible aetiological significance of folate deficiency in mental illness might appear.

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Method and Material

Serum folate estimations were carried out on consecutive admissions to two psychiatric units 20 miles (32 km.) apart, one a general hospital unit and the other a mental hospital. They were all under my personal care and were admitted over a period slightly exceeding a year. Though the hospitals served the same geographical area they dealt with somewhat different psychiatric populations, the mental hospital tending to admit the more disturbed and more chronic patients. The intakes of both units were studied concurrently in order to ensure that the whole group was representative with respect to diagnosis, age, and sex of those psychiatric patients within the catchment area for whom admission to hospital was judged to be needed. Within individual subcategories of patients there was little variation in folate levels between the two hospitals.

Serum folate estimations were carried out by an adaptation of the method of Waters and Mollin (1961) by which folate activity was measured by reading turbidimetrically the growth of *Lactobacillus casei* A.T.C.C. 7469 after incubation in the sample solution for 48 hours at 37° C.: the results were calculated from a standard graph. These estimations were carried out in two different laboratories, but the procedures in both were identical.