generating decisions. They set the tone for the rest of the organisation. They cannot be told to do something they don't believe in. They need to lead in the development of efficient care." With NHS consultants in danger of losing out in the Griffiths management reforms (pp 1062, 1065), this message has an added urgency.

On Griffiths Enthoven's understated style is particularly devastating. "While I am sympathetic to the thrust of the report . . . if the structure and incentives in the NHS are not changed more fundamentally, these recommendations are not likely to change much." For those grappling with the consequences of this "reform"—described as the biggest reorganisation the NHS has undergone—these words will bring no comfort. He identifies national uniformity and political haste as stultifying the aims of the management changes. With the departure of Kenneth Clarke from the Department of Health and Social Security the pressure for haste may lessen—though much damage has already been done.[3] Even so, the Whitehall tradition of uniformity will be hard to overcome. Enthoven sees the solution in wider but more effective use of competitive tendering for catering, cleaning, and laundry services—the "entering wedge for a great deal of management improvement"; the purchase by districts of private sector medical care when this can be bought at a "good price"; a widespread use of pilot schemes before changes are introduced; and—the most provocative proposal of all—the substitution of positive incentives for existing perverse incentives, with the introduction of an "internal market model" for the NHS.

What does this last suggestion mean? The aim would be to enable managers to use resources most efficiently and this would be achieved as follows. Each district would receive RAWP based per capita revenue and capital allowances and would be responsible, as now, for providing and paying for comprehensive care for its resident population. It would be paid for emergency services to "outsiders" at a standard cost and for non-emergency services at negotiated prices. Hence in effect each authority would resemble an American health maintenance organisation (p 1068). Pay and working conditions would preferably be negotiated locally. Consultants and general practitioners would be contracted to district authorities, which could negotiate variable term contracts with appropriate incentives. Districts would be allowed, within limits, to borrow at government long term interest rates and to keep the proceeds of property sales. Services and assets could be bought and sold between districts, which would also be free to introduce management innovations.

Enthoven believes that such a market model would force the development of proper costing schemes and create much more cost efficiency and cost sensitivity among health authorities. He acknowledges that the model lacks incentives for decisions to be taken in the best interests of patients rather than of the authority. Though attracted by the idea of the patient choice available in America through competing hospital maintenance organisations—in themselves mini NHS's—he accepts that this would not be workable in Britain. But patients would be no worse off than they are already, and if the internal market model was found to be effective—presumably after suitable pilot studies—patients should benefit from a more effective and locally oriented service.

Medicopoliticians may well reject Enthoven's diagnosis and suggested treatment of the NHS's management ills. Ideological opponents of the private sector as well as sceptics who doubt its capabilities will also be critical. But, even shorn of its suggested links with the private sector, the internal market model could promote better management and loosen the gridlock in the NHS. It would be a tragedy if his ideas were not taken seriously, weighed in the balance, and tested in the small pilot schemes he advocates so powerfully.

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Regular Review

Treatment of chronic heart failure: a review of recent drug trials

DAVID P LIPKIN, PHILIP A POOLE-WILSON

The conventional treatment for congestive heart failure is diuretics (either a thiazide or a loop diuretic), some form of potassium replacement, and digoxin. Digoxin is specifically indicated for the control of atrial fibrillation but is also widely used in patients with heart failure who are in sinus rhythm. For mild, moderate, and even severe heart failure this treatment is effective in most patients. Fluid overload producing either peripheral oedema or pulmonary congestion is controlled, and symptoms are improved. A clinical problem exists only when despite conventional treatment patients continue to have symptoms, usually shortness of breath or fatigue.

What further treatment should then be introduced? New inotropic drugs have been and are being investigated in the belief that a more powerful positive inotropic agent without the toxic side effects of digoxin might be valuable in heart failure. Vasodilators have also been studied, since unloading the heart might directly relieve symptoms and retard the progressive functional deterioration of myocardial muscle. Numerous reports of the acute and chronic haemodynamic

effects of these drugs have been published, but few fulfil criteria advocated for clinical trials. We have reassessed the value of oral inotropic and vasodilator drugs in heart failure by analysing those papers which report randomised, blind, and controlled trials.

Review of published work

Thirty trials were identified in which a control group was included, patients were randomised, the assessment was double blind, and the duration exceeded 48 hours. Of these 30 trials, 10 reported on a positive inotropic drug, 18 on a vasodilator, and two on β blockers. The trials were evaluated in terms of diagnostic criteria, selection criteria, drug treatment, sample size, duration, withdrawals, and methods of assessment of the end point. Tables I and II summarise the details of the 30 trials. The duration of the shortest trial was two weeks.

Of the 18 trials on vasodilators, three concerned nitrates, two hydralazine, five prazosin, two trimazosin, three captopril, two enalapril, and one minoxidil.

Two of the three trials on nitrates reported on the same group of patients at rest[1] and exercise.[2] Treatment with nitrates did not modify the increase of cardiac output during exercise.[1 3] Pulmonary capillary wedge pressure fell[3] or was unaltered.[2] The durations of exercise and maximal oxygen uptake were not improved immediately but increased with long term treatment.[2 3] Treatment with diuretics was altered during all three trials.

In a study lasting six months hydralazine did not alter resting haemodynamics, exercise capacity, ejection fraction as asessed by radionuclide scanning, or exercise capacity.[4] A later trial lasting 12 months failed to show a persistent increase of exercise capacity measured on a bicycle ergometer, but symptoms assessed by the New York Heart Association criteria improved in 11 out of 17 patients in the hydralazine treated group compared with seven out of 18 patients in the control group.[5] Forty four per cent of patients initially included in the trial failed to complete the study. The clinical relevance of the difference between the groups is unclear.

In two out of five trials prazosin, an inhibitor of α adrenergic receptors, increased exercise capacity.[6-10] In one of these trials 10 patients taking prazosin required an increase in treatment with diuretics as compared with one out of 12 in the placebo group.[8] The other study was the only one to show unequivocal long term benefit with prazosin, in that exercise duration increased and left ventricular ejection fraction improved.[9]

Trimazosin improved exercise capacity and reduced symptoms,[11 12] but in one of these trials four out of 13 patients were not randomly allocated to treatment and the outcome of all patients was not assessed blindly.[12]

Three trials of captopril[13-15] and two of enalapril,[16 17] both angiotensin converting enzyme inhibitors, showed benefit to patients after long term treatment of heart failure. Captopril improved symptoms (New York Heart Association criteria), exercise duration, left ventricular ejection fraction, exercise haemodynamics, and maximal oxygen consumption. The frequency of ventricular arrhythmias was reduced during long term treatment with captopril, possibly owing to improvement in left ventricular function.[13] In a multicentre study there were no deaths in 50 patients treated with captopril as compared with four out of 42 in those treated by placebo.[14] Similar results have been obtained with enalapril. Treatment with diuretics was altered in both trials,[16 17] but in the larger and more convincing study treatment was increased in only one out of 16 patients treated with enalapril as compared with seven out of 14 in the control group.[16]

Minoxidil caused an appreciable worsening of heart failure, increased the need for diuretics, and increased the incidence of ventricular arrhythmias.[18] The outcome was not assessed blindly.

The trials of inotropic drugs included three on digoxin,[19-21] two on amrinone,[22 23] one on pirbuterol, four on prenalterol, and two on β blockers.

Dobbs *et al* found that 16 of 46 patients deteriorated when placebo was substituted for digoxin, and concluded that treatment with digoxin was warranted in patients with heart failure.[21] Thirteen patients with atrial fibrillation were included in the trial, but the report left unclear how many of the patients who deteriorated had atrial fibrillation. Eighteen patients were not receiving diuretics, and the aetiology of heart failure was heterogeneous, including 10 patients with bronchitis and emphysema. The end point was clinical deterioration. Body weight increased in the 16 patients who deteriorated while taking placebo and did not increase in those who did not deteriorate. How other treatments were altered during the trial was not made clear. Fleg *et al* found no effect on exercise duration or left ventricular function after withdrawal of digoxin.[19] Treatment allocation was not in random order. The drop out rate was 25%, which reduced the likelihood of detecting a clinically important difference from placebo. Lee *et al* reported that 14 out of 25 patients with heart failure in sinus rhythm deteriorated while taking placebo.[20] Those who responded to digoxin were characterised by more severe heart failure and a third sound. Clinical improvement with digoxin was associated with a loss of body weight ($p<0{\cdot}01$), and in most patients equal benefit might have been obtained by increase of diuretics alone. Only 10 patients were taking more than 80 mg frusemide, and three were receiving no diuretic at all.

A multicentre trial of amrinone selected 52 out of 173 "acute responders" for long term treatment.[23] No benefit was found after prolonged treatment in this selected group. Pirbuterol[24] and prenalterol[25-28] failed to improve exercise haemodynamics or exercise capacity.

Waagstein *et al* claimed on the basis of uncontrolled studies that patients with cardiomyopathy improved long term when treated with β blockers.[29-32] Neither of the two controlled trials published showed any benefit from β blockade in terms of exercise capacity or left ventricular function.[33 34]

Conclusions

Many papers have been published on the effects of newer inotropic or vasodilator drugs in the treatment of patients with heart failure. Often they have reported the haemodynamic consequences of acute administration of the drug. Some attempt to show that these acute haemodynamic changes are maintained after long term treatment and are accompanied by clinical improvement or an increase in treadmill exercise time. Few papers report controlled, double blind, and randomised trials. The apparent reluctance to undertake such trials is almost certainly related to the predictable difficulties. The mortality from severe heart failure is high, so that patients are lost to the study if the end point is exercise tolerance. Deterioration of the patient due to progression of heart disease necessitates withdrawal from the

trial. The need to increase diuretics during the trial complicates the interpretation of the results. Blinding may be difficult if drugs such as digoxin are to be used, and the use of digoxin complicates a study of an alleged inotropic drug. The aetiology of heart failure is rarely the same in all patients. Previous drug treatment may have a carryover effect in the trial. The end point for an exercise test may be breathlessness, fatigue, or even angina[28] in different patients and be altered by the drug by different mechanisms.

In this paper we have reviewed the published studies in heart failure which have included a control group of patients. It is immediately apparent that the results from these selected trials do not support the enthusiastic claims from uncontrolled studies.

exercise testing as a means of assessing ability of patients to lead an acceptable if restricted life is not yet clear.

The response to treatment is commonly assessed not only by symptoms and exercise capacity but also by cardiac function (haemodynamics and ventricular ejection fraction). These should not be regarded as synonymous. Franciosa *et al* could show no correlation among patients between exercise capacity and resting haemodynamics or left ventricular end diastolic pressure on exercise.[38] Within patients a poor correlation exists.[39] Caution is necessary in making claims about drug efficacy on the basis of haemodynamic data alone, though studies showing an increase of exercise capacity have in general shown an improvement of haemodynamics (tables I and II).

TABLE I—*Randomised double blind placebo controlled trials of vasodilators in chronic heart failure*

Drug	Year	Trial	Duration (weeks)	Sample size	Severity of heart failure (NYHA)	Withdrawals	Diagnostic criteria	Selection criteria	Methods of assessment of end point	Result: Exercise capacity	Result: Haemodynamics, left ventricular function	Comments
Nitrate	1980	Franciosa and Cohn[1]	12	24 (12 D, 12 P)	NS	5 (3 D, 2 P)	S	S	H (rest)	Resting study	↑ (rest)	Diuretic dose altered
Nitrate	1980	Franciosa *et al*[2]	12	16 (8 D, 8 P)	II-IV	Nil	S	S	Vo_2, H	↑	→	Diuretic dose altered
Nitrate	1983	Leier *et al*[3]	12	39 (18 D, 21 P)	III-IV	9 (5 D, 4 P)	S	S	NYHA, ED, H	↑	↑	Diuretic dose altered
Hydralazine	1982	Franciosa *et al*[4]	26	32 (16 D, 16 P)	III-IV	11 (5 D, 6 P)	S	S	NYHA, ED, RNA	→	→	Diuretic dose altered
Hydralazine	1984	Conradson *et al*[5]	52	62 (32 D, 30 P)	III	27 (15 D, 12 P)	S	S	NYHA, ED, CXR	? ↑	0	
Prazosin	1983	Higginbotham *et al*[6]	26	22 (11 D, 11 P)	III	4 (2 D, 2 P)	S	S	ED, RNA	→	→	Diuretic dose altered
Prazosin	1983	Markham *et al*[7]	26	23 (11 D, 12 P)	III	7 (3 D, 4 P)	S	S	NYHA, ED, RNA	→	→	
Prazosin	1980	Colucci *et al*[8]	8	22 (10 D, 12 P)	III-IV	5 (P)	S	S	NYHA, RNA, ECHO	↑	↑	Diuretic dose altered
Prazosin	1978	Aronow *et al*[9]	6	24 (12D, 12 P)	NS	Nil	S	S	ED, ECHO	↑	↑	
Prazosin	1980	Harper *et al*[10]	4	12 (crossover)	NS	3 (1 D, 2 P)	NS	NS	ED, H	→	↑	
Trimazosin	1977	Aronow *et al*[11]	6	16 (8 D, 8 P)	NS	1 (D)	S	S	ED	↑	→	
Trimazosin	1980	Weber *et al*[12]	6	23 (10 D, 13 P)	I-IV	1 (P)	S	S	ED, Vo_2	↑	↑	4/13 not randomly allocated. Outcome of all patients not assessed blindly
Captopril	1984	Cleland *et al*[13]	6	15 (crossover)	III-III	1 (P)	S	S	NYHA, ED, ECHO, ECG	↑	↑	
Captopril	1983	Multicentre[14]	12	92 (50 D, 42 P)	II-III	16 (2 D, 14 P)	S	S	NYHA, ED, RNA	↑	↑	
Captopril	1983	Kramer *et al*[15]	12	16 (8 D, 8 P)	II-IV	4 (P)	S	S	ED, Vo_2, H	↑	↑	
Enalapril	1984	Sharpe *et al*[16]	12	36 (18 D, 18 P)	II-III	6 (2 D, 4 P)	S	S	NYHA, ED, ECHO	↑	↑	
Enalapril	1985	Franciosa *et al*[17]	12	17 (9 D, 8 P)	III-IV	1 (D)	S	S	Functional class (Yale), ED, Vo_2	↑	0	Diuretic dose altered
Minoxidil	1984	Franciosa *et al*[18]	12	17 (9 D, 8 P)	II-III	4 (3 D, 1 P)	S	S	NYHA, ED, Vo_2, H	→	→	Diuretic dose altered. Outcome not assessed blindly

D = Drug. P = Placebo. W = Withdrawal. S = Specified. NS = Not specified. H = Haemodynamics. Vo_2 = Oxygen consumption. ED = Exercise duration. NYHA = Criteria of New York Heart Association. RNA = Radionuclide assessment of left ventricular function. CXR = Chest x ray evaluation. ECHO = Echocardiography. ↑ = Improvement. → = No change. 0 = Not determined.

TABLE II—*Randomised double blind placebo controlled trials of inotropic agents in chronic heart failure*

Drug	Year	Trial	Duration (weeks)	Sample size	Severity of heart failure (NYHA)	Withdrawals	Diagnostic criteria	Selection criteria	Methods of assessment of end point	Result: Exercise capacity	Result: Haemodynamics, left ventricular function	Comments
Digoxin	1982	Fleg *et al*[19]	24	40 (crossover)	II-III	10	S	S	ED, ECHO	→	→	Patients not allocated in random order
Digoxin	1982	Lee *et al*[20]	4-22	35 (crossover)	II-III	10	S	S	Scoring system, ECHO	0	0	Patients with third heart sound benefit. Clinical assessment
Digoxin	1977	Dobbs *et al*[21]	12	46 (crossover)	III	Nil	NS	NS	Scoring system, ECHO	0	↑	Unclear which patients in atrial fibrillation. Clinical assessment
Amrinone	1984	Likoff *et al*[22]	26	9 (5 D, 4 P)	Moderate-severe	1	S	S	Vo_2	? ↑	→	
Amrinone	1982	Dibianco *et al*[23]	12	52 (31 D, 21 W)	II-IV	8	S	S	NYHA, ED, Vo_2, ECHO	→	→	
Pirbuterol	1982	Weber *et al*[24]	7	15 (7 D, 8 P)	III-III	?	S	S	ED, Vo_2, ECHO	→	→	
Prenalterol	1984	Currie *et al*[25]	2	8 (crossover)	II-III	2	S	S	NYHA, ED, H, RNA	→	→	
Prenalterol	1984	Lambertz *et al*[26]	12	16 (8 D, 8 P)	III-IV	2	S	S	NYHA, H, ECHO	→	→	
Prenalterol	1984	Roubin *et al*[27]	2	11 (crossover)	II-III	Nil	S	S	Vo_2, H, RNA	→	→	
Prenalterol	1984	Glover *et al*[28]	26	37 (18 D, 19 P)	III	9	S	S	NYHA, scoring system, RNA	→	→	
Acebutolol	1981	Ikram and Fitzpatrick[33]	4	17 (crossover)	II-III	2	S	S	NYHA, ED, Vo_2, ECHO	→	→	7/17 had alcoholic heart muscle disease
Metoprolol	1984	Currie *et al*[34]	4	10 (crossover)	III	Nil	S	S	NYHA, ED, H, RNA	→	→	All patients had cardiomyopathy

D = Drug. P = Placebo. W = Withdrawal. S = Specified. NS = Not specified. H = Haemodynamics. Vo_2 = Oxygen consumption. ED = Exercise duration. NYHA = Criteria of New York Heart Association. RNA = Radionuclide assessment of left ventricular function. CXR = Chest x ray evaluation. ECHO = Echocardiography. ↑ = Improvement. → = No change. 0 = Not determined.

The purpose of treatment in patients with chronic heart failure is to relieve symptoms and reduce mortality. The trials have included too few patients and been too short to determine whether treatment prolongs life.[35] Evidence suggests that captopril may favourably influence mortality,[14] whereas at least one inotropic drug, amrinone, may be harmful.[36]

The intended outcome of treatment is an improvement in physical activity and a reduction of symptoms. Symptomatic assessment is not reproducible among observers. Measurement of exercise duration on a treadmill is more objective but is influenced by the nature of the exercise protocol, familiarity of the patient with the test, and the enthusiasm of the doctor supervising the test. Measurement of maximal oxygen consumption on exercise has recently been described, is reproducible, relates to functional class, and may replace invasive haemodynamic monitoring.[37] The place of

Drugs with a positive inotropic effect on the heart (some also have vasodilator properties) have not been shown to be helpful for patients with chronic severe heart failure. Out of 10 trials only three claimed a positive result.[20-22] The study on amrinone included only five patients taking the active drug.[22] These five patients were selected from a group of responders to amrinone, and the statistical analysis was unsatisfactory. The other two positive trials were on digoxin and the end point was clinical assessment.[20,21] Both studies included patients with heart failure of different aetiology and the severity of heart failure was variable. Those who benefited from digoxin in the study of Lee *et al* were a subset of patients with a third heart sound, who might have responded to a small increase of diuretic alone without the need to introduce an additional drug such as digoxin.[20] Inotropic drugs hasten cell death in the myocardium in pathological conditions.[40] Digoxin may have the advantage over other inotropic drugs

that its inotropic effect is small and limited by the appearance of toxicity so that any harmful effect due to overstimulation of the myocardium is minimised. Many withdrawal studies on digoxin have been undertaken and have shown the proportion of patients deteriorating to be from nil to 56%.[41] Digoxin remains the only inotropic drug in which there is reasonable evidence of efficacy. What is less clear is whether the benefit derived from digoxin still accrues in patients optimally treated with diuretics.

The results of studies with vasodilating drugs are more complex. In one positive study of prazosin the diuretic dosage was altered.[8] In a study on trimazosin the strict criteria for a double blind randomised trial were not fulfilled.[12] Only two studies, those by Aronow *et al*, show that α blockade increases exercise capacity.[9 11] The evidence for the efficacy of nitrates is also not compelling, since in all three studies the diuretic dosage was altered. Hydralazine may be marginally superior to placebo in its ability to improve symptoms, though this effect may not be apparent until after one year of treatment.[5] Possible reasons for these disappointing effects of some vasodilators on exercise capacity are that drug tolerance developed long term by whatever mechanism, that symptoms were not determined solely by haemodynamic variables, and that, though vasodilatation often increases cardiac output, blood flow is increased to the skin and splanchnic circulation rather than altering the blood flow to exercising skeletal muscle.[42]

The word "vasodilators" has been used to group together a variety of drugs with very different pharmacological properties. The concept of characterising drugs on the basis of haemodynamic effect may be misleading in a disease as complex as heart failure. Five studies have shown that angiotensin converting enzyme inhibitors are beneficial to patients with severe heart failure, and in these studies there was a correspondence between the improvement of the clinical state of the patient and the change in haemodynamics.[15] The acute haemodynamic effect of these drugs is similar to that of other vasodilators. The reason why they are so advantageous in contrast with the other vasodilators is not known, but it may be due to specific effects on the kidney and peripheral circulation and to inhibition of the increase in plasma renin activity brought about by the use of high doses of diuretics. The haemodynamic changes long term may be partly a consequence of such effects rather than the direct cause of clinical improvement. It is also possible, though improbable, that the specific advantage of this class of drug is solely because the trials, having been undertaken more recently, have been better designed and include one large study.[14]

DAVID P LIPKIN
Research registrar

PHILIP A POOLE-WILSON
Professor of cardiology

Cardiothoracic Institute and National Heart Hospital, London W1N 2DX

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Correspondence and requests for reprints to: Dr Lipkin.

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