possibly as many as 200,000 people with cases distributed throughout the city and suburbs. Thus far, there have been approximately 300 cases requiring medical attention, and 15 deaths. No microfocus has yet been found. If a microfocus is found it is possible it will little resemble the original microfocus if the history of the houses around the collected soil samples is not known. In any case, it is reassuring to know that the sometimes adversely criticized serologic tests are as effective in picking up the primary pulmonary cases in a large city population as they were originally in the smaller, more rural communities.\textsuperscript{1,11,12}

It is therefore increasingly urgent that legislation be enacted that will require treatment of the well-known potential microfoci of \emph{H capsulatum} before they are disrupted, especially those sites among the densely milling populations of the cities. Killing the fungus in its microfocus before soil upheaval is the only protection currently at our disposal, not only for the participants in and the observers of soil moving activities, but also for the citizens at large who may only be passing by or only in the vicinity of such activities, unaware that they are inhaling infective “dust particles” that can produce severe infection, occasionally death and at the very least damaged lungs. Goodwin and Des Prez\textsuperscript{18} recently reviewed the pathogenesis and complete clinical spectrum of infection and disease caused by \emph{H capsulatum}.

Successful treatment of microfoci of \emph{H capsulatum} in soil might substantially lower the number of cases of acute flu-like or upper respiratory infections usually attributed to “viruses,” which in reality are undifferentiated; and in time significantly reduce the costly and incapacitating disease in compromised hosts now caused by \emph{H capsulatum}.\textsuperscript{14}

Such a precaution might also reduce the disease and death toll from cryptococcosis, caused by another fungal air pollutant, \emph{Cryptococcus neoformans}, whose association with pigeon excreta is well recognized. Microfoci for both histoplasmosis and cryptococcosis have been found to be essentially global in distribution.

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\textbf{Is There a Drug of Choice for Vasodilator Therapy in Patients with Refractory Heart Failure?}

\textbf{Is there a Drug of Choice for Vasodilator Therapy in Patients with Refractory Heart Failure?}

It is now well established that the administration of peripheral vasodilator agents improves hemodynamic and clinical performance in many patients with severe chronic heart failure. We have an increasing number of drugs which either alone or in combination can produce substantial decreases in ventricular filling pressures and systemic vascular resistance and thereby acutely reduce symptoms of pulmonary congestion and low cardiac output. The response to vasodilator therapy, however, is variable, and all of the presently available agents have major limitations that affect their clinical usefulness.

The most commonly administered vasodilator agents are the organic nitrates which rapidly decrease ventricular filling pressures in many patients with severe heart failure.\textsuperscript{14} However, their effects on arteriolar resistance vessels are highly variable, so that only a small number of treated patients demonstrate significant improvements in cardiac output or
relief of fatigue.1 Substantial increases in forward output can be achieved only in patients with a markedly diminished pretreatment cardiac index at rest (<1.8 L/min/m²) and only when very high doses are utilized.2,4 In addition, the duration of effectiveness of all nitrate preparations is brief in my experience, usually less than four hours even with oral administration. Only by the administration of doses of 40 to 100 mg of isosorbide dinitrate orally every two to four hours can sustained longterm hemodynamic benefits be achieved.4 These large doses are surprisingly well tolerated in patients with severe heart failure, provided that the pretreatment left ventricular filling pressure is over 20 mm Hg, so that the minimum filling pressure needed to maintain forward output is not compromised.9 Because of the need for repeated doses at frequent dosing intervals, however, longterm outpatient therapy with nitrate preparations is difficult.

In contrast to nitrates, arterial vasodilators, such as hydralazine, consistently reduce systemic vascular resistance in patients with severe congestive heart failure and thereby produce marked improvements in cardiac output and stroke work with short and longterm administration.5,8 However, although significant increases in exercise tolerance have been observed by some investigators, others have suggested that objective clinical benefit fails to occur,7 and that many patients demonstrate only minimal hemodynamic responses.8,9 To a large extent this seems to be due to the administration of doses of hydralazine too small to produce any hemodynamic effects. Of nearly 50 patients evaluated at Mount Sinai Hospital, over 40 percent required doses of the drug more than 300 mg daily in order to reduce systemic vascular resistance significantly. These very high dose requirements seem particularly common in patients with elevated mean right atrial pressures suggesting that malabsorption of the drug due to mesenteric venous congestion may be important, since intravenous administration of small doses of the drug in these patients produces rapid hemodynamic effects. This great variability in dose requirements of hydralazine makes evaluation of the drug with empirically determined doses difficult, since invasive techniques are needed to substantiate hemodynamic improvement and permit individualization of an effective dosage regimen.

Even if significant systemic vasodilatation is achieved by sufficiently large doses of hydralazine, beneficial clinical responses are not consistently observed with longterm therapy with the drug.10,11 In patients with markedly dilated left ventricular chambers or severe mitral or aortic regurgitation, the decrease in systemic vascular resistance results in substantial increases in forward output and decreases in left ventricular filling pressure with minimal decreases in systemic blood pressure. These patients demonstrate a rapid increase in exercise tolerance associated with a decline in diuretic requirements and an improvement in prerenal azotemia.12 However, in patients with only mildly dilated left ventricular chambers, without primary valvular regurgitation, the decrease in systemic vascular resistance results in substantial decreases in blood pressure with modest increases in cardiac output and without improvement in stroke work. These patients commonly experience clinical deterioration upon institution of hydralazine therapy with precipitation of myocardial ischemic events, exacerbation of prerenal azotemia and progressive fluid retention.10,11 Determination of the left ventricular end-diastolic dimension echocardiographically seems to be able to predict the type of response to hydralazine before initiation of longterm therapy.12

In the continuing search for an agent with balanced effects of preload and afterload, recent investigators have focused on prazosin, an alpha sympathetic blocking drug with actions similar to nitroprusside. Although a marked improvement in cardiac performance is observed with first doses of prazosin,13 several reports utilizing invasive techniques have demonstrated the rapid development of hemodynamic tachyphylaxis after two to three days of maintenance therapy.14-16 In my experience, even rapid increments in dosage up to 30 to 45 mg daily are not accompanied by sustained hemodynamic benefits in the majority of patients.14 Nevertheless, several reports have appeared claiming longterm effectiveness of prazosin in patients with severe heart failure.17-19 Invasive confirmation of sustained hemodynamic benefit was not performed, however, and ventricular function was evaluated in two of these studies by M mode echocardiography which is particularly unreliable in patients with left ventricular asynergy.17-18 Furthermore, since improvements in exercise tolerance are seen with placebo therapy in heart failure patients,7 reports of improved exercise tolerance in uncontrolled studies must also be viewed with considerable caution.17

Finally, there is phentolamine. It was the first vasodilator specifically utilized for preload and afterload reduction in patients with severe heart failure in 1968.20 Although it produced marked decreases in ventricular filling pressures and increases in cardiac output, its tendency to produce tachycardia led to its rapid replacement by nitroprusside as the drug of choice for acute intravenous vasodilator therapy, and therefore, it is used infrequently now.
Its reintroduction in oral form, as suggested by Schreiber et al in the November, 1979 issue of Chest (76:571) represents a touch of irony in the evaluation of progress in this field. In the search for a long-term, orally effective equivalent of nitroprusside, we have come full circle. Unfortunately, the problem of tachycardia is present with oral phentolamine as well, and longterm effectiveness and usefulness still needs to be demonstrated.

There is, indeed, no drug of choice for oral vasodilator therapy in patients with severe congestive heart failure. Each patient presents a different set of problems, each drug has its unique limitations, and selection of the proper agent to achieve optimal clinical results is only possible through a highly individualized approach. The dosages of all available agents need to be individually titrated for each patient in order to ensure the administration of hemodynamically effective quantities. The pretreatment hemodynamic or pathophysiologic state is an important determinant of the responses observed as well, making certain patients unlikely to benefit from certain agents. Longterm therapy is complicated by an inconvenient dosing schedule for nitrates, potentially dangerous adverse reactions with hydralazine, and the rapid development of drug tolerance when prazosin is used. Although most patients may improve acutely with any vasodilator agent, well tolerated, sustained, longterm benefits are observed in relatively few. This is the real challenge which faces every old and new vasodilator drug.

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