Demeclocycline therapy for resistant oedema in advanced cardiac failure

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Summary
A patient with long-standing ischaemic heart disease and severe low output congestive cardiac failure received numerous diuretics, which gradually became ineffective. Resistant oedema was treated by adding demeclocycline to the current diuretic regime of frusemide and metolazone. Diuresis resulted, oedema disappeared and body weight fell. This drug combination was continued without complication for a further 6 months until his death.

Introduction
As cardiac output declines in congestive cardiac failure, response to diuretic therapy progressively diminishes. In advanced cardiac failure, demeclocycline, a relatively non-toxic tetracycline derivative (7-chloro-6-demethyl tetracycline), may effect a diuresis where conventional diuretics have failed. Short term metabolic studies employing a daily dose of 1200 mg increased urinary sodium and water excretion in intractable cardiac failure (Zegers de Beyl, Naeije and de Troyer, 1978). However, prolonged use of high dose demeclocycline may provoke uraemia, in oedematous states (Carrilho et al., 1977). The present authors noted that conventional diuretics with low dose demeclocycline may be less nephrotoxic and still capable of mobilizing resistant oedema.

Case report
A 62-year-old male had an extensive anterior myocardial infarction 10 years previously, which was followed by persistent mild cardiac failure easily controlled by small doses of frusemide. Suddenly, over the last 2 years, gross congestive cardiac failure developed, which required increasing doses of frusemide, eventually combined with metolazone for its potentiative effect. While oedema-free, as a result of frusemide and metolazone, a water load (20 ml/kg body weight) produced a maximal urine volume of 2·0 ml/min and a minimal urine osmolality of 363 mosmol/kg. Body space estimations with radio-isotope dilution were as follows: total exchangeable sodium 62·7 mmol/kg (normal 43·4), total exchangeable potassium 26·1 mmol/kg (normal 42·1), total body water 38·4 litres (normal 34·3). Even this combination eventually failed to control peripheral oedema, and resistant oedema had been present for 3 or 4 months. Demeclocycline, initially in a daily dose of 150 mg, and later in a daily dose of 300 mg, was added to frusemide and metolazone (Fig. 1). This combined diuretic therapy kept the patient oedema-free for 6 months. During this period, serum sodium concentration remained stable at 137 mmol/l and urea concentration at 10 mmol/l.

Discussion
The various factors responsible for oedema in low output congestive cardiac failure are not precisely defined. However, empirical treatment with conventional diuretic drugs, which act on the renal tubule to inhibit reabsorption of sodium or chloride, is effective in reducing oedema as a result of excretion of these ions (Burg, 1976). Furthermore, potentiation of the high-ceiling diuretic frusemide, which acts by inhibiting active chloride transport across the thick ascending limb of the loop of Henle, has been noted with addition of metolazone, a relatively weak diuretic which inhibits active sodium transport in the cortical diluting segment (Epstein et al. (1977). This diuretic combination has been shown to be successful in the treatment of resistant cardiac oedema (Asscher, 1974), and was employed with good effect for many months in the present case. When resistance developed, demeclocycline once again restored diuresis by a natriuretic effect, probably acting on the collecting duct. Combined diuretic therapy, acting at multiple sites along the nephron, may exert undesirable systemic haemodynamic effects by critically reducing extracellular fluid volume, and causing a further fall in cardiac output and systemic blood pressure.

Demeclocycline interferes with the cellular action of anti-diuretic hormone as a result of an effect
proximal and distal to the generation of 3,5'-adenosine monophosphate (cyclic AMP). In man and experimental animal the drug induces partial or complete nephrogenic diabetes insipidus, acting to block the effect of anti-diuretic hormone on the collecting duct (Dousa and Wilson, 1974; Wilson et al., 1973), by an effect which is dose-dependent and reversible (Singer and Rotenberg, 1973).

In a variety of oedematous disease states, demeclocycline in addition to increasing water diuresis may also increase urinary sodium excretion (de Troyer et al., 1976; Poupon, Gustot and Darnis, 1976). Natriuresis has also been observed with high dose demeclocycline in severe congestive cardiac failure in a patient who had become resistant to frusemide and metolazone (Ghose and Bonser, 1978). Successful action of low dose demeclocycline in the present case suggests that titration of demeclocycline dosage is possible.

Azotaemia is the main complication of high dose...
demeclocycline therapy when used in the treatment of oedematous patients. It was noted within weeks of commencing treatment with 1200 mg/day in severe congestive cardiac failure (Cox et al., 1977). Fortunately, azotaemia is quickly reversed by stopping the drug. Oligaemia, drug-induced nephrotoxicity, or anti-anabolic action may all contribute to this complication. A low dosage schedule, which is facilitated by concomitant conventional diuretic therapy, may prevent the development of azotaemia and still retain its diuretic properties.

Acknowledgments
The authors are grateful to Sister Kemp, Ward 9, for careful nursing; Dr A. L. Wells for biochemical investigations; and to Miss L. A. Grove for secretarial assistance.

References
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Postgrad Med J 1980 56: 121-123
doi: 10.1136/pgmj.56.652.121

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