

Reduction of excessive haematocrit levels in patients with polycythaemia due to hypoxic lung diseases by phenylhydrazine hydrochloride and pyrimethamine*

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Summary

A series of fourteen patients with polycythaemia due to hypoxic lung disease has been treated with a combination of phenylhydrazine hydrochloride and pyrimethamine to reduce the haematocrit level, with doses usually of up to 100 mg/day (and rarely up to 150 mg/day) of the former and never more than 12.5 mg/day of the latter.

Successful reduction of the haematocrit level was achieved in every case without any significant thrombocytopenia, the lowest level ever occurring being 100,000 platelets/mm³ in two patients.

All the patients were improved symptomatically.

Introduction

Reduction of the haematocrit and red-cell volume in patients with polycythaemia secondary to hypoxic lung disease is now an accepted method of treatment (Chamberlain & Millard, 1963; Pengelly, 1966) leading to general clinical improvement, even though little demonstrable improvement in tests of respiratory function occurs (Chamberlain & Millard, 1963).

Pengelly (1966) effectively used a combination of dapsone and pyrimethamine, using doses of up to 50 mg/day and very occasionally 75 mg/day of the latter. The principle of the drug combination was to reduce the red-cell life-span and at the same time inhibit red-cell production from the bone marrow, but sometimes thrombocytopenia occurred which was clearly due to the pyrimethamine. Although there was never any apparent ill-effect from the thrombocytopenia it is clearly not a desirable complication and is potentially fraught with the danger of internal or external bleeding. It would be safer if the drug therapy were entirely free from this risk.

Dapsone does not cause very much reduction in the red-cell life-span (Pengelly, 1963), and the use of a more powerfully haemolytic drug would mean

that the dosage of pyrimethamine could be reduced to a level which, while still causing some inhibition of red-cell production, would fail to reduce the platelet count significantly.

Phenylhydrazine hydrochloride (British Pharmaceutical Codex) is a haemolytic drug with a direct damaging effect on the red cells and the production of Heinz bodies. It used to be employed in the treatment of polycythaemia vera, but most people have discarded it because its effect was said to be too unpredictable (Britton, 1963) or too toxic (de Gruchy, 1964). The official dosage is 100-450 mg/day (British Pharmaceutical Codex, 1949) but Cumming *et al.* (1967) found that 100 mg/day produced a mild haemolytic anaemia in one patient and that 75 mg/day caused definite haemolysis in their other nine patients. I found that two red-cell survival trials by the method of Mollison & Veall (1955) in a mild diabetic volunteer gave mean red-cell life-spans (Method A, Mollison, 1956) of approximately 30 days and 20 days when 50 and 100 mg/day, respectively, of phenylhydrazine hydrochloride were administered by mouth. These red-cell life-spans were definitely lower than those occurring when conventional doses of dapsone were used (Pengelly, 1963).

This paper describes the use of phenylhydrazine hydrochloride in combination with a daily dose of 12.5 mg of pyrimethamine or less in fourteen patients with secondary polycythaemia. The usual dosage was 25-100 mg/day though rarely 125-150 mg/day had to be used. At this level of pyrimethamine dosage, thrombocytopenia of significance did not occur in any of the patients, though a level of 100,000 platelets/mm³ occurred occasionally.

The phenylhydrazine hydrochloride was obtained as a powder, and dispensed by the hospital pharmacist in capsules each containing 25 mg.

Methods

Haematocrit values were measured by the method of Wintrobe (1933), the tubes being centrifuged for

*An abridged version of the winning entry submitted by C.D.R.P. for the Nathaniel Bishop Harman Prize of the British Medical Association 1968.

30 min at 3000 rev/min in an M.S.E. Minor Centrifuge, and the results expressed without any correction for trapped plasma.

Platelets were counted by the 'basic method using formol-citrate red-cell diluent' (Dacie & Lewis, 1966). (Methods involving haemolysis of red cells were not used as the presence of Heinz bodies caused difficulties in counting platelets accurately.)

Red-cell survival testing was carried out by the method of Mollison & Veall (1955), the results being expressed as mean red-cell life-span by Method A (Mollison, 1956).

Haemoglobin is expressed as a percentage; 100% = 14.6 g/100 ml.

Case reports and results

Case 1

Chronic bronchitis and emphysema, arterio-sclerotic heart disease. Male 67 years. Chest expansion 1 in. BP 140/80 mmHg. Generalized cardiac enlargement. Left bundle branch block. PCV 57%. Treatment with phenylhydrazine hydrochloride and pyrimethamine resulted in satisfactory falls in PCV (Fig. 1). He was comfortable and less dyspnoeic with a PCV of 50% or just below.

Case 2

Asthmatic bronchitis and emphysema. Female 61 years. Chest expansion $\frac{1}{2}$ in. BP 150/90 mmHg. Congestive heart failure. PCV 56%. Two good responses occurred with phenylhydrazine hydrochloride and pyrimethamine therapy and there was clinical improvement (Fig. 2), but the third time she failed to respond and died. Necropsy showed marked right ventricular hypertrophy and severe bronchitis.

Case 3

Chronic bronchitis and emphysema. Male 59 years. Chest expansion $1\frac{1}{2}$ in. Scattered moist sounds in lungs. BP 150/90 mmHg. PCV 57%. Good response to phenylhydrazine hydrochloride and pyrimethamine (Fig. 3). He was always better with PCV about 50%.

Case 4

Chronic bronchitis and emphysema. Male 52 years. Scattered moist sounds in lungs. Chest expansion less than $\frac{1}{2}$ in. BP 130/80 mmHg. Moderate cardiomegaly. PCV 58%. Good response to phenylhydrazine hydrochloride and pyrimethamine (Fig. 4) with general improvement. He later died of an exacerbation of his bronchitis. Necropsy showed right ventricular hypertrophy and purulent bronchitis.

Case 5

Chronic bronchitis and emphysema; obesity. Male 58 years. Weight $15\frac{1}{2}$ stones. BP 150/90 mmHg. Chest expansion $\frac{1}{2}$ in. Some left ventricular enlargement. PCV 55%. Phenylhydrazine hydrochloride and pyrimethamine were given with good falls in PCV (Fig. 5). He was always more comfortable and less dyspnoeic with a PCV of about 50%.

Case 6

Chronic bronchitis and emphysema. Male 62 years. BP 130/80 mmHg. Chest expansion 1 in. Some cardiac enlargement and pulmonary congestion. PCV 61% (Fig. 6). Phenylhydrazine hydrochloride and pyrimethamine resulted in a good fall in PCV and he has been better with a level of about 50%.

Case 7

Chronic asthmatic bronchitis and emphysema. Female 56 years. Scattered moist sounds in chest. Expansion $1\frac{1}{2}$ in. BP 140/80 mmHg. Some generalized cardiac enlargement. PCV 57.5%. Phenylhydrazine hydrochloride and pyrimethamine given with good falls in PCV but a more sustained fall seemed to be achieved when phenylhydrazine hydrochloride was given as a powder in milk (Fig. 7). She was less dyspnoeic with a PCV of about 50%.

Case 8

Chronic bronchitis and emphysema. Female 61 years. Chest expansion $\frac{1}{2}$ in. BP 175/80 mmHg. Some oedema of feet. Gross cardiac enlargement. Pleural effusions. PCV 57%. Phenylhydrazine hydrochloride and pyrimethamine given with good falls in PCV (Fig. 8). She was better with PCV about 45-50%.

Case 9

Chronic bronchitis and emphysema. Male 53 years. Chest expansion 1 in. BP 120/70 mmHg. Heart considerably enlarged. ECG: P-pulmonale and T-wave inversion in precordial leads. PCV 57%. Treatment with phenylhydrazine hydrochloride and pyrimethamine gave falls in PCV but resistance developed later. When phenylhydrazine hydrochloride was taken as a powder in milk, the effect was enhanced and a satisfactory fall in PCV occurred (Fig. 9). Thereafter his dyspnoea became less and he became generally more comfortable.

Case 10

Chronic bronchitis and emphysema. Male 64 years. Auricular fibrillation. Scattered moist sounds in chest. Expansion 2 in. BP 150/80 mmHg. PCV 56.5%. Treatment with phenylhydrazine hydrochloride and pyrimethamine gave a satisfactory fall in PCV which remained about 50% (Fig. 10), and the patient became less dyspnoeic and more comfortable.

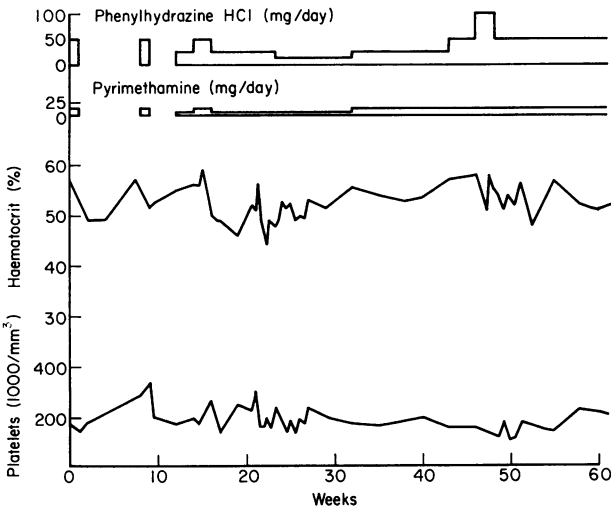


FIG. 1. Therapy, haematocrit levels and platelet counts in Case 1.

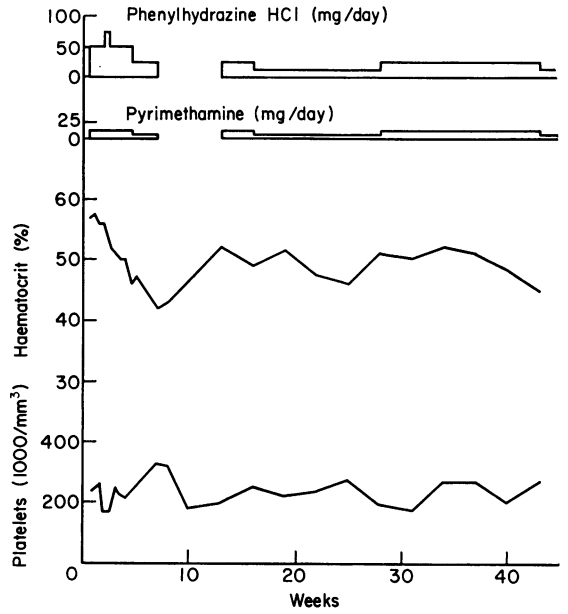


FIG. 3. Therapy, haematocrit levels and platelet counts in Case 3.

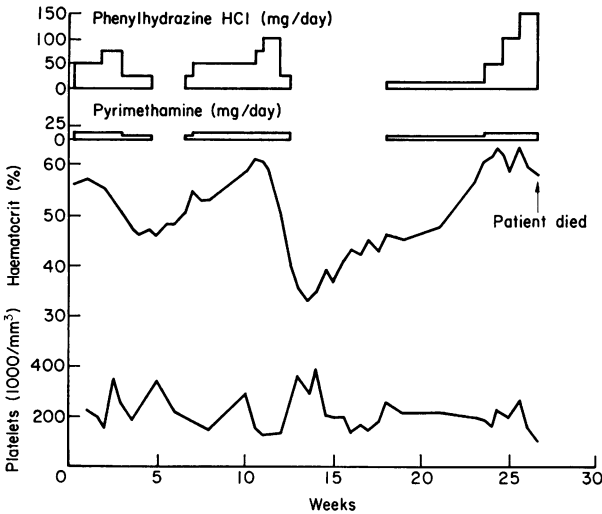


FIG. 2. Therapy, haematocrit levels and platelet counts in Case 2.

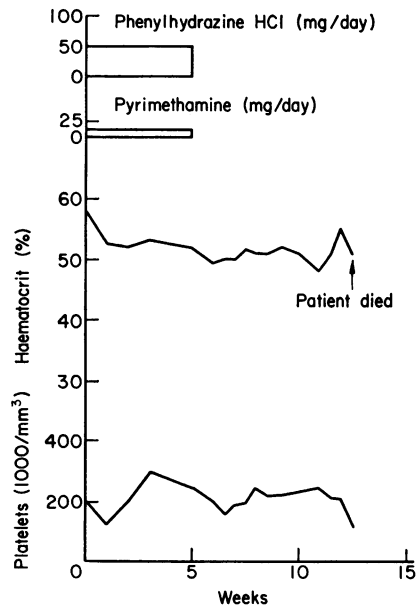


FIG. 4. Therapy, haematocrit levels and platelet counts in Case 4.

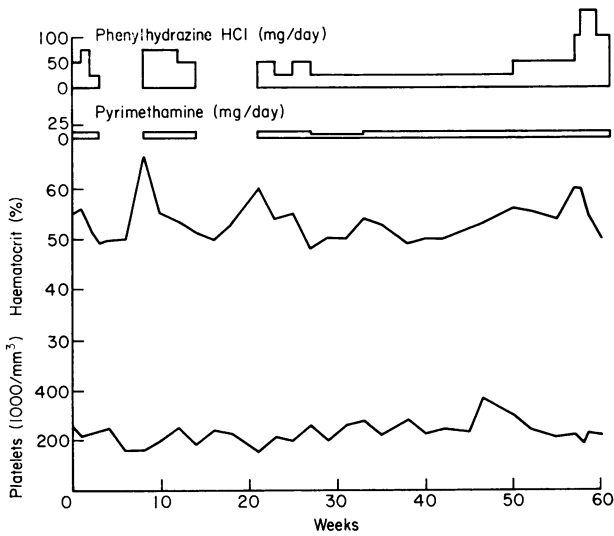


FIG. 5. Therapy, haematocrit levels and platelet counts in Case 5.

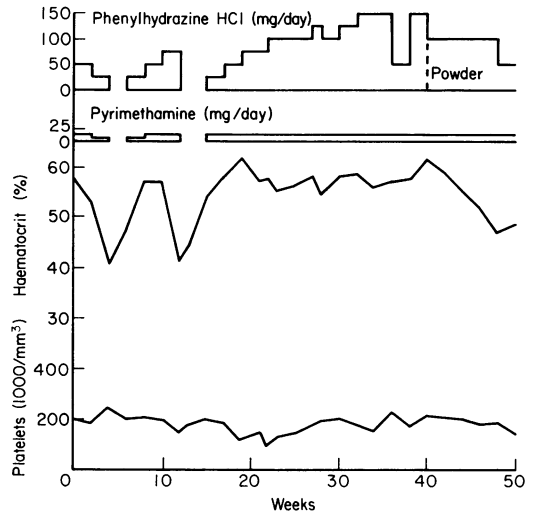


FIG. 7. Therapy, haematocrit levels and platelet counts in Case 7.

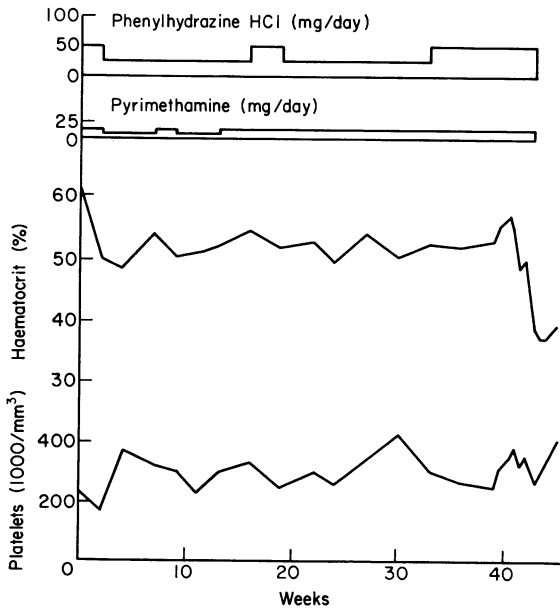


FIG. 6. Therapy, haematocrit levels and platelet counts in Case 6.

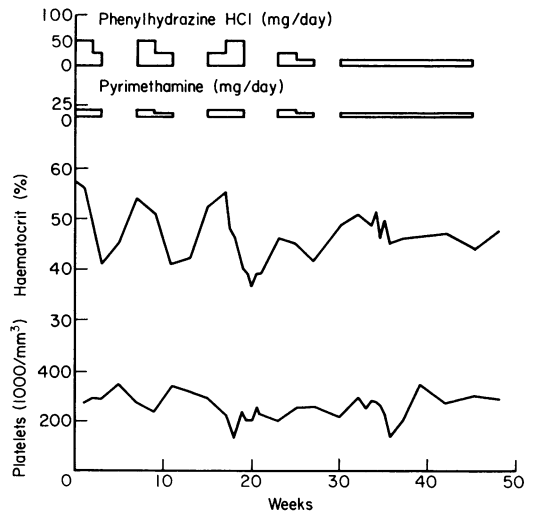


FIG. 8. Therapy, haematocrit levels and platelet counts in Case 8.

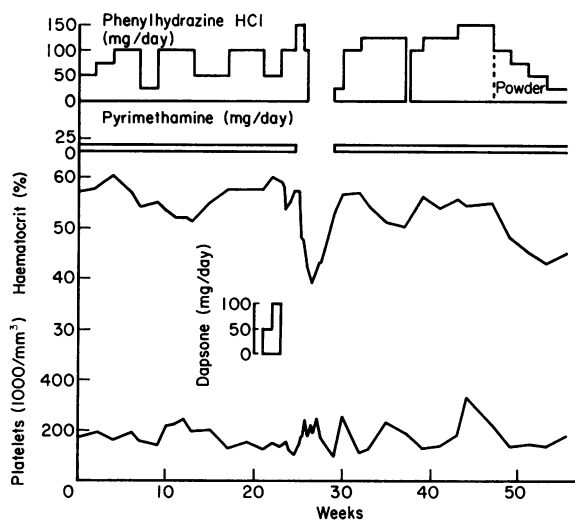


FIG. 9. Therapy, haematocrit levels and platelet counts in Case 9.

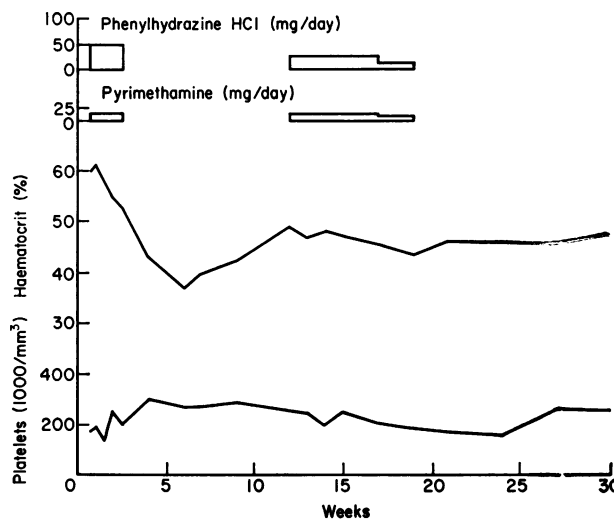


FIG. 11. Therapy, haematocrit levels and platelet counts in Case 11.

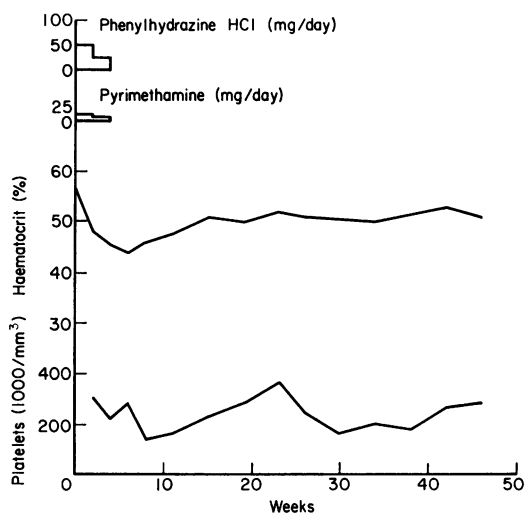


FIG. 10. Therapy, haematocrit levels and platelet counts in Case 10.

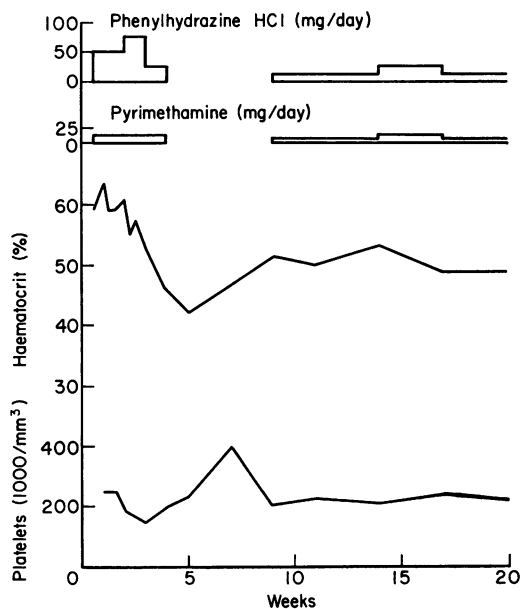


FIG. 12. Therapy, haematocrit levels and platelet counts in Case 12.

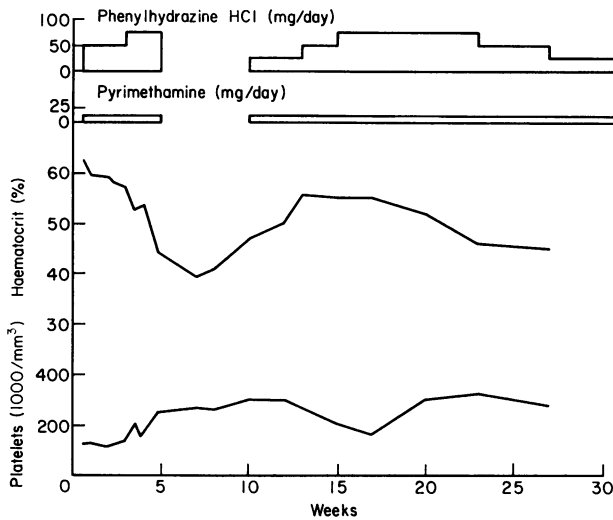


FIG. 13. Therapy, haematocrit levels and platelet counts in Case 13.

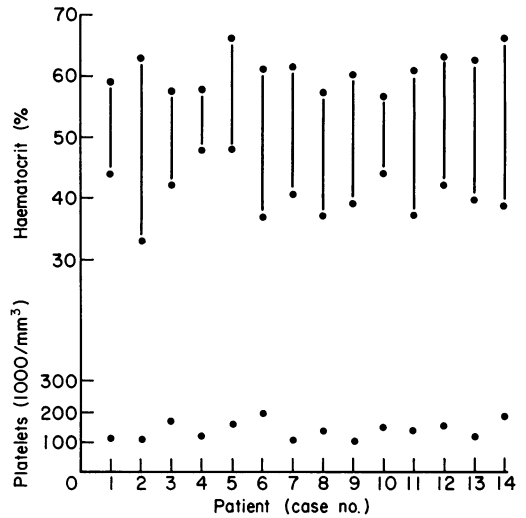


FIG. 15. Maximum and minimum haematocrit levels and lowest platelet count in the fourteen patients treated with phenylhydrazine hydrochloride and pyrimethamine.

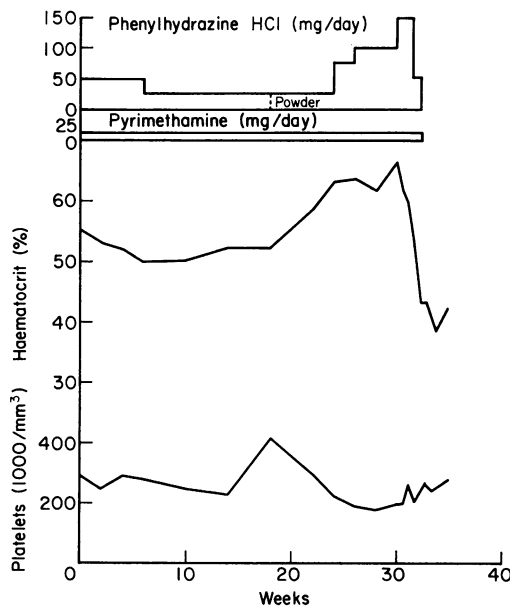


FIG. 14. Therapy, haematocrit levels and platelet counts in Case 14.

Case 11

Chronic bronchitis and emphysema; chronic rheumatoid arthritis. Female 62 years. Chest expansion $\frac{1}{2}$ in. BP 190/90 mmHg. Heart considerably enlarged. PCV 60%. Good response to phenylhydrazine hydrochloride and pyrimethamine (Fig. 11). She was less dyspnoeic and more comfortable with PCV of about 45–50%.

Case 12

Bronchitis and emphysema; coronary artery disease. Male 73 years. Scattered moist sounds in chest. Expansion 1 in. Heart considerably enlarged with gallop rhythm. ECG: Right ventricular enlargement. BP 180/110 mmHg. PCV 59%. Treatment with phenylhydrazine hydrochloride and pyrimethamine gave good fall in PCV (Fig. 12). He was more comfortable and less dyspnoeic with PCV about 50%.

Case 13

Chronic bronchitis and emphysema; cor pulmonale. Male 44 years. Ankle oedema and neck vein congestion. BP 150/110 mmHg. Chest expansion $\frac{1}{2}$ in. PCV 62.5%. Treatment with phenylhydrazine hydrochloride and pyrimethamine resulted in good falls in PCV with clinical improvement (Fig. 13).

TABLE 1. Respiratory function tests before and/or after therapy

Case no.		VC (litres)	FEV ₁ (%)	MBC (l/min)	PFR (l/min)
5	Before treatment	2.0	47	14.4	70
6	Before treatment	1.3	50	14.4	80
	After treatment	1.2	70	15.6	80
7	Before treatment	1.1	59	12.6	120
9	Before treatment	1.3	32	12.0	60
	After treatment	1.0	40	8.8	85
10	Before treatment	2.7	83	15.6	160
	After treatment	2.4	55	11.4	240
12	Before treatment	2.0	30	24.0	180
13	Before treatment	1.4	28	12.6	110
	After treatment	2.5	39	23.0	160
14	After treatment	1.8	30	14.4	120

VC, Vital capacity; FEV₁, forced expiratory volume at 1 sec; MBC, maximum breathing capacity; PFR, peak flow rate.

Case 14

Chronic bronchitis and emphysema; cor pulmonale.

Male 62 years. Ankle oedema and neck vein congestion. BP 130/85 mmHg. PCV 55%. Treatment with phenylhydrazine hydrochloride and pyrimethamine gave falls in PCV. The response appeared to be better when the phenylhydrazine hydrochloride was given as a powder in milk (Fig. 14). He was comfortable and less dyspnoeic with a PCV of about 50%.

Maximum and minimum haematocrit levels and the lowest observed platelet count for each case are shown in Fig. 15.

Tests for vital capacity (VC), forced expiratory volume at 1 sec (FEV₁), maximum breathing capacity (MBC) and peak flow rate (PFR) were done in Cases 5, 6, 7, 9, 10, 12, 13 and 14 and the results are shown in Table 1.

Sternal marrow examination was carried out in Cases 3, 5, 6, 9, 11 and 13, at the approximate time of the maximum effect of the drugs on the haematocrit level. In Cases 3 and 11, no abnormality was recognized. In Cases 5 and 9 Howell-Jolly bodies were seen, Case 6 showed normoblastic hyperplasia and Case 9 some macronormoblasts. Frankly megaloblastic changes were not seen in any of the marrow smears.

Discussion

Chamberlain & Millard (1963) found that reduction of the PCV in polycythaemia secondary to hypoxic lung disease could benefit the patient; the method used was prolonged oxygen inhalation. Pengelly (1966) showed that satisfactory reduction in PCV could be achieved by the administration of dapsone and pyrimethamine by mouth, but that in the dosage of pyrimethamine used (up to 50–75 mg/day), thrombocytopenia was sometimes a side-

effect which interfered with the therapy. Only five patients were treated.

In this series of fourteen patients the dose of pyrimethamine used was only 12.5 mg/day or less and phenylhydrazine hydrochloride was used as the haemolytic drug. The reducing effect on the PCV was satisfactory in most of the patients and in only two patients did the platelet count ever become as low as 100,000/mm³. The usual dosage of phenylhydrazine hydrochloride (25–100 mg/day) only just reached the lowest official dose of 100–450 mg/day (British Pharmaceutical Codex, 1949) and probably explains why no instance of a haemolytic crisis occurred. The maximum dosage employed was 150 mg/day in Cases 2, 5, 7, 9 and 14 which is not much above the lowest official dose. One patient (Case 9) seemed rather resistant to the drug therapy (Fig. 9) and a red-cell survival test while he was having 100 mg of phenylhydrazine hydrochloride per day indicated a mean red-cell life-span of about 70 days. Whether this apparent resistance to haemolysis was due to poor absorption, to a lower than usual blood level of the drug or to abnormally resistant red cells was not clear. Dapsone in addition to the other drugs did not seem to help (Fig. 9). Recently he has been taking the phenylhydrazine hydrochloride in milk as a powder and the drug seems to have been more effective, thus suggesting that the gelatine capsules may not have been digesting adequately (Fig. 9). The same phenomenon may have been present in Cases 7 and 14, though the results are not quite so clearcut (Figs. 7 and 14).

The maximum dosage of pyrimethamine used was 12.5 mg/day which represents the lowest dose which has been recommended for the treatment of polycythaemia vera (Britton, 1963). The effectiveness of this drug was demonstrated by falls in the platelet count to 100,000 mm³ in Cases 7 and 9 (Figs. 7 and 9),

and although frank megaloblastic changes were not seen in the bone-marrow smears examined, Howell-Jolly bodies were seen in two (Cases 5 and 9) and macronormoblasts in one (Case 9). (Pyrimethamine is an anti-folic acid drug.) These rather low platelet counts did not appear to bear any particular relationship to the larger doses of phenylhydrazine hydrochloride (Figs. 7 and 9).

Systematic tests of respiratory function were not carried out in this series of patients though some were done in Cases 5, 6, 7, 9, 10, 12, 13 and 14 (see Table 1). Diffusion capacity could not be carried out owing to lack of suitable apparatus, but it seems to be mainly the diffusion capacity which is improved by lowering excessive haematocrit levels (Chamberlain & Millard, 1963). Tests of VC, FEV₁, MBC and PFR were done before and after treatment in Cases 6, 9, 10 and 13. Case 13 showed a consistent all-round improvement, but there was no good evidence of improvement in any of the others (see Table 1).

Measurements of red-cell volume were not carried out in these patients but studies by Pengelly (1966) indicated that there were considerable reductions in the circulating red-cell volume in the patients treated with dapsone and pyrimethamine in whom the haematocrit levels fell. There is no reason to believe that in this series of patients the results would be dissimilar. Demonstrations of falls in red-cell volume would therefore be solely of academic interest and it can reasonably be assumed that such falls in red-cell volume did occur as the haematocrit levels were lowered.

Only two patients (Cases 2 and 4) have died. Both were very ill and had bronchitis for over 40 years and Case 4 had had episodes of heart failure for 3 years. Therapy with phenylhydrazine hydrochloride and pyrimethamine was only used as a last resort. There was right ventricular hypertrophy in both patients at necropsy. On the other hand, since being treated with the phenylhydrazine

hydrochloride and pyrimethamine, six patients have been able to work (Cases 3, 6, 9, 10, 12 and 13).

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