a penicillamine-induced immune complex nephropathy (Tribe *et al.*, 1974).

The mode action of penicillamine in R.A. is unknown. Thymus-derived lymphocytes are known to play an important part in the pathogenesis of autoimmune diseases, including R.A. In view of the finding of pathological changes in the thymus in 70-80% of patients with myasthenia gravis the effect of penicillamine in apparently precipitating myasthenia gravis in R.A. may therefore be of more than anecdotal interest.

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ADDENDUM

In case 3 pyridostigmine was subsequently withdrawn without any recurrence of myasthenic symptoms.

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Changes in Haemoglobin Binding Curve and Oxygen Transport in Chronic Hypoxic Lung Disease

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Summary

Direct measurements of the factors determining blood oxygen transport in 10 patients with chronic hypoxic respiratory failure led to the conclusion that wide differences in the position of their oxygen binding curves, due to spontaneous differences in red-cell 2, 3-diphosphoglycerate, had little effect on oxygen delivery to the tissues, as assessed by the mixed venous oxygen tension when they were breathing air. This result arises from the shape of the oxygen binding curve. A drug which could shift the curve to the right would help tissue oxygenation in cardiogenic and other forms of shock, when a low cardiac output can not be improved though arterial blood can be well oxygenated.

Introduction

The discovery that variations in red-cell concentrations of 2, 3-diphosphoglycerate (2,3-DPG) could alter the affinity of haemoglobin for oxygen (Benesch and Benesch, 1967; Chanutin and Curnish, 1967) has led to intensive study of the binding of ligands to the haemoglobin molecule (Kilmartin and Rossi-Bernardi, 1973). Nevertheless, less attention has been paid to the effects of variations in 2, 3-DPG concentrations on oxygen transport in vivo, particularly in patients with hypoxaemia resulting from chronic lung disease. Transport of oxygen by the blood depends on the concentration of haemoglobin, the arterial oxygen tension (Pao_2), arterial pH, and the cardiac output in addition to the oxygen binding curve. The position of this curve can be described by the oxygen tension necessary to obtain 50% full saturation (P_{50}). We have measured all these variables in 10 hypoxaemic patients during right heart catherization to assess the effects of their different 2, 3-DPG levels on oxygen transport.

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Patients and Methods

We studied 10 patients aged from 43 to 70 years, who were in a stable state of chronic hypoxaemia (mean Pao_2 (±S.D.) 6·4±1·03 kPa (48·1±7·7 mm Hg)), with different levels of chronic Co_2 retention ($Paco_2$ 7·3±1·6 kPa (54·9±11·9 mm Hg)). All had irreversible airways obstruction (FEV_1 0·49±0·21 l, FEV % 33·7±11·0%) and hyperinflation of the lungs (residual volume 66·5±10·6% of total lung capacity). This confirmed the clinical diagnosis of cor pulmonale (pulmonary arterial mean pressure 4·8±1·5 kPa (35·8±11·5 mm Hg)) resulting from chronic bronchitis and emphysema, with different degrees of secondary polycythaemia (red cell mass 51·4±19·5 ml/kg). Right heart catherization and the other measurements were part of their assessment for long-term domiciliary oxygen therapy, and all patients gave informed consent to the procedures after the study had been approved by the local ethical committee.

When the patients were resting supine and breathing air simultaneous blood samples were taken from catheters in the brachial and pulmonary arteries, and oxygen uptake, by collection and analysis of expired gas, and cardiac output (green dye dilution) were measured. Blood gas tensions and pH were measured by IL 113 electrodes calibrated with tonometered blood (Flenley *et al.*, 1967); oxygen capacity by spectrophotometry (King and Wooton, 1956) calibrated against the method of Van Slyke and Neill (1924); P_{50} by a modification of the mixing technique (Edwards and Martin, 1956); red-cell mass by ^{51}Cr dilution; and 2,3-DPG by a modification of Krimsky's (1963) enzymatic assay. Details of these methods and their precision are given by Fairweather *et al.* (1974).

Measured and Calculated Indices of Oxygen Transport in 10 Patients with Respiratory Failure.

Case No.	P_{50}(7·4) (kPa)	2, 3-DPG in Red Cells $\times 10^{-6}$mol/g Hb)	Arterial Blood			Cardiac Output (l/min)	Oxygen Uptake (ml/min)	Mixed Venous Blood	
			Po_2 (kPa)	pH	Oxygen Capacity of Arterial Blood (ml/l)			Venous pH	$P\bar{v}o_2$ (kPa)
1	3·42	16·1	5·1	7·45	231	9·42	184	7·39	4·7
2	3·60	16·0	8·7	7·44	240	6·17	260	7·38	5·6
3	3·69	18·9	5·7	7·42	208	5·67	205	7·41	4·3
4	3·64	14·7	6·0	7·33	233	6·10	251	7·30	4·5
5	3·64	18·3	5·2	7·35	212	5·03	201	7·34	3·7
6	3·81	19·1	7·1	7·37	175	7·39	153	7·36	5·6
7	3·40	12·6	5·9	7·37	243	6·34	325	7·36	4·3
8	3·53	13·5	5·7	7·35	197	7·47	313	7·31	4·3
9	3·11	13·2	6·3	7·36	186	5·29	242	7·35	4·0
10	3·46	18·1	7·2	7·40	221	3·75	224	7·39	4·8

Conversion: SI to Traditional Units—kPa $\approx$ 7·5 mm Hg.

Results

P_{50} was expressed at pH of 7·40 using a Bohr effect of −0·50, the actual arterial pH varying only between 7·45 and 7·33. P_{50} (7·4) in these 10 patients ranged from 3·1 to 4·0 kPa (23·3-29·7 mm Hg). In 10 normal subjects P_{50} (7·4) averaged 3·6 $\pm$ 0·009 kPa (26·7 $\pm$ 0·65 mm Hg) in our hands. The 2,3-DPG levels of our patients correlated with P_{50} (7·4) values, varying from 13·2 to 18·9 $\times 10^{-6}$ mol/g haemoglobin and in normal subjects averaging 12·8 $\pm 10^{-6} \times$ mol/g haemoglobin.

The measured determinants of oxygen transport are shown in the table. The mixed venous Po_2 ($P\bar{v}o_2$) was derived as follows: Arterial Po_2, Pco_2, and pH allowed the arterial oxygen saturation (Sao_2) to be calculated at the measured P_{50}; the oxygen capacity allowed derivation of the arterial oxygen content, and cardiac output and oxygen uptake then led by the Fick principle to the arteriovenous oxygen content difference, and so to the mixed venous oxygen content and saturation. Again using the measured P_{50} and the pH measured in the pulmonary arterial (mixed venous) blood sample we calculated the $P\bar{v}o_2$ by means of the Bohr effect of −0·50. When the $P\bar{v}o_2$ value calculated by these methods was compared with that actually measured in the mixed venous blood and also with the value derived from a standard normal binding curve with a P_{50} of 3·5 kPa (26·7 mm Hg) (Severinghaus, 1966) these values did not differ by more than 0·53 kPa (4 mm Hg) in any of the patients, which is very close to the 95% confidence limits of our error of measurement of Po_2 in blood, at $\pm$0·47 kPa ($\pm$3·5 mm Hg) (Flenley *et al.*, 1967).

Discussion

These observations imply that in our patients, most of whom had chronic stable hypercapnia and compensated respiratory acidosis, spontaneously arising wide variations in 2, 3-DPG concentrations were associated with considerable changes in the position of the binding curve, as measured by P_{50}. Nevertheless, such variations had comparatively little effect on oxygen transport when these patients were breathing air, for both the measured and calculated $P\bar{v}o_2$ varied by only 0·53 kPa (4 mm Hg) at most from the value calculated using a standard normal binding curve with a P_{50} of 3·6 kPa (26·7 mm Hg).

The mechanism of this apparent paradox lies in the shape of the binding curve, as shown in fig. 1, where two curves with a P_{50} (7·4) of 2·7 and 4·0 kPa (20 and 30 mm Hg) are drawn. If we take an Pao_2 of 5·3 kPa (40 mm Hg) the arterial points are already "over the knee" of the binding curve (fig. 1a). Thus with a slightly wide arteriovenous oxygen content difference of 50 ml/l—that is, a normal to low cardiac output—the venous points on the curve are relatively close in terms of $P\bar{v}o_2$ despite the difference in position of the curves as shown by their P_{50} (7·4). As fig. 1 b shows, however, the same arteriovenous oxygen content difference when the Pao_2 is higher—for example, 13·3 kPa (100 mm Hg)—results in considerable separation of $P\bar{v}o_2$ when the P_{50} (7·4) changes from 2·7 to 4·0 kPa (20 to 30 mm Hg).

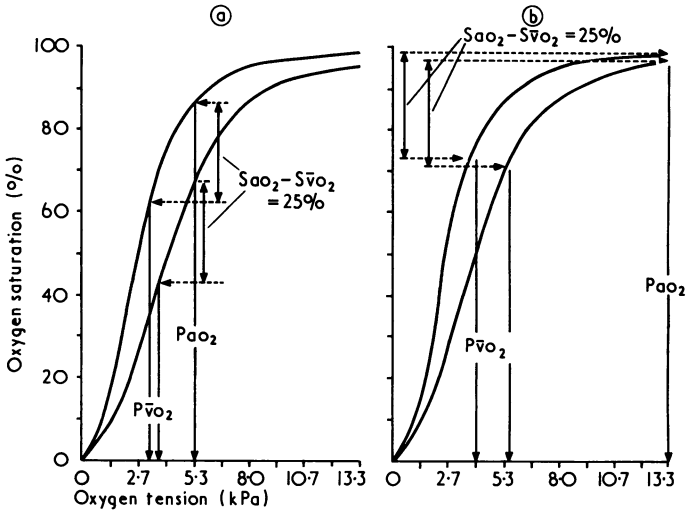

FIG. 1—Oxygen binding curves with P_{50} (7·4) of 2·7 kPa (left curve) and 4·0 kPa (right curve). $P\bar{v}o_2$ for each curve is shown, assuming arteriovenous saturation difference ($Sao_2 - S\bar{v}o_2$) of 25%, when the arterial Po_2 is (a) 5·3 kPa and (b) 13·3 kPa.

Conversion: SI to Traditional Units—kPa $\approx$ 7·5 mm Hg.

These interactions between P_{50}, Pao_2, arteriovenous oxygen content difference (inversely related to cardiac output), and the resultant $P\bar{v}o_2$ can be described graphically. The effects of a change in P_{50} (7·4) from 2·7 to 4·0 kPa (20 to 30 mm Hg) on the resultant $P\bar{v}o_2$ at PaO^2 13·3, 9·3, 6·7, and 5·3 kPa (100, 70, 50, and 40 mm Hg) are shown in fig. 2. Arteriovenous oxygen content differences of 40 ml/l and 60 ml/l blood are shown. In each case the oxygen capacity was taken as 200 ml/l blood and the arterial pH as 7·40.

Clearly changes in P_{50} (7·4) have considerable effects on oxygen transport when the Pao_2 is high but minimal effects, amounting to only 0·26-0·40 kPa (2-3 mm Hg) differences in $P\bar{v}o_2$, when the Pao_2 is low. Turek *et al.* (1973) reached a similar conclusion from theoretical studies of the binding curve.

A rise in P_{50} (7·4) from 2·7 to 4·0 kPa (20 to 30 mm Hg) could have a considerable effect on blood oxygen transport when a high Pao_2 is associated with a low cardiac output—for example, by raising $P\bar{v}o_2$ from the dangerously low value of 3·7 kPa (28 mm Hg) to a near normal value of 5·7 (43 mm Hg)—without a change in cardiac output. These deductions from the shape of the oxygen binding curve, which provide an explanation for our observations in chronic hypoxaemia, lead us to propose a potentially valuable role for a therapeutically induced rise in P_{50} in the treatment of cardiogenic or other forms of shock, where the cardiac output is usually low and cannot be increased

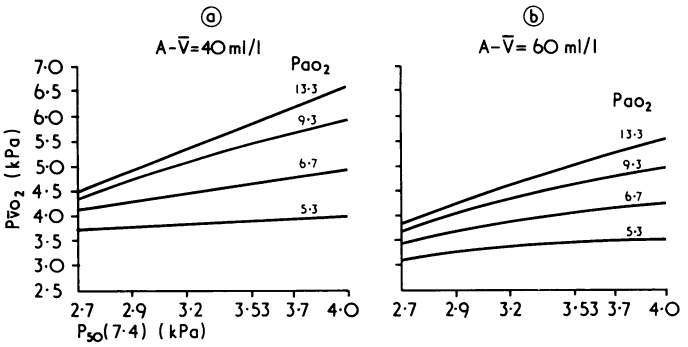

FIG. 2—Calculated relationships between P_{50} (7·4) and $P\bar{v}O_2$ for Pao_2 of 13·3, 9·3, 6·7, and 5·3 kPa. Oxygen capacity of 200 ml/l blood and arterial pH of 7·40 are assumed. In (a) arteriovenous content difference ($a-\bar{v}$) is 60 ml/l and in (b) 40 ml/l.

Conversion: SI to Traditional Units—1kPa ≈ 7·5 mm Hg.

(McKenzie *et al.*, 1964). If high-concentration oxygen therapy could provide a Pao_2 of around 13·3 kPa (100 mm Hg) in such shocked patients the transport of oxygen to the cells of the body could be facilitated by an increase in P_{50}, which would then allow oxygen to be delivered with a higher $P\bar{v}O_2$ (fig. 2 b). This would cause an improvement in the Po_2 gradient driving diffusion of oxygen from capillaries to the site of oxygen usage in the cellular mitochondria (Flenley, 1967). This suggestion now awaits direct trial when a therapeutic agent to raise P_{50} becomes available.

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Prolactin Studies in "Functionless" Pituitary Tumours

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Summary

Hyperprolactinaemia was found in all 17 women and in one out of six men who presented with hypogonadism and a radiologically enlarged sella turcica but no other clinical endocrine dysfunction. Some of the women also had galactorrhoea. The greater the level of hyperprolactinaemia in these 18 patients the larger their sellae turcica except in two patients with unusual features. The sella turcica was usually asymmetrically enlarged and there was rarely an upward extension of tumour, though the sella floor often showed some erosion on tomography. An oral dose of bromocriptine suppressed the hyperprolactinaemia in most patients at the same rate as in normal post-partum women.

Nine of the 18 patients with hyperprolactinaemia had low basal luteinizing hormone (LH) levels. The LH responsiveness to 100 μg of LH-releasing hormone (LHRH) was tested in 12, and eight showed subnormal values. Of eight biopsy specimens obtained four showed acidophil granules on light microscopy, and in five granules of various sizes were seen on electron microscopy.

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Introduction

Amenorrhoea with or without galactorrhoea has long been known to be common in women with radiologically evident pituitary tumours (Forbes *et al.*, 1954), and when there is no associated acromegaly or Cushing's disease it has been customary to refer to these as "functionless" pituitary tumours. Lewis and van Noorden (1974) have commented that not all these tumours are chromophobes histologically, and on both light and electron microscopy the tumours may vary from being inactive to showing intense secretory activity. Thus, histological evidence or serum hormone levels can show that these tumours may not be "functionless".

The frequency of hyperprolactinaemia with these tumours is not precisely known though Jacobs and Daughaday (1973) put it at 30%. Hyperprolactinaemia occurs in some men with functionless pituitary tumours (Thorner *et al.*, 1974), but again its frequency has not been determined. Vezina and Sutton (1974) found that all 20 of their patients with hyperprolactinaemia and associated amenorrhoea and galactorrhoea had radiological evidence of a pituitary tumour after careful tomography, even though a plain *x*-ray examination of the pituitary fossa showed it to be of normal size in 14 patients. All their patients subsequently had transphenoidal surgery, and pituitary tumours were found in each case.

We report here an analysis of 18 patients with hypogonadism or visual field defects or both who also had hyperprolactinaemia.

Patients and Methods

Six men and 17 women all presented with hypogonadism or visual field defects or both, and all also had radiologically enlarged sellae. None had received any treatment directed to the pituitary gland. Their clinical features are summarized in the table. All 17 women and one man had hyperprolactinaemia. Eight of these patients were later treated by pituitary implantation of yttrium-90.