blood flow in each part of the lungs. From this, values of relative underventilation (summed for both lungs) were calculated and plotted against arterial oxygen tension for each patient (fig 3). The extent of the relative underventilation correlated well with the degree of arterial hypoxaemia. A slight refinement of allowing for the age dependence of normal arterial oxygen tension in calculating the degree of hypoxaemia attributable in each patient to the pulmonary embolism further improved this correlation.

In view of the above considerations we postulate that the development of ventilation-perfusion mismatching in regions of non-embolised lung was an important cause of hypoxaemia in our patients. There has been no general agreement about the cause of hypoxaemia in acute pulmonary embolism in man, and evidence has been provided for right to left intrapulmonary shunting^{1 11} and impairment of gas diffusion.¹² These results are not necessarily incompatible with ours. Localised atelectasis and prolonged breathing of oxygen may produce shunting. We were at pains to exclude these in the present study, whereas one or more of them appears to have been present in most patients in other studies.^{1 11 12} Furthermore, other mechanisms of hypoxaemia might be operating in massive pulmonary embolism accompanied by appreciable haemodynamic disturbances, which were not detected in our mild cases.

One possible way of exploring the relative roles of mismatching and shunting would be to use 100% oxygen breathing as a discriminatory test.¹³ Observations of this kind do not appear to have been reported to date and were not possible in the present series because we studied the patients retrospectively.

Finally, some support for our hypothesis may be drawn from animal studies in which pulmonary embolisation with autologous

clot^{14 15} or gas bubbles¹⁶ caused hypoxaemia by disturbing ventilation-perfusion ratios in the direction that we postulate.

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Persistent fetal haemoglobin and falsely high glycosylated haemoglobin levels

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Abstract

Some of the routine methods of measuring glycosylated haemoglobin depend on its difference in charge from haemoglobin A and do not distinguish between glycosylated haemoglobin and fetal haemoglobin. Two insulin dependent diabetics showed persistent discrepancies between their capillary blood glucose values and their glycosylated haemoglobin values measured by agar gel electrophoresis: the blood values were normal but the glycosylated haemoglobin values were raised. In one patient increases in insulin dose in response to the glycosylated haemoglobin results repeatedly produced hypoglycaemia. Both patients were found to have higher than normal concentrations of fetal haemoglobin; and when measured by the thiobarbituric acid reaction their glycosylated haemoglobin levels were almost normal.

This problem may be avoided by using a method that distinguishes between fetal and glycosylated haemoglobin or by testing glycosylation of hair or serum albumin if discrepancies arise. This is particularly important during pregnancy, when some women have an increase in fetal haemoglobin.

Introduction

Glycosylated haemoglobin is widely used as a measure of diabetic control in insulin treated patients, often in conjunction with home blood glucose monitoring. Some of the methods routinely used for measuring glycosylated haemoglobin depend on its separation from haemoglobin A by a difference in charge—for example, column techniques and agar gel electrophoresis. With all of these methods fetal haemoglobin (HbF) will migrate with glycosylated haemoglobin and, if present, give a falsely high reading.¹

Case 1

A 24 year old research assistant had been diabetic for 15 years. She adjusted her dose of twice daily quick and intermediate acting insulins according to home blood glucose concentrations measured by BM 20-800 strips and confirmed by filter paper capillary blood glucose measurement. These consistently showed normal or near

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normal results. In contrast, her glycosylated haemoglobin concentrations measured by agar gel electrophoresis were always between 13% and 16% (normal range 5.5-7.5%), indicating poor diabetic control. Increases in her insulin dose and dietary restrictions repeatedly led to troublesome hypoglycaemia.

Because of this disparity, fetal haemoglobin estimation was performed,² which showed 2.7% HbF (normal less than 0.6%). Simultaneous measurement of glycosylated haemoglobin by agar gel electrophoresis and by the thiobarbituric acid reaction gave results of 14.5% and 9.0% respectively. As a further independent assessment

avoided by measuring glycosylated haemoglobin by a chemical method, such as the thiobarbituric acid reaction; by the more precise electrophoretic technique of isoelectric focusing; or by affinity chromatography. Alternatively, in cases in which discrepancies arise between glycosylated haemoglobin and carefully documented home blood glucose analyses, glycosylation of another protein or tissue such as serum albumin or hair could be used. The issue is of particular importance in the management of diabetic women during pregnancy as maternal

Capillary blood glucose, hair, and haemoglobin glycosylation studies in two diabetic patients. Figures in parentheses after thiobarbituric acid incubation result are expected % glycosylated Hb from the figure

Case No	Date	Mean capillary blood glucose (mmol/l)	Hair glycosylation (μ mol fructosamine/100 mg)	Glycosylated haemoglobin		
				Agar gel (%)	Thiobarbituric acid reaction (μ mol fructosamine/100 mg)	% HbF
1	Jan 1984	7.2	0.055	14.5	0.27 (9.0%)	2.7
	May 1984	8.1		15.3	0.33 (10.5%)	2.7
2	March 1984	11.2	0.09	18	0.41 (12.5%)	5.0
	May 1984	10.1		16.4	0.39 (11.6%)	1.6
Normal ranges		< 6.0	0.032-0.070	5.5-7.5	0.13-0.25	< 0.6

Conversion: SI to traditional units—Blood glucose: 1 mmol/l $\approx$ 18 mg/100 ml.

Relation between glycosylated haemoglobin measured by agar gel electrophoresis and the thiobarbituric acid incubation in 58 patients, with results from cases 1 and 2. $r = 0.76$; $p < 0.01$.

of chronic hyperglycaemia, glycosylation of scalp hair was assayed and found to be within the normal range at 0.055 μ mol fructosamine/100 mg (normal range 0.035-0.07).³

Case 2

The first patient's mother, aged 48, had been diabetic for 27 years and also had coeliac disease. Her glycosylated haemoglobin values were consistently grossly raised at 16-18% as compared with filter paper blood glucose concentrations of 10-11 mmol/l (180-198 mg/100 ml). Her fetal haemoglobin level was 5%, and simultaneous measurements of glycosylated haemoglobin by agar gel electrophoresis and by the thiobarbituric acid reaction showed values of 18% and 12.5% respectively.

The table shows these results in full, repeated on two occasions, and the figure the normal relation between glycosylated Hb concentrations measured by the two methods.

Discussion

Persistent fetal haemoglobin is found as an isolated anomaly in 1% of white patients⁴ and is not in itself clinically important. In our two patients, however, inappropriate advice to increase their insulin doses was given because of the overestimation of glycosylated haemoglobin by a method which included fetal haemoglobin in the measurement. This difficulty can be

fetal haemoglobin concentrations rise from the 10th week in a small proportion of women.⁵

Furthermore, some patients with more serious inherited genetic variants of haemoglobin synthesis such as thalassaemias and sickle cell disease have increased levels of HbF.

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ONE HUNDRED YEARS AGO

The native press have (says the *India Medical Gazette*) lately been discussing a subject of immense practical importance. With reference to the death of the Honourable Rai Cristo Das Pal, at the comparatively early age of 45, the question arose, Why do all the leaders of native thought in India die young? The majority of the papers answered it by pointing to the unhealthy conditions under which an intelligent Hindu is born and is obliged to work. His mother—probably his father also—was a mere child at his birth; he himself marries as a mere child, and at twenty-one or twenty-two has the cares of a large and increasing family upon him. He has no breathing-time, or happy independence in early manhood, like the youth of Europe. He is forced by necessity to be precociously old; and in what we should call early middle life he finds himself prematurely worn out and exhausted. Thus the burden of the complaint is the custom of child-marriage. Certain educated Hindu gentlemen are calling upon the Government to legislate against these enforced child-marriages; but these are matters in which the Government cannot interfere. Such social reform must be brought about within the society itself; and, although its accomplishment is unlikely to be speedy, the educated part of the community should be encouraged to persevere in their crusade against ignorance and prejudice, in the hope of ultimate success. (*British Medical Journal* 1884;iii:872.)