Europ. J. Cancer Vol. 17, pp. 123–124

0014-2964/81/0101-0123 $02.00/0

Letter to the Editor

Glycosylated Haemoglobins in Advanced Malignancy

M. KOÇAK, L. J. HIPKIN and J. C. DAVIS

University Sub-Department of Endocrine Pathology, Alder Hey Hospital, Eaton Rd., Liverpool, United Kingdom

WE HAVE suggested [1] that in disseminated malignancy the level of many glycoproteins in the blood is raised, and that this leads to 'coating' of the cell surface membrances. In turn, this causes masking of the surface receptors for hormones, and so to a blunting of the action of hormones on their target organs. In the case of insulin, this leads to a state of insulin resistance, which might account for the increased incidence of diabetes that has been reported in cancer patients [2]. A convenient method of testing the prevalence of carbohydrate intolerance in such patients is to estimate the level of glycosylated haemoglobins (HbA_{Ia+b+c}), which provide an index of the integrated blood glucose levels over the preceding weeks [3]. We have done this in 22 cancer patients and in 18 control subjects.

The patients had disseminated malignancies with primaries in various sites [14 men, 8 women: primary tumours of breast (3), cervix (1), testis (1), prostate (1), bronchus (8), stomach (1), rectum (1), bladder (1), lymphosarcoma (2), and uncertain origin (3)]. None of the patients had glycosuria but glucose tolerance tests were not performed. None were on cytotoxic drugs or radiotherapy at the time. The normal controls were healthy volunteers (11 men, 7 women, age range 22–61 yr).

The blood level of total glycosylated haemoglobins (HbA_1) was estimated using the assay system supplied by Bio-Rad Laboratories. Following haemolysis with an aqueous solution of polyoxyethylene ether (0.33% v/v), the haemolysate was applied to a disposable column (2.5 × 0.7 cm) of weakly acidic cation exchange resin. An elution-developing reagent (phosphate buffer pH 6.7, 0.01 M KCN) was then added to the column to separate the 'fast' moving HbA_1 from the remaining slower moving haemoglobin fraction. The relative concentrations of HbA_1 and total haemoglobin (obtained from mixing an aliquot of haemolysate with elution/developing reagent directly) were determined spectrophotometrically (415 nm) and the percentage of glycosylated haemoglobulins calculated. The procedure was carried out between temperatures of 20 and 25°C and one or more control bloods was assayed with each batch of cancer patient blood, all in duplicate.

The normal subjects had a mean level of HbA_1 of 7.24% (S.D. ±0.79), comparable to the findings of others [3]. The cancer patients showed a mean level of 8.22% (S.D. ±0.75). The means were compared using a *t*-test for small samples, assuming variances not equal [4]; the difference was highly significant ($P < 0.001$). The results are plotted in Fig. 1.

The level of HbA_1 is influenced by the level of plasma glucose and by the length of time the red corpuscles are exposed to the

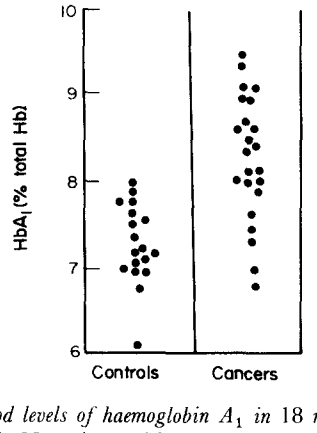

Fig. 1. Blood levels of haemoglobin A_1 in 18 normal controls and in 22 patients with advanced malignancy.

Accepted 1 September 1980.

glucose. Thus the survival time of red cells affects the results. In malignancy, however, the red cell survival time is usually shortened [5], which would tend to lower the HbA_1 level, so that this factor certainly does not explain the elevated levels found. Two general explanations can be suggested. (a) The malignancy causes, by an unknown mechanism, the increased synthesis of some plasma glycoproteins that is known to occur [6]; this leads to coating of the cells and their hormone receptors, insulin resistance, and hyperglycaemia. The latter leads to the elevated HbA_1 reported here. (b) The malignancy causes glucose intolerence by some mechanisms other than insulin resistance in the end organs; the resulting hyperglycaemia causes both the HbA_1 increase and, by glycosylation of other proteins, the elevated plasma glycoprotein levels. A post-ribosomal synthesis of glycoproteins has in fact been suggested by other workers [7].

REFERENCES

1. J. C. Davis, L. J. Hipkin, R. Finn and C. A. St. Hill, Do plasma glycoproteins induce lymphocyte hyporesponsiveness and insulin resistance? *Lancet* **ii,** 1343 (1978).
2. A. Marble, P. White, R. F. Bradley and L. P. Krall, Cancer and diabetes. In *Joslin's Diabetes Mellitus.* 11th Edn., p. 695. Lea & Febiger, Philadelphia (1971).
3. K. H. Gabbay, K. Hasty, J. L. Breslow, R. C. Ellison, H. F. Bunn and P. M. Gallop, Glycosylated hemoglobins and long-term blood glucose control in diabetes mellitus. *J. clin. Endocr.* **44,** 859 (1977).
4. N. T. J. Bailey, The use of *t*-tests for small samples. In *Statistical Methods in Biology.* p. 43. English Universities Press Ltd., London (1959).
5. D. J. Weatherall and J. Bradley, The blood in systemic disease. In *Blood and its Disorders.* (Edited by R. M. Hardisty and D. J. Weatherall) p. 1377. Blackwell Scientific Publications, Oxford (1974).
6. S. Synder and G. Ashwell, Quantitation of specific serum glycoproteins in malignancy. *Clin. chim. Acta* **34,** 449 (1971).
7. C. M. Peterson and R. L. Jones, Minor hemoglobins, diabetic control and diseases of post-synthetic protein modification. *Ann. intern. Med.* **87,** 489 (1977).