TABLE VIII—*Comparison of risk estimates from studies of Japanese atomic bomb survivors, National Registry for Radiation Workers, and combined cohort of nuclear workers in United States*

	Atomic bomb survivors[16]		National Registry for Radiation Workers	American workers*
	Whole cohort	Doses ≤500 mSv		
Cohort size	75 991		95 217	35 933
Person years	2 185 000		1 218 000	705 000
Collective dose (man Sv)	18 000		3 198	1 140
Range of doses	0-4 or more	0-0·5	0-0·5 or more	0-0·5 or more
Excess relative risk per Sv (90% confidence interval):				
All malignant neoplasms	0·41† (0·32 to 0·52)	0·38‡	0·47 (−0·12 to 1·20)	−0·99 (<−1·6 to 0·38)
Leukaemia	5·2‡ (3·8 to 7·1)	2·4‡	4·3 (0·40 to 13·6)	<−1·5 (<−1·5 to 3·4)
Lifetime risks, % per Sv (90% confidence interval):				
All malignant neoplasms	4§ (3 to 5)‖		10 (<0 to 26)	<0 (<0 to 8·2)
Leukaemia	0·4§ (0·3 to 0·55)‖		0·76 (0·07 to 2·4)	<0 (<0 to 0·60)

*Workers at Hanford, Oak Ridge and Rocky Flats.[19]
†All malignant neoplasms excluding leukaemia, based on all ages.
‡All ages at exposure.
§Derived by the International Commission on Radiological Protection applying dose and dose rate effectiveness factor of 2 to data on Japanese survivors.
‖Approximate values based on Japanese data.

estimate from the registry and was similar to that predicted by the Committee on the Biological Effects of Ionising Radiation from the fit of a linear quadratic dose-response model to the Japanese data[17 20]; this corresponds to a lifetime risk for a British population of 0·6%/Sv.[21] By contrast, the lower limit of the 90% confidence interval in the analysis of the registry is just above zero in the case of leukaemia and less than zero for all malignant neoplasms. Thus, although the confidence limits for the registry and the American study overlap, the American study points toward lower risks. Thirdly, the risk per unit dose derived from the registry may be subject to some uncertainty because only external dose was considered, and it has not been possible to take into account the possible effects of occupational exposures to other carcinogenic agents (both physical and chemical). However, if the 13 500 workers with a collective external recorded dose of about 700 man Sv and known to have been monitored for internal contamination are excluded from the analysis the results are not materially different.

Thus the risk estimates recommended by the International Commission on Radiological Protection, which were derived from high dose and high dose rate exposures, with a dose and dose rate effectiveness factor of 2, occupy a middle position between the risk estimates from two comprehensive studies of workers receiving low doses and low dose rates of radiation.[2 19] Given the statistical uncertainties, the results from these studies do not indicate that the commission's risk estimates are materially wrong. Nevertheless, the results from the first analysis of the National Registry for Radiation Workers provide valuable evidence, and future analysis of the registry, which will incorporate all registered cohorts and updated dose histories (including internal doses) and have a longer follow up, will provide a firmer basis for deriving risk estimates from low dose and low dose rate exposures.

From its inception the registry has been guided by an advisory committee of eminent epidemiologists. We are grateful to them for their guidance over many years, to Sir Richard Doll for advice, and to Dr Ethel Gilbert for making available some unpublished data.

The registry has relied on cooperation from many individuals and organisations, both within the nuclear industry and outside. We cannot thank here all those who have helped the study, but more detailed acknowledgements can be found elsewhere.[2]

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Detection of functional iron deficiency during erythropoietin treatment: a new approach

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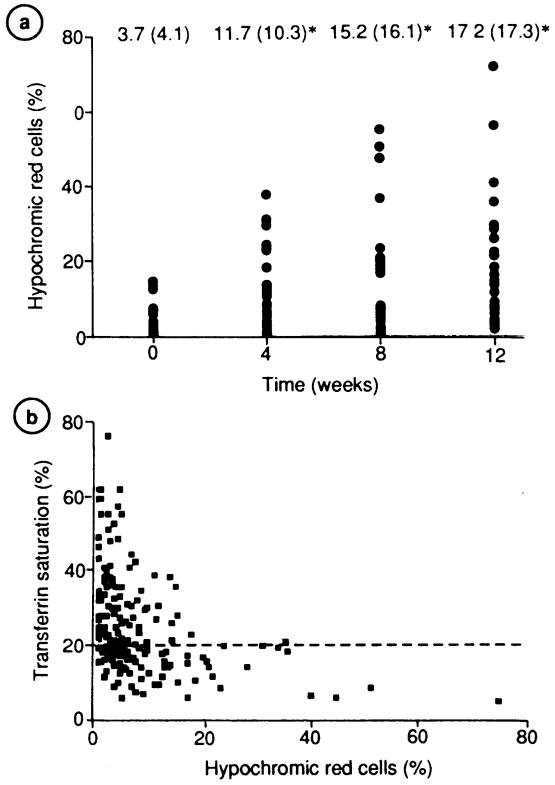
Erythropoietin treatment may cause functional iron deficiency in patients receiving long term dialysis.[1-3] Such deficiency is currently detected by low transferrin saturation,[1-3] which has considerable limitations because saturation varies substantially even in normal, healthy subjects.[4 5]

We conducted a multicentre prospective study of a new and more direct method of detecting iron deficient erythropoiesis. This entailed serial measurement of the percentage of hypochromic and microcytic red cells in the circulation with an automated blood count analyser.

Patients, methods, and results

Forty six patients were studied (17 from Cardiff Royal Infirmary; 15 from St Mary's Hospital, London; five from the Western Infirmary, Glasgow; and nine from West Wales General Hospital, Carmarthen). Twenty two were male and 24 female; 30 were receiving regular haemodialysis and 16 continuous ambulatory peritoneal dialysis. Nineteen patients were treated with intravenous erythropoietin 1200-4000 units thrice weekly and 27 with subcutaneous erythro-



*(a) Progressive increase in percentage of hypochromic red cells after erythropoietin treatment in patients receiving dialysis. Data are also given as means (SD) for whole group; *p<0·05 compared with results for week 0 (paired t test). (b) Relation between transferrin saturation and percentage of hypochromic red cells in same patients during erythropoietin treatment*

poietin (10 units/kg daily for five days a week, 2000 units twice weekly, or 50 units/kg thrice weekly, depending on the centre). All except six patients received oral iron supplementation throughout the study. Blood samples were taken every fortnight for full blood counts including red cell indices (mean cell volume, mean cell haemoglobin, and mean cell haemoglobin concentration); serum ferritin concentration; transferrin saturation; and percentages of microcytic (cell volume <60 fl) and hypochromic (haemoglobin concentration <280 g/l) red cells, the upper limit of normal for both these measurements being 2·5%. Full blood counts and red cell analyses were determined with a Technicon H1 automated blood count analyser (Bayer Diagnostics, Basingstoke), which uses laser technology and flow cytometry to measure the volume and internal haemoglobin concentration of between 40 000 and 60 000 individual red cells.

The mean haemoglobin concentration rose from a pretreatment value of 62 (SD 8) g/l to 70 (9) g/l at four weeks, 79 (11) g/l at eight weeks, and 92 (13) g/l at 12 weeks. There were no changes during this time in mean cell volume (91·6 (5·1) fl to 93·5 (5·7) fl), mean cell haemoglobin (30·0 (2·3) pg to 29·6 (2·3) pg), or mean cell haemoglobin concentration (325 (17) g/l to 315 (13) g/l). Similarly, the percentage of microcytic red cells in the sample did not change and remained within the normal range (1·0% (0·8%) before treatment, 0·9% (0·7%) at four weeks, 0·8% (0·6%) at eight weeks, and 1·1% (0·8%) at 12 weeks). The proportion of hypochromic red cells progressively increased during the first 12 weeks of treatment (figure, a). In 15 patients the proportion was >2·5% before starting treatment, and in nine it was >20% after 12 weeks of treatment. Serum transferrin saturation and the percentage of hypochromic red cells showed a loose inverse correlation ($r=-0·47$; $p<0·001$), but in the 15 instances when the percentage of hypochromic red cells was >20% serum transferrin saturation was consistently <20% (figure, b). Serum ferritin concentration and the percentage of hypochromic red cells were not correlated ($r=-0·14$; $p=0·09$).

Five of the 14 patients who had >10% of hypochromic red cells at 12 weeks were treated with parenteral iron supplementation (2 ml iron dextran (Imferon, Fisons Pharmaceuticals, Loughborough) weekly for four weeks). In all cases the percentage hypochromia subsequently fell to within the normal range after six to 14 weeks, with a corresponding increase in the haemoglobin concentration.

Comment

Our method of detecting functional iron deficiency in patients given erythropoietin uses some of the recent technological advances in automated blood count analysers. The measurements reflect the iron content of circulating red cells, which is a more direct indicator of iron delivery to the developing erythron than is transferrin saturation or serum ferritin concentration. Furthermore, the test can be performed on the same sample as the full blood count and the results are immediate.

The proportion of hypochromic red cells progressively increased with erythropoietin treatment, in some instances running parallel with a fall in transferrin saturation and in others preceding it. The loose correlation between the two variables is probably due to the biological variability in transferrin saturation,[4] but in extreme cases (percentage of hypochromic red cells >20%) transferrin saturation was consistently in the range associated with iron deficiency (<20%).[1-3] In addition, the fact that the proportion of hypochromic red cells fell in association with improved haemoglobin concentration after intravenous iron—albeit in only five patients—is further evidence that the percentage of hypochromic red cells is a true indicator of iron insufficiency. Further studies are, however, required to evaluate this approach in more patients.

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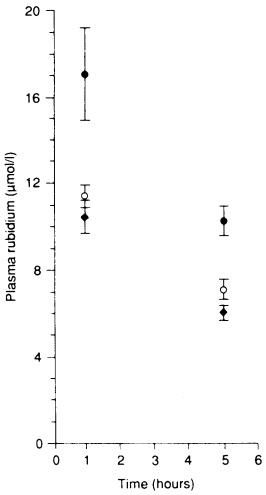
Correction

In vivo and in vitro sodium pump activity in subjects with thyrotoxic periodic paralysis

Several editorial errors occurred in the figure in this paper by A Chan and others (2 November, p 1096). The correct figure and legend are given below.



Plasma rubidium concentrations in six healthy subjects (●), eight thyrotoxic subjects (○), and seven thyrotoxic subjects with periodic paralysis (◆) after oral administration of rubidium chloride (8 mg/kg body weight). Vertical bars represent 95% confidence intervals