expected in the absence of screening as this stabilises the denominator, allowing a more valid comparison to be made. When the number of squamous cell carcinomas expected in the absence of screening was used as the denominator in our study no significant difference in the proportion of cases accounted for by interval cancer was found between the two age groups (6·8% *v* 4·8%, p>0·10).

This problem would be overcome if the number of interval cancers was related to the number of negative screening tests issued for each age group. Under these circumstances if the test had equal sensitivity in all age groups the rate of diagnosis of interval cancer per 100 000 negative tests should be directly proportional to the underlying risk of cervical cancer for each age group. If the risk of cervical cancer does increase with age the rate of diagnosis of interval cancer per 100 000 negative tests should be higher in older women than in younger women. Our study confirmed this.

REVIEW OF THE CYTOLOGY

Our review of the negative smears disclosed that only 1·1% to 1·6% of all registrations of cervical cancer during 1982-6 were associated with a negative test of optimal quality as reported by the Victorian Cytology Gynaecological Service during the 36 months before the cancer was diagnosed. Our results are in accord with those of other studies, showing that most of the negative cytology reports that are issued in close proximity to a diagnosis of cancer being made are accounted for by difficulties in the sampling and reporting processes.[1 12 13] None of the smears that were considered to have been suboptimal at review because of a lack of endocervical cells or metaplastic cells, or both, had been reported as such at the time of the original reporting. The Victorian Cytology Gynaecological Service began routinely to comment on the absence of endocervical cells in 1987; women whose smears lack these cells are now recommended to have a repeat test after one year.

Our study also showed that among interval cancers a higher proportion of cases were adeno or adeno-squamous carcinomas, possibly confirming other evidence that cervical cytology has a lower sensitivity for the detection or prevention of these histological types.[14]

CONCLUSION

In conclusion, we consider three points to be of importance in relation to interval cancers. Firstly, it is necessary to determine the role of sampling difficulties and reporting errors before concluding that all interval cancers represent a rapid transition from a normal cervix to a malignant one. Though all interval cancers might be regarded as failures of the screening system, difficulties with sampling and reporting errors might be overcome by measures other than shortening the rescreening interval. When a hospital, laboratory, or clinician is concerned about a high incidence of diagnoses of cancer after negative cytology, rather than assuming that this provides evidence of the rapid onset of cancer, the negatively reported slides should be re-examined. It is likely that most of the cases will be accounted for by suboptimal sampling and by errors in reporting; evidence remains that the rapid biological development of cervical cancer is infrequent.

Secondly, the establishment of record systems that allow continuous monitoring of the rate of diagnosis of interval cancer in women who have been screened is preferable to relying on analyses that are based on crude numbers and proportions. This is particularly important when comparisons are made between age groups in which there are differential uptakes of screening.

Finally, this study has shown that the probability of a woman having cervical cancer diagnosed in the 36 months after a negative smear was substantially lower in women aged less than 35 than in women aged 35-69. These data agree with the traditional view that younger women are at lower risk of cervical cancer than are older women.

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Changes in determinants of blood rheology during treatment with haemodialysis and recombinant human erythropoietin

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The two main side effects of treatment with recombinant human erythropoietin in anaemic patients receiving regular haemodialysis are the aggravation of hypertension and thrombosis at the site of vascular access.[1] Changes in blood rheology during the treatment might contribute to these complications. Thus we studied the behaviour of various determinants of blood rheology in relation to the occurrence of side effects in patients receiving haemodialysis who were being treated with recombinant human erythropoietin.

Patients, methods, and results

We studied 21 clinically stable patients (seven men, 14 women; mean age 55 (range 23-74)) who had been receiving maintenance haemodialysis three times a week for a mean of 42 (6-120) months. Fifteen patients had hypertension that was well controlled with drugs. The starting dose of recombinant human erythropoietin (Boehringer Mannheim) was 80 units/kg administered as an intravenous bolus after each dialysis session; when the target packed cell volume (0·30-0·35) was

Mean (SD) haemorrheological variables during treatment with recombinant human erythropoietin in 21 patients receiving regular haemodialysis

	Before treatment	Week 4	Week 8	Week 12	Week 16	p Value	Mean change in values at week 16 (95% confidence interval)
Packed cell volume	0·22 (0·03)	0·25 (0·05)	0·28 (0·06)	0·29 (0·05)	0·30 (0·05)	0·0000	0·08 (0·06 to 0·11)
Red cell aggregation (arbitrary units):							
At high shear rate	4·26 (1·2)	4·53 (1·2)	5·14 (1·3)	5·35 (1·3)	5·79 (1·3)	0·0000	1·52 (0·82 to 2·22)
At low shear rate	7·89 (1·9)	8·23 (1·9)	8·68 (1·7)	9·14 (2·1)	9·59 (1·3)	0·0005	1·69 (0·75 to 2·63)
Fibrinogen (g/l)	3·94 (1·6)	3·87 (1·2)	3·85 (1·3)	3·76 (1·1)	3·92 (1·3)	0·94	−0·02 (−0·67 to 0·63)
Plasma viscosity (mPa·s)	1·61 (0·1)	1·63 (0·1)	1·64 (0·1)	1·63 (0·1)	1·62 (0·1)	0·54	0·01 (−0·04 to 0·06)

reached the dose was adjusted individually to avoid a further rise in packed cell volume. Haemorrheological determinants were monitored before and every four weeks during treatment with recombinant human erythropoietin up to four months; 12 patients were followed up until seven months. Venous blood samples were taken from the antecubital vein before a dialysis session for analysis of fibrinogen concentration[2]; red cell aggregation at low (3/s) and high (600/s) shear rates (MA1 aggregometer, Myrenne, Roetgen) after heparin 10×10^3 U/l had been added to the samples[3]; packed cell volume (microhaematocrit); and plasma viscosity (Coulter-Harkness viscometer) at 25°C.[4] Nineteen apparently normal subjects (six men, 13 women; mean age 56 (range 20-75)) served as controls.

Results are given as means (SD). Differences in mean values between the patients and controls were analysed by the two sample *t* test; single factor analysis of variance (time) with repeated measures (biomedical programs data package 2V, University of California Press, 1985) was used to study changes in the variables during treatment with recombinant human erythropoietin.

Baseline values of several of the variables were lower in the patients than the controls: packed cell volume 0·22 (0·03) *v* 0·44 (0·04) (t=19·40, p=0·0001); red cell aggregation at the high shear rate 4·26 (1·2) *v* 6·98 (1·9) arbitrary units (t=5·37, p=0·0001); and plasma viscosity 1·61 (0·1) *v* 1·68 (0·1) mPa·s (t=2·20, p=0·033). By contrast, the baseline fibrinogen concentration was considerably higher in the patients (3·94 (1·6) *v* 2·90 (0·7) g/l (t=2·53, p=0·016)). Treatment resulted in a progressive increase in red cell aggregation at both the low and high shear rates and in the packed cell volume (table). After four months of treatment red cell aggregation at the low shear rate, which is predominantly determined by the plasma fibrinogen concentration, exceeded the value seen in the controls (9·59 (1·3) *v* 8·21 (2·0) arbitrary units, p<0·01), although the packed cell volume, the second main determinant of red cell aggregation, was below the normal range (0·30 (0·05)). No further changes occurred in red cell aggregation at either shear rate in the 12 patients followed up until seven months of treatment, who had a constant packed cell volume. Fibrinogen concentration and plasma viscosity remained unchanged throughout the four months of treatment (table).

Five patients developed an exacerbation of their hypertension during treatment, and six had a thrombosis at the site of vascular access; these side effects did not occur before the fourth month of treatment. The baseline fibrinogen concentration and baseline red cell aggregation at the low shear rate were higher in the patients who developed side effects than in those who did not (fibrinogen concentration 4·53 (1·9) *v* 3·28 (0·7) g/l (t=1·96, p=0·064); red cell aggregation at low shear rate 8·69 (1·9) *v* 7·01 (1·6) arbitrary units (t=2·10, p=0·049)).

Comment

We found that correcting these patients' anaemia slowly by giving recombinant human erythropoietin induced abnormally high red cell aggregation at a low shear rate. This was probably due to hyperfibrinogenaemia as fibrinogen is a major determinant of red cell aggregation, acting as a "bridging" macromolecule between the cells.[5] The increased red cell aggregation may have contributed to the side effects of treatment as these did not occur before the fourth month of treatment, when red cell aggregation at the low shear rate had risen above the value seen in normal controls. A long term study is needed of patients receiving haemodialysis who are treated with recombinant human eythropoietin to see whether there is an increased incidence of complications of the treatment in patients with high fibrinogen concentrations or high red cell aggregation at a low shear rate, or both, at the start of treatment.

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Recombinant human erythropoietin as adjuvant treatment for autologous blood donation

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Homologous blood transfusions are associated with a considerable risk of transmission of a variety of diseases. An alternative is to bank autologous blood before an elective surgical intervention.[1] Goodenough *et al* recently showed that with intravenous human recombinant erythropoietin the preoperative collection of autologous blood could be increased greatly.[2] We investigated the potential of subcutaneous recombinant erythropoietin as adjuvant treatment for autologous blood transfusions in patients waiting for total hip replacement.

Patients, methods, and results

Ten patients (three men, seven women) waiting for total hip replacement gave informed consent to take part in the study. The operating orthopaedic surgeon assessed the number of units of blood necessary for each procedure. This varied from two to seven units. Autologous blood collection took from two and a half