Correspondence

Cytological changes preceding cervical cancer

Dr Robertson and colleagues must be congratulated for holding up the "red flag of classification" to the "bulls of gynaecological cytology".¹ Their timing is excellent, particularly as the frailty of the current reporting system becomes increasingly evident.

A basic premise in the currently recommended terminology and management of cervical smears is that the degree of dyskaryosis correlates with the grade of cervical intraepithelial neoplasia (CIN).^{2,3} However, published information⁴ and KC61 returns for the Department of Health indicate that this is far from the case. Reasonable correlation occurs between severe dyskaryosis and CIN3, but considerably more variation is observed as the degree of dyskaryosis and CIN diminishes. Whether or not dyskaryosis and CIN should correlate is debatable, as the definitions involved are purely arbitrary. However, a principal reason why they do not must be the considerable interobserver variation in the histopathological diagnosis of CIN.^{4,5} Health Service guidelines emphasise the important requirement to compare cytology and biopsy results.⁶ However, the crucial audit is whether cytological findings identify clinically relevant histopathological abnormalities and whether the false positive rate is accordingly kept to a minimum.

Surprisingly, with only one or two exceptions,^{7,8} there has been little discussion with regard to the possible introduction of the American Bethesda system for reporting cervical smears.⁹ Indeed, some cynics believe that any potential introduction was doomed following the timing of the publication, which coincided with the printing of several million new HMR forms. However, although the Bethesda system uses the terms low and high grade squamous intraepithelial lesions, its overall complexity and content is analogous to that of the current British system. Accordingly, unlike Dr Robertson, I share previous authors' views^{7,8} that the Bethesda system has little to commend it.

I suspect that many gynaecological cytopathologists already perceive nuclear changes as either low or high grade abnormalities. It is therefore reassuring to see that Dr Robertson's scientific conclusion supports this view. With little difficulty, current national recommendations for terminology and management of cervical smears could be amalgamated along the following lines:

Borderline changes, wart virus, and mild dyskaryosis could be grouped together as low grade abnormalities. These would necessitate a six month repeat smear and, if persistent, require referral for colposcopy.

Moderate and severe dyskaryosis could be grouped together as high grade abnormalities with the necessity for immediate referral for colposcopy.

Gynaecological cytology has now become a nationalised industry with a propagated aura of sophisticated diagnostic accuracy. This has resulted in undoubted success in the field of "cytology job and working party creation schemes". However, as the diag-

nistic gold standard of CIN has partially collapsed, it is hard to believe that gynaecological cytology can emerge unscathed. Which cytopathologist, with their hands on their hearts, can deny that accurate distinction between borderline changes, wart virus, and mild dyskaryosis is a difficult, often impossible, time consuming, and a largely pointless pursuit? These changes are all far more realistically grouped together as low grade abnormalities, requiring the same clinical management. The hours saved by avoiding such mental contemplation would be enormous.

We should not lose sight of the fact that the basic function of gynaecological cytology is merely to screen for relevant disease that will require subsequent histopathological diagnosis and clinical management. It must be seriously questioned whether the existence of multiple, closely related, diagnostic categories is warranted. Furthermore, it is rumoured that this problem is about to be compounded by division of the category of borderline changes. Superficially, credibility for the existence of the current terminology seems to be provided by the mass of statistical returns requested annually and the requirement for these subtle distinctions to be assessed in quality assurance schemes. It is also questionable as to whether this complex blinkered dogma should continue to be the staple of cytology training schools.

My proposition is simple: back to cytological basics, before it is too late.

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Drs Robertson, Woodend, and Elliott comment: We agree with most of Dr Slater's comments, but would never have dared make them. They draw attention to the Emperor's new clothes and suggest rebellion in the ranks. We also have long regarded cervical cytology as a screening procedure with little diagnostic precision apart from its detection of severe dyskaryosis.

In advocating a low and high grade method of reporting, the Bethesda system is cited by us only as an example. We accept that it is rather too elaborate. However, unlike Dr Slater, we hesitate to include "borderline changes", with wart virus and mild dyskaryosis as a low grade abnormality. Among cytopathologists "borderline" seems almost to have achieved the status of a diagnostic entity. Our experience is that in practice it merely reflects uncertainty in interpretation of a smear. Reparative changes in the cervix, papillomavirus infection, or atypical cells due to inflammation can all present difficulties. The latter may occasionally be confused with invasive cancer, and a six month repeat smear would be inappropriate. We feel that such reports should describe the diagnostic difficulty, advise on further action, and be summarised as "no diagnosis".

To the lay person the term "borderline" is unsatisfactory. It could be quite frightening for some women, giving the impression of a limbo bordering on (?) the abyss. It is not a diagnostic entity and, like the unicorn which had similar problems of identity, should be allowed to pass into mythology.

Pregnancy in von Willebrand's disease

The guidelines on the investigation and management of haemorrhagic disorders in pregnancy are welcome.¹ With reference to the management of von Willebrand's disease, we have recently studied 23 pregnancies managed at a single centre,² and add the following comments.

We believe that there is a tendency towards complacency in the management of pregnant women with von Willebrand's disease due to an excessive reliance on improvement in the coagulation deficit. The coagulation parameters improve in many instances, but we and others³ have noted exceptions, particularly in those more severely affected with low factor VIII (VIII:C) before conception. In our series, those patients with low baseline VIII:C values (<15 IU/dl; four cases) had only limited improvement in VIII:C by the third trimester, the maximum attained being 54 IU/dl in the group. Bleeding times shortened significantly in only one of seven cases studied, and similar findings have been noted by others.^{4,5} In addition, our observations support the view that type II patients carry a higher risk of primary postpartum haemorrhage (PPH) than type I patients (3/11 type II v 0/12 type I). This seems to be independent of the value of VIII:C in the third trimester, and presumably is explained by a failure of the primary haemostatic defect to improve in pregnancy. Importantly, secondary PPH occurred to a similar extent in both groups (2/12 type I and 3/11 type II—22% overall) and may be more dangerous as it often occurs after discharge from hospital.

The guidelines should serve to raise awareness and maintain vigilance in the management of von Willebrand's disease in pregnancy. We would add that with reference to secondary PPH, while the administration of prophylactic von Willebrand factor (vWF) containing

products in the puerperium is not necessary, patients should receive careful instructions to report excessive vaginal blood loss, so that measure to increase the vWF:Ag and VIII:C can be instigated without delay.

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Haemorrhagic disorders in pregnancy

The guidelines produced by the Haemostasis and Thrombosis Task Force mention the management of congenital platelet disorders.¹ For those patients who do require platelet transfusions, single donor platelets or platelet type specific donor platelets are advised.

I have recently treated a 16 year old girl with storage pool deficiency, during labour, by using a single infusion of ABO compatible but otherwise unmatched leucocyte depleted single donor platelets (Cobe Spectra Blood Processor) containing a platelet content of $2.8 \times 10^9/l$ and a leucocyte content of $0.5 \times 10^9/l$.

There was little bleeding after giving birth.

I suggest that such depleted platelets are a practical alternative to infusing single leucocyte undepleted donor or type specific platelets when the aim is to reduce the incidence of platelet antigen specific and HLA alloimmunisation.¹ An added advantage is the reduced risk of transmission of cytomegalovirus.²

Although DDAVP has been used without complication during labour, cases of maternal water retention precipitating grand mal seizure (after repeated treatment) have been reported.³

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Zinc assays in patients with α and β thalassaemia trait

We read with interest the investigations by Tillyer and Tillyer on the interpretation of zinc protoporphyrin (ZPP) assays in patients with α and β thalassaemia trait.¹ We have been using ZPP assays (protofluorimeter, Helena laboratories) as a screen for iron deficiency since July 1991.

The normal range quoted by Tillyer and Tillyer is much wider than we would expect from our own experience, and presume that some of their "normals" with high ZPP values were indeed iron deficient, especially as 25% of subjects were pregnant. Other reasons for an increase in ZPP must also be considered, such as interfering substances and, rarely, lead poisoning. Our 95% confidence range is 30-65, rather than 38-104 $\mu\text{mol/mol}$ haem.

We agree that in β thalassaemia trait the ZPP is wider and merges into those ranges found in iron deficiency. It may indicate some impaired iron utilisation in thalassaemia trait. In 58 consecutive patients with β thalassaemia trait (microcytosis + $\text{HbA}_2 \geq 3.6\%$) our mean (SD) ZPP is 63.7 (19.7) $\mu\text{mol/mol}$ haem. A ZPP of > 120 is likely to indicate iron deficiency in thalassaemia trait and we usually request postponing haemoglobinopathy studies until the patient has received a trial of iron treatment. If the ZPP value is raised out of clinical context, it may be useful to make repeat measurements with washed red cells to remove interfering substances.²

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Drs M L and C R Tillyer comment:

The "normals" we studied were not clinically iron deficient: the MCV and MCH of this group corresponded exactly to established reference ranges and all had plasma ferritin values well within the accepted normal range.

We found, as stated in the paper, no evidence that ZPP in pregnant women was higher than in non-pregnant women, and exclusion of pregnant women from the group gives exactly the same reference ranges. Pre-washing the red cells, as proposed by Hastka *et al*¹ lowers all ZPP values by about 15 $\mu\text{mol/mol}$ so this procedure could not be used without establishing new reference ranges. Furthermore, not only were the drugs causing substantial interference, which is extremely unlikely in the outpatient and general practice population we studied, but the washing procedure failed to remove completely the interference from some of these drugs. Lead poisoning would also be rare in this adult population.

Labbe *et al*², using the ProtoFluor system quote a reference range of 30-80 $\mu\text{mol/mol}$ haem. Our upper reference limit is 24

$\mu\text{mol/mol}$ haem higher than this, and Paul and Brumfitt's 15 $\mu\text{mol/mol}$ haem is lower. It is difficult, however, to compare reference ranges without knowing about the number and manner of selection of subjects or the nature of the frequency distributions, and Paul and Brumfitt give us no information on theirs. If iron stores fall below 50 $\mu\text{g/l}$ of ferritin then the ZPP starts to rise.³ If the proportion of subjects with ferritin concentrations below this differs in the populations studied, the ranges, and particularly the upper reference ranges, could differ. The populations may not be functionally iron deficient, but can vary in the extent of their iron stores as measured by ferritin. Populations from South Asia, like the one we studied, suffer from a greater prevalence of iron deficiency than European and American populations, largely for nutritional reasons, and women in general have a greater prevalence of iron deficiency than men. Their storage iron may be within the "normal" range but in many cases is only just above this.

The ZPP value of women was about 13 $\mu\text{mol/mol}$ haem higher than the men, on average, in our study. If separate reference ranges are calculated for men and women, the 95% non-parametric ranges are 37-75 $\mu\text{mol/mol}$ haem ($n = 196$) and 41-115 $\mu\text{mol/mol}$ haem ($n = 381$), respectively. On re-calculating our reference ranges using only male-female pairs matched for ferritin (to within $\pm 2.5\%$) we found that the 95% non-parametric ranges were 37-79 $\mu\text{mol/mol}$ haem for men and 43-110 $\mu\text{mol/mol}$ haem for non-pregnant women ($n = 129$). This sex difference is highly significant ($p < 0.0005$; Mann-Whitney U test) and is not explained by differences in ferritin concentrations. The pooled estimate of the reference range from this group, which consisted of equal numbers of men and women, was 38-102 $\mu\text{mol/mol}$ haem ($n = 258$), so an uneven mix of the sexes could not account for any significant bias in our reference range.

The original purpose of our study was to establish the extent of iron deficiency and prevalence of haemoglobinopathies in our population: It was therefore important to study an unselected group of subjects as seen in clinical practice and to assign them to diagnostic groups with reliable criteria which we regularly use. Using these criteria, over 40% of our subjects were classified as iron deficient. Haemoglobinopathy screening must take this into account. We found that the diagnosis of β thalassaemia trait was unaffected by coincident iron deficiency, and we therefore do not delay HbA_2 quantitation in its presence. Rapid results are clearly important when screening an antenatal population where the genetic risk is high.

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