questions whether most should be biopsied in the first place other than for research purposes; the reproducibility and accuracy of their cytological management are probably much more important.

The difficulty in establishing a diagnosis of low grade cervical intraepithelial neoplasia is not the only problem with the classification. Further studies in this department and of pathologists attending a colposcopic pathology course at this hospital have shown disagreement over the diagnosis of a high grade (grade III) lesion versus a low grade (grade I) lesion in about 15% of cases. This difficulty arises from the interpretation of changes that have been designated atypical immature metaplasia, a diagnostic category that is not included in the classification, which affects areas of immature metaplasia in the transformation zone alongside all grades of cervical intraepithelial neoplasia.[5] Difficulty in diagnosis arises because immature cells with large atypical nuclei are not stratified to the bottom third like cervical intraepithelial neoplasia grade I in mature squamous epithelium, although the behaviour of this category is probably equivalent to that of low grade cervical intraepithelial neoplasia rather than cervical intraepithelial neoplasia grade III, which it partially mimics.

Another problem arises from the use only of grade in histological classification and the failure to take into account the role of the size of a lesion. We have recently shown that size is at least as important as grade in determining the grade of cytological abnormality[6] and the rate of false negative smears.[7] A study in New Zealand showed that the risk of progression of cervical intraepithelial neoplasia grade III to invasive cancer was closely linked to persistent severe dyskaryosis,[8] which we have shown to be related to the size of this grade of lesion. Further work is in progress on the role of size.

The cervical intraepithelial neoplasia classification was intended to be "of descriptive value only and lacking any prognostic connotations or therapeutic implications."[9] It is now used as the standard for clinical management, interpretation of screening methods, and scientific research. The time is ripe to rethink the separate needs of each of these for a pathological classification of cervical precancer: the needs for straightforward routine diagnosis are probably for simplification[3] whereas research demands more detailed understanding of the three dimensional structure of cervical intraepithelial neoplasia. A full solution requires new, more objective methods not only for histology but for cytology.

D JENKINS
M R JARMULOWICZ

Whittington Hospital,
London N19 5NF

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SIR,—The paper by Dr Sezgin M Ismail and colleagues[1] is interesting as there have been marked changes in cervical smear reporting since our practice of 12 000 patients changed its histopathological department.

In March 1987, 72 cervical smears were reported at one hospital (A), of which 36 needed to be followed up within one year. In March 1988, 55 cervical smears were reported at a second hospital (B), and 16 needed to be followed up within one year. In June 1987 hospital A received 93 smears, of which 65 needed to be followed up within one year, and in June 1988 hospital B received 73 smears, of which 26 needed to be followed up. This difference in reporting (a 20% reduction of abnormalities at hospital B) probably reflects departmental style and variability among observers in grading cervical smears. The departments of both hospitals are keen and committed, yet hospital B rarely reports inflammatory smears and more frequently reports the finding of no malignant cells seen.

Such differences affect women and family doctors. The reporting style of hospital B means that women can be reassured that no cancer has been found and that the laboratory has advised recall, which is mostly three yearly. At hospital A detailed information on mild dyskaryosis and inflammation has often confused and frightened women and general practitioners and has led to demands of frequent colposcopy. At present the cervical smear workload is much reduced and the need for colposcopy is infrequent. As a hard pressed urban general practitioner I am happy to stay with our new histopathology department and its reporting style.

NIGEL MASTERS

Thamesmead,
London SE2 9UQ

1 Ismail SM, Colclough AB, Dinnen JS, *et al.* Observer variation in histopathological diagnosis and grading of cervical intraepithelial neoplasia. *Br Med J* 1989;**298**:707-10. (18 March.)

SIR,—The results of Dr Sezgin M Ismail and colleagues[1] are similar to those of our study in Scotland.[2] We disagree, however, with their recommendations to abandon grading of cervical intraepithelial neoplasia and introduce a borderline category. We and they have shown that cervical intraepithelial neoplasia grade III can be identified reliably and that agreement is poorer in the diagnosis of cervical intraepithelial neoplasia grades I and II. We have shown that grades I and II when amalgamated can be diagnosed with reasonable confidence. We have therefore recommended that the present grading system should be replaced by high (current cervical intraepithelial neoplasia grade III) and low (current cervical intraepithelial neoplasia grades I and II) grades.

Although the role of human papillomavirus in causing cervical carcinoma has still to be fully elucidated, evidence is increasing that cervical intraepithelial neoplasia grade III is commonly associated with human papillomavirus types 16 and 18.[3] Regression of these lesions is uncommon, and persistence and progression are the norm. In lesions morphologically diagnosed as cervical intraepithelial neoplasia grades I and II the human papillomavirus is usually of types 6 and 11 and there is a high regression rate and little progression. We believe, therefore, that the group of lesions currently regarded as cervical intraepithelial neoplasia grades I and II, although including a small group of true early premalignancy destined to progress to cervical intraepithelial neoplasia grade III, is largely benign. Hence it seems to be a mistake to place all cervical intraepithelial neoplasia lesions into a single diagnostic category. We accept that all these cases must be treated as there is no reliable method for distinguishing histologically the cases of low grade cervical intraepithelial neoplasia that have the potential to progress. It should be recognised that this policy means that many women may be receiving unnecessary treatment with its attendant psychosexual stress.[4]

The principal advantage of our proposed classification of premalignant lesions of the cervix into low grade and high grade cervical intraepithelial neoplasia is that it permits a clinical management triage separating the well defined high grade cases, which must receive priority treatment and intensive cytological follow up, from the lower grade cases in which assessment is not as urgent and follow up need not be so intensive.

There is undoubtedly difficulty in distinguishing some low grade cervical intraepithelial neoplasia from benign lesions such as immature squamous metaplasia. Nevertheless, we do not support the introduction of a borderline category because when there is doubt whether a lesion is totally benign it must surely be treated. We have shown that assessment of human papillomavirus infection from sections stained with haematoxylin and eosin is extremely poor, and almost certainly much of the disagreement in diagnosis of low grade cervical intraepithelial neoplasia is the result of this difficulty. We hope, therefore, that methods of tissue localisation and subtyping of human papillomavirus infection will soon become readily available. The number of women having cervical intraepithelial neoplasia diagnosed is steadily increasing, and this has major resource implications for the health service: the establishment of reliable and robust criteria for histological diagnosis is therefore important.

A J ROBERTSON — K M MCLAREN
J SWANSON BECK — S M MOSS
J M ANDERSON — J G SIMPSON
R A BURNETT — G D SMITH
S R HOWATSON — H B TAVADIA
F D LEE — F WALKER
A M LESSELLS

Department of Pathology,
University of Dundee,
Ninewells Hospital and Medical School,
Dundee DD1 9SY

1 Ismail SM, Colclough AB, Dinnen JS, *et al.* Observer variation in histopathological diagnosis and grading of cervical intraepithelial neoplasia. *Br Med J* 1989;**298**:707-10. (18 March.)
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Does constitutional hypotension exist?

SIR,—Dr John Pemberton has rightly pointed out that constitutional hypotension, as diagnosed in West Germany, France, and other west European countries, is usually no more than the occurrence of blood pressure values at the lower end of the distribution range.[1]

Such hypotension, far from being a sign of disease, could perhaps more appropriately be regarded as a sign of health. This shows a rather extraordinary and fundamental difference in approach to diagnosis and treatment and as the number of the patients in west Europe accorded the diagnosis and hence treated runs into millions the possible consequences after the further integration between Britain and west Europe should be examined. As Dr Pemberton suggests other examples of such disparate practice probably exist.

Dr Pemberton has, however, not mentioned some rare organic diseases that may present as postural hypotension.[2] For example, pure autonomic failure (formerly known as idiopathic orthostatic hypotension), first described by Bradbury and Eggleston in 1925,[3] is an entirely respectable

diagnosis by British and American criteria. It results in an inability to release noradrenaline from sympathetic nerve endings, owing in part to a selective neuronal degeneration affecting intermediolateral column cells of the spinal cord. Other autonomic defects apart from the postural hypotension may not be apparent. Recently we have seen siblings with another disease, congenital dopamine β hydroxylase deficiency, first described in 1986,[4 5] in which the enzyme that converts dopamine to noradrenaline is missing from the plasma. As the structural gene for the enzyme has been localised to chromosome 9q34 there is a prospect of identifying the cause of the disease precisely. Fortunately, the defect can be partially corrected by the use of DL-threo-dihydroxyphenylserine, a synthetic amino acid which can be converted to noradrenaline by non-specific dopamine decarboxylase in the tissue.

Though in most instances Dr Pemberton's constitutional hypotension can be safely dismissed as a disease according to British and American criteria, it is important to recognise that measuring the blood pressure on standing should be a part of the routine examination of all patients with vague symptoms of tiredness, giddiness, and fainting. A fall in blood pressure of more than 20 mm Hg may, on further investigation, prove to be due to one of these rare organic diseases, which can be treated and might otherwise run the risk of receiving a psychiatric label.

ROGER BANNISTER
CHRISTOPHER MATHIAS

Autonomic Investigation Unit,
National Hospital for Nervous Diseases,
London WC1

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SIR,—Dr John Pemberton[1] leaps to conclusions that are unsupported by his evidence. The Australian data presented shed little light on whether there is or is not a disease characterised by constant hypotension and a symptom complex including physical and mental tiredness, giddiness, and fainting.

The Germans, Italians, and Spanish believe in this syndrome and treat it with coffee, cold showers, Swedish drill, and, if necessary, drugs. Is Dr Pemberton sure that this treatment is ineffective? Has he any evidence that our practice of attributing the symptoms mentioned to psychogenic factors and treating them accordingly is effective? Surely the question is simple. What approach achieves the best results for the individual patient who knocks at the surgery doors?

Dr Pemberton is worried that recognition of low blood pressure as a disease will lead to a rise in our drug bill. Hypertension is, however, sometimes treated with meditation or biofeedback. For hypotension we could cheerfully prescribe cold showers, coffee, and even Swedish drill. Surely it is unfair to avoid identifying a disease in a patient with symptoms for fear of increasing our drug bill. To label such a person as neurotic is adding insult to injury.

J K ANAND
BARRY TENNISON

Peterborough PE1 1LN

1 Pemberton J. Does constitutional hypotension exist? *Br Med J* 1989;**298**:660-2. (11 March.)

Stress and relapse of breast cancer

SIR,—The findings reported by Dr Amanda J Ramirez and colleagues[1] seem to support a widely popular view and might prove to be true when a larger study is available.

There is, however, a methodological point that should be raised. Were the women reported as being under stress receiving any tranquillisers, antidepressive drugs, or hypnotics and if so for how long and at what doses? Most of these drugs are prolactin inducers,[2] which is also the case for reserpine.[3 4] In France, unfortunately, these drugs are widely used, which makes epidemiological studies difficult, but I suspect that high peaks of prolactin every day for years may contribute to the proliferation of "dormant" breast cancer cells, as is the case in several cell lines.[5 6] Avoiding such drugs might be a useful measure in preventing relapses and perhaps preventing or delaying breast cancer.

LUCIEN ISRAËL

Clinique de Cancérologie,
Institut d'Oncologie Cellulaire et Moléculaire Humaine,
Hôpital Avicenne,
9300 Bobigny,
Paris

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AUTHORS' REPLY,—Dr Israël suggests that the effect of stress on relapse of breast cancer that we have shown may be due to prolactin induction by psychoactive treatment of the women experiencing severe stress. This raises several important issues, though it is an unlikely explanation for our results.

Prolactin has been shown to promote growth of breast tumours in women as well as in the in vitro studies described by Dr Israël. High prolactin concentrations have been associated with poor prognosis in early[1] and advanced[2] breast cancer. Also preliminary data suggest that perioperative bromocriptine given to women undergoing mastectomy appreciably reduces their increased prolactin concentration and reduces the proportion of tumour cells in the S phase.[3]

Certain psychoactive drugs do induce prolactin, in particular antipsychotic drugs.[4] Epidemiological studies have, however, so far failed to show an increased risk of cancer associated with their use.[5] None of the women in our study received these drugs. In France antipsychotic drugs, particularly sulpiride, are widely used in managing neurotic disorders. One case and one control in our study had received a tricyclic antidepressant (imipramine and dothiepin respectively), and seven cases and five controls had been treated with benzodiazepines. Consumption of these drugs was not controlled for as there was little evidence that they are associated with long term prolactin stimulation.[4] In general antidepressants do not affect basal prolactin concentration.[6] Exceptions include dopamine agonists, such as nomifensine, which induce marked prolactin inhibition, and the selective serotonin uptake inhibitors, such as clovoxamine and fluvoxamine, which induce a moderate rise in basal prolactin in the short term but not in the long term. Long term treatment with amitriptyline increases prolactin inhibition induced by bromocriptine in depressed patients.[7] Similarly, there is little evidence to suggest that benzodiazepines induce prolactin. In general such γ aminobutyric acid mimetic drugs induce a biphasic effect on plasma prolactin concentration in humans, causing an initial increase followed by long lasting decrease.

The intriguing possibility remains that prolactin secretion may be induced by psychological stress of the nature associated with the relapse of breast cancer described in our investigations. Studies in rats have shown an association between various psychological stresses, such as immobilisation or cold swimming, and increased prolactin release. There is, however, a striking lack of information on the effect of psychological stress on prolactin release in humans.[8] The role of prolactin as a potential mediator of the effects of stress on relapse of breast cancer requires further investigation as do other possible neuroendocrine and immunological intermediaries.

AMANDA J RAMIREZ IAN S FENTIMAN
T K CRAIG MICHAEL RICHARDS
J P WATSON W R S NORTH
R D RUBENS

Imperial Cancer Research Fund Clinical Oncology Unit and Department of Psychiatry,
Guy's Hospital,
London SE1 9RT

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All must audit

SIR,—Having sat in at a surgical death and morbidity meeting on the late Professor Sir James Learmonth's unit at Edinburgh in 1948, I shortly afterwards started such meetings at St Albans and later at the Royal Northern Hospital. This type of audit was then supplemented by a variety of other clinical and pathological meetings. Only those who have carried out such reviews over many years can appreciate the work entailed.

These meetings are often much easier to organise on a unit basis and in smaller regional hospitals and where a large proportion of the staff are "geographically whole time," with NHS private beds. I remain an enthusiastic supporter of such meetings while recognising some of their limitations—for example, that certain staff tend to be conspicuous by their absence. More recently, it has been the custom of Royal College of Surgeons assessors, when visiting hospitals in connection with FRCS regulations, to inquire about surgical audit and related meetings.

But the type of audit now called for by the Secretary of State is of a very different sort, and, as one who has consistently (and sometimes tiresomely) called for doctors to develop a better appreciation of the economic facts of life, let me say that in principle I am in support of medicoeconomic