Tower Hamlets health district is one of the most deprived in Britain, with many medical and social problems, and it has already overspent considerably in this financial year. It is therefore difficult for this district to allocate funding for zidovudine from its very limited resources. Current studies on the treatment of asymptomatic patients infected with the human immunodeficiency virus have even greater financial implications. We are fast reaching the point where patients are denied effective treatment because of limited financial resources, as has been shown by the hepatitis B vaccine.[1]

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1 Adler MW, Belsey EM, McCutchan JA, Mindel A. Should homosexuals be vaccinated against hepatitis B virus? Cost and benefit assessment. *Br Med J* 1983;**286**:1921-4.

SIR,—The treatment of choice for toxoplasmosis in patients with the acquired immune deficiency syndrome (AIDS) is a combination of sulphadiazine and pyrimethamine,[1] as mentioned by Dr Ian V D Weller (18 July, p 200). It should be emphasised, however, that folinic acid supplements are given concurrently during treatment of toxoplasmosis in any patients. This is particularly important for AIDS victims, who show defective folate metabolism associated with poor diet, malabsorption, and possibly persistent macrophage activation.[2]

Pyrimethamine treatment is associated with dose related bone marrow suppression, and so blood cell and platelet counts should be monitored during treatment. Folinic acid supplements reduce the severity of these side effects. Response rates to sulphonamide and pyrimethamine treatment are high, and clinical improvement is rapid, often within one day of administration.[3] Doses may be increased to 8 g sulphadiazine and 50 mg pyrimethamine daily if the initial response is poor.[4] Drug reactions during treatment may prompt the withdrawal of sulphonamides, although alternative treatment is contentious.

Spiramycin has been used extensively for the management of toxoplasmosis in pregnancy, but there is little experience of its use in patients with AIDS, and penetration into the cerebrospinal fluid is poor. A high incidence of treatment failure has been seen with pyrimethamine monotherapy.[3] The combination of clindamycin and pyrimethamine has been used in North America for the management of toxoplasmosis in patients with AIDS with documented sulphonamide reactions. Cerebrospinal fluid concentrations of clindamycin after oral treatment are erratic, and, although cerebral toxoplasmosis has been treated successfully, failure of treatment has also been reported.[5] The more familiar combination of sulphonamide plus trimethoprim is significantly less active than that of sulphonamide with pyrimethamine in the treatment of toxoplasma infection, and patients with AIDS have failed to respond to cotrimoxazole.[6]

A reliable alternative to treatment with sulphonamide plus pyrimethamine for toxoplasmosis in patients with AIDS has not been defined. Sulphonamide desensitisation has, however, been achieved in such patients and may be considered when drug reactions cause serious problems.[7]

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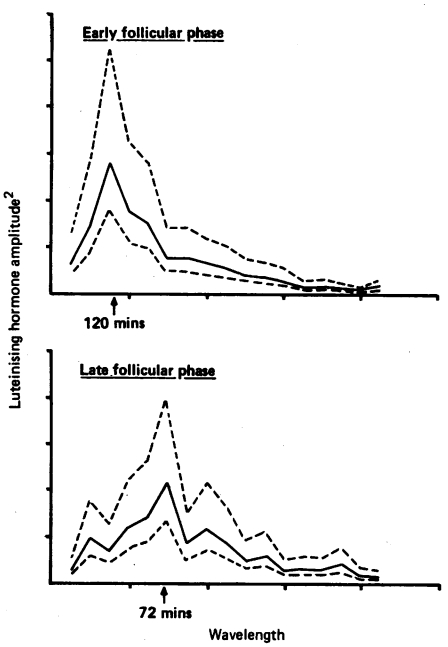
Is changing hypothalamic activity important for control of ovulation?

SIR,—The lack of change in luteinising hormone pulse frequency during folliculogenesis reported by Dr R N Clayton and colleagues (4 July, p 7) contrasts with observations of an increasing frequency in previous longitudinal studies that used similar iterative methods of pulse detection.[1,2] When such methods are used it is difficult to distinguish pulses of small amplitude from assay variation. While this may explain some of the discrepancies, it is noteworthy that the new program described by Dr Clayton and coworkers was expected to generate 2·5 peaks by chance during the series in which they detected only some 7·5 pulses.

Spectral analysis treats this problem in a different way, attempting to identify harmonic patterns in serial data.[3] The method is highly sensitive, and spectra from individual series of data must be interpreted with considerable caution, as Dr Clayton and colleagues point out. When comparisons of spectra between individual series suggest no significant differences,[4] however, normalised results may be pooled to identify consistent features between subjects.

We have applied these methods to the results of a study similar to that of Dr Clayton and colleagues (A P Murdoch *et al*, findings presented at 24th British congress of obstetrics and gynaecology, Cardiff 1986). Five healthy women were investigated in the early (day 2-4) and late (day 10-12) follicular phases of two ovulatory cycles. Blood samples were taken at 10 minute intervals for six hours. No differences could be shown within the subjects at the same stage of the cycle, but there were significant differences between early and late follicular phases in all subjects ($p<0·05$). Pooled spectral estimates showed a dominant pulse frequency during the early follicular phase of about two hours, whereas that during the late follicular phase was faster at about one hour (figure). These observations are in keeping with the results of the earlier studies.[1,2]



Pooled spectra from five normal women.

In support of their suggestion that changing hypothalamic activity is not important for control of ovulation, Dr Clayton and coworkers suggest that folliculogenesis and ovulation may be induced by constant pulses of exogenous luteinising hormone releasing hormone. This pharmacological observation does not, however, preclude the possibility that physiological regulation may entail a more complicated pattern of hypothalamic activity. In view of our results, we think it unwise to underestimate the role of hypothalamic factors in the control of ovulation.

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1 Reame N Sauder SE, Kelch RP, Marshall JC. Pulsatile gonadotrophin secretion during the human menstrual cycle: evidence for altered frequency of gonadotrophin releasing hormone secretion. *J Clin Endocrinol Metab* 1984;**59**:328-37.
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"Patients with terminal cancer" who have neither terminal illness nor cancer

SIR,—Dr W D Rees and colleagues (1 August, p 318) report on four patients who were wrongly referred for terminal care with a misdiagnosis of cancer. They highlight incorrect or misinterpreted histopathological data as the cause in three cases. My own records suggest, however, that the other illustrated cause—namely, incomplete laboratory confirmation—could occur far more often than their paper implies.

During the past five years I have recorded my necropsy findings in all cases of "clinical" carcinomatosis in which no pathological diagnosis of malignancy had been established during life. Of 41 such patients, 14 were found to have non-malignant diseases, which included chest infections (five including two tuberculosis), ischaemic heart disease (three), cirrhosis (three), pulmonary emboli (two), and sarcoidosis (one).

The commonest clinical error seems to be a tendency to consider the clinical presentation of either jaundice (eight) or femoral neck fractures (three) as a manifestation of disseminated malignancy. In addition, as described by Dr Rees and coworkers (case 4), five patients had abnormal isotope liver scans, which retrospectively reflected changes in vascular perfusion rather than space occupying lesions. Whether a more accurate diagnosis during life would have altered the fatal

outcome is difficult to judge, but certainly many of the final necropsy diagnoses would have been amenable to active medical treatment. Interestingly, the incidence of clinical misdiagnosis was similar in both teaching and non-teaching hospitals. Three additional cases in my records also illustrate that jaundice in a patient with a previously established diagnosis of malignancy should not be attributed to carcinomatosis in the absence of histological evidence of spread, the final necropsy diagnoses in these cases being chest infection, cirrhosis, and amyloidosis. It is particularly important that a false positive isotope liver scan was again the main cause of clinical difficulty.

During the same period my necropsies have shown only one histopathological misdiagnosis of malignancy, although four cases of cytopathological error are recorded, an error surprisingly not experienced by Dr Rees and colleagues in their 1635 admissions.

Dr Rees and coworkers support my long held view that a clinical diagnosis of terminal cancer must always be supported by a definitive histopathological diagnosis. In addition, it would seem desirable for cytopathological diagnoses to receive tissue confirmation whenever possible.

For reasons that remain obscure, the unqualified and grossly inadequate term "carcinomatosis" remains acceptable to both registrars and referees on death and cremation certificates. Fortunately, however, some coroners place histologically unproved carcinomatosis in the "cause of death which appears to be unknown" category and request the performance of a necropsy in such cases. My statistics illustrate that such a policy is well founded and should receive wider, if not national, acceptance by all those concerned with certification of death.

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Pinch skin grafting or porcine dermis in venous ulcers

SIR,—We would like to address the first two paragraphs of Dr L O Simpson's letter (4 July, p 53).

Our preliminary findings after measuring transcutaneous oxygen tension at 43°C (in the inner aspect of the lower third of the leg) in patients with venous, mixed arteriovenous, and arterial ulcers enabled us to discriminate between patients and controls as well as between ulcers of venous and other aetiologies.[1]

In the same preliminary communication we also reported our inability to agree with the findings of Dodd *et al*, who measured oxygen tension at 37°C on the dorsum of the foot and found very low absolute values.[2] The point that we would like to emphasise, as Dr Simpson draws support from Dodd *et al*, is that transcutaneous oxygen tension measured at 37°C yields very low absolute values (2-10 mm Hg), and changes within such small absolute values must be interpreted cautiously.

*Percentage change in blood flow on dorsum. Information in parentheses indicates change on dependence**

	Mean (SD)	Range
Patients with venous disease and ulcers (n=19)	43 (17) (decrease)	11·0- 66·6
Controls (n=9)	55·2 (27·2) (decrease)	26·6-100
Patients with venous disease and ulcers (n=3)	386·2 (increase)	87·5-700

*% Change=(supine−dependent)/supine.

We have obtained many results using the protocol described in our preliminary communication, and at present our findings are consistent with the concept of a barrier to oxygen transport in the legs of patients with venous disease. Clyne *et al*, who reported findings of oxygen tension similar to ours, support the concept of the fibrin barrier proposed by Professor Browse.[3] Other workers, notably Bollinger *et al*[4] and Fagrell,[5] have used sodium fluorescene to image the veins and have reported observing "haloes" of micro-oedema around capillaries in the skin of patients with chronic venous incompetence. These workers suggest that such "haloes" may act as barriers to the transport of oxygen to tissues.

Dr Simpson has also extrapolated from Dodd *et al*'s findings to say that "it is unlikely that vascular changes occurred when the body changed from the horizontal to the vertical plane." We have investigated the change in blood flow in the dorsum of the foot after a passive lowering of the foot from the supine position through 50 cm. The table shows the changes in cutaneous blood flow measured on the dorsum with a laser Doppler flowmeter (Periflux PF1C, Perimed, Sweden). The decrease in blood flow agrees with the findings of Hassan and Tooke.[6] The increase measured in the three patients was absent when experiments were repeated with patients wearing graduated compression bandaging.

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Cervical carcinoma: prognosis in younger patients

SIR,—The review by Dr J M Russell and colleagues (1 August, p 300) of 2870 patients with cervical carcinoma showed results that were compatible with the Office of Population Censuses and Surveys' returns for similar years.[1] The age related incidence of cervical cancer is, however, now different. Individual gynaecologists have for some years been aware of a dramatic increase in the disease in very young women. This is now apparent in the Office of Population Censuses and Surveys' returns and since 1985 figures for women aged 15-24 have been cited. Compared with 1976-80 the number of reported cases of carcinoma of the cervix in women aged 25-34 rose from 348 to 492, an increase of 41%. This increase has continued after the period of analysis covered by the paper by Dr Russell and coworkers.[2]

In young women the degree of tumour differentiation and the rate of tumour progression are likely to dictate outcome. Hall and Monaghan reported on a small series of women under 35 years with cervical carcinoma; all five with microinvasion were alive, but of the remaining 37 patients with squamous carcinoma, 34 had poorly differentiated or anaplastic tumours and 17 were dead.[3] Although it does not give survivals at five years, this report is alarming. The study by Dr Russell and colleagues, valuable as it is, is a retrospective analysis of a retrospective situation. A similar study in 1997 may well tell a different story.

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SIR,—Dr M Ashby (27 June, p 1688) and Dr J M Russell and colleagues (1 August, p 300) suggest that the prognosis for young women with cervical carcinoma is as good as, if not better than, that in older women, despite previous reports to the contrary.[1]

I reviewed the records of all patients with invasive squamous cancer of the cervix presenting to the radiation oncology unit at the Western General Hospital in Edinburgh in the years 1974 and 1983. Though the overall numbers had altered little (75 patients in 1974, 83 in 1983), the proportion of women under 35 had increased from 4% in 1974 to 18% in 1983. Only three cases (4%) in 1974 and five (6%) in 1983 were detected by routine cervical cytology; the rest of the women had symptoms at the time of diagnosis.

Of the young women who presented in 1983, most presented with International Federation of Gynaecology and Obstetrics stage Ib (67%) or II (27%) disease, and 54% of all patients had stage Ib and II disease. Of the women under 35, half were shown to have lymph node disease by lymphangiography or node biopsy. Treatment was by external beam radiotherapy and intracavitary caesium or by radical hysterectomy and external beam radiotherapy (eight patients).

After one year 27% of those under 35 had died of their disease (all had had lymph node disease). By contrast, only 11% of women over 35 with stage Ib and II disease had died at one year, and three of these four women were in the 36 to 40 age group. Though the numbers are small and figures for five year survival cannot be given, these findings do not support the suggestion that stage for stage survival in women under 35 is as good as that in older women.

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1 Stanhope CR, Smith JP, Wharton JT, Rutledge FN, Fletcher GH, Gallagher HS. Carcinoma of the cervix: the effect of age on survival. *Gynecol Oncol* 1980;10:188-93.

Ruptured abdominal aortic aneurysm presenting as ureteric colic

SIR,—We believe that the presentation of a ruptured abdominal aneurysm as ureteric colic, as discussed by Mr C G Moran and colleagues (16 May, p 1279) and Dr J B Roussak and Mr E R C T Owen (25 July, p 267), is so common that all the staff in the urology department are routinely told consciously to exclude a leaking aneurysm in all cases of ureteric colic in patients over 50 years old. To our knowledge there have been four such cases in the past 12 months in Bristol.

We would also like to point out the hazards of relying on ultrasound for the diagnosis of ruptured abdominal aortic aneurysm. Recently, a 60 year old man was referred to the department of urology from the accident and emergency department