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 folic 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. Folic 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.⁵ 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.⁶ 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}

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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"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" carcinoma 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

Pooled spectra from five normal women.