of endometrial cancer in this country. We could not recall having made any such suggestion, but memory is fickle and we reread our article with renewed interest. We found that the article contained a figure showing the trends in mortality attributed to cancer of the corpus uteri in England and Wales from 1955 to 1971 in three age groups. No comment was made on the data, which were included only to show that the reduction in mortality from cancer of the cervix uteri (which was the subject of the article) was not obviously due to more exact localisation of the site of origin of the cancer. Any "analysis" of the mortality rates would have required, first, a consideration of fatality (since we were dealing with mortality rather than incidence), and, secondly, as you rightly point out, some consideration of the prevalence of hysterectomy—which we noted was important for the interpretation of the trend in mortality from cervix cancer. Is it possible, perhaps, that you based your comments on Ziel and Finkle's misapprehension rather than on our original text?

In fact the latest available data on endometrial cancer in England and Wales show no increase in either mortality, up to 1973,² or in incidence, up to 1970,³ nor do the incidence data for residents of the old SE and SW Metropolitan Regions up to 1974.⁴ This, however, may not be surprising even if medically prescribed oestrogens do cause some cancers, as they have been prescribed here on a much smaller scale than in the USA. A study of prescriptions in a general practice population of approximately 40 000 people, which one of us is carrying out, shows that in the year preceding April 1975 the percentages of women who received at least one prescription for oestrogens other than oral contraceptives in the age groups 40-49, 50-59, 60-69, and 70-79 years were respectively 4.6, 5.9, 1.1, and 1.0%. The proportion of women who received regular repeat prescriptions is not yet available to us, but is likely to have been appreciably less.

RICHARD DOLL
L J KINLEN
D C G SKEGG

Radcliffe Infirmary,
Oxford

¹ Kinlen, L J, and Doll, R, *British Journal of Preventive Social Medicine*, 1973, 27, 156.

² Registrar-General's Statistical Reviews for England and Wales, Part I, Mortality Tables, 1960-73. London, HMSO.

³ Registrar-General's Statistical Review for England and Wales, Supplement on Cancer. London, HMSO, 1975.

⁴ Payne, P, 1976, personal communication.

Methaqualone and urinary steroids

SIR,—We should like to draw readers' attention to the possibility of spuriously high results of urinary 17-oxosteroid (17-OS) and 17-oxogenic steroid (17-OGS) estimations in patients receiving methaqualone therapy.

A patient taking two Mandrax tablets nightly was found to have apparent 17-OS excretion of 50 μ mol/24 h (14 mg/24 h) and 17-OGS excretion of 44 μ mol/24 h (13 mg/24 h). This was confirmed by analysis of a second urine specimen, but cessation of Mandrax treatment for a week resulted in lower values—28 μ mol/24 h (8 mg/24 h) for 17-OS and 30 μ mol/24 h (9 mg/24 h) for 17-OGS. This again was confirmed in a further specimen.

Each Mandrax tablet contains 250 mg of methaqualone and 25 mg of diphenhydramine. When solutions of these compounds were

separately subjected to the 17-OS and 17-OGS estimation procedures no effect was observed in the case of diphenhydramine, but methaqualone did produce considerable interference. The method of analysis for 17-OS was as described by Gray *et al.*¹ and for 17-OGS according to Metcalf.² Chloroform was employed as extraction solvent in both cases and the Zimmermann procedure of James and De Jong³ was used. When an alternative Zimmermann procedure⁴ was tried the interference seen with pure methaqualone was approximately doubled.

In view of these observations it seems prudent to stop methaqualone therapy at least several days before collecting urine for steroid estimations and we should like to endorse the recommendation¹ that, when possible, patients should not be receiving any drugs when such collections are made.

K WIENER
C H FOOT

Department of Pathology,
North Manchester General Hospital,
Manchester

¹ Gray, C H, *et al*, *Lancet*, 1969, 1, 124.

² Metcalf, M G, *Journal of Endocrinology*, 1963, 26, 415.

³ James, V H T, and De Jong, M, *Journal of Clinical Pathology*, 1961, 14, 425.

⁴ Beale, R N, Bostrom, J O, and Croft, D, *Journal of Clinical Pathology*, 1962, 15, 574.

Vaccination against meningitis

SIR,—In your excellent leading article on vaccination against meningitis (17 April, p 919) the name of Arstenstein is mentioned. In fact he is the only research worker mentioned specifically in the editorial. Your readers who are interested in this disease and its prevention will be sad to be informed that this brilliant and still comparatively young investigator has just died.

WALLY VELLA

Purley, Surrey

Herpesvirus and cancer of the uterine cervix

SIR,—We note with interest your leading article on this subject (20 March, p 671).

It is well known that some women with dysplasia of the uterine cervix will develop carcinoma-in-situ or invasive cancer while in others the lesion remains stationary or regresses. The work of Skinner and his colleagues¹ at the University of Birmingham has shown that neutralising antibody activity against herpes simplex virus type 2 increases with the severity of cervical neoplasia—that is, from dysplasia through carcinoma-in-situ to invasive cancer. These observations suggest to us that the women with increased antibody activity against herpesvirus type 2 may be those with the dysplasias which progress to carcinoma-in-situ.

In conjunction with Dr G R B Skinner in Birmingham and Dr S D Gardner at the Central Public Health Laboratory, Colindale, we are carrying out a study to test this hypothesis by regular follow-up of women with dysplasia detected during routine cervical screening at venereal disease clinics and gynaecological clinics at this hospital. The women are being investigated by cytology, colposcopy, and virology at 3-monthly intervals to determine whether present or past infection with herpes simplex virus type 2

alters the risk of progression of dysplasia to carcinoma-in-situ. In this way we hope to establish a role for herpesvirus in cervical carcinogenesis and thus identify a group of women who are at particular risk.

The design of this study is, we feel, more effective and less costly than that proposed by Kessler² or Nahmias,³ who recommend close regular cytological and virological surveillance of 10 000 well women for 5-10 years. We estimate that close surveillance of 700-1000 women with mild or moderate dysplasia over a period of 3-5 years will provide valid results, assuming that approximately 10% of minor dysplasias progress to carcinoma-in-situ in this time.

D V COLEMAN
M ANDERSON

Department of Experimental Pathology,
St Mary's Hospital Medical School,
London W2

¹ Skinner, G R B, Thouless, M E, and Jordan, J A, *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1971, 78, 1031.

² Kessler, I I, *Cancer Research*, 1974, 34, 1091.

³ Nahmias, A J, *et al*, *Cancer Research*, 1973, 33, 1491.

Suppressor cells and human malignant disease

SIR,—It is most impressive to read the report by Drs I T Magrath and J L Ziegler (13 March, p 615) of a clinical trial of human tumour immunotherapy that contradicts the now widely held tenet that non-specific immunostimulation is clinically beneficial in the treatment of almost any human neoplasm. Among the possible mechanisms that invalidate non-specific immunostimulation is the activity of suppressor lymphoid cells.

At least two pathological conditions are known in which overactive suppressor cells play an aetiological role: one form of hypogammaglobulinaemia¹ and Hodgkin's disease.² Since the suppressor activity directed against the blastogenic response to Hodgkin's lymphocytes of normal lymphocytes parallels the clinical activity of the disease² it is possible that the neoplastic cells in Hodgkin's disease are a clone of suppressor T lymphocytes.

At least two physiological conditions could be listed whose maintenance depends in part on normal suppressor-cell function: self-tolerance and pregnancy with an allogeneic conceptus. As tumours imitate fetal growth morphologically and biochemically it is plausible to assume that the mammalian immune system responds to tumours as the mother responds to paternal antigens of the fetus.³ In a former, unpublished, study we observed enhanced growth of a virally induced murine lymphoma in mice pretreated with murine embryo cells. We propose that the physiological function of early-phase embryonic antigens is the activation of suppressor-cell clones in order that tolerance to (or even enhancement of) the allogeneic conceptus be mediated. Further, we propose that oncofetal antigen expression in tumours serves the same purpose: activation of appropriate suppressor cells and thus the induction of one type of immune tolerance towards the tumour. This immunosuppression may encompass a broad spectrum of reactivities or it may be limited to tumour-specific reactivity only. Thus the profound immunosuppression of patients with colorectal or bronchogenic carcinomas may be the result of excessive oncofetal antigen production. Patients with much less production of oncofetal

antigens, as with sarcomas and melanomas,¹ acute leukaemias,² and Burkitt's lymphoma (Drs Magrath and Ziegler), often retain good immune reactivity to common antigens; thus the general immune status often fails to correlate with the host-tumour relationship. We assume that in these cases suppressor cells specifically inhibit tumour rejection mechanisms. For the demonstration of this activity suppression of lymphocyte blastogenesis to autologous tumour cells by a clone of lymphoid cells added to the mixture of reactor and tumour cells would be necessary.

This oversimplified view is in need of experimental support, but the basic techniques for the detection of human suppressor cells are already available.^{1,2} Means of deactivating suppressor cells could develop into an innovative modality of tumour immunotherapy, whereas activation of suppressor cells (by administration of fetal antigens?) may be useful for organ transplant acceptance. The hormonal milieu of the immediate post-partum period, selective immunosuppression during tumour chemotherapy,⁶ and ablative procedures (splenectomy, lymphadenectomy, adult thymectomy) come to mind as possible procedures of deactivation and elimination of suppressor cells.

Our work is supported by the Kelsey-Leary Foundation, the Dr C D Howe Fund, and the Lippmann Fund.

J G SINKOVICS

Department of Medicine,
University of Texas System Cancer Center,
M D Anderson Hospital and Tumor Institute,
Houston, Texas

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- ³ Sinkovics, J G, *et al*, *Lancet*, 1970, 2, 1190.
- ⁴ Pinsky, C M, *et al*, *Recent Results in Cancer Research*, 1974, 47, 37.
- ⁵ Schneider, M, *et al*, *Recent Results in Cancer Research*, 1974, 47, 42.
- ⁶ Mott, M G, *Lancet*, 1973, 1, 1092.

Co-trimoxazole and cephalexin in urinary tract infection

SIR,—A plausible explanation is to hand for the superior performance of co-trimoxazole compared with cephalexin in the urinary tract infection trial of Drs P E Gower and P R W Tasker (20 March, p 684).

Contrary to their statement that "cephalexin readily induces spheroplast formation," it has repeatedly been shown¹⁻⁴ that the sole effect of therapeutically useful concentrations of cephalexin (and the related cephradine and cephaloglycin) is to cause filamentation of enterobacteria by inhibiting the division process. Because of this cephalexin is more slowly bactericidal than other β -lactam antibiotics and more bacteria are likely to survive in the urine, where, as Drs Gower and Tasker rightly point out, a twice-daily dosage may achieve only transient high levels.

In addition, all cephalosporins now available are somewhat susceptible to enterobacterial β -lactamases, including a slow-acting enzyme characteristic of ampicillin-sensitive *Escherichia coli* strains.⁴ Consequently tests of sensitivity of enterobacteria to cephalosporins are affected by inoculum size; this is particularly marked with ampicillin-resistant strains.^{4,5} Infected urine frequently contains more than 10^8 bacteria/ml. Concentrations of cephalosporins achievable in urine only

transiently suppress such a bacterial population, recovery occurring as the antibiotic is broken down.^{4,5} Disc sensitivity tests may give an over-optimistic view of the sensitivity of such strains to cephalosporins, even when conventional "high inocula" are used, as in the Bauer-Kirby test.⁶

Sulphonamides and trimethoprim are also susceptible to inoculum effects, but this is unrelated to degradation of the drugs.^{7,8} In contrast to β -lactam antibiotics, the components of co-trimoxazole are excreted into the urine slowly and the antibacterial activity is maintained in support of intrinsic clearance mechanisms.

Evidence for the validity of these considerations has been provided by experiments employing an in-vitro model in which some important aspects of the treatment of bacterial cystitis can be simulated.^{7,9-11} Such studies have shown that cephalosporins perform less well than penicillins (including benzyl- and phenoxymethyl-penicillin) in the dynamic conditions of the urinary bladder, using an initially dense, but ostensibly sensitive, bacterial population.⁹ Tested against ampicillin-resistant strains judged "cephalosporin-sensitive" on the basis of disc tests, cephalosporins exhibited a further reduced capacity to suppress bacterial growth.¹⁰ In both these studies cephalexin was the least effective cephalosporin tested. When sulphamethoxazole and trimethoprim were tested in the model their efficiency in clearing infection was rather better than predicted by conventional tests.⁷

DAVID GREENWOOD
FRANCIS O'GRADY

University Department of Microbiology,
City Hospital,
Nottingham

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- ² Russell, A D, and Fountain, R H, *Postgraduate Medical Journal*, 1970, 46, October supplement, p 43.
- ³ Fujii, R, Konno, M, and Ubukata, K, in *Progress in Antimicrobial and Anticancer Chemotherapy*, vol 1, p 374. Baltimore, University Park Press, 1970.
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- ⁸ Greenwood, D, *Journal of Antimicrobial Chemotherapy*, 1976, 2, 87.
- ⁹ Greenwood, D, and O'Grady, F, *British Journal of Experimental Pathology*, 1974, 55, 245.
- ¹⁰ Greenwood, D, and O'Grady, F, *British Journal of Experimental Pathology*, 1975, 56, 167.
- ¹¹ Greenwood, D, in *Chemotherapy*, vol 2, p 241. New York and London, Plenum Press, 1976.

Preventing animal diseases

SIR,—In a letter (14 February, p 393) Sir James Howie referred to a statement by Mr M E Hugh-Jones, of the Central Veterinary Laboratory, Weybridge, which posed five basic questions to be answered before monitoring systems are introduced in the zoonoses field. In a leading article (p 355) you took up the challenge and focused attention on the particular problem of salmonella infection from poultry.

In a subsequent letter (28 February, p 521) Dr D J H Payne and Mr E Lowes referred to the formation of liaison groups with medical, veterinary, and environmental health representation. The Eastern Regional Medical-Veterinary Liaison Group is such a body and has been in existence for over three years. Throughout that time a major concern has

been the recognition of numerous outbreaks of food poisoning in human populations where chicken or turkey has been the vehicle of infection and the evidence of enzootic salmonella infection in poultry establishments in the area covered by the professional groups represented on the committee. Following the references to the problem in the *BMJ* our committee has had further discussion and we wish to make two suggestions additional to those in your leading article on the information that is needed.

We recognise that many poultry establishments have voluntarily instituted their own monitoring programmes and that information on salmonella isolations resulting from such programmes is being made available through the implementation of the Zoonoses Order, 1975. However, we feel that there are large sections of the poultry industry from which no information is available and we would urge medical officers of environmental health/community medicine specialists and environmental health officers to introduce regular bacteriological monitoring at poultry processing plants and retail outlets. In this way a more complete picture of the size of the problem could be built up.

We also suggest that there is a need for a requirement upon the poultry trade that birds entering the market carry a batch number or other identification mark so that in the event of human infection or the discovery of a bacteriologically positive carcass the source of infection can be traced to the poultry unit concerned. Under the present system investigations can rarely be taken beyond the point where the particular brand has been established, and in the case of the very large poultry firms this information of itself is inadequate.

RAMSEY G SMALL
Secretary,
Eastern Regional Medical
Veterinary Committee

Tayside Health Board,
Dundee

Rheumatoid arthritis and ankylosing spondylitis occurring together

SIR,—The paper by Professor G H Fallet and others (3 April, p 804) documents a series of patients who had the clinical picture of both rheumatoid arthritis and ankylosing spondylitis. They describe as extremely unlikely the possibility that these patients represent the random occurrence of two separate disease entities. Critical examination of the argument shows that coincidental occurrence is certainly not ruled out.

An accurate estimate of the real prevalence of ankylosing spondylitis is not available. The study of West¹ which Professor Fallet and his colleagues quote gives an extremely unreliable estimate. They also quote de Blécourt *et al*,² but the frequency of ankylosing spondylitis in the controls used in that study is of no value in estimating the prevalence in the population as these controls were families of probands without spondylitis. The data of Lawrence³ offer the best available estimate of the prevalence of ankylosing spondylitis, but even here there are methodological problems which suggest that his prevalence figures are only an approximation and probably an underestimate.

The figure given by the authors for the a priori probability that an individual will have both severe rheumatoid arthritis and ankylosing spondylitis is unreliable and probably too