antigens, as with sarcomas and melanomas,[1] acute leukaemias,[5] 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.

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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 shown[1-4] 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]

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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 carcase 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.

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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 West[1] 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 Lawrence[3] 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

low. It is difficult to know what the second figure "1 in 450 000 to 1 in 1 800 000" is intended to denote. It is presumably meant to imply that the average size of population expected to include nine such patients is 450 000-1 800 000. This figure is probably too high but in any case the total population from which the nine patients were ascertained is undefined and presumably unknown. The probability that the size of this population falls within 95% confidence limits of the above estimate is likely to be quite high. Moreover, three specialised rheumatological centres were involved so that the likelihood of biased ascertainment is considerable.

Among 104 successive men with ankylosing spondylitis ascertained here, one has seropositive peripheral erosive polyarthritis with a rheumatoid olecranon nodule, his HLA typing including B27. The prevalence of this grade of rheumatoid arthritis is 1% in males.[4]

We therefore interpret the evidence as providing no support for a non-random association of the two diseases and indeed it would be surprising and even more interesting if such cases were *not* encountered. All the present clinical, immunological, and genetic evidence points to the likelihood that there is no aetiological connection between rheumatoid arthritis and ankylosing spondylitis.

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Aplastic anaemia and hair dye

SIR,—The anecdotal report by Drs P J Toghill and R G Wilcox (28 February, p 502) implies a relationship between the occurrence of aplastic anaemia and use of a hair dye. The authors reported prior exposure of the patient to oxytetracycline and penicillin but state that it is unlikely that either antibiotic caused the patient's aplastic anaemia. Aplastic anaemia has been recorded in conjunction with use of tetracycline, chlortetracycline, demethyl chlortetracycline, and doxycycline as well as phenoxymethyl penicillin, cloxacillin, and ampicillin.[1] Attention is drawn to the risk of thrombocytopenia and neutropenia in connection with use of oxytetracycline,[2] and a fatal case of aplastic anaemia possibly due to oxytetracycline has been described.[3]

Three publications dealing with long-term exposure of mice,[4] rats,[5] and dogs[6] to hair dyes give no indication of deleterious effects on bone marrow or peripheral blood elements. Data from current industry studies,[7] which include *para*-toluenediamine at a concentration as high as 6% and both nitrophenylenediamines, show no evidence of toxic effects of these or any other hair dyes on bone marrow. Most of these data were discussed by Burnett at the 1975 meeting of the European Cancer Society in Nottingham.

Karch and Lasagna[8] emphasise the difficulties in relating specific untoward events to drugs. They categorise adverse drug reactions into definite, probable, conditional, and doubtful subgroups. In the light of the data referred to above one is forced to conclude, using these definitions, that the fatal case of aplastic anaemia described by Drs Toghill and Wilcox was probably if not definitely due to either oxytetracycline or penicillin and that it is doubtful that the hair dye in question was causal. Moreover, since 20% of women in the United Kingdom are current users of hair colouring products (and many more have used these products at some time) one would expect to find a history of hair colour usage clearly associated with several cases of a disease before drawing any conclusion. Thus I would support Drs Toghill and Wilcox's plea for careful questioning and continuing inquiry in the case of any unusual phenomenon.

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Spasmolytics for postoperative bowel contractions

SIR,—I am grateful to Dr J W H Watt for his comments and suggestions (10 April, p 901) concerning our letter about hyoscine butylbromide used as a spasmolytic for postoperative bowel contractions (13 March, p 646). I agree that a torn suture line directly due to prostigmine is probably not a common complication of bowel anastomosis, so any remedy must carry a low risk to the patient. One of the drugs that Dr Watt suggests, papaverine, does not do this.

About 20 years ago, and for other reasons, I used intravenous papaverine in doses of 10-40 mg during general anaesthesia but encountered the following complications. Tracheal intubation was more difficult because of failure of pharyngeal and laryngeal muscles to relax even with suxamethonium, haemorrhage was considerably increased, abdominal exposure and closure of the peritoneum were made more difficult because of an apparent failure of the transverse muscles of the abdomen to relax, and reactionary haemorrhage and haematomas were common.

These effects were reduced but not abolished by intramuscular injection. It would seem that despite its theoretical advantages papaverine should not be used as an intestinal spasmolytic after abdominal surgery.

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Assessment of results of surgery

SIR,—Patients' assessment of their symptoms by linear analogue techniques, although appropriate in some situations, such as the assessment of postoperative pain, is not a suitable instrument in the outpatient clinic as described by Mr R Hall and others (3 April, p 814).

In this study patients were asked to rate their own postoperative status on a linear scale ranging from "awful" to "perfect." There are intrinsic biases in this: (1) patients find it difficult to admit that an operation has done them harm because this implies blame on their surgeon; (2) it allows patients to please the surgeon by stating their condition to be "perfect." These biases may be sufficient to explain the tendency of patients who have suffered less than perfect operations to class the result as perfect.

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Iatrogenic gall stones

SIR,—I must take issue with your leading article on this subject (10 April, p 859). You infer that risk of gall stones should make the physician wary of prescribing oral contraceptives. By means of our feature card morbidity recording system I have determined that of the 9000 patients in this practice 474 are on oral contraceptives and not one of these presented with gall stones during the year ending 1 March 1976. Many of these women have been on the pill for more than 10 years.

As you state, "other methods for preventing pregnancy are available," but none combines the merits of effectiveness, reversibility, and convenience. A good deal more evidence than exists at present of risk of gall stones will need to be produced before sexually active women whose family is not yet complete should be denied the peace of mind which the pill usually brings.

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Metronidazole in treatment of empyema

SIR,—Little information is available at present on the penetration of systemic antibiotics into empyemas and we can find no reference on metronidazole in this context. This is perhaps surprising as in one recent study of 83 patients anaerobic bacteria were recovered from 76% of cases (these were the exclusive isolates in 35%)[1] and metronidazole has been increasingly recognised for its role in dealing with anaerobic organisms.[2] Being a relatively non-toxic antibiotic, well absorbed when given by mouth, we feel its use in empyemas is worthy of consideration. We would like to report our experience with this drug.

An 81-year-old man was admitted with right middle lobe pneumonitis. He subsequently developed a right-sided empyema which was drained with an intercostal tube. An anaerobic bacteroides organism particularly sensitive to metronidazole and also to clindamycin was cultured from the pus. Metronidazole 400 mg and clindamycin 300 mg were given orally six-hourly and the patient made a good recovery. A sample from the intercostal drain taken 3½ days after starting this regimen showed a metronidazole concentration of 24·2 μg/ml. The minimum inhibitory and bactericidal concentrations of metronidazole against *Bacteroides fragilis* isolated from clinical material, as determined by Whelan and Hale,[3] were almost identical in several types of