do not know the difference in cost between Distalgesic, Cosalgic, and dextropropoxyphene and paracetamol tablets; or between Paramol and dihydrocodeine and paracetamol tablets. I doubt if it is very much. Would the Minister care to specify? I do know that every time I have to write these longwinded prescriptions my irritation will increase, and all my previous resolutions to keep down drug costs (and mine have usually been below average) will be dissipated. If the Minister was concerned to antagonise us for a very meagre and possibly non-existent financial saving then he has succeeded, and lost my vote.

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Threat to the PHLS

SIR,—Sir James Howie, a former director of the Public Health Laboratory Service, has drawn attention to the importance of maintaining this national network of laboratories, some or all of which are now threatened, for reasons of supposed economy, with transfer to health authorities (23 February, p 579). As director of one of the constituent laboratories of the PHLS I am in complete agreement with the case put forward by Sir James.

The PHLS is concerned with the control of microbial infections, which differ from other human diseases in being communicable from one person to another, to many people from single sources, or from animals to man. Thus they often cross geographical and administrative boundaries and may present as outbreaks, sudden and unpredictable, which require deployment of laboratory resources on a scale greater than may be calculated to be necessary for any one health district on the basis of population "norms." As one example among many, this laboratory recently accepted responsibility for screening large numbers of patients and staff in another district where there was an outbreak of salmonella infection at a mental hospital. PHLS laboratories provide services not only for health districts but also for the environmental health departments of local authorities (six in the case of this laboratory) from whom the demand in specimen numbers is smaller than that from hospitals and general practitioners but often requires more epidemiological detective work.

Our experience is that PHLS laboratories are regarded not only as factories processing specimens (although training in techniques used in them is much sought after) but as sources of information and advice. PHLS staff are consulted frequently by hospital staff, general practitioners, community physicians, environmental health officers, and, from time to time, others in the community, including dentists, veterinarians, port health staff, police, and prison staff, whose problems in relation to communicable disease often overlap. We are well placed to give help because we are part of a national organisation but at the same time familiar with the local situation and its problems.

If PHLS laboratories were assigned to regions and became district administered units there would be considerable financial and administrative problems if all these diverse functions were to be maintained as they should be for the well being of the community. District treasurers hard pressed to find money to keep clinical services going would rightly

wish to exercise tight control over the funding of services extending beyond the boundaries and normal functions of a district health authority. To achieve this it would certainly be necessary to employ more administrative staff with a consequent reduction in resources available for medical and scientific staff. There could hardly be a better example of false economy.

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New hepatitis B vaccines

SIR,—The comprehensive review of prospects for new hepatitis B vaccines by Professor A J Zuckerman (16 February, p 492) was very welcome, particularly as some of the innovations are likely to find wider applications. However, it will be some years before any hepatitis B vaccine other than that currently available is ready. The indications for use and efficacy of the present vaccine therefore need to be kept under scrutiny. This is particularly true of the United Kingdom, where the very low prevalence of hepatitis B virus makes it possible for a vaccine to appear to be effective when it is not. In a previous leading article Professor Zuckerman offered detailed recommendations for the use of the conventional serum derived hepatitis B surface antigen vaccine.¹ These recommendations were written within the context of the worldwide problem of hepatitis B infection, but they ought, for British purposes, to have some elaboration.

Firstly, the use of vaccine alone in the management of single exposures to hepatitis B virus, whether needlestick or sexual, is of unproved value. There is considerable delay before antibody is produced in response to vaccination and such incidents therefore also require early treatment with specific hepatitis B immunoglobulin. Until recently hepatitis B immunoglobulin alone has been given in these circumstances and indeed there is insufficient evidence to warrant abandoning its use. However, especially if further exposures are likely in the future, it seems reasonable to begin a course of vaccine (injected at a different site) at the same time as the hepatitis B immunoglobulin is given.

In fact exposure in Britain to hepatitis B virus is infrequent even in hospital practice. In 1983-4 we tested over 1000 members of hospital staff selected locally as being at increased risk of infection with the virus. Radioimmunoassays for antibodies to the surface antigen (anti-HBs) and to the core antigen (anti-HBc) were used. Only 6% were found to be immune—that is, had levels of anti-HBs >50 IU/l alone or of 10-50 IU/l plus anti-HBc. Thus antibody prevalences even among staff thought to be at special risk from hepatitis B virus showed no evidence of widespread infection. They were too low to justify routine antibody screening before hepatitis B virus vaccination and they argue against the liberal use of hepatitis B vaccine among British hospital staff.

In units that treat significant numbers of HBsAg carriers, however, the risk of hepatitis B is considerable and screening for immunity (and subsequent vaccination of susceptible people) is worth while. In one large hospital for the mentally handicapped we investigated 101 patients in the unit for treating younger patients (under 30 years). Twelve were HBsAg positive and 36 anti-HBs and anti-HBc positive. Of 47 staff tested, one was HBsAg positive and six anti-HBs and anti-HBc positive. Thus 48% of the patients and 15% of the staff had evidence of infection with hepatitis B virus. In British hospital staff antibody prevalences greater than 10% seem likely to be found only in parts of hospitals for the mentally handicapped and in other special units—for example, for the treatment of liver disease. Antibody prevalences elsewhere are much lower and

screening of these individuals for immunity to hepatitis B virus is financially unjustifiable.

Professor Zuckerman also failed to discuss the efficacy of the current HBV vaccine. Of 136 subjects tested by us after a course of H-B-VAX, 71% responded well (>100 IU/l of anti-HBs), 19% responded poorly (<100 IU/l of anti-HBs), and 10% failed to show any response (see table). The poor responders

Anti-HBs response to a course of hepatitis B vaccine in 136 subjects

Anti-HBs response	No	Mean age (years)	Sex M:F
> 100 IU/ml	97	35	47:46
< 100 IU/l	25	42	6:18
Negative	14	49	6:8

tended to be older and female. In view of the expense of the vaccine (the basic cost to the NHS is £63.50 per course), the very low risk of exposure in most sorts of hospitals in Britain, and the weak antibody response and presumably less permanently protective effect in some vaccinees each request for vaccine should be critically examined. The six groups defined in the editorial include all for whom the presently available hepatitis B virus vaccine can properly be contemplated. Even for them the risk of infection may be small. It is unjustifiable to use the vaccine widely until its long term efficacy is better established or the pattern of risk in Britain changes.

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1 Zuckerman AJ. Who should be immunised against hepatitis B? *Br Med J* 1984;289:1243-4.

Anti-inflammatory drugs and bowel perforations and haemorrhage

SIR,—Following the report by Professor M J S Langman and others (2 February, p 347), on the suggested relation between the ingestion of anti-inflammatory drugs and colonic or small bowel perforation or haemorrhage we would like to report our experience of a patient who developed multiple perforations after the ingestion of indomethacin.

A previously fit, 38 year old man received indomethacin 50 mg, three times a day for a painful toe. After one day he experienced generalised abdominal pain and diarrhoea but continued to take the drug. Three days later his pain had become more severe and he was admitted to hospital with peritonitis. At laparotomy there was a single perforation in the sigmoid colon and multiple sigmoid diverticulae. A localised sigmoid colectomy was performed, but after operation he continued to have pain and developed signs of generalised sepsis and his abdominal wound began discharging faeculent fluid.

He underwent a second laparotomy 13 days later, when extensive peritonitis was found, with pus and faeces throughout the abdomen, and the formation of interloop abscesses. Three small perforations in the small bowel were oversewn, but there were also multiple areas of necrosis and perforation throughout the large bowel. A total colectomy was performed, the rectum was oversewn, and an ileostomy created. Four days later a third laparotomy was required, at which several small bowel perforations were again oversewn. After this his nutritional state was so poor that he was transferred to our unit for parenteral nutrition.

Unfortunately he continued to drain small bowel contents from his original wound and once again developed peritonitis. At his fourth laparotomy

several new perforations in the small bowel were repaired. Apart from the persistence of an enterocutaneous fistula there were no further abdominal problems. Following three months of total parenteral nutrition his fistula closed, and enteral feeding was reintroduced without any problems.

A multitude of investigations, including histological examination of the resected bowel, has not provided any explanation for the spontaneous development of multiple large and small bowel perforations in this man. We suggest that ingestion of indomethacin may have been responsible.

Reports of lower gastrointestinal tract lesions attributable to non-steroidal anti-inflammatory agents are uncommon. The Committee on Safety of Medicines has recorded 12 cases of intestinal perforation (with 7 deaths) attributed to indomethacin, as well as 5 cases (1 death) of intestinal ulceration, and 2 cases (no deaths) of intestinal ulceration and perforation since January 1965. There has also been one report (1 death) of perforated diverticula (personal communication). It is not known how many of these cases were due to conventional formulations of indomethacin and how many were due to delayed release preparations such as Osmosin. The case reported here has been notified to the Committee on Safety of Medicines.

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SIR,—We read with interest the paper by Professor M J S Langman and his colleagues on the use of anti-inflammatory drugs by patients with small and large bowel perforation or haemorrhage. We have recently studied a series of 54 patients with small bowel perforation and obtained details of drug ingestion from the case records of each patient. Fifteen were on regular medication or were recorded as having taken drugs within two weeks of presentation: five were on corticosteroids and five were taking non-steroidal anti-inflammatory drugs (total 10 (17%)). Ten patients underwent a complete clinical and pathological review, but no specific cause for perforation was identified. Only one of these 10 was taking an anti-inflammatory drug, this being mefenamic acid. When we further investigated the patients taking non-steroidal anti-inflammatory drugs we found that their histories were longer than those of the remaining patients and that their initial symptoms had been rather non-specific. Presumably some of these patients were treated with anti-inflammatory drugs for symptom relief, and this could well be the reason for the increased use of these agents in this group of patients.

Six patients in our series re-perforated, and all of these were taking steroids or had disorders predisposing to poor wound healing. None were taking non-steroidal anti-inflammatory drugs.

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SIR,—I have described elsewhere a possible bleed into the caecal wall of a marathon runner.¹ It may have been due to a prolongation of the bleeding time on account of a little known

interaction between non-steroidal anti-inflammatory drugs and ethyl alcohol.^{2,3} It would not have been possible for Professor M J S Langman and his colleagues (2 February, p 347) to have determined the recent alcohol intake for the patients in their retrospective study, but perhaps this interaction sometimes played a part.

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Domperidone

SIR,—Drs J Lesser and D N Bateman question the use of domperidone as an antiemetic in Parkinson's disease (19 January, p 241) and suggest that it may affect adversely symptoms of parkinsonism. Levodopa and dopamine agonists cause nausea and vomiting in up to 80% of patients with parkinsonism. Vomiting is often severe and prolonged and may limit or entirely prevent effective treatment. The use of decarboxylase inhibitors with levodopa reduces the incidence of vomiting to 10-20%, but no such remedy is available with bromocriptine, lysuride, or pergolide. Despite decarboxylase inhibitors, mild or severe nausea sometimes emerges late in treatment.

An effective antiemetic is thus a sine qua non in the management of parkinsonism. Domperidone has many advantages over other antiemetics. Experience with domperidone in Parkinson's disease now extends to several hundred patients.¹⁻³ We ourselves have treated over 100 such patients with oral domperidone, 10-120 mg daily, for the prophylaxis or treatment of drug induced sickness, and we have never encountered any extrapyramidal reaction, severe side effect, or reduction of anti-parkinsonian drug effect. Indeed, the opposite may be true. Acute studies suggest that domperidone speeds the delivery of levodopa to the main absorption site, the small bowel, with a consequent increase in immediate bio-availability of levodopa.⁴ This is also the case with bromocriptine. In contrast to domperidone, metoclopramide 60 mg daily, although an effective antiemetic, may slightly impair the levodopa-bromocriptine response.⁵ We consider domperidone given orally a most useful adjunct in the management of Parkinson's disease.

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Overview of randomised trials of diuretics in pregnancy

SIR,—We read the paper of Dr Rory Collins and others (5 January, p 17) with interest, in particular the reference to our study.¹ Perinatal mortality may not be the best indicator of outcome in trials of antihypertensive therapy in pregnancy. At the gestational age (more than 30 weeks) at which most cases present the fetus can nearly always be electively delivered and will almost certainly survive given the recent advances in perinatal care. For example, the fetal loss rates associated with pre-eclampsia in the UK declined from 4.3 per 1000 in 1958 (when most of the studies cited by Dr Collins and others would have been in progress) to 0.8 per 1000 in 1981-2.² Other outcomes such as gestational age at birth, birth weight, and mother's time spent in hospital before delivery should therefore be considered. These outcomes are still important to mothers and their infants, and the use of such measures may not entail such large numbers as are clearly necessary to study perinatal mortality.

For these reasons our study was primarily concerned with birth weight.¹ However, it was obviously necessary to indicate the numbers of abortions and stillbirths, together with other characteristics of birth such as method of delivery. As indicated above, we did not expect antihypertensive therapy or its effects on blood pressure to influence the numbers of deaths. If a difference had been found our comparison of birth weights might have been biased and difficult to interpret. Accordingly, although we analysed and described birth weight in detail no formal analysis of deaths was presented and no p values were given. We merely observed that the groups were comparable but did not discuss the relevance or importance of this lack of difference in outcome.

The authors' statement that we concluded that there was no difference in final fetal outcome because there was no difference in stillbirth rates in the treatment group was inappropriate. Our chief concern was birth weight, not perinatal mortality. In any case it is inappropriate to compare our findings with those of Rubin *et al* (see accompanying letter) since our studies were quite different in concept.

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SIR,—The review by Dr Rory Collins and others on trials of diuretic use in pregnancy is comprehensive and useful, but I would take issue with three points made in the discussion.

Firstly, these authors support their view that most drug trials in pregnancy hypertension are too small by stating that the studies by Fidler *et al*¹ and ourselves² on β blockers reached opposite conclusions. This is incorrect since we were investigating different problems. Fidler *et al* addressed the question of whether