think that the conclusions drawn can be accepted uncritically.

PETER J WILLIAMSON
PETER M HAWKEY

Department of Microbiology,
Bristol Royal Infirmary,
Bristol BS2 8HW

* * We sent a copy of this letter to Dr Lakic, who replies below.—Ed, *BMJ*.

SIR,—Our group practice shares 15 403 patients, and the incidence of glandular fever during the year in which my survey was conducted was 1.03 per 1000 patients. With such small numbers of confirmed cases of glandular fever it was impossible, within the scope of this paper, to satisfy all the statistical requirements. Any future study will obviously have to include placebo and control groups.

A tabular display of results is subject to many interpretations. Confirmed cases of glandular fever initially treated with "other antibiotics" made no progress during the first week. These seven cases were deliberately not subdivided because of the small numbers and were considered as a whole group. This is yet another pitfall of an evolving study (as opposed to a true crossover trial).

I fully appreciate the final sentence of the letter of Dr Williamson and Dr Hawkey. Their scientific criticism is accepted and will be taken into consideration in future work. My impression of the effect of cephalexin in the treatment of glandular fever is that of a practising general practitioner.

JOVO LAKIC

Barton on Humber,
South Humberside DN18 5EP

SIR,—The day after reading the article by Dr Jovo Lakic (21 May, p 1617) I saw an 18 year old girl with typical glandular fever (later confirmed by laboratory tests). She had been prescribed phenethicillin for an inflamed throat on 19 May. On 23 May I started her on cephalexin 500 mg four times daily, and by 26 May she was much improved. By 30 May she said she was feeling fine, and her large cervical glands were no longer palpable. A florid morbilliform rash had developed, however, similar to that commonly affecting patients who are inadvertently given ampicillin when they have glandular fever. Rashes due to cephalexin are said to be rare. The rapid improvement in the signs and symptoms of glandular fever is, in my experience, most unusual.

P M ELWIN

Bridgwater,
Somerset TA5 1RJ

One man's burden

SIR,—Professor R B Zachary (4 June, p 1821) accuses me of misrepresenting the views of the Surgeon General in the United States, Dr C Everett Koop. He is able to describe Dr Koop's views so precisely that he clearly has ready access to them, perhaps through personal acquaintance. I, like most American doctors, had to judge the man's views from the words attributed to him. Every American newspaper I read reported Dr Koop as describing the practice of ending life support for terminally ill newborn babies as either infanticide or murder, or both.

I should add that my misinterpretation—or,

in Professor Zachary's eyes, "misrepresentation"—was shared by the American Pediatric Association, the American Medical Association, and the many doctors who wrote "open replies" to newspapers and journals.

MICHAEL O'DONNELL

Weybridge,
Surrey KT13 8SJ

Clinical and biochemical manifestations of digoxin toxicity

SIR,—Was it justified in this interesting study of the clinical and biochemical manifestations of digoxin toxicity (2 April, p 1089) to illustrate the paper with a figure referring to the raw data and including two patients who appeared in two groups when the method specifically states that they were excluded from the analysis for that very reason? In the same illustration I note that the line representing the upper limit of the therapeutic range for serum digoxin was drawn at 2.1 $\mu\text{g/l}$, not 2.0 $\mu\text{g/l}$, as stated in the text.

It would be interesting and relevant to know the number of patients in each group undergoing arterial puncture for blood gas estimation and the indications for the procedure. Could the higher average arterial pH in the patients with cardiac automaticity be secondary to alveolar hyperventilation caused by left ventricular failure, precipitated or maintained by arrhythmias? Even in the absence of a respiratory cause for the extracellular alkalosis it is difficult to ascribe a role for the alkalosis, per se, in the genesis of cardiac automaticity since the arterial pH is causally related to intracellular hydrogen and potassium ion concentration, as mentioned in the discussion. Indeed, if hypokalaemia is the underlying cause, an intracellular acidosis may be found.¹ Knowing the measured arterial bicarbonate concentration and Paco_2 would answer the first question and also confirm or exclude the presence of the transient hyperventilation which is often seen with the trauma of arterial puncture but apparently not in evidence in this study.

Lastly, is there any reason why there were no patients with both cardiac automaticity and cardiotoxicity? Are the two mutually exclusive, is this a chance finding, or was some pre-selection of patients undertaken? This could be of therapeutic significance in view of the different mechanisms of pathogenesis at a cellular level.

C M BYATT

¹ Zilva JF, Panall PR. *Clinical chemistry in diagnosis and treatment*. London: Lloyd-Duke, 1979.

* * We sent a copy of this letter to the authors, who reply below.—Ed, *BMJ*.

SIR,—We illustrated our paper with the figure in order to emphasise the differences in serum digoxin concentrations between patients with gastroenterological symptoms and those with enhanced automaticity. It is indeed surprising that we found only two patients with mixed presentations of digoxin toxicity, and our figure was meant to emphasise this.

Dr Byatt quite rightly points out the discrepancy in the upper limit of the therapeutic range for serum digoxin, and the figure of 2.0 $\mu\text{g/l}$ in the text should read 2.1 $\mu\text{g/l}$.

The numbers of patients who underwent arterial puncture were nine, seven, and six in

the gastroenterological, automaticity, and cardiotoxicity groups respectively. It is difficult retrospectively to establish the cause of the alkalosis in the patients with cardiac automaticity. Although hyperventilation could certainly account for part of this rise in arterial pH, the average Paco_2 in this group being 34.7 ± 2.5 mm Hg, the group with gastroenterological symptoms also had a mean Paco_2 of 29.7 ± 1.7 mm Hg. Whether the alkalosis itself is in any way directly responsible for the increased automaticity or not needs investigation. Although acidosis is usually accepted as a cause of cardiac arrhythmias, Brater and Morrelli¹ have also shown a higher incidence of digoxin toxicity in states of alkalosis. We agree with Dr Byatt, however, that in patients with hypokalaemia the shift of hydrogen ions intracellularly can give rise to an intracellular acidosis, which in turn will aggravate the extracellular alkalosis.

Lastly, Dr Byatt asks why there were no patients with both cardiac automaticity and cardiotoxicity. As previously stated, it is indeed surprising how patients manifest one particular symptom of toxicity and not another. In all the previous studies on digoxin toxicity no attempt was made to classify patients in this manner, but as we have shown it is possible that it has a physiological basis. Our understanding of the effects of other electrolytes or brain digoxin concentrations are, as yet, too meagre to establish whether these groups really do have a physiological basis.

M SONNENBLICK
ABRAHAM S ABRAHAM
Z MESHULAM
U EYLATH

Department of Medicine,
Shaare Zedek Medical Center,
Jerusalem 91002, Israel

¹ Brater DC, Morrelli HF. Systemic alkalosis and digitalis related arrhythmias. *Acta Med Scand* 1981;**647** (suppl):79-85.

Digitalis intoxication

SIR,—The treatment of digitalis toxicity by digoxin specific antibodies, which was reviewed by Professor C F George (14 May, p 1533), clearly is an advance. Avoidance of digoxin overdosage and toxicity must remain the prime consideration.

We are concerned about the prescribing advice for digoxin given in the *British National Formulary*.¹ We quote: "When very rapid control is required, which is seldom, digoxin may be given intravenously in a digitalising dose of 0.75-1.25 mg followed by 250 μg intravenously every four hours, with electrocardiographic monitoring." If these guidelines were followed to the letter, up to 2.5 mg of digoxin could be given in 24 hours, a dose we consider dangerously high. The *British National Formulary* recommends that for rapid oral digitalisation 1 mg is given over 24 hours. In its present form 85% of oral digoxin may be absorbed in healthy subjects.² For Lanoxin tablets the amount absorbed is about 65-75%, and in patients in heart failure this may be further reduced to about 50%. Logically, therefore, an intravenous loading dose should be about 500 μg . We also suggest that the *British National Formulary* should recommend that intravenous digoxin be given slowly³ and that a caution should be given over its use in patients who are already receiving digoxin.

With regard to oral treatment, advice in the *British National Formulary* lacks consistency. In the main text we read, "In patients with moderate heart failure a loading dose is not required and a satisfactory concentration can be achieved over a period of about a week of 125-250 μg twice daily which can then be reduced." Whereas, in the summary we read: "Dose by mouth 250 μg twice daily until digitalised then 125-500 μg daily." This ambiguity could lead to the prescription of 500 μg daily for a week, which would result in a potentially toxic total dose of 3.5 mg.

We appreciate that general cautionary advice on the use of digoxin is included but think this entry in the *British National Formulary* needs revision. Simplified instructions on loading doses as discussed by Jelliffe⁴ could then be supplemented by fuller guidance on estimation of maintenance dose.⁵

M G THORNE
CLIVE E BOWMAN

Torbay Hospital,
Torquay TQ2 7AA

¹ British Medical Association and Pharmaceutical Society of Great Britain. *British national formulary*, No 5. London: BMA. 1983:63.

² Doherty JE. Clinical pharmacology of the cardiac glycosides. *Ann Rev Med* 1975;26:159-71.

³ Aronson JK, Grahame Smith DG. Digoxin therapy textbooks, theory and practice. *Br J Clin Pharmacol* 1976;3:639-48.

⁴ Jelliffe RW. An improved method of digoxin therapy. *Ann Int Med* 1968;69:703-17.

⁵ Dobbs SM, Nicholson PW, Rodgers EM, Mawer GE, Kenyon WI. Digoxin prescribing: an evaluation of clinical judgment. *Br Med J* 1978;iii:668-9.

*.*The joint secretary of the Joint Formulary Committee writes: "The letter from Dr Thorne and Dr Bowman will be considered by the Joint Formulary Committee at its next meeting. Meanwhile, however, the text of the chapter on drugs used in the treatment of diseases of the cardiovascular system has been extensively revised and most of the points made in the above letter have in fact been incorporated in the next edition of the *British National Formulary* to be published in September of this year."—ED, *BMJ*.

Spontaneous abortions in hospital sterilising staff

SIR,—Dr K Hemminki and others (20 November, p 1461) reported on research which suggests that women occupationally exposed to ethylene oxide may be at increased risk of spontaneous abortions. This is the first report to indicate that ethylene oxide may affect human reproduction, and these provocative findings add to the concern about the potential carcinogenicity of this agent. There are, however, some questions we would like to raise regarding the findings.

This particular study was complicated by the fact that the study women could report pregnancies which occurred as far back as 1951. Can women recall such distant events without bias? Furthermore, can we presume that a current nursing supervisor can retrieve and reliably report each woman's exposure to sterilising agents and concurrent exposure to other agents in the hospital environment—for example, anaesthetic gases, x rays, biological and chemical agents—over a period of 30 years? Did the patterns of use of sterilising agents vary over 30 years? Likewise, can she have identified whether any such exposures did or did not occur during each pregnancy, for each woman, during this time? We are also concerned about the possibility that biased misclassification of exposure could have occurred if the supervisors also knew

the results of pregnancies occurring to the women they helped identify for study.

Although not emphasised by the authors, table I and figure 1 show clearly that spontaneous abortions among the "controls" fell midway between the categories of the "exposed" and "unexposed" pregnancies in the sterilising staff. This suggests that there may in fact have been some other agent in the hospitals which may have affected spontaneous abortion or that the "controls" were somehow exposed to the sterilising agents in question.

We are further troubled by lack of sufficient information regarding: (a) adjustment for age and parity; (b) classification of smoking habits, alcohol, and coffee consumption, and whether the duration and degree of these three consumption patterns were accounted for at the time of each pregnancy, particularly during the first trimester. It would have been useful if the authors had used the Finnish hospital discharge register to validate the women's self reported information and not only to attempt to confirm their findings.

The authors did not report the actual number of women in their study. If the number of women, by gravidity, had been given in a table, the rate of repeat pregnancy in this cohort would have been clear. We are concerned with this issue because clearly a woman's pregnancies are not independent events and cannot automatically be assumed to be so in a statistical analysis.

Lastly, in an attempt to rearrange some of the reported data (from table II) for the purpose of making some supplementary statistical tests, we could not discern how the reported pregnancies among the sterilising staff in the various exposure categories might be related. It seemed to us that a single pregnancy could be counted more than once in a table if a woman had one or more types of exposure; if she had more than one pregnancy, but her exposure during each was different, each person and each pregnancy could appear several times in the same table.

A fuller interpretation of the original study findings would be of great use to all of us researching reproductive hazards in general, and of ethylene oxide in particular.

JANE E GORDON
THEODORE J MEINHARDT

Division of Surveillance, Hazard
Evaluations and Field Studies,
National Institute for Occupational
Safety and Health,
Cincinnati,
Ohio 45226

SIR,—Dr K Hemminki and others (20 November, p 1461) suggest that exposure to ethylene oxide in hospitals may be related to an increased risk of spontaneous abortions among sterilising staff. A number of points arising from this report merit clarification.

Firstly, the authors suggested that complications in pregnancy may be related to exposures as low as 0.1 to 0.5 parts per million (TWA-8) and short term peaks of 250 parts per million. The authors state: "Ethylene oxide concentrations have been measured in many sterilising units in Finnish hospitals; eight hour weighted mean concentrations have ranged from 0.1 to 0.5 parts per million with peak concentrations up to 250 parts per million (measurements by Institute of Occupational Health)." The authors do not indicate whether these measurements were representative of the hospitals and women included in the study. If the measurements were made recently, they may have little relevance to the study, which focused on the women's retrospective histories and included pregnancies dating back to the 1950s. Additional information on how these exposure levels were determined would be useful.

I am also concerned about the possibility that the women surveyed were aware of the purpose of the study. If the questionnaire stated that the study was investigating sterilisation gases, this could have introduced a stimulus for differential reporting of

adverse outcomes between controls and sterilising staff and for differential reporting of adverse outcomes between the sterilisers' and unexposed pregnancies. The direction of the bias that could have been introduced would be consistent with the observed excess of spontaneous abortions among exposed pregnancies. Although the hospital discharge data suggest that the observed rise in abortion rates may be real, the data shown in table III were crude, rather than adjusted, rates and were based on smaller numbers of pregnancies than encompassed by the questionnaire.

The way in which the questionnaire and hospital data were analysed may also have introduced some biases. For example, the authors use two different methods for comparing in their analyses, which yield conflicting results. When spontaneous abortion rates are compared between "all sterilising staff pregnancies" and "all control group pregnancies" little difference is seen (sterilising staff = 9.7%; controls = 10.5%). Internal comparison of the "exposed" and "non-exposed" pregnancies of the sterilisation staff group, however, reveals some rather large inexplicable differences (exposed = 15.1%; not exposed = 4.6%).

The authors do not explain why the non-exposed pregnancies of the sterilising staff should have lower abortion rates than the control group (which was also non-exposed); however, several possibilities seem likely. Firstly, the authors indicate that there was a relation between exposure and year of pregnancy such that recent pregnancies were more likely to be exposed and recalled more accurately. This would have resulted in a concentration of the pregnancies of non-exposed sterilising staff in the earlier years, 1950 to 1960, where recall was thought to be poorest. It is likely that the younger maternal age and lower parity of these pregnancies would be reflected in a lowered risk. Secondly, it is possible that the non-exposed pregnancies of the sterilising staff occurred among women who were largely unemployed at the start of their pregnancy, whereas the control group would include both employed and unemployed pregnant women. If employment status affects the risk of spontaneous abortion then the higher proportion of unemployed pregnant women in the non-exposed sterilising staff group might further confound the comparison. Additional data are needed to resolve these issues.

Although the rates of spontaneous abortion of the non-exposed sterilising staff and control groups have been adjusted for a number of variables—including age, parity, year (decade) of pregnancy, coffee drinking, smoking status, and alcohol consumption—the resulting rates continue to reflect considerable disparity. A possible explanation is that the adjustment procedure used was inadequate. If a high proportion of all pregnancies fell within the 20-34 years age group, it is questionable how useful the control for age was, since within this category no further age adjustment was made. Secondly, no control for employment status or history of previous spontaneous abortion was included, and controls for alcohol, smoking and drinking habits were related to "current" habits and not to habits at the start of each pregnancy.

In view of these problems it is questionable whether or not an exposure specific effect has been observed. Although the spontaneous abortion rates for the group of sterilising workers exposed to ethylene oxide appear to be increased, it is unclear what the appropriate reference rate should be.

SUSAN G AUSTIN
Chairman

Epidemiology Subcommittee,
Ethylene Oxide Industry Council,
Union Carbide Corporation,
Danbury,
Connecticut 06817

*.*We sent copies of these letters to the authors, who reply below.—ED, *BMJ*.

SIR,—Our article on spontaneous abortions in staff engaged in sterilising instruments with chemical agents came out at a time when one of the agents studied, ethylene oxide, was a focus