ing retinopathy after the institution of diabetic control is concerned, we have only one lead: longstanding uncontrolled diabetes with^{1,5} or without³ pre-existent retinopathy is probably a risk factor. Whether "platelet activation" is a marker for the development of microangiopathy will be revealed by future prospective studies on similar patients. It is worth mentioning that hypoglycaemia "activates" platelets in normal⁷ and diabetic subjects.⁸ Other coagulation factors like factor VIII may also increase during hypoglycaemia.^{9,10} Whether a reduction of blood glucose concentrations to normal levels after a spell of uncontrolled diabetes has a similar effect on platelet function and coagulation factors has yet to be shown.

P DANDONA

Royal Free Hospital and School of Medicine,
London NW3 2QG

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Treatment for teenagers with epilepsy

SIR,—Professor C B S Wood's answer to the question "What treatment is advised for a teenage girl who has recently developed grand mal epilepsy?" (2 March, p 707) is unsatisfactory and ignores many of the advances in the drug treatment of epilepsy which have occurred over the past 15 years.¹

Professor Wood is correct in stating that phenytoin may no longer be the drug of first choice in a teenage girl, because cosmetic effects may be troublesome and mood changes occasionally occur. Teratogenic effects are also of concern; the evidence indicates that anti-epileptic therapy is associated with an increase in the incidence of congenital malformation in the offspring of epileptic mothers, and phenytoin is one of the drugs most likely to be implicated. Professor Wood, however, misses the point over the kinetics of phenytoin. The development of plasma concentration monitoring has made this drug one of the easiest to use, because, with a little knowledge of its kinetics, the correct dose can be selected very precisely, thereby avoiding the ataxia, nystagmus, and slurred speech associated with overdosage. In adults with epilepsy it is still a widely used and effective agent.

Professor Wood suggests sodium valproate as an

alternative, with which we agree. One point of concern, however, is that irreversible hepatic damage may rarely occur, and over 50 patients have so far died of hepatic necrosis, which was possibly due to sodium valproate. Most of these patients were children with severe epilepsy accompanied by an associated neurological handicap and on multiple drug therapy.² This is probably an idiosyncratic reaction, possibly from the formation of a minor toxic metabolite. There is no evidence, as Professor Wood suggests, that pre-existing liver disease is worsened. Neither is there any evidence that monitoring liver function tests helps to identify susceptible patients at an early stage (although the manufacturers were obliged to recommend routine measurement in their data sheet). Mild increases in transaminase enzymes and blood ammonia values occur frequently but are simply a reflection of the drug's effect on intrinsic metabolic pathways, not a prelude to hepatic necrosis. Recently there has been evidence that sodium valproate taken during pregnancy may be associated with an increased incidence of spina bifida in the newborn³; this needs to be borne in mind when prescribing for the teenage girl, but alternative drugs may not themselves be free of teratogenic effects.

Professor Wood mentions drug concentration monitoring with sodium valproate. Unfortunately the evidence to date is that these measurements are unhelpful in regulating the dose or avoiding toxicity, and there is little to recommend regular monitoring of this drug, in contrast to phenytoin.

As alternatives Professor Wood suggests primidone, sulthiame, or benzodiazepines. The first is related to phenobarbitone (and is converted partly to this drug in vivo) and is regarded in authoritative sources as a drug of third choice because of its adverse effects on mood and learning. Sulthiame is now virtually obsolete because of its inhibitory effect on drug metabolism and the frequency of adverse effects such as hyperventilation, paraesthesiae, and mood changes. Benzodiazepines are highly effective in status epilepticus when given as single doses or in myoclonic epilepsies when given chronically. In tonic-clonic (grand mal) seizures they are less satisfactory because tolerance and breakthrough occur.

Why does Professor Wood not mention one of the most popular and effective drugs, carbamazepine? There is extensive evidence that this drug is as effective as phenytoin in tonic-clonic seizures and is now widely used by paediatricians and neurologists because of its low incidence of toxicity particularly on mood and intellectual function. This drug stands alongside sodium valproate as a drug of first choice, particularly in teenage girls because the evidence for teratogenicity of carbamazepine is minimal.

The correct answer to the question should therefore have been that carbamazepine and sodium valproate are drugs of first choice in this patient, phenytoin second choice, and phenobarbitone and primidone third choice. The other drugs have only a subsidiary role. It should also be emphasised that treatment means more than just prescribing drugs and is incomplete without, for example, counselling the girl and her parents on a wide range of potential problems related to having epilepsy. In any case "grand mal epilepsy" is an outdated term and is not a complete diagnosis. There may thus be clinical or other evidence of a cause which requires medical or surgical investigation and treatment. Treatment should also include possible preventive measures—that is, the identification and elimination of any provocative factors such as drug, solvent, or alcohol abuse and sleep deprivation.

MICHAEL ESPIR

Charing Cross Hospital,
London W6

ALAN RICHENS

Department of Pharmacology and Therapeutics,
University of Wales College of Medicine,
Cardiff CF4 4XN

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* * * Professor Wood replies below.—Ed, BMJ.

SIR,—Professor Richens's and Dr Espir's comments are most useful and go into the subject more fully than was possible in the initial short answer. I acknowledge that carbamazepine has become an increasing claimant for a place among first line treatments for major epilepsy and its use is said to be associated with relatively good school performance. It is therefore being given an expanded role, having been initially introduced more specifically in the context of temporal lobe epilepsy, for which it remains of prime use. It goes without saying that a doctor prescribing medication for a teenage girl will spend some time in counselling her and her parents for there will be many questions to be answered about prognosis, side effects, educational and career prospects, driving, etc.

C B S WOOD

Academic Department of Child Health,
Queen Elizabeth Hospital for Children,
London E2 8PS

Invasive cervical cancer and combined oral contraceptives

SIR,—The report of the WHO collaborative survey on cervical cancer and oral contraception (30 March, p 961) has inevitably attracted much attention, not all of it well informed. Greater attention to some aspects of trial design and statistical analysis would have reduced this danger.

The abstract states that the finding supports a causal relation, and this statement featured prominently in the *Guardian* report. It is a fundamental principle of statistical analysis that association does not prove causation, and there are many well known examples to emphasise this. The association reported from Holland between the number of storks' nests on a house and the number of children in the house is perhaps the most relevant.

The authors state that in all centres the controls were younger than the cases and that estimates of relative risk were therefore adjusted for age. No details are given of the method of adjustment, nor is there a reference. Since social and sexual attitudes have changed with time, no doubt at different rates in different countries, and since these changes are generally thought to have affected different age groups to differing degrees, any such adjustment will be complex and needs validation. Without information on the methods used it is impossible to assess the validity of the results presented.

The participating centres must see a very small proportion of the cases of cervical cancer that occur in their own countries. It might be supposed that these are more academically oriented centres, possibly with a special interest in malignant disease. No evidence is given that the participating centres were seeing a representative sample of local patients.

The figures from Israel given in table I are remarkable. It appears that about 3% of the cases were Israeli and nearly 20% of the controls. It has been suggested that Jewish women (or at least women from a

subgroup within the Jewish community) have a particularly low incidence of carcinoma of the cervix. It is theoretically possible that all the apparent differences are the result of the proportions of Israeli women in the two groups.

The authors state that the overall relative risk is of borderline significance. This must be some new use of the word significance. The 95% confidence interval of the risk factor includes 1, and it would be more usual to state that the study had failed to show any significant difference between the two groups.

It is clearly important that studies like this are published, even when, as in this case, the results are essentially negative and even when factors such as smoking and the sexual history of the partners are unaccountably ignored. However, to present associations which do not reach statistical significance as if they proved a causal relation is irresponsible. Editors should be on the lookout for pitfalls and use expert statistical advisers more often than they do.¹

JOHN V PARKIN

II University Department of Surgery,
Krankenhaus Merheim,
5000 Cologne 91, West Germany

¹ Lock S. In: Gore SM, Altman DG. *Statistics in practice*. London: British Medical Journal, 1982.

*.*Dr Thomas replies below.—Ed, *BMJ*.

SIR,—Dr Parkin has raised a number of issues. He states that no details of the method of age adjustment are given. This is clearly described in reference 17 of the paper, which is referred to in the last paragraph of the methods section; we see no reason to provide details of such standard statistical procedures when they are readily available elsewhere. They are certainly not needed, as Dr Parkin asserts, to assess the validity of the results presented.

We recognise that the cases seen in the participating centres may not be representative of all cases in the populations of the countries in which the study was conducted. It was for this reason that the controls were selected not from the general populations of those countries but from among women admitted to the participating hospitals for conditions other than those under study. This procedure was instituted specifically to control for factors that are related to hospitalisation in the participating institutions.

The fact that only 3% of the cases but 20% of the controls came from Israel does not explain our results. Risks were increased in oral contraceptive users in most countries, and the overall relative risk was adjusted for both age and centre.

The 95% confidence interval of the relative risk of 1.19 was 0.99 to 1.44. Rounding 0.99 to one significant figure gives us a lower 95% confidence limit of 1. By convention this would be considered borderline by most people.

Smoking was not unaccountably ignored as Dr Parkin implies. Information on this factor was, unfortunately, not collected but we address this at considerable length in the discussion. Information on the sexual behaviour of the subjects' partners was also not collected. However, for such behaviour to be a source of confounding a woman's choice of contraceptives would have to vary depending on the number of partners her husband had. Although this is certainly a theoretical possibility, it seems unlikely and certainly provides

no reason for us to have refrained from publishing our results.

Dr Parkin questions the statistical methods that we used. We have used the most up to date techniques available and have had the privilege of consulting some of the finest statistical minds in the world today.

Finally, I should like to indicate that our final conclusions were written after considerable thought and discussion and represent a consensus reached by the participating investigators.

DAVID B THOMAS

Professor and Head,
Program in Epidemiology

Fred Hutchinson Cancer Research Center,
Seattle, Washington 98104, USA

SIR,—It is unfortunate that the recent WHO collaborative study on oral contraception and cervical cancer (30 March, p 961) discounted the potential effect of smoking. As the authors conceded, smoking has been shown to be an independent risk factor for cervical cancer that is dose related and increases with time. Neither is it appropriate to conclude that women in the study were unlikely to be smokers simply because low smoking rates have been reported for Third World women in a study on an unrelated topic. Firstly, the British study in general practice of oral contraception showed that oral contraceptives users had higher smoking rates than non-users. But, more importantly, smoking is already a substantial problem among Australian women (to be included in the study), and smoking rates among women from several of the Third World countries already included in the study are rapidly approaching those in the developed world. The most recent data available from WHO¹ and elsewhere show that 30% of women smoke in Australia,² 26% in Chile (Santiago), 20% in Colombia (Bogota), 16% in Mexico (Mexico City), 3% in Nigeria (Lagos), and 4-20% in Thailand.

The above rates do not include traditional forms of tobacco use which are popular among men and women in Nigeria, Thailand, and the Philippines. In the early studies on the cardiovascular risks of oral contraception the key role of smoking was underemphasised because women in the initial studies were not asked about their smoking habits. It would be sad if history repeated itself.

BOBBIE JACOBSON

London NW1 8EY

¹ Masironi R, Roy L. *Smoking in developing countries*. Geneva: WHO, 1983.

² Hill D, Gray N. Australian patterns of tobacco smoking and related health beliefs. *Community Health Studies* 1984;8:No. 3.

Doctors' dilemmas

SIR,—I was sorry to see the correspondence between Ms Sheila McKechnie and Dr Peter Taylor on some of the ethical problems of occupational physicians (20 April, p 1216) become an exchange of quotations with a defensive reply by Dr Taylor. The underlying issue is too important and ought to be debated.

Ms McKechnie has a point: when employed by companies occupational physicians have salaries and fringe benefits—for example, cars, pensions, management social activities—which to many eyes identify them with management. Furthermore, the firm employs them to advise management. (I know that they

may give medical advice to individual workers but seldom do they separately give advice to workpeople as a group.) Furthermore, some of these occupational physicians also act as advisers to such bodies as the Chemical Industries Association and the Engineering Employers Confederation—a proper and important function; in a similar way the Trades Union Congress has its own medical adviser.

As a consequence of that status and of those duties it is not surprising that workpeople, some managers, and, in my experience, some hospital and general practitioners perceive the occupational physician as part of management. When he is, however, advising an individual worker the occupational physician regards himself as an independent doctor, but he does not always recognise the difficulty that a worker (now a patient?) may have in accepting that mental switch and that leads him to worry over confidentiality. Faculty guidelines (despite their name) partly enshrine practice; they do not, nor should they, instruct how this problem should be made tractable.

Changing names by itself does not help unless it betokens an underlying change of attitudes and functions. "Refuse collectors" are still dustmen, but with changing social attitudes mental hospitals are no longer asylums. Are occupational physicians different from industrial medical officers, or are they the same doctors with a less pejorative title?

That change in title signifies a recognition of what the better ones have been doing for some time. They are doctors, trying to work as doctors, in industry. But that does not help the misperception of them by the workforce. In over 25 years' experience in hospital outpatient departments and as a "neutral" observer going into industry from a university, I find that workpeople are more and more, but not entirely, recognising the occupational physician as a doctor in the workplace rather than "the firm's medical officer." But how is this change to be encouraged and developed in the present industrial set up in the UK? By education of occupational physicians in these matters, not simply by lectures, guidelines, and articles but by conscious demonstration by supervisors during training. By trades union leaders helping this change of attitude, where they see it in operation? By other means? My own teaching, which is not very original, is that each occupational physician must, by his total conduct, earn the acknowledgement that he is acting as an "occupational physician." He cannot expect it to be given automatically just because he belongs to the medical profession (or for that matter because of what the General Medical Council or the faculty guidelines say).

Both Sheila McKechnie and Peter Taylor have made signal contributions to the development of health and safety in Britain. I hope that their minds, and those of your other readers, may be turned to constructive debate on the problems underlying ethical issues in occupational medicine and on their solution.

W R LEE

Department of Occupational Health,
University of Manchester,
Manchester M13 9PT

Preventing infant deaths

SIR,—Assessing and managing symptomatic infants at home is anxiety provoking for all concerned; while most consultations are associated with self limiting complaints, the same symptoms may herald progressive illness and, once in 10 years for an individual general practitioner, an unexpected infant death.

Dr Bernard Valman has argued (2 February, p 339) that improved assessment and management of symptomatic infants in general practice could save lives and that this management should include referral to hospital of all infants with certain "sinister" symptoms or