and a review of systems in only seven. A clear statement of the indications for treatment with lithium was found in 18 of the notes, while an explicit treatment plan had been preserved in only five.

In none of the case notes was there a record suggesting that the patient had been informed of the possible side effects or toxicity of lithium, nor of the need to have regular blood tests and to maintain adequate fluid intake. Lithium is known to be a toxic drug and patients are undoubtedly given information about its use, but this should be recorded, particularly in view of recent medicolegal interest in the use of lithium.

Kehoe and Mander comment that certain aspects of lithium prescribing and monitoring habits give cause for concern; our audit suggests that this concern should also be extended to the period when lithium is first prescribed and to the recording of treatment and advice given.

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1 Kehoe RF, Mander AJ. Lithium treatment: prescribing and monitoring habits in hospital and general practice. *BMJ* 1992;304:552-4. (29 February.)

Is *Bordetella pertussis* clonal?

SIR,—M N Khattak and colleagues were right to finish their title with a question mark.¹ Although their elegant study shows the discriminatory power of genotype analysis by restriction enzyme digestion and pulsed field gel electrophoresis and its suitability for typing and epidemiological tracing, we do not agree with the conclusion that their results fail to support the hypothesis that this organism is essentially clonal.

The operational definition of clones provided by Ørskov and Ørskov describes them as "bacterial cultures isolated independently from different sources, in different locations and perhaps at different times, but showing so many identical phenotypic and genetic traits that the most likely explanation for this identity is a common origin."² Implicit in this concept is the requirement that the specific combinations of chromosomal genes coding for characters identifying clones are not rapidly broken down by recombination and mutation.³ The authors' demonstration that six of the seven DNA types found in German strains—accounting for 22 of the 23 strains studied—were also found in the United Kingdom indicates to us that for these markers the rates of change caused by recombination and mutation are slower than the rates of spread of these organisms through western Europe, thus leading to the occurrence of statistically overrepresented, widespread, identical genotypes, a coincidence of features which is a strong criterion of clonality.⁴ Our view is that rather than refuting the clonal concept for *Bordetella pertussis* the pulsed field gel electrophoresis data provide quite good evidence favouring the hypothesis that in genetic terms this organism has a relatively stable, and clonal, population structure.

The inability of simple electrophoresis of restriction fragments of whole DNA produced by *Eco*RI, *Sma*I, *Nci*I, *Bam*HI, *Ava*I and *Bgl*II to discriminate between strains suggests that they are very closely related. Whether these European strains are members of a single clone with pulsed field gel electropherotypes defining subclones, or whether these define clones in themselves, cannot be answered from the data to hand; information on the extent of linkage disequilibrium and further studies using other markers of genotype and phenotype would clarify this situation. It seems to us that the authors have answered the question posed by the title of their paper in the affirmative;

the really important question that remains—albeit one that they have begun to address—is whether whooping cough in Britain and Germany is caused by one, or several, clones of *B pertussis*.

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AUTHORS' REPLY.—T H Pennington and K J Forbes suggest that the 17 distinct DNA types generated by pulsed field gel electrophoresis identify "subclones" and that *Bordetella pertussis* is essentially stable and clonal. It is unclear as to how they make the distinction between clones and subclones. Phenotypically *B pertussis* is not particularly stable. It shows striking colonial variation on repeated subculture;¹ changes in agglutinin type occur both during infection and in response to vaccination;² and phase variation (loss of virulence factors) occurs at a frequency of one per 10³ or 10⁶ organisms.³

The types isolated by pulsed field gel electrophoresis that we describe were stable on repeated subculture and persisted after cross infection between siblings, yet they were clearly distinguishable in the four different pairs of siblings. In the light of these distinct, stable genetic differences it seems difficult to argue the case for clonality. Pennington and Forbes cite "the occurrence of statistically overrepresented, widespread, identical genotypes" as a strong criterion of clonality, yet we showed that the predominant genotype in the United Kingdom was not found among the 23 isolates examined from Germany.

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Physiotherapy intervention late after stroke

SIR,—In their paper on the effectiveness of physiotherapy on mobility late after stroke, Derick T Wade and colleagues went to great pains to develop a cross over study design which introduced blind assessment and controls.¹ This attention to design is not typical of research in stroke rehabilitation and the authors are to be congratulated. However, the results are ambiguous.

The study showed that mobility (as measured by time to walk 10 metres) decreased by about four seconds during the treatment phase but increased after treatment. This would be expected if the physiotherapy intervention was very active and required regular and specialised exercises. However, table II shows that much of the intervention was of an advisory and educational nature, including the provision of more appropriate aids. It is

therefore worrying to note a decline in mobility in the period immediately after treatment in both groups (6.5 seconds in the early treatment group and 2.6 seconds in the late treatment group). The fact that these increases are not statistically significant is due to the acknowledged low power of the study.

These results strongly suggest that the improvement during treatment might be a placebo effect due purely to the attention given by the physiotherapist rather than the direct result of the interventions mentioned. The fact that the possible placebo effect was confined to changes in gait speed is probably a reflection of the lack of sensitivity to change of the other outcome measures, as is acknowledged by the authors.

A cross over design in drug treatment trials is invariably associated with the use of either a placebo or an alternative treatment. In such trials the differences in outcome between the treatment period and non-treatment period can be more confidently attributed to the treatment. In this study, because patients received no treatment or placebo in the non-treatment period it is impossible to disentangle the treatment effects of physiotherapy from any placebo effects.

Physiotherapy consists of more than direct physical treatment, also having a significant psychological component. Therefore the authors must be careful when they attribute the positive outcome to the more physical aspects of the intervention, for it is possible that a similar outcome could have been achieved by using other personnel such as well motivated and supervised volunteers, as has been shown in speech therapy after stroke.²

Although we recognise that finding placebos for physical and counselling interventions is much more difficult than in pharmacological areas, it is important that attempts are made to develop ways of controlling for placebo effects in an area where attention and care are likely to have significant beneficial effects on patients' performance.

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- 1 Wade DT, Cullen FM, Robb GF, Warlow CP. Physiotherapy intervention late after stroke and mobility. *BMJ* 1992;304:609-13. (7 March.)
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AUTHOR'S REPLY.—Trevor A Sheldon and his colleagues should reread the first sentence of our abstract: "To determine whether the intervention of a physiotherapist improved mobility. . . ." Rehabilitation is a problem-solving, educational process aiming to minimise handicap. Its reiterative components include assessment, planning (goal setting), intervention, and evaluation (reassessment) and each of these can be further subdivided. Few components of this process can be so isolated that effects can be attributed to one specific item. We were very careful to state throughout that the trial investigated the effect of being seen by a physiotherapist.

Next, if attention alone had caused improvement in gait speed why was no change seen in manual dexterity or mood? Why should attention specifically and only improve gait speed?

One cannot assume that volunteers might be as effective without further trials. The volunteers in speech therapy trials were given the results of assessments and were supervised by trained therapists. The equivalent would be for the first "assessment" visits to be undertaken by a trained therapist, followed by visits by volunteers with trained therapists supervising. As the average number of visits was four, this seems uneconomic.

Volunteers (or families) might, however, have a role in maintaining benefit, and indeed the aim of all rehabilitation should be to involve families in longer term support. To this extent we failed, and further studies are needed to confirm our results and investigate ways of maintaining mobility.

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Lipoprotein(a) in cirrhosis

SIR,—The primary site of synthesis of lipoprotein(a) has not been clearly identified. Like J Feely and colleagues,¹ we have measured lipoprotein(a) concentrations using an enzyme linked immunosorbent assay (Immuno, Heidelberg). We studied 18 patients with severe cirrhosis as assessed by the Child Turcotte classification. Cirrhosis was due to chronic active hepatitis in 12 patients and to primary biliary cirrhosis in four; in two others it was associated with hepatocellular carcinoma.

In 14 of the 18 patients lipoprotein(a) concentrations were almost not detectable (mean 23 mg/l, range 0-60 mg/l), which supports the hypothesis that lipoprotein(a) is synthesised primarily by the liver. In contrast, the four other patients had high normal or raised concentrations of lipoprotein(a) (ranging from 150 to 360 mg/l). The cirrhosis in these four patients was due to chronic active hepatitis in two and to primary biliary cirrhosis in one and was associated with hepatocellular carcinoma in one.

Therefore, we support the hypothesis that lipoprotein(a) is synthesised primarily in the liver; non-hepatic tissue may, however, contribute to the concentration of lipoprotein(a) in the serum.

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Hospital admission and start of benzodiazepine use

SIR,—D Surendrakumar and colleagues present data from three general hospitals in which a total of 65 patients had been supplied benzodiazepines when discharged.¹ There is no indication as to what proportion of total discharges this represents and seven (11%) of the relevant records were not scrutinised and no reason was given for their omission. The mean age of patients scrutinised was 74 years, and 60% were male, an unusual population distribution about which no comment was made. Only 17 patients were found to have been first prescribed benzodiazepines during the index admission; five patients had been taking the drugs for up to two months, seven for up to a year, and 20 for over a year. That leaves only nine of the 58 unaccountable, although it had been said that for 12 of the cases details of when the drug had been started were not ascertained.

Discrepant or not, these are trivia. What is not trivial is to report finding evidence of dependence in eight out of 10 patients said to have taken the drugs for more than two years. What evidence is not stated, nor why attempts to stop the drug had been made in only five patients, nor what were the withdrawal symptoms which had occurred in only two patients. Such symptoms, the mainstay of a diagnosis of dependence, can be difficult to extricate both from symptoms for which the drugs were prescribed and from "pseudowithdrawal" symptoms.^{2,4} Nor is it trivial to accuse colleagues

both of unwarranted prescribing and prescribing without assessment of need: in effect, of negligence. The former is supported by minimal details of just three cases, the latter by no data at all.

It is true that some doctors have a righteous concern about the allegedly careless prescribing habits of other doctors, as referenced in the paper. It is also true that some doctors are equally concerned that prejudiced reporting has led to a situation where patients in need may be denied appropriate treatment.^{5,7} The promotion of medicines should reflect accurately and clearly an up to date evaluation of all the evidence. Might it not be appropriate for similar requirements to apply to publications in influential medical journals?

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AUTHOR'S REPLY,—K Woodcock's attitude towards medical audit is unacceptable. Making accusations of inconsistency in data without carefully reading the article is inappropriate. The data are correct and consistent. As is evident from the paper, in 12 cases it was not possible to ascertain whether the patient had started benzodiazepines in hospital or in the community. This number is not applicable to the question of when they started.

It is surprising that Woodcock does not appreciate the brevity of the presentation of results and discussion required for a short report. However, I can now fill in the details he requests. The reasons for not scrutinising some notes were simple administrative difficulties and refusal by one consultant to give permission. Dependence was implied by the presence of statements in the notes to the effect that the patient could not manage without the tablets. A clear statement of increased insomnia or anxiety in the period immediately following a dose reduction was considered to be a withdrawal effect. Although I can be positive that the benzodiazepine medication had been reduced in five cases because of concern, that this was not attempted in the others cannot be ruled out.

It is only through examination of its prescribing habits that the medical profession can move towards rationalisation in therapeutics. Benzodiazepines have done enough harm. The publication of studies whose conclusions encourage doctors to keep within nationally agreed policies can only result in good.

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Side of origin of ovarian cancer

SIR,—D J Cruickshank recently suggested that ovarian cancer arises more frequently on the right than on the left ovary.¹ This finding was discussed in terms of the incessant ovulation hypothesis, on the basis of the observation that ovulation occurs

more frequently on the right.² Along this line, a paper by C B Johannes and colleagues based on about 300 ovarian cancer cases has shown that 53% of cancers were right sided in origin (compared with 59% in Cruickshank's study).³

To offer further data on the issue we have reviewed the pathological diagnosis in 556 cases of ovarian cancer consecutively observed for first line treatment between 1980 and 1991 at two obstetric and gynaecology clinics of the University of Milan. Information on the side of origin of the tumour, histological type, stage of the disease, age, and menopausal status at surgery were retrieved from clinical records. Of the 556 cases, 235 were at stage I, 35 at stage II, 237 at stage III, and 24 at stage IV; in 25 cases the stage was not reported in the clinical records.

The side of origin of the tumour was determined in 333 (unilateral) cases. Of those, 172 (52%) were of right sided origin and 161 (48%) of left ($z=0.55$, $p>0.05$). The tumour was bilateral in 212 cases, and in 11 the data on the side of tumour were missing. The proportion of right and left sided unilateral tumours was largely similar in strata of menopausal status, stage, and histological type of the disease.

Our analysis was based on pathological data reported in the clinical records, and the hypothesis of the study was not known to the pathologists who performed the histological analysis or to the clinicians who recorded the data. We had no information on right and left dominance in bilateral tumours. This is of some concern, since both in Cruickshank's and in Johannes *et al*'s series the greater proportion of right sided cancers was mainly accounted for by right dominance in bilateral tumours. It should be pointed out, however, that the assumption with bilateral tumours that the side with the larger tumour is the side of origin is merely speculative.

In conclusion, our analysis gives little support to the hypothesis that ovarian cancer is more common in the right ovary.

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Medicine in Europe

SIR,—The interesting series of articles on medicine in Europe will have struck a chord in many of those involved in this scene. Many of Tessa Richards's misgivings of the current structures¹ are widely shared.

One of the weakest links is that between the European Union of Medical Specialists (UEMS) and its monospecialist committees, and one can legitimately question both the value and the need for this relationship. The UEMS is constituted on the basis of national representation—which is incompatible with its role as a representative specialist body. One can have either national or specialist representation, but not both.

The figure shows a simplistic view of a medical advisory structure for a country (with the "matching" British organisations shown in brackets) and