2 Norgaard-Pedersen B, Schultz HP, Arends J, *et al.* Tumour markers in testicular germ cell tumours. Five year experience from the DATECA study 1976-1980. *Acta Radiol [Oncol]* 1984;23:287-95.
3 Bagshawe KD, Lawler SD. Unmasking moles. *Br J Obstet Gynaecol* 1982;89:255-7.
4 Rustin GJS, Bagshawe KD, Newlands ESN, Begent RHJ, Dent J. Organisation of tumour marker follow up and prognostic implications in patients with germ cell tumours. In: Jones WG, Ward AM, Anderson CK, eds. *Germ cell tumours II*. Oxford: Pergamon Press (in press).
5 Lange PH, Millan JL, Stigbrand T, Vessella RL, Ruoslahti E, Fishman WH. Placental alkaline phosphatase as a tumor marker for seminoma. *Cancer Res* 1982;42:3244-7.
6 Tucker DF, Oliver RT, Travers P, Bodmer WF. Serum marker potential of placental alkaline phosphatase-like activity in testicular germ cell tumours evaluated by H17E2 monoclonal antibody assay. *Br J Cancer* 1985;51:631-9.
7 Lippert MC, Javadpour N. Lactic dehydrogenase in the monitoring and prognosis of testicular cancer. *Cancer* 1981;48:2272-8.
8 Bosl GJ, Geller NL, Cirrincione C, *et al.* Multivariate analysis of prognostic variables in patients with metastatic testicular cancer. *Cancer Res* 1983;43:3403-7.
9 Germa-Lluch JR, Begent RHJ, Bagshawe KD. Tumour marker levels and prognosis in malignant teratoma of the testis. *Br J Cancer* 1980;42:850-5.
10 Medical Research Council Working Party on Testicular Tumours. Prognostic factors in advanced non-seminomatous germ-cell testicular tumours: results of a multi-centre study. *Lancet* 1985;i:8-11.
11 Newlands ES, Begent RHJ, Rustin GJS, Parker D, Bagshawe KD. Further advances in the management of malignant teratomas of the testis and other sites. *Lancet* 1983;i:948-51.

Ampoules, infusions, and filters

Particulate contamination of intravenous fluids has been recognised for years.[1] It is mostly due to manufacturing and packaging debris—rubber, cotton, plastic, particles of drug, and glass. Improvements in the manufacturing processes have reduced the numbers of these particles but not eliminated them.[2-4] When drugs (including multivitamin preparations) or electrolyte solutions are added to an intravenous infusion there is a disproportionately large increase in particulate contamination.[4] Some at least of this is associated with the opening of ampoules, the breaking of container seals, and the insertion of syringes or needles during transfer of the additive to the infusion. The risks of these particles have not been well defined.

Particulate contamination plays a part in the development of phlebitis related to infusion, the most common complication of intravenous treatment. The many other factors include the site of infusion, the size of the vein, the composition of the solution being infused (especially its tonicity), the duration of the infusion, the nature of the cannula, and the rate of flow or injection of material through this.[5] The contribution of particulate matter may be reduced by "in line filters," with pore sizes varying between 0·2 and 0·5 μm. This type of filtration reduces the incidence of phlebitis during infusions of large volumes,[6-9] and similar reductions have occurred with in line filtration of antibiotic infusions.[7 10] Uncertainty remains about the relative importance of particles in the infusion fluid and those contributed by the additives. Dorris *et al* showed that filtrates of a solution of cephalothin sodium produced more inflammatory changes in the vein wall than did filtrates of a solution of dextrose.[11] This was consistent with observations by Allcutt *et al,* who found that a filter prolonged "phlebitis free survival" of the drip only in those patients who had antibiotics injected above the filter.[12] Persistence of the drip at five days was improved from about 17% to 58%. No such difference was noted, however, in a similar study by Falchuk *et al.*[9] They concluded that filtration reduced phlebitis from 58% to 25% after three days irrespective of the addition of antibiotics.

Even less is known about the systemic effects of infused particles. Garvan and Gunner described the formation of granulomas in rabbits' lungs after intravenous infusion, and they suggested that these might represent a long term foreign body reaction to particulate matter.[1] They described similar granulomas in human lungs removed at necropsy. Other reports of pulmonary lesions have appeared, and infused particles have also been linked with lesions of the kidney, spleen, liver, and brain.[13] The clinical importance of these lesions is unknown, and improvements in manufacturing processes since they were first identified may be sufficient to prevent similar complications occurring with modern intravenous treatment.

Turco and Davis first noted that glass fragments greater than 5 μm could be aspirated from opened ampoules of frusemide.[14] A paper by Shaw and Lyall published last year in the *BMJ* reopened the debate on the importance of this contamination from intravenous additives drawn up from glass ampoules.[15] These workers identified glass particles with diameters of over 20 μm—and some visible to the naked eye, which are probably over 75 μm diameter. Such particles might lodge in the pulmonary capillaries, which have an average size of 10-12 μm. Clearly further research is needed into the possible consequences of these particles being injected intravenously. Until such studies have been carried out what conclusions or recommendations may be made? Firstly, in line filtration will reduce the risks of contamination with micro-organisms and may prolong the phlebitis free survival of intravenous drips. It follows that filtration is a sensible precaution in any patient who needs a prolonged infusion and who is susceptible to infection either by virtue of systemic disease or as a result of cancer chemotherapy. Most patients of this type will be located in "high care" areas of the hospital, and most will be receiving regular intravenous treatment. Phlebitis may also, however, be prevented by regular resiting of the infusion, and this may be more appropriate in many patients.

The potential benefits of in line filters must be weighed against their possible disadvantages. They cost more, they restrict the flow of colloid solutions and lipid suspensions, and they add an extra potential site for disconnection. Some "final in line" filters are produced with injection ports below the filter itself. Use of these ports for injections drawn from glass ampoules may diminish any gains to be expected from filtering infusions. Some drugs may be retained in filters, notably insulin and vincristine sulphate.[16] The latest filter designs, however, do not greatly restrict flow of crystalloids and microvent air bubbles to prevent their infusion.

Another approach may be to look for alternatives to glass for drug packaging. Not only might these overcome any problems associated with the infusion of glass particles but they should also prevent the problems of injury to staff. Lacerations occurring during the opening of glass ampoules represent an important potential site of entry of bacteria and viruses.

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1 Garvan JM, Gunner BW. The harmful effects of particles in intravenous fluids. *Med J Aust* 1964;ii:1-6.
2 Davis NM, Turco S, Sivelly E. A study of particulate matter in IV infusion fluids. *Am J Hosp Pharm* 1970;27:822-6.

3 Davis NM, Turco S. A study of particulate matter in IV infusion fluids—phase 2. *Am J Hosp Pharm* 1971;28:620-3.
4 Turco S, Davis NM. Particulate matter in intravenous infusion fluids—phase 3. *Am J Hosp Pharm* 1973;30:611-3.
5 Lewis GBH, Hecker JF. Infusion thrombophlebitis. *Br J Anaesth* 1985;57:220-33.
6 DeLuca PP, Rapp RP, Bivins B, McKean HE, Griffen WO. Filtration and infusion phlebitis: a double-blind prospective clinical study. *Am J Hosp Pharm* 1975;32:1001-7.
7 Bivins BA, Rapp RP, DeLuca PP, McKean H, Griffen WO Jr. Final in-line filtration: a means of decreasing the incidence of infusion phlebitis. *Surgery* 1979;85:388-94.
8 Rusho WJ, Bain JW. Effects of filtration on complications of post-operative intravenous therapy. *Am J Hosp Pharm* 1979;36:1355-6.
9 Falchuk KH, Peterson L, McNeil BJ. Microparticulate-induced phlebitis: its prevention by in-line filtration. *N Engl J Med* 1985;312:78-82.
10 Maddox RR, Rush DR, Rapp RP, Foster TS, Mazella V, McKean HE. Double-blind study to investigate methods to prevent cephalothin-induced phlebitis. *Am J Hosp Pharm* 1977;34: 29-34.
11 Dorris GG, Bivins BA, Rapp RP, Weiss DL, DeLuca PP, Ravin MB. Inflammatory potential of foreign particulates in parenteral drugs. *Anesth Analg* 1977;56:422-8.
12 Allcutt DA, Lort D, McCollum CN. Final inline filtration for intravenous infusions: a prospective hospital study. *Br J Surg* 1983;70:111-3.
13 Turco S, Davis NM. Clinical significance of particulate matter: a review of the literature. *Hospital Pharmacy* 1973;8:137-40.
14 Turco S, Davis NM. Glass particles in intravenous injections. *N Engl J Med* 1972;287:1204-5.
15 Shaw NJ, Lyall EGH. Hazards of glass ampoules. *Br Med J* 1985;291:1390.
16 Butler LD, Munson JM, DeLuca PP. Effect of inline filtration on the potency of low-dose drugs. *Am J Hosp Pharm* 1980;37:935-41.

Drugs for poor sleepers?

Some people have always been poor sleepers, but nowadays there are more of them—because there are more elderly people. Patients have always wanted sleep inducing drugs, from Shakespeare's drowsy syrups to the benzodiazepines of today. If doctors accept recent criticisms of benzodiazepines are they justified in always withholding the drugs? I think not.

Patients who say that they have hardly slept a wink for a month or that they always take two hours to fall asleep are inaccurate. Monitoring with an electroencephalogram shows that such people are usually asleep within 20 minutes and sleep for six hours. Indeed, the impressive finding in the laboratory is the overlap in the amounts of sleep between those who complain and their matched controls. Yet, though the expert can say for how many minutes a patient slept, he can say almost nothing about the restorative intensity of the sleep. The patient maintains something is amiss; the expert cannot say he or she is wrong.

When matched groups are compared with the electroencephalograph people who complain of poor sleep do on average get half an hour less and do wake up more frequently than people who say that they sleep well. The poor sleepers are also hotter by night and by day,[1-3] which would imply a higher rate of catabolism—and the greater need for restoration; yet their sleep is somewhat shorter and more broken. Evidently they are not mere complainers: they know something that we cannot fully measure. Also we do not know why people who say they habitually have under six hours a night when followed up for nine years should have had a mortality rate 1·3 times higher than expected.[4 5]

The simple guides to better sleep are regularity in time of getting up in the morning, not smoking, minimising alcohol intake, taking regular exercise, forgiving your enemies, and deliberately planning happy thoughts at bedtime.[6 7] Irregular times of evening food should be avoided—these disturb sleep—while the milk and cereal drink Horlicks at bedtime really does bring benefit.[8] But none of these recipes rivals the potency of a modern hypnotic drug.[9]

What about alternative techniques? Biofeedback training sessions use the tension in the muscles to produce a rate of clicks that informs the listener that she is or is not relaxing. Poor sleepers average high scores for tension and anxiety. Can training in relaxation improve their sleep? Nicassio *et al* trained poor sleepers in progressive relaxation or gave biofeedback or bogus biofeedback (the rate of clicks varying without relation to muscle tension).[9] The genuine biofeedback and the progressive relaxation were no more effective than the bogus biofeedback. Hauri assessed 165 poor sleepers and thought that 54 might benefit from biofeedback.[10] Yet after an average of 25 hours of training neither subjectively nor in the laboratory was there an overall advantage compared with one hour of simple counselling.

The subjective and laboratory evidence that modern hypnotics improve sleep is extensive. Statements that benzodiazepines do not long remain effective may be refuted[11 12]: tolerance certainly occurs, but it is only partial. The trouble is that with regular dosage the brain adapts its machinery to provide the partial tolerance. If the drug is then abruptly stopped a rebound occurs because of the changes in the brain, so sleep is temporarily worse than it would have been had the drug never been taken.[11] Once these facts are understood the drugs can be used accordingly.

A recent leading article in the *BMJ* asserted that benzodiazepines should not be prescribed at times of bereavement or divorce,[13] but I think that it would be inhumane to pursue such a policy rigorously in the face of distress. Certainly patients should be told that hypnotics should be taken only in small dosages during short periods and preferably not every night. Time sorts out human troubles, the dosage may then be cut, and the drug stopped, rebound sleep troubles being balanced out by the amelioration of stress.

Many people keep a few sleeping pills at home for the odd occasion when experience suggests that the day's events will cause a troubled night. Today's hypnotics are safe and are as much modern facilities as telephones or videos. In Britain an effective hypnotic may now be purchased over the counter as Sominex (promethazine), and sufficient for several nights. I do not see why short acting benzodiazepine hypnotics should not be similarly available in Britain—where any adult is free to buy a bottle of vodka. Doctors need not always be intermediaries. If asked to prescribe they can take the opportunity to educate.

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1 Monroe LJ. Psychological and physiological differences between good and poor sleepers. *J Abnorm Psychol* 1967;72:255-64.
2 Mendelson WB, Garnett D, Gillin JC, Weingartner H. The experience of insomnia and daytime and nighttime functioning. *Psychiatry Res* 1984;12:235-50.
3 Adam K. Are poor sleepers changed into good sleepers by hypnotic drugs? In: Hindmarch I, Ott H, Roth T, eds. *Sleep, benzodiazepines and performance*. Berlin: Springer-Verlag, 1984.
4 Kripke DF, Simons RN, Garfinkel L, Hammond EC. Short and long sleep and sleeping pills: is increased mortality associated? *Arch Gen Psychiatry* 1979;36:103-16.
5 Wingard DL, Berkman LF. Mortality risk associated with sleeping patterns among adults. *Sleep* 1983;6:102-7.
6 Schwartz AK, Aaron NS. *Somnniquest: the five types of sleeplessness and how to overcome them*. London: Wildwood House, 1980.
7 Oswald I, Adam K. *Get a better night's sleep*. London: Martin Dunitz, 1983.
8 Adam K. Dietary habits and sleep after bedtime food drinks. *Sleep* 1980;3:47-58.
9 Nicassio PM, Boylan MB, McCabe TG. Progressive relaxation, EMG feedback and biofeedback placebo in the treatment of sleep-onset insomnia. *Br J Med Psychol* 1982;55:159-66.
10 Hauri P. Treating psychophysiologic insomnia with biofeedback. *Arch Gen Psychiatry* 1981; 38:752-8.
11 Adam K, Adamson L, Brezinova V, Hunter WM, Oswald I. Nitrazepam: lastingly effective but trouble on withdrawal. *Br Med J* 1976;i:1558-60.
12 Oswald I, French C, Adam K, Gilham J. Benzodiazepine hypnotics remain effective for 24 weeks. *Br Med J* 1982;284:860-3.
13 Higgit AC, Lader MH, Fonagy P. Clinical management of benzodiazepine dependence. *Br Med J* 1985;291:688-90.