difference of 2·0 cm between social classes I and V. The age standardised difference between manual and non-manual groups was 0·9 cm. Differences between manual and non-manual groups showed a tendency to increase with age, from 0·64 cm in 5 year olds to 1·96 cm in 7 year olds, although the effect did not reach conventional levels of statistical significance (p=0·09).

An analysis of height differences in the national child development study cohort (born in 1958) at age 7 showed a mean difference of 3·3 cm between social classes I and II and social class V.[3] A study of 5-11 year-olds born in 1960-7 suggested a median difference of 2 cm between manual and non-manual groups.[4] Although the differences appear smaller in our study, comparisons require cautious interpretation because of differences in population selection and because of the suggestion in our data that social class differences in height increase with age. What the results show clearly is that important inequalities in height are still present in the first decade of life in Great Britain.

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3 Goldstein H. Factors influencing the height of seven year old children—results from the national child development study. *Human Biology* 1971;**43**:92-111.
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Depression resistant to tricyclic antidepressants

As Dr P J Cowen (13 August, p 435) points out, adding lithium to tricyclic antidepressants may produce remission in patients who have failed to respond to an adequate trial of tricyclics alone. Usually this observation is interpreted as being due to some sort of "lithium augmentation" of the tricyclic, though what exactly this means is rarely explained. As Dr Cowen admits, the alternative hypothesis, which is somewhat more economical, is that lithium itself has an acute antidepressant effect. Although there is some evidence against this view,[1] other studies are strongly in favour.[2-4] Although lithium has proved efficacy as an acute treatment for mania and in the prophylaxis of recurrent bipolar illness, there has been considerable resistance to the idea that it may also have potential as an acute antidepressant treatment. This is despite experimental evidence that release of 5-hydroxytryptamine in the hippocampus is increased by lithium,[5,6] perhaps through increased transport of L-tryptophan into that brain region, and that lithium facilitates the postsynaptic function of 5-hydroxytryptamine in the brain.[7] Clearly, the potential of lithium as an acute antidepressant needs to be reappraised. The treatment of resistant depression is usually pragmatic but often rather muddled, and more logical approaches are clearly indicated; before being given lithium in combination with a tricyclic patients, especially those with bipolar depression, should be given a trial of lithium alone.

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A milestone for myocardial infarction

The leading article by Dr Desmond G Julian and others (20-27 August, p 497) showed yet again how aspirin is an effective component of the treatment regimen of patients with ischaemic heart disease. Dr Chamberlain and others discussed the contraindications to treatment with thrombolytic agents and aspirin, but one problem that is often overlooked by the prescribing physician is the size of aspirin's effect on haemostasis after surgery. Cardiac surgeons have been all too aware of this since aspirin became fashionable treatment for patients with coronary artery disease.

A recent prospective study of 209 patients having coronary surgery at this hospital has highlighted this problem. Postoperative bleeding was significantly greater in patients who had been taking low doses of aspirin (75-300 mg a day) up to five days before surgery (mean blood loss 1440 ml) compared with that in those who had not taken aspirin during this time (mean blood loss 939 ml; p=0·0001, Mann-Whitney test). This has also had an impact on the need for blood component replacement in such patients, and it belies the extra operating time needed to achieve haemostasis.

So, although the benefits of aspirin to patients with coronary artery disease—especially in unstable angina or during the postinfarction period—cannot be denied, it does cause major problems with haemostasis in those submitted to surgery. We would thus ask physicians to consider not using aspirin in patients who are likely to require urgent surgery and to withdraw it at least five days before elective operations.

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Disciplining midwives

Mr James Owen Drife's editorial (1 October, p 806) on the disciplinary arrangements for midwives will draw strong criticism from their professional bodies, and for some reasons should certainly do so. As a former medical member of the England and Wales Central Midwives Board, and also of the United Kingdom Central Council, with some experience of their disciplinary roles, I would refute his suggestion that the disciplinary process covering doctors, as exercised by the General Medical Council, should be more closely followed for nurses because it has advantages.

Doctors (apart from those in training) function as individuals in their clinical practice and not as part of a professional hierarchy; their accountability is significantly different from that of the registered midwife, whose practice is not only governed by rules relating to her clinical responsibilities but is also subject to supervision by a system that is kept distinct from her duty to her manager. This much closer oversight of the midwife's practice is matched with a simpler and more precise disciplinary process. Doctors may offer defence of their actions on grounds that there is a lack of clinical guidelines; for nurses and midwives their rules are more tightly drawn, and in general I imagine that the public at large sees benefit in this as their purpose is to serve its safety.

Whether the findings in a particular case are just or not may be debated, though the strength of their side as publicly urged by partisans on behalf of defendants seem often to show a bias these days for individuals against institutions, and this may be very noticeable to others directly concerned with the disciplinary proceedings. Nevertheless, Mr Drife makes a strong point that the judging of professionals may be aided by those outside their narrow discipline. I would not agree with him that this purpose could best be served simply by including lay people in membership of disciplinary panels. In my view the impartiality of the professional tribunal (which normally draws on advice from its own legal sources) could be enhanced by inclusion of an experienced magistrate capable of seeing justice in the wider context of contemporary non-professional attitudes. As midwives have indicated through their representatives that they do not wish the assistance of doctors in judging their competence or the breach of their practice rules I think that it is impertinent to urge this upon them.

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Drug Tariff increases

I had noticed that over the past year or so I was getting a monthly copy of the *Drug Tariff*, which recently has taken the form of a book, the yearly subscription being £30.

As it is a publication I rarely refer to I wrote to the appropriate minister saying that one or two copies a year would be quite adequate for my needs and for those of my colleagues I had spoken to. In reply his representative stated that general medical practitioners received a monthly copy after negotiations with our representatives.

I find it very wasteful to throw away a book of some 380 pages every month and wonder if colleagues feel the same. Perhaps the nation's money could be better spent.

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Computer viruses

Dr Patrick J R Harkin (10 September, p 688) doubts the hypothesis described by one of us (JC) (13 August, p 488) that computer viruses may evolve (and may already have evolved) by random substitution and cumulative selection from pre-existing pieces of software.

Firstly, the hypothesis is not that a computer virus could spring into being from nowhere by random chance alone, as Dr Harkin assumes, but that it could evolve from a pre-existing piece of software in its host computer in the same way that human viruses probably evolved from a host organism's DNA. Our study of viruses in the computers that use the CP/M operating system has led us to believe that a specific two byte point mutation occurring in memory at the right place at the right time might be enough to start a spontaneous virus on its way.

Secondly, within some long established computer networks, in which evolution has had plenty of time to occur, the phenomenon of "ghosts" is well known. Ghosts are fragments of old, deleted programs that have accidentally attached themselves to other programs and occasionally become activated by accident. Ghosts and viruses differ only in their kinetics of transmission.

Thirdly, Dr Harkin estimates that, in the current industry standard microcomputers—for example, IBM personal computers—that use the MS-DOS operating system, the minimum size for a computer virus is 97 bytes. Following his example, one of us created a virus this morning. From the initial idea it took only 20 minutes of work and the virus was up and running and infectious, capable of spreading spontaneously from disk to disk. Its minimal size for infectious behaviour was only 32 bytes; to ensure minimal pathogenesis and therefore probably long term survival a more sophisticated version of about 64 bytes was necessary.

Finally, may we point out that Dr Harkin himself is the result of an extremely unlikely event. The odds against his creation by the normal random reshuffling of his parents' chromosomes are one in 2^{46}—that is, one in 70 368 744 177 664. Yet that, we presume, is exactly what happened.

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Points

Complications of central venous cannulation

Dr R A F LINTON (Department of Anaesthetics, St Thomas's Hospital, London SE1 7EH) writes: Drs C G Kaye and D R Smith (3 September, p 572) state that most central venous catheters are inserted into the subclavian vein. Why do we expose patients to such unnecessary risks? When inserting a catheter into the subclavian vein (by infraclavicular or supraclavicular approach) there is a chance of puncturing the subclavian artery or lung however careful and experienced you may be. Countless patients have suffered these avoidable complications, which may be lethal. Puncture of the internal jugular vein carries no risk of haemothorax or pneumothorax in competent hands.

Dr KEITH JUDKINS (McIndoe Burn Centre, Queen Victoria Hospital, East Grinstead, Sussex RH19 3DZ) writes: I found the editorial by Drs C G Kaye and D R Smith (3 September, p 572) a useful, succinct summary of the complications of central venous cannulation. I have to say, however, that their recommendation of two dimensional echocardiography for all patients in whom sepsis occurs is a little daunting. In patients who have been burnt the procedure would have to be carried out frequently as sepsis is almost a universal problem in such patients. I would suggest that in burns and perhaps other forms of trauma it is more sensible to recommend echocardiography when sepsis is accompanied by signs indicating myocardial complications.

Professor A P HEMINGWAY (Academic Department of Radiology, Royal Hallamshire Hospital, Sheffield S10 2JF) writes: The editorial by Drs C G Kaye and D R Smith (3 September, p 572) was a timely reminder that the invaluable techniques of central venous catheterisation may be accompanied by a horrific list of major and minor complications. One important and potentially lethal complication that the authors did not discuss is fracture of the long line with subsequent retention of an intravascular foreign body. Such intravascular foreign bodies cause a wide range of complications ranging from arrhythmias to myocardial perforation, endocarditis, pulmonary embolism, and death. Recognition that this complication has occurred and prompt referral to an experienced vascular interventional radiologist will invariably result in successful percutaneous retrieval.[1,2]

1 Mehta AB, Goldman JN, Hemingway AP, Allison DJ. Percutaneous retrieval of catheter fragments from the heart and great vessels: five cases. *Br Med J* 1983;286:937.
2 Kadir S, Athanasoulis CA. Percutaneous retrieval of intervascular foreign bodies. In: Athanasoulis CA, Pfister RC, Greene RE, Roberson GH, eds. *Interventional radiology*. Philadelphia: Saunders, 1982:379-90.

Predictive value of a positive result

Dr ROBERT CARLEN (Sayville, NY 11782-2501, United States) writes: Errors in interpreting diagnostic tests have crept into the *BMJ* of 3 September. On p 617 Dr D Simmons discusses urine analysis and capillary blood sampling to detect diabetes mellitus. He writes, "90% of diabetic patients had no glycosuria on random urine sampling and would have been missed by this screening procedure. Furthermore, two thirds of those with glycosuria who undergo an oral glucose tolerance test are not diabetic. Hence urine sampling is neither sensitive nor specific." Dr Simmons properly indicates that the sensitivity of random urine sampling is 10% but he confuses specificity with the predictive value of a positive result, here 33%. Predictive value depends on both the characteristics of the test itself (sensitivity and specificity) and on the prevalence of the particular disease in the population being tested.[1] The test's predictive value is the posterior probability of disease—the chance that a member of that particular population who has a positive test will actually have the disease. The posterior probability must be substantially higher than the prior probability for the test to be worth doing in that group of people. He goes on to make a similar error in his last sentence, confusing predictive value with both sensitivity and specificity. On p 619 Dr Peter Davies writes, "Ultrasound examination is not good at detecting dilatation of the pelvicaliceal system because it is subject to false negative and false positive results." In considering the ability of a test to detect disease (its sensitivity) false negatives are all that matter. False positives refer to its specificity, which, by definition has nothing to do with detection.

1 Carlen R. AIDS antibody testing and counselling. *Br Med J* 1986;292:699.

Bovine spongiform encephalopathy

Mr A J LAWRENCE (Ministry of Agriculture, Fisheries, and Foods, Surbiton, Surrey KT6 7NF) writes: Dr J C M Sharp (3 September, p 626) refers to the government's announcement (on 7 July) that it had accepted the recommendation of Sir Richard Southwood's expert working party that as a precautionary measure carcases of affected cattle should be destroyed. Dr Sharp then states "it is therefore somewhat surprising that to date (1 August) no action has yet been taken and that affected cows are still being slaughtered and are entering the human food chain." The Ministry of Agriculture, Fisheries, and Food did in fact announce on 28 July that a compulsory slaughter with compensation policy and the subsequent disposal of carcases would be introduced on 8 August, four weeks before the publication of Dr Sharp's point in the *BMJ*. I write simply to dispel any mistaken impression that nothing had been done by 3 September and to indicate, too, that in the month from the initial announcement to the introduction of the slaughter policy there was considerable action, including the drawing up of the necessary legislation and administrative arrangements.

Prenatal diagnosis of common genetic disorders

Dr ANN HARRIS (Paediatric Research Unit, Division of Medical and Molecular Genetics, United Medical and Dental Schools of Guy's and St Thomas's Hospitals, Guy's Tower, London SE1 9RT) writes: As the subject of human molecular genetics is moving so fast it is disappointing to see review articles in the *BMJ* that are more than a year out of date, particularly as it is one of the main avenues through which the potential clinical power of the new genetics can be conveyed to the medical profession at large. I refer specifically to the review by Dr M d'A Crawfurd (20-27 August, p 502) and the section on cystic fibrosis. Dr d'A Crawfurd quotes rates of false negative results of 2% and of false positive results of 6% for prenatal diagnosis of cystic fibrosis after DNA tests. In most laboratories screening for cystic fibrosis, however, most families have been counselled on error risks of less than 1% for the past year since the new probes pXV2C and KM19,[1,2] which are extremely close to the cystic fibrosis gene, became available for use. For example, of the 61 families who have been fully typed in our unit, 55 families can be counselled at error risks of about or much less than 1%. Many of these, referred for screening before October 1987, were previously counselled at risks of 1·4-5·6%, but all these families have been retyped with the new probes to lower their risk values. Of the remaining six families, one still has an error risk of about 5% and the five others are only partially informative for all the polymorphic probes we have that are linked to the cystic fibrosis gene—that is, one parent is homozygous for all probes tested. To summarise, in families in whom prenatal diagnosis of cystic fibrosis is possible with existing probes error risks of 1% are the order of the day.

1 Estivill X, Farrall M, Scambler PJ, *et al.* A candidate for the cystic fibrosis locus isolated by selection for methylation-free islands. *Nature* 1987;326:840-5.
2 Estivill X, *et al. Genomics* 1987;1:257-63.

AUTHOR'S REPLY,—Dr Ann Harris's comments on the recent advances in prenatal diagnosis of cystic fibrosis that were not incorporated in my review are entirely valid. The probes pXV2C and KM19 to which she refers had not been used for prenatal diagnosis at the time the review was written, some time before it was published. The way in which these probes were quickly used both for prenatal diagnosis and, utilising the fact that they are in linkage disequilibrium with the cystic fibrosis gene, for carrier detection provides an excellent illustration of the rapidity of current advances in both research in and the clinical application of DNA analysis of human disease. Another area that has been overtaken by events is tuberous sclerosis, in which more recent studies have shown that the frequency of recombination between the currently available linked DNA polymorphisms and the tuberous sclerosis gene is too high to provide reliable prenatal diagnosis. Such advances were anticipated in the review in the advice given to check with a genetic centre before taking decisions in individual cases.

Ectopic pregnancy

Dr ADEL A A ISMAIL and Mr PAUL L WALKER (Department of Clinical Biochemistry, Pinderfields General Hospital, Wakefield, West Yorkshire WF1 4DG) write: Professor John Newton (10 September, p 633) suggested that to be useful in detecting ectopic pregnancy a hormone assay should be rapid, sensitive, and widely available. Measuring serum concentrations of human chorionic gonadotrophin by immunoassay was proposed, although this assay is not widely available, so it would require additional resources. We suggest that instead of introducing a new assay laboratories in district general hospitals wishing to detect ectopic pregnancy could employ a method of detecting luteinising hormone that has high cross reactivity with human chorionic gonadotrophin. Assays of serum luteinising hormone concentration are widely available using many methods; results are available within hours. Some methods show high cross reactivity with human chorionic gonadotrophin (up to 96%) whereas some are almost totally specific for luteinising hormone (J Seth, personal communication). Luteinising hormone concentration is required in various clinical conditions, and in many of them an indication of raised human chorionic gonadotrophin values would be useful—for example, in undiagnosed pregnancy in the investigation of amenorrhoea and in detecting tumours producing human chorionic gonadotrophin in precocious puberty as well as ectopic pregnancy. A method measuring luteinising hormone concentration that has high cross reactivity provides this information at no extra cost; interpreting the results is simple and straightforward as in these patients the concentrations of luteinising hormone would be extremely high (but not the concentrations of follicle stimulating hormone if measured), strongly suggesting a source producing human chorionic gonadotrophin. From our experience of a method measuring luteinising hormone values with 30% cross reactivity with human chorionic gonadotrophin we believe that a specific method detecting luteinising hormone has little or no practical advantages as the first line investigation of luteinising hormone values. We think that the cost and effort would not justify introducing human chorionic gonadotrophin assays as an additional test to a laboratory in a district general hospital for detecting ectopic pregnancy.