The suggestion that the "requirement for profound anaesthesia will decline" certainly does not apply to laparoscopic surgery—indeed, for laparoscopic herniorraphy the opposite is true. Sedoanalgesia is not, in any case, inherently better, safer, or preferred by patients, nor would its widespread application allow operator-sedationists to free themselves from the shackles of their former anaesthetists.

The most disturbing vignette of the future is, however, plausible unlike the foregoing. This is of a large team of people who pass the patient among each other. The "director" has a brief interview and passes the patient on. The tedious task of preoperative and postoperative care is given to the otherwise redundant anaesthetist. The operators in both open and minimal access surgery, freed from the tedium of actually seeing, diagnosing, and caring for patients, practise their skills in the theatre. The patients are no longer cared for by one practitioner who (in theory at least) looks after them as a whole person. The new process might be efficient but would be bad for patients.

Named nurses now look after each patient. Allocation of tasks has ended; personal care is here. Medicine neither wants nor needs to step away from personal care, it needs to step towards it. Patients need named doctors as well as named nurses.

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Laparoscopic nephrectomy unproved in controlled clinical trials

EDITOR,—An italic paragraph accompanying the series of articles on minimally invasive surgery states that the "articles have been written to inform non-specialists of developments in this rapidly moving subject." Two of the authors of the article on laparoscopic nephrectomy,[1] Ralph V Clayman and Louis R Kavoussi, are known by urologists to be innovators, and without such people urology would not advance. Certain points should, however, be made.

The summary of the article says that "laparoscopic nephrectomy for benign disease has become widely accepted."[1] This is not so, and the authors' figures show this: the fact that only 30 laparoscopic procedures have been performed in St Louis and "more than 100 worldwide" shows that almost all nephrectomies for benign disease are open operations.

It is appropriate that the authors comment on the learning curve for laparoscopic nephrectomy, but to imply that three major complications in the first 12 patients and then one in the second 12 represents an improvement due to experience is incorrect. There is no significant difference between these complication rates ($\chi^2=1{\cdot}2$, $P=0{\cdot}27$). A rate of major complications of 16% in the first 24 patients in the hands of presumably outstandingly good operators suggests that for most urologists the complication rate for their first 24 patients will be even higher; this may make many urologists sceptical about using the technique. It also suggests that a period of formal training should be required for urologists of any grade who wish to use this technique to avoid subjecting excessive numbers of patients to the same learning curve.

The authors' final paragraph contains entirely reasonable comments. The authors should, however, follow their own advice, with "careful critical comparison of each newly developed procedure with its counterpart in open surgery." It is intuitively obvious that an uncomplicated laparoscopic nephrectomy will result in a shorter and less painful convalescence than an open operation. Whether the complications of the two forms of surgery favour laparoscopy remains to be seen. This can be answered satisfactorily only by controlled clinical trials and not by comparison with contemporary series of patients, as the authors have attempted.

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Renal failure after topical use of NSAIDs

EDITOR,—We wish to amplify the case reports of C A O'Callaghan and colleagues[1] by reporting on a patient who developed acute renal failure twice: once after taking ibuprofen orally and once after topical administration of the drug.

A 76 year old man was admitted with acute anuric renal failure five days after taking four tablets of ibuprofen for a muscle strain. In the 48 hours before admission he had vomited repeatedly, and at presentation he was clinically dehydrated. The platelet count on admission was 35×10^9/l, and a blood film showed microangiopathic haemolytic anaemia without eosinophilia. Renal biopsy showed evidence of acute interstitial nephritis and acute tubular necrosis. After four days of haemodialysis his renal function recovered and the serum creatinine concentration fell to 128 μmol/l.

Three years later the patient applied topical ibuprofen once to his shoulders because of muscle aches after he had cut a hedge. Thirty six hours later he was admitted with acute anuric renal failure. The platelet count fell transiently to 72×10^9/l, and a blood film showed microangiopathic haemolysis with no eosinophilia. Methylprednisolone (0·5 g) was given intravenously on admission. After 13 days, during which haemodialysis was required, the patient's renal function recovered, and nine months after discharge his serum creatinine concentration was 571 μmol/l.

Unlike O'Callaghan and colleagues, we observed only limited renal recovery after a single topical application of a non-steroidal anti-inflammatory drug. Severe idiosyncratic renal syndromes are recognised after administration of non-steroidal anti-inflammatory drugs, and mechanisms other than interference with vasodilatation mediated by prostaglandin have been implicated.[2] In this case sensitivity to oral ibuprofen had been shown previously. Haemolysis and thrombocytopenia, which were prominent features after each exposure to ibuprofen, have been reported after oral administration of non-steroidal anti-inflammatory drugs.[3,4]

Abrupt renal impairment may occur after modest exposure to oral or topical non-steroidal anti-inflammatory drugs, and patients with a history of this should be warned to avoid these drugs irrespective of the route of administration or dose.

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Long term use of sumatriptan

EDITOR,—M J Osborne and colleagues report on a patient who developed a pattern of daily headaches and used excessive daily doses of sumatriptan.[1] They suggest that the long term use of sumatriptan could have led to a dependent state. The patient had a 50 year history of incapacitating migraine attacks refractory to other treatments, but his attacks were rapidly and effectively treated with sumatriptan.

People who suffer from migraine report changes in the frequency and nature of attacks over time and also experience other types of headache. The authors note that this patient experienced mild headaches every morning and that these frequently progressed to migraine. The patient took sumatriptan daily in anticipation of these attacks, in clear contrast to the recommendation on the datasheet. This does not suggest dependence on the effects of sumatriptan.

Data have been published on long term experience with sumatriptan.[2] In three studies lasting up to one year the tolerability profile of sumatriptan (the incidence and nature of reported adverse events) was similar to that reported in short term studies. There was no evidence of an escalation of the dose, irrespective of the number of attacks of migraine treated. Two of these studies (one of subcutaneous and one of oral treatment) were extended up to two years. There was no evidence of an increased frequency of migraine over the two years (table). Additionally, no evidence of dependence has been noted from spontaneous postmarketing reports.

Median number of attacks of migraine per patient in months 1, 2, 23, and 24 of two year studies of use of subcutaneous or oral sumatriptan

	Subcutaneous	Oral
Months 1, 2	6	7
Months 23, 24	5	7

Sumatriptan is indicated only for intermittent short term treatment of migraine. When it is used appropriately there is no evidence of dependence developing during long term treatment. Sumatriptan should not be used daily as prophylaxis against migraine.

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Mesalazine toxicity

EDITOR,—The case reported by A G Lim and K R Hine, in which a patient developed a reaction to mesalazine,[1] prompts me to describe a case.

A 30 year old woman presented with a five week history of bilateral pleuritic chest pain. She had increasing shortness of breath (though no wheezing), a non-productive cough, and intermittent fevers and had lost 7 kg in weight. She had a 14 year history of ulcerative colitis, which had remained

quiescent for 18 months. Her drug treatment consisted of oral mesalazine 800 mg twice daily, which she had been taking for the past eight months. She had previously taken sulphasalazine for several years but had stopped this after developing arthralgia.

On examination there was decreased air entry at both lung bases and no other abnormality. Investigations showed a white cell count of $11{\cdot}3 \times 10^9$/l with 16% eosinophils and a high plasma viscosity; she was negative for rheumatoid factor, weakly positive for antinuclear factor, and strongly positive for antibody to neutrophil cytoplasm (titre 1/400). The pattern of staining of the antibody to neutrophil cytoplasm was cytoplasmic, and the neutrophils were negative for antibodies to myeloperoxidase, lactoferrin, and cathepsin G. Initial urine testing showed microscopic haematuria, an isotope lung scan did not show any abnormality, and an electrocardiogram was normal. She was unable to perform lung function tests because of coughing. A chest *x* ray film showed bilateral lung infiltrates, especially at the apexes, and bilateral small pleural effusions.

In view of the picture of pulmonary eosinophilia, haematuria, and strongly positive titre of antibodies to neutrophil cytoplasm a thoracoscopic lung biopsy specimen was taken from the right upper lobe. It showed no evidence of Wegener's granulomatosis or pneumonia due to bronchiolitis obliterans: appearances were those of a chronic eosinophilic pneumonia. Mesalazine was stopped, and the patient refused steroid treatment. Her condition improved over the next few weeks, and the abnormalities in the chest *x* ray film and blood eosinophilia resolved. The titre of antibody to neutrophil cytoplasm was still 1/400 three weeks after she stopped taking mesalazine but had fallen to 1/25 a few months later.

This patient's illness was probably caused by mesalazine. Pulmonary side effects from this drug are rare and may occur soon after the drug is started, as in the case described by Lim and Hine, or after many months of exposure,[2] as in this case. One report mentions a strongly positive titre of antinuclear anbitody, which fell after mesalazine was stopped.[3] Ulcerative colitis may cause a positive result in a test for antibodies to neutrophil cytoplasm, but the staining is usually perinuclear.[4] The high titre of antibody to neutrophil cytoplasm with a cytoplasmic staining pattern, which fell when mesalazine was stopped, raises the possibility of a link with the drug.

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Safety of tamoxifen

EDITOR,—V Craig Jordan reports some of the preclinical toxicological findings on tamoxifen in his editorial.[1] Though he states that tamoxifen "promotes hepatic tumours in rats," he fails to note that tamoxifen is a strong liver carcinogen by itself in rats, producing tumours within six months and a high incidence by one year at doses that yield blood concentrations comparable to those in treated women.[2] In addition to causing the formation of DNA adducts in the liver of rats, which Jordan mentions, tamoxifen causes the formation of DNA adducts in the liver of hamsters and mice. This feature is characteristic of human carcinogens. In fact, tamoxifen is associated with increases in cancers of the endometrium[3,4] and possibly liver[3] in treated patients.

In answer to the question "Is tamoxifen safe?" Jordan compares the risk of tamoxifen with that of use of oral contraceptives on the basis of his conclusion that it is the oestrogenic properties of tamoxifen that result in the assumed, but not proved, ability of tamoxifen to promote hepatic tumours in rats. This conclusion fails to take into account other aspects of the toxicology of tamoxifen, as noted above, which are different from the effects of oestrogens. The weakness of the comparison with oestrogens is further illustrated by the fact that toremifene, which is related to tamoxifen and has comparable oestrogenic properties in liver, is not hepatocarcinogenic.[2]

It is important to ascertain whether breast cancer can be prevented without the potential risks of tamoxifen being imposed. Considerable evidence supports the view that breast cancer can be substantially prevented by reduction of dietary consumption of fat,[5] which entails no risk and affords other benefits. If chemical intervention is deemed necessary the antioestrogen toremifene could be used.

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Genetic susceptibility to non-insulin dependent diabetes

EDITOR,—Eva Tuomilehto-Wolf and coworkers have presented the interesting hypothesis that genetic susceptibility to non-insulin dependent diabetes mellitus is located in the HLA region. Their conclusions are based on findings in 157 elderly Finnish men (age 70-89), in whom HLA haplotypes associated with insulin dependent diabetes could explain 98% of non-insulin dependent diabetes and 79% of impaired glucose tolerance. This association depended strongly on the presence of HLA-DR4, which was observed in 57% (56/98) of patients with non-insulin dependent diabetes but only 13% (3/23) of controls ($P = 0{\cdot}003$). The frequency of HLA-DR4 in the patients with non-insulin dependent diabetes is in the same range as that previously reported from Finland[2] and the United States[5] (table). The frequency in the control population is considerably lower than that previously reported, but this is most probably due to the small number of control subjects studied.

Prevalence of HLA-DR4 in patients with non-insulin dependent diabetes. Figures are numbers (percentages) of patients

Study	Controls	Non-insulin dependent diabetes	P value
Groop *et al*[2]	86/322(28)	51/121(51)	0·02
Rich *et al*[5]	62/221(27)	36/86 (42)	0·02
Tuomilehto-Wolf *et al*[1]	3/23 (13)	56/98 (57)	0·03

If patients with non-insulin dependent diabetes are divided into insulin requiring and non-insulin requiring on the basis of a glucagon stimulated C peptide concentration $< 0{\cdot}6$ nmol/l, however, only the insulin requiring patients show an increased frequency of HLA-DR4 (54% (37/69) compared with 32% (41/127) in patients whose condition was controlled with oral antidiabetic agents).[4] Patients with DR4 had lower C peptide concentrations than patients with other HLA-DR antigens.[2]

Since high insulin and C peptide concentrations are associated with an increased risk of cardiovascular disease we propose that these patients represented a subgroup of patients with non-insulin dependent diabetes protected against cardiovascular disease. Therefore, the increase in frequency of HLA-DR4 is due to an admixture of patients with genes conferring susceptibility to insulin dependent diabetes rather than a general feature of patients with non-insulin dependent diabetes. In the search for genes for non-insulin dependent diabetes correct definition of the phenotype is critical, since the disease is likely to be heterogenous.

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Breast feeding and diabetes mellitus

EDITOR,—K G M M Alberti briefly mentions that "breast feeding has been shown to protect against the development of insulin dependent diabetes mellitus."[1] Two papers have strongly suggested that infants born into families with a family history of diabetes have a lesser chance of developing insulin dependent diabetes if they are breast fed up to the age of 9-12 months.[2,3] This breast feeding must be exclusive of top up formula milk feeds as these initiate the autoimmune process that may result in insulin dependent diabetes in later life. This message seems not to be getting across to diabetic people in the community. Doctors, health visitors, and midwives must try to make breast feeding the norm in diabetic families.

Alberti mentions a possible link between consumption of bovine serum albumin and the development of insulin dependent diabetes. Karjalainen *et al* found raised antibodies to bovine serum albumin in most newly diagnosed insulin dependent diabetic patients.[4] More importantly, Dahl-Jørgensen *et al* showed a close correlation between the amounts of cows' milk consumed per head of the population in various countries and the incidence of insulin dependent diabetes.[5] This leaves little doubt that consumption of cows' milk is a trigger for diabetes mellitus. Bovine serum albumin is 97% denatured by ultraheat treatment of milk. We are assessing data to see whether ultraheat treated milk is less diabetogenic than pasteurised milk.