Extrapolation from this data suggests that only some 10% of postoperative liver damage is likely to be attributable to anaesthetic agents. Furthermore, we are currently engaged in a study of postoperative jaundice occurring in Great Britain and Eire. Up to the present time, in the majority of cases investigated, the jaundice is probably due to factors other than the anaesthetic agent used. However, it can be seen from Table IV on p. 21 that every case reported to the Committee on Safety of Drugs has been included in Figure 2, p. 19. It is highly unlikely, therefore, that all of these cases are unexplained, and an "excess" of cases in which a cause and effect relationship is attributable to halothane may not exist. The high incidence of jaundice after operations repeated within a month remains of interest and concern. (Similar arguments may be applied to Figure 3.)

We endorse the view that "the rare occurrence of jaundice after halothane anaesthesia is of much concern to anaesthetists." Regrettably, however, we conclude that the paper by Professor Mushin and his colleagues does not reduce the uncertainty as to whether or not halothane hepatitis exists. Indeed, the statement that "this complication could be avoided if the use of halothane were stopped altogether" is open to misinterpretation by non-anaesthetists who may not appreciate that most anaesthetic agents and techniques have been incriminated following the occurrence of postoperative liver damage. It may well be that, if the advice not to repeat halothane is taken "because of the possible greater overall safety of administration of two halothane anesthetics as opposed to administration of one halothane followed or preceded by one non-halothane anesthetic, the epidemiologic consequences of withholding halothane from almost all patients returning for a second surgical procedure might well be the opposite of those intended."[3]—We are, etc.,

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Functions of the G.M.C.

SIR,—Dr. J. Fry (10 July, p. 116) paints too complacent a picture of the present situation of the G.M.C. As one who, so far as I know, was entirely unsponsored in the recent election, I feel entitled to say something about sponsorship. If the B.M.A. opts out it leaves the field open to others who do sponsor, and while this may result, as Dr. Fry modestly states, in a reasonable choice it does not necessarily represent the profession but is loaded in favour of those groups who sponsored candidates. It strikes me as odd that the largest and most important association of doctors should abandon the field, particularly when it has policies to pursue and perhaps even more important has the responsibility to advise the profession on the vexed questions of the retention fee and postgraduate registration.

Dr. Fry seems satisfied with the Brynmor Jones Report. I am not, and in this respect I am in agreement with Dr. J. F. G. Pigott (3 July, p. 52). The G.M.C. is already too big and although the majority of elected members has been accepted in the report, it would mean a council of about 70 as a start, with an extra two for each new medical school or college that is accepted in future.

The arguments for each university having a seat are much weakened by the firm views of London University to stick to only one representative for all the medical schools in London. It strikes me as incongruous that the universities for whose standards of medical education the G.M.C. is responsible should be so heavily represented on the only body which can call them to account. If it is seriously suggested that they are needed to such an extent, then medical schools in India, Pakistan, and Egypt, whose degrees the G.M.C. accept as registerable, should also be represented. Some, because of the large numbers of graduates they send here, may even claim a greater entitlement.

We really need a much smaller G.M.C., with less but still an overall majority of elected members. If the universities and the colleges feel so strongly about membership, one could be accommodating, but at a price. They should make a proportionate contribution to the finance of the G.M.C. It is entirely unfair that the registered doctors should be asked to subsidize privileged classes. The Government should also be asked to make its contribution on behalf of Privy Council members. This would not give us the most efficient G.M.C., but at least the financial burden would be shared.—I am, etc.,

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Lymphocyte Sensitization

SIR,—We have read the recent study of lymphocyte sensitization in sarcoidosis by Dr. E. A. Caspary and Professor E. J. Field (17 April, p. 143) as shown by inhibition of macrophage migration. These authors also report two other patients who repeatedly failed to "convert" to tuberculin sensitivity after B.C.G., and who had lymphocytes sensitized to the same cell antigens as patients with sarcoidosis. This finding leads them to suggest that an extended study might show that "non-converted," although apparently healthy, subjects may exhibit the immunopathology of sarcoidosis.

We have investigated the phenomenon of apparently healthy subjects who remain "non-converted" to tuberculin sensitivity following two vaccinations,[1 2] using both liquid and freeze-dried B.C.G. vaccine; each of our subjects showed satisfactory vaccination scars. In our first study[1] 7 out of 10 subjects who were vaccinated twice and who remained non-converted had positive Kveim tests. These seven subjects also showed marked depression of delayed-type skin hypersensitivity following intracutaneous tests with a *Candida albicans* suspension. Further tests three years later showed marked regression of Kveim reactivity. A similar waning of the Kveim response with persistence of tuberculin anergy is frequently seen in regressing clinical sarcoidosis. However, none of these seven subjects had a history suggestive of erythema nodosum or arthralgia or showed any other evidence of sarcoidosis on physical examination. Moreover, miniature chest radiographs extending back to the initial B.C.G. vaccinations 10 years previously, and chest radiographs taken within six months of the positive Kveim tests, were normal. Serum calcium, IgG, IgM, and IgA were normal and all the ABO blood groups were represented.

The lymphocyte transformation test carried out in four of these seven subjects showed no response to Kveim material used as antigen after five or seven days' culture, or to tuberculin or B.C.G.[3] A similar lack of response was reported by Brandt, Bouveng, and Norden[4] on a healthy "non-converter," using tuberculin as antigen.

No tests were made on our subjects using a migration inhibition technique. In this context it is of interest that Lockshin and Bombarieri[5] using tuberculin and *Candida albicans* antigens, found that the macrophage migration inhibition test was sometimes positive in subjects with reduced skin reactivity to these materials. The dissociation between cell sensitization of cutaneous reactivity disclosed by Dr. Caspary and Professor Field would appear to be in line with these findings. Hardt and Wanstrup,[6] also using a migration inhibition technique, were able to mediate a specific response to sarcoid spleen suspensions, and more recently Willoughby and Mitchell[7] have found inhibition of leucocyte migration in sarcoidosis and Crohn's disease, with sarcoid but not with normal spleen suspensions.

In discussing our own findings[2] we suggested that healthy "non-converted" subjects seem most likely to represent a minute proportion of the healthy population who reflect an unusual immunological change brought about by B.C.G. itself and in some way related to tuberculin sensitivity, being especially prominent among subjects with persistent tuberculin anergy. We still favour this hypothesis.—We are, etc.,

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Vitamin B_{12} and Metformin

SIR,—We welcomed the paper by Dr. G. H. Tomkin and others (19 June, p. 685) for its convincing demonstration of the causative association between malabsorption of vitamin B_{12} and long-term therapy with metformin. These authors showed that 30% of 71 diabetic patients on such treatment had

malabsorption of vitamin B_{12} and four of these had abnormally low serum levels of the vitamin. We have data on 114 diabetic patients who have had at least 2 g of metformin daily for at least two years and of these no less than 17·5% had serum levels of vitamin B_{12} at or below the lowest level of the normal range (160-900 $\mu\mu$/ml). The fact that this figure is considerably above the 5·6% of the Belfast workers may be owing to the relatively larger mean daily dose of metformin used in the Aberdeen series (3·3 g versus 1·8 g). Just under 10% of the Aberdeen series also had abnormally low levels of serum folate, but in all but one instance this occurred with normal serum vitamin B_{12} levels. The mean duration of biguanide therapy was similar in both series (4·6 and 4·4 years for Belfast and Aberdeen respectively) but in Aberdeen most of the patients had had phenformin in preference to metformin before 1968. The change-over to metformin for those requiring more than 100 mg of phenformin a day was effected because of a few cases of serious lactic acidosis associated with the use of larger doses of phenformin, especially after an alcoholic spree. We have not seen lactic acidosis in patients taking up to 4·5 g of metformin a day.

We would like to support the recommendation of Dr. Tomkin and others that all patients on long-term therapy with metformin should have an annual estimation of serum vitamin B_{12}, for it is otherwise quite easy to miss cases of classical macrocytic anaemia and/or signs of subacute combined degeneration of the cord.

We would like to thank Dr. Audrey Dawson and her staff for undertaking the haematological investigations.

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Vagotomy Diarrhoea

SIR,—There has been considerable debate concerning the incidence of incapacitating explosive diarrhoea after truncal vagotomy for peptic ulcer (1 February 1969, p. 302; and 14 February 1970, p. 412).

I would like to report the case of a 42-year-old man who was admitted to hospital in September 1970 with the clinical presentation of a perforated chronic duodenal ulcer. This was confirmed and treated at laparotomy by simple suture. Two months later, with no improvement in his symptoms, a truncal vagotomy and gastroenterostomy were performed. After this he immediately developed explosive incapacitating diarrhoea, up to 15 times daily, which failed to respond to any medical treatment. A diagnosis of vagotomy diarrhoea was made. Four months later it was clear that, from physical, occupational, and social aspects, the patient could not tolerate continuation of his symptoms. He was admitted to hospital for full reinvestigation. The further relevant findings were a history of intense hunger, not satisfied by any amount of food; the presence of undigested food in the stool; and on barium meal and follow through, the passage of barium from the hypopharynx to the caecum in 4½ minutes.

At laparotomy a terminal ileogastrostomy was found. This was converted to a proximal jejunogastrostomy. The patient made an uninterrupted recovery, and is continuing to have a normal bowel action and to regain weight.

Mistakes are made. This is not a criticism but a cautionary tale. Diarrhoea does occur after truncal vagotomy, but, before it is given a diagnostic label of "vagotomy diarrhoea," the patient must be thoroughly reinvestigated.—I am, etc.,

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Genital Herpes Infection and Non-specific Urethritis

SIR,—Dr. C. S. Goodwin and others (28 November, 1970, p. 558) discussed the asymptomatic infection of the male urethra with herpes simplex virus (H.S.V.). H.S.V. was isolated from 2 out of 12 males with urethral discharge. The patients had no clinical signs or symptoms of herpes genitalis.

At Karolinska Sjukhuset since 1968 we have studied the incidence of genital H.S.V. infection in patients attending the V.D. clinic because of suspected venereal disease.[1] The specimens for virus isolation were taken from the urethra and collected on the patients' first visit to the clinic. Immediately after sampling the urethral swab was placed in a tissue culture tube with GMK-AH 1 cells (established line of Green monkey kidney cells).[2] In 29 out of 688 males H.S.V. was isolated. Seven of the males with verified H.S.V. infection had no clinical signs or symptoms of herpes genitalis. Their only symptom was urethral discharge. The Table indicates symptoms and histories in all our cases of virologically verified genital H.S.V. infection (figures in brackets give the number of patients with gonorrhoea in the respective groups).

No typical herpes symptoms No anamnesis of herpes	6 (1)
No typical herpes symptoms * Anamnesis of herpes	1 (1)
† Suspect herpes symptoms No anamnesis of herpes	12 (2)
Suspect herpes symptoms * Anamnesis of herpes	2 (1)
*† Typical herpes symptoms No anamnesis of herpes	5 (1)
*† Typical herpes symptoms * Anamnesis of herpes	3 (0)
Total	29 (6)

* History of clinical H.S.V. infection in the genital region
† A few minor lesions, similar to H.S.V. infection, in the genital region
*† Grouped vesicles or grouped shallow ulcerations in the genital region

The same technique for virus isolation has been used in a control group.[1] One hundred and thirty three young males without venereal disease and without history or clinical signs of genital H.S.V. infection were investigated. The rate of genital H.S.V. infection in the control group was none (no virus isolated).

From the Table it is obvious that in five patients without typical symptoms and history of genital H.S.V. infection, all with urethral discharge, H.S.V. was the only agent that could be isolated. If virus isolation had not been performed these patients might well have been classified as suffering from non-specific urethritis.

To our knowledge none of the authors who previously have reported negative virus isolations from males with non-specific urethritis[2 3] have used a comparable technique. Nahmias *et al.*[4] have reported a prevalence of 0·3% genital H.S.V. infection in males attending a venereal disease clinic. Virus isolation was done only from genital lesions in males with clinical symptoms of genital H.S.V., and the swabs were placed into Hank's buffered salt solution before inoculation of the specimens into tissue culture tubes. Considering the relative lability of H.S.V. Type 2[5] it is to be expected that a method with direct inoculation of the specimen into the tissue culture tube will be a more sensitive method of detecting the virus.—We are, etc.,

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Haemodialysis/Transplantation Programme

SIR,—I have been interested in the logistics of renal dialysis units and I should like to raise a few points regarding the paper by Dr. S. C. Farrow and others on a statistical approach to planning an integrated haemodialysis-transplantation programme (19 June, p. 671).

Firstly, certain important probabilities used in the matrix do not appear to fit the data from which they were derived. The Table giving survival figures should be corrected in the columns given below. It is appreciated that a monthly survival greater than 1·00 is unreal, but such parameters are meaningful when the average "matrix survival" for months 7 to 30 is calculated; this is 0·9897 (or 0·99) not 0·98 as given in the Table. (A simple graph of the survivals for these months illustrates that 0·99 gives a closer fit than does 0·98). It should be noted that this is the monthly survival for all states, and includes poorer survivals from states with poorer prognoses, such as the months following transplantation.

Table Corrections

Months	10	16	19	21	22	24	26
Patients surviving	38	25	19	17	15	12	9
Patients observed	47	36	29	25	23	18	12
Overall survival	0·81	0·69	0·66	0·68	0·65	0·67	0·75
Monthly survival	1·01	0·99	0·98	1·04	0·96	1·03	1·13
Matrix survival	←			0·99			→

The probabilities inserted in the matrix for the survival of patients following transplantation do not agree with those obtained from the Edinburgh data.[1] The Edinburgh data (for 35 patients) indicate survival at 1, 2, and 3 months of 86%, 70%, and 64% respectively. However, in the matrix higher probabilities lead from states 8, 9, and 10 to rejection (state 11) than to death (state 0). Analysis of the matrix in this region leads to survival at 1, 2, and 3 months following transplantation of 97%, 94%, and 90%