seven kidneys (5%), however, showed severe arterial beading of the type previously reported in rejection^{1,2}; and in another nine kidneys (7%) there were irregularities in the small renal arteries ranging from minor variations in vessel calibre and course to obvious segments of constriction or dilatation with abrupt terminations to the vessels. All the transplanted kidneys demonstrating these vascular abnormalities were undergoing rejection. One of the patients in whom aneurysms were demonstrated had arteriography of the transplanted kidney performed on two occasions; the first arteriogram showed normal intrarenal vessels, the second study one year later showed multiple small aneurysms which had developed during the course of rejection of the kidney.

There was considerable overlap between the different types of arteriographic abnormality seen in rejecting transplant kidneys; the 20 kidneys comprising the three groups described above demonstrated a spectrum of vascular changes ranging from mild variations in vessel calibre at one extreme to multiple aneurysms at the other. In summary, multiple intrarenal aneurysms or severe preaneurysmal beading were demonstrated in 8% of 136 arteriograms performed on malfunctioning transplanted kidneys. In a total series of 918 renal arteriograms rejection of a transplant was second only to polyarteritis nodosa as a cause of this type of aneurysm. Many causes of renal aneurysm are known,³ but the aneurysms seen in transplant rejection are most similar in their arteriographic appearance to those occurring in polyarteritis nodosa³ or drug abuse.⁴

Our findings support the contention of Dr Walker and his colleagues that transplant rejection can be a cause of intrarenal aneurysms, and we believe that such aneurysms represent one extreme of the wide spectrum of arteriopathic changes that can be demonstrated by arteriography during transplant rejection.⁵

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¹ Vinik M, Smellie WAB, Freed TA, Hume DM, Weidner WA. *Radiology* 1969;92:873.

² Raphael MJ, Steiner RE. In: *Recent advances in radiology*. Fifth edn. Lodge T, Steiner RE, eds. Edinburgh: Churchill Livingstone, 1975:159.

³ Travers RL, Allison DJ, Brettell RP, Hughes GRV. *Semin Arthritis Rheum* 1979;8:184.

⁴ Halpern M, Citron P. *Am J Roentgenol* 1971;iii:663.

⁵ Raphael MJ, Steiner RE, Stockman R, Ware RG. *Br J Radiol* 1969;42:873.

Elemental diets in treatment of acute Crohn's disease

SIR,—The difficulties in conducting controlled trials in Crohn's disease do not diminish the need for cautious interpretation of uncontrolled data such as those provided by Dr C O'Morain and colleagues (1 November, p 1173). The induction of remission claimed for the elemental diet may equally have been the result of bed rest or due to the drugs that 16 out of the 24 patients were taking.

Whether any beneficial effect of elemental diets is attributable to the characteristics peculiar to these formulations is similarly in doubt, and the much cheaper whole-protein low-residue liquid diets may be equally efficacious. Recently a trial of bowel rest in Crohn's disease using parenteral nutrition alone showed no significant improvement over results obtained using parenteral nutrition plus oral food (H Lochs *et al*, abstract PF7, European Congress of Parenteral and Enteral Nutrition, Newcastle, 1980). Both methods reduced the Crohn's disease activity index, which was attributed to improvement in nutritional status. But the property of having

no or low residue, with resultant bowel rest, may be important in the healing of local perianal lesions when nutritional deficiency is not a feature.¹

Elemental diets are not without hazards,² and before they are accepted as useful therapy in Crohn's disease controlled data on their efficacy must be obtained³ and comparisons with the cheaper whole-protein liquid diets undertaken.

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¹ Russell RI, Hall MJ. *Scot Med J* 1979;24:291-5.

² Hall MJ. In: Russell RI, ed. *Elemental Diets*. Cleveland Ohio: Chemical Rubber Company (in press).

³ Koretz RL, Meyer JH. *Gastroenterology* 1980;78:393-410.

Psychiatric morbidity and physical toxicity associated with adjuvant chemotherapy

SIR,—We were most interested in the report by Dr G P Maguire and others (1 November, p 1179) of a study of psychiatric morbidity associated with adjuvant chemotherapy following mastectomy, which is similar to the investigation already reported by us.¹ However, we should like to draw attention to an ambiguity which occurs in the first sentence. The wording and the grouping together of the first two references^{1,2} suggest that both papers make the claim that adjuvant combination chemotherapy causes little physical toxicity and psychiatric morbidity in patients with breast cancer.

In fact, our results, based on a series of 39 patients, showed that in those free from recurrent disease psychiatric morbidity, particularly depression, was significantly greater in patients completing a one-year course of chemotherapy than in those who had radiotherapy alone. Furthermore, data from a longer follow-up study involving 52 patients indicate that the psychiatric morbidity associated with chemotherapy persists for at least 12 months following the cessation of treatment.³ In the paper by Dr Maguire and his colleagues it is not clear when the differences in morbidity between the groups became evident, whether patients were still having chemotherapy at the time of the 12-18 month assessment, or whether they were free from recurrent disease. It is possible that part of the psychiatric morbidity observed by them could be related to the physical symptoms arising from recurrence of disease as well as those associated with drug toxicity.

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¹ Cooper AF, McArdle CS, Russell AR, Smith DC. *Br J Surg* 1979;66:362.

² Bonnadonna G, Brusamolino E, Valagussa P, *et al*. *N Engl J Med* 1976;294:405-10.

³ Hughson AVMH, Cooper AF, McArdle CS, Russell AR, Smith DC. *Br J Surg* 1980;67:370.

* * * We sent this letter to the authors, whose reply is printed below.—ED, *BMJ*.

SIR,—We welcome the letter from Dr Cooper and his colleagues for it enables us to cover points which were not included in our short report.

Our investigation was part of a larger study, which aimed to determine whether counselling by a specialist nurse reduced the psychiatric morbidity associated with the treatment of breast cancer.¹ Women about to undergo mastectomy were randomised to routine care or routine care plus counselling. Those whose lymph nodes had been invaded by cancer were further randomised to treatment with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF), melphalan or no therapy.

Counselling failed to prevent psychiatric morbidity. So we considered that our findings accurately reflected the incidence of such morbidity in patients on adjuvant chemotherapy. The high morbidity in patients on CMF was not attributable to recurrence of disease since this had occurred in 4/18 (22%) of those on no treatment, 1/14 (7%) of patients on melphalan, and 1/26 (4%) of those given CMF. Regular monitoring by the specialist nurse led her to detect and refer for help most of those in the counselled group who needed psychiatric treatment. In view of this the questions posed about the duration of psychiatric morbidity in patients on CMF can be answered only by considering what happened in the non-counselled group.

The mood disturbance generally became evident two to three months after starting the 12-month course of CMF. It reached a peak six to eight months after starting treatment. The course thereafter was variable. The extent to which it persisted once treatment was completed is shown in the accompanying table. This persisting psychiatric morbidity has to be judged against the incidence in the "no treatment" group of patients, who suffered a greater incidence of recurrence (two patients within the follow-up period and one shortly after, compared with no patients in the CMF or melphalan groups).

Presence or absence of psychiatric morbidity at the end of the follow-up period. Figures in parenthesis give percentage of treatment group showing morbidity

Treatment group	Anxiety		Depression	
	+	-	+	-
Mastectomy alone	5 (50)	5	5 (50)	5
Mastectomy and melphalan	1 (14)	6	1 (14)	6
Mastectomy and CMF	7 (47)	8	5 (33)	10

CMF = Cyclophosphamide, methotrexate, and 5-fluorouracil.

Thus we believe that, while patients given CMF pay a considerable price for the possibility of improved survival, this is offset to a considerable extent by the problems they would have encountered through recurrence had they been given no further treatment. Further, more extensive studies are needed to confirm that this is so.

Finally we would like to correct an error which appeared in the table. The figures for the incidence of depression in the "mastectomy alone" group should have read:

+ - + -
9 (50) 9 and not 9 (32) 19

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¹ Maguire P, Tait A, Brooke M, Thomas C, Sellwood R. *Br Med J* 1980;281:1454-6.

Heart rate variations in the Guillain-Barré syndrome

SIR,—Dr Shirley A Smith and Professor S E Smith (11 October, p 1009) writing about our paper (6 September, p 649) say that "the difference in the size of the standard deviation between the two groups studied [patients

with Guillain-Barré syndrome and normal subjects] could be explained, at least in part, by a tachycardia in the Guillain-Barré patients."

In our work the mean heart rate at the moment of the measurement of the beat-to-beat variation was 74.94 ± 12.6 for controls and 101.36 ± 9.1 for patients, the difference between the groups being significant. We think that this difference could influence, at least in part, the measurement of standard deviation of the beat-to-beat variation, although it is unlikely that this is the only possible cause of the significant difference found in the standard deviation (SD) and the mean square successive difference (MSSD) of the beat-to-beat variations in both groups.

In three of our control subjects, with heart rates of 84, 88, and 98 beats/min respectively, the individual SD, and MSSDs were 1.79 and 1.50, 2.20 and 1.66, and 1.70 and 1.42; while in three patients with the Guillain-Barré syndrome the SDs and MSSDs were 1.60 and 0.91 (82 beats/min), 0.82 and 0.66 (96 beats/min), and 0.50 and 0.48 (102 beats/min). The figure shows the results of the measurement of 45 successive beat-to-beat intervals in a control and a patient.

Beat-to-beat intervals in a patient with Guillain-Barré syndrome and a normal subject.

It is likely that the work that is to be published by Dr S A Smith and Dr S E Smith concerning normal subjects will be useful for estimating the influence of the heart rate variation when comparing healthy subjects with heart rates between 60-70 and 90-100 beats/min.

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Fenclofenac and thyroid function tests

SIR,—We wish to report the occurrence of severe hypoglycaemia in a diabetic patient after the addition of fenclofenac to her drug therapy. In view of the effect of fenclofenac on the displacement of thyroxine from protein binding sites (4 October, p 911; 8 November, p 1282) it is probable that the hypoglycaemia was due to a potentially lethal drug interaction not hitherto reported.

A 68-year-old diabetic woman was admitted to hospital on 1 November 1980 for assessment and treatment of rheumatoid arthritis. Her diabetes mellitus had been well controlled by diet, chlorpropamide 500 mg daily, and metformin 850 mg twice daily for two years. This treatment was maintained in hospital and bed rest was commenced. On 5 November, before lunch, her blood glucose was 8.5 mmol/l (153 mg/100 ml). Antirheumatic therapy was continued with flurbiprofen 50 mg three times daily and sustained-release indomethacin 75 mg twice daily until 6 November, when fenclofenac 600 mg twice daily was substituted for both drugs. After supper on 9 November she became confused and clammy and blood

glucose estimation by Dextrostix was less than 1.4 mmol/l (25 mg/100 ml). She was able to take glucose by mouth and she became rational again quickly. Next day the antidiabetic drugs were stopped and she ate normal meals for breakfast and lunch. Blood glucose estimations taken at intervals throughout the day were 1.7 mmol/l (31 mg/100 ml), 3.1 mmol/l (56 mg/100 ml), 2.1 mmol/l (38 mg/100 ml) and 1.7 mmol/l (31 mg/100 ml). Before supper she suddenly became deeply unconscious and responded to an intravenous injection of 15 g of glucose. An intravenous infusion of glucose was maintained until the next day. There have been no further hypoglycaemic episodes but by 17 November antidiabetic drugs had not been resumed. The only change in drug therapy before this reaction was the substitution of fenclofenac for indomethacin and flurbiprofen. Afterwards she asserted that her food intake before the event was greater than her diet at home. She had also been inactive, resting in bed, as part of the treatment of her acute rheumatoid arthritis.

The action of chlorpropamide is known to be potentiated by highly protein-bound drugs such as phenylbutazone and so we suggest that a similar interaction takes place between fenclofenac and chlorpropamide. As most changes in antirheumatic drug therapy are made out of hospital we feel that this probable interaction should be reported urgently without awaiting confirmation.

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Indomethacin-propranolol interaction

SIR,—I recently reported an attenuation of the hypotensive effect of propranolol by indomethacin (13 September, p 702). Dr R J Mangini has suggested (15 November, p 1353) that the coincident administration of aluminium hydroxide, by reducing the bioavailability of propranolol in the indomethacin-treated patients, may have contributed to this effect.

No increase in heart rate was seen during indomethacin therapy despite the increase in blood pressure. This strongly suggests that the bioavailability of propranolol was unaffected. Only three of the eight propranolol-treated patients actually took any aluminium hydroxide while on indomethacin (patient No 5, 6, and 8), and their results were very similar to those of the other patients in this group.

While I would agree with Dr Mangini that careful consideration should be given to the use of drugs such as aluminium hydroxide in studies of this sort, the acute gastric erosion which developed in patient No 11 during indomethacin therapy in the absence of an antacid I feel fully justified its use in this study.

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Anaphylactic reaction to desensitisation

SIR,—Drs R J Ancill and Gillian R Wainscott (22 November, p 1429) point out that asthma causes between 1000 and 2000 deaths annually in the UK and state that, "this can be compared with only 13 reported deaths following anaphylactic reaction to hyposensitisation with Bencard vaccines since 1966." In what way is comparison of these figures relevant or useful?

With immunisation against infectious disease valid comparison can be made between the number of deaths or serious complications prevented and the occasional fatalities resulting from the therapy. With immunotherapy for asthma the only fact we are given is that 13 deaths directly attributable to Bencard vaccines have been reported (how many have resulted from vaccines of other manufacturers?)—where is the evidence that a single death has been prevented?

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Primary biliary cirrhosis: an epidemiological study

SIR,—Dr G F Batstone and his colleagues (22 November, p 1427) make some interesting comments on recent communications by Dr David R Triger (20 September, p 772) and myself (18 October, p 1069) on primary biliary cirrhosis. It is certainly true that liver biopsies in primary biliary cirrhosis may not have a consistent pathognomonic pattern that is seen in other forms of liver disease, the most important differential histological diagnosis being cryptogenic cirrhosis and cholestatic forms of chronic active hepatitis.¹ If, however, damaged septal or interlobular bile ducts are seen in the biopsy specimen, as was the case in the majority of the Tayside patients, the diagnosis may be made with a high degree of certainty.

The clinical features of primary biliary cirrhosis may also overlap with other conditions—notably, again, chronic active hepatitis and cryptogenic cirrhosis, but also sclerosing cholangitis (seen in several rheumatic conditions) and occasionally Wilson's disease. The presence of antimitochondrial antibodies will not necessarily exclude chronic active hepatitis or cryptogenic cirrhosis.

Primary biliary cirrhosis is associated with some morbidity, especially from bone disease and pruritus. Therapeutically, recent work suggests that D-penicillamine may provide benefit, especially in severely cholestatic cases.² In contrast, chronic active hepatitis usually responds to corticosteroid therapy. Neither of these regimens is free of side effects, and should not be embarked on without strong evidence of accuracy of diagnosis.

Although the clinician may be very confident from clinical features, biochemistry, and serology that a patient has primary biliary cirrhosis, most hepatologists would now agree that liver biopsy is desirable, as this is the one procedure that can provide unequivocal proof of primary biliary cirrhosis, thus preventing the dangers of inappropriate therapy and enabling the physician and patient to be more aware of the likely prognosis and complications.

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¹ Scheuer PJ. *Liver biopsy interpretation*. London: Ballière, 1980.

² Jain S, Scheuer PJ, McGee JO'D, Sherlock S. *Lancet* 1977;i:831-4.

SIR,—May we be permitted to reply to the letter of Dr G F Batstone and colleagues (22 November, p 1427) concerning the contribution of liver biopsy to the diagnosis of primary biliary cirrhosis, since they raise a point which