norphine 3 µg and fentanyl 1 µg/kg body weight peroperatively with minimal intravenous induction agents and halogenated vapours. Postoperatively I give papaveretum 10-20 mg intramuscularly as soon as full consciousness returns but before severe pain is felt.³ Occasionally severe spasms of pain require injection of orphenadrine.⁴ This technique provides analgesia comparable, as assessed by hourly pain scores, with continuous infusion. There was no detectable depression of respiration measured by counting, by Wright's respirometer, or by random blood gas samples.

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¹ Fry ENS. *Br Med J* 1976;ii:817.

² Fry ENS. *Ann R Coll Surg Engl* 1979;61:371-2.

³ Fry ENS. *Br J Anaesth* (in press).

⁴ Fry ENS. *Br J Anaesth* 1977;50:841.

SIR,—Too much narcotic analgesic, like too little gruel, is not a good thing. The opportunity to ask for less would have been of benefit to the group of patients given continuous papaveretum infusions by Dr J A Catling and others (16 August, p 478).

Disturbances in respiration, apnoeic episodes, and low respiratory rates seen in five of seven patients, combined with high overall pain scores suggest that constant infusion results in either overdosing or underdosing. This is an inevitable consequence of inflexible administration techniques, where analgesic requirements for up to 48 hours postoperatively are calculated on the effect of a single loading dose given early in the postanesthetic period. No allowance can be made for the varying requirement for analgesia which come with elimination of anaesthetic agents, the effect of antiemetic drugs, physiotherapy, or the onset of sleep.

The only logical way to control analgesic dosage is by reference to the degree of pain felt by the patient. While on-demand systems have been shown to result in lower overall pain score it is now important to know whether patients using systems like the Cardiff Palliator are demonstrably "better" using the respiratory parameters which Catling and others have defined.

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Impotence in diabetic and non-diabetic hospital outpatients

SIR,—Dr Eva Lester and others (2 August, p 354) demonstrated a 23% incidence of impotence in 83 male diabetic outpatients as compared with a similar incidence of 20% in 50 non-diabetic outpatients. This would seem to indicate that the high incidence of impotence in diabetic men previously claimed has been exaggerated.

Recently we have shown that hypoxia in men with chronic obstructive airways disease is associated with low testosterone values¹ and that the degree of testosterone depression is related to the severity of arterial hypoxia.² The majority of men thus affected are impotent and lack early morning penile erections.³ In view of this and the fact that

patients with chronic obstructive airways disease are one of the largest medical outpatient groups it would be of interest to know from which non-diabetic clinics Dr Lester and her colleagues took their "controls." For if these included a significant proportion of men with chronic obstructive airways disease it might suggest that diabetic men are indeed more frequently impotent than non-diabetic patients excepting those with hypoxia and chronic obstructive airways disease.

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¹ Semple Pd'A, Watson WS, Beastall GH, et al. *Thorax* 1979;34:783-8.

² Semple Pd'A, Beastall GH, Watson WS, Hume R. *Clin Sci* 1980;58:105-6.

³ Semple Pd'A, Beastall GH, Hume R. *Br J Sex Med* 1980;62:48 and 53.

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

SIR,—Our 50 controls came from a variety of medical and surgical clinics. None of them were from the large and active chest clinic here. Although we did not record detailed clinical findings in the controls it is therefore very unlikely that a significant number had chronic obstructive airways disease.

We do feel that the prevalence of impotence in diabetics has been exaggerated. The figure of 55% which is quoted from paper to paper is an overall figure from a study of 198 men of whom 111 were under 60 years and 87 were aged 60 to 90 years.¹ The prevalence of impotence in the men under 60 years in this study was 26.4% which is very similar to our own figure of 23%.

The findings of Dr Semple and his colleagues of impotence in men with chronic obstructive airways disease and severe hypoxia confirm our feeling that "there is a lot of it about" in men who are unwell. Although four of their seven patients with chronic obstructive airways disease and erectile difficulty had low or low normal testosterone concentrations, they found normal gonadotrophin concentrations so that evidence for a hypothalamic-pituitary mechanism is lacking. This seems to indicate that the question as to whether impotence in patients attending hospital with a variety of disorders including diabetes mellitus is organic, functional, or perhaps even "normal" remains open and we cannot claim to have answered it.

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¹ Rubin A, Babbott D. *JAMA* 1958;168:498-500.

Is methotrexate carcinogenic?

SIR,—We wish to comment on the assertion of Mr R S Knowles and Mr J E Virden (30 August, p 589) that methotrexate is carcinogenic.

Five comprehensive methotrexate toxicology studies in different species of laboratory animals have failed to demonstrate carcino-

genic activity.¹⁻⁵ Roschlau and Justus found that methotrexate induced lung tumours in mice.⁶ These findings are questionable, however, since there were no concurrent untreated controls and spontaneous tumour development in the species used is well documented.

While a number of case histories describing tumour occurrence after methotrexate treatment for psoriasis and one report of a hepatocellular carcinoma found at autopsy in a patient with acute lymphoblastic leukaemia have appeared in the literature, definitive cause-and-effect judgments cannot be made on the basis of isolated reports, especially if one considers that some 25% of the population may be expected to develop malignant disease in the course of their lives. Analysis of a series of 205 psoriasis patients treated with methotrexate for periods of two to seven years with a minimum follow-up of seven years showed no increase in the incidence of internal tumours over a matched population control.⁷ Furthermore, Bagshawe has reported only one second tumour in over 400 methotrexate-treated choriocarcinoma patients followed up since the late 1950s⁸; similarly follow-up of choriocarcinoma patients treated at the United States National Institutes of Health over the last 22 years shows no evidence of increased susceptibility to develop malignant disease after successful chemotherapy, which presumably included methotrexate.⁹

Logically, one would not expect methotrexate to be carcinogenic since, unlike most cytotoxic drugs, it neither reacts chemically with, nor is incorporated into, nucleic acids.

In view of the substantial animal toxicology data and clinical evidence, we submit that it is unjustified to describe methotrexate as carcinogenic and that it should be considered a non-carcinogenic drug.

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¹ Ryan TJ, Buddington MM, Spriggs AI. *Br J Dermatol* 1965;77:541-55.

² Von Schmoll D, Osswald H. *Arzneim Forsch* 1970;20:1461-7.

³ Rustia M, Shubik P. *Toxicol Appl Pharmacol* 1973;26:329-38.

⁴ Data on file, Lederle Laboratories.

⁵ Weisberger EK. *Cancer* 1977;40:1935-49.

⁶ Roschlau G, Justus J. *Dtsch Gesundheitsw* 1971;26:219-22.

⁷ Bailin PL, Tindall JP, Roenigk HH, Hogan MD. *JAMA* 1975;232:359-62.

⁸ Bagshawe KD. *Proc Roy Soc Med* 1977;70:303-6.

⁹ Lewis JL. *Am J Obstet Gynaecol* 1980;136:163-72.

Rugger player's ear

SIR,—Your reply to the question "what is rugger player's ear?" (Any Questions, 16 August, p 498) could perhaps have mentioned two other conditions in addition to the "cauliflower ear" described. Chondrodermatitis helices nodularis is generally considered to be caused by repeated minor trauma to the ear, and I have seen the typical painful papules of this condition in four patients who had played rugby football until after the age of 40. All of them had been forwards and therefore involved with the scrummage, and there was no other likely cause of trauma in their cases. In addition, they all had cauliflower ears to a greater or lesser degree.

More commonly, I have seen multiple herpes simplex lesions on the ears and adjacent areas of neck and scalp in several medical students following rugby football

matches. Contact tracing has been possible with the help of a fixture list and the medical student health officer of the "opposing" hospital. The condition is known as scum pox locally.

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Why don't venereologists like prophylactic antibiotics?

SIR,—Minerva asks, "Why don't venereologists like prophylactic antibiotics?" (16 August, p 524).

My reasons for not issuing prophylactic antibiotics are: (1) Reasonable precautions against acquiring venereal infections are possible. (2) The patient may not be infected. Better a short wait to know this than an eternity of doubt because antibiotic prophylaxis was attempted. (3) Venereal diseases are not life threatening. Therefore to my mind there is no reason for what could be the indiscriminate and injudicious use of antibiotic agents to protect a patient. (4) There are a variety of venereal infections, with varying incubation periods, which may coexist and which are sensitive to different agents. There is no acceptable blunderbuss therapy which would eliminate all possible infections. (5) Until one is aware of the type or types of infection, one important function of a venereal disease clinic—contact tracing—is hardly possible. (6) The use of certain agents, while eliminating particular infections, may obscure the development of others so that, in the long term, to offer prophylactic treatment might not be in the best interests of the patient. (7) If I did ever agree to give prophylactic antibiotics I would be submerged with requests.

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Protein synthesis and breakdown after vaccination

SIR,—The attempt of Dr Peter J Garlick and others (26 July, p 263) to measure by ethical means the rates of human protein synthesis and degradation is a laudable one, but a bit puzzling. Theirs is an inferential method, as tissue sampling would be required for direct measurement of the rate of incorporation of label into protein, and of the specific activity of the labelled amino acid in the precursor pool. Any inferential method, to be valid, should produce results in agreement with those obtained by direct methods.

Dr Garlick and his colleagues write, "Rates of protein synthesis are acutely responsive to the rate of dietary protein intake . . . the rates of turnover shown . . . applied to fed subjects. Protein synthesis is *therefore* greater than breakdown . . ." (our italics). The conclusion derives only from the use of their own formula and its assumptions. In animal studies, using direct measurements of the rates of protein synthesis, it is found that there is a rhythm in the rate of protein synthesis over the 24 hours, with the highest rates at times when food intake is least, during the sleeping and resting period. Examples are protein synthesis in brain,¹ skin,² bone,³ and heart muscle.⁴ The only exception is the liver,

where the synthesis of short half-life proteins associated with the metabolism of incoming nutrients is very sensitive to food intake.

The discrepancy between the results obtained by direct methods and what Dr Garlick and others wrote of whole-body protein synthesis leaves an uneasy feeling that their indirect method may not be valid. One of their assumptions is that there is a constant metabolic pool of amino nitrogen from which amino-acids are removed for protein synthesis or are deaminated and excreted. This does not reflect the true picture—levels of plasma amino-acid vary considerably over the 24 hours and do so independently of protein intake.⁵ Amino-acids are actively transported into tissues against a concentration gradient. Plasma levels do not correlate with tissue levels, let alone with the intracellular pool of amino-acids that are charged with transfer RNA and that are the actual precursors for protein synthesis. In reality, intracellular amino-acids are again highest while food intake is least.⁶

We wonder whether the method of Dr Garlick and his colleagues is really reflecting glycine metabolism in the liver and not the whole-body protein turnover of which they wrote in their article.

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Porphyria cutanea tarda and beta-thalassaemia minor with iron overload

SIR,—We wish to comment on the recent report by Dr R W G Chapman (24 May, p 1255) concerning the simultaneous occurrence of familial porphyria cutanea tarda and beta-thalassaemia in a Turkish mother and daughter. Dr Chapman suggested that iron overload, a rare result of the thalassaemia trait, may have precipitated porphyria cutanea tarda in these patients, who were presumably genetically predisposed to the condition.

The biochemical evidence supplied to support the diagnosis of porphyria cutanea tarda in the mother is a urinary uroporphyrin level of 218 nmol (182 µg)/day, which is above normal but is very low for overt porphyria cutanea tarda in our experience.¹ Furthermore, a full porphyrin analysis of the patient is necessary to confirm the diagnosis since elevated urinary uroporphyrin levels can occur in several other conditions, including some stages of variegated porphyria,¹ where the cutaneous symptoms are identical.² In fact, if this criterion alone is used false-positives for porphyria cutanea tarda are at least as common as the disease itself; and a diagnosis of overt or subclinical biochemically positive porphyria cutanea tarda must be verified by demonstrating a marked isocoporphyrin fraction in the faeces,³ using thin layer chromatographic separation of the porphyrin methyl esters.⁴

In the daughter no excess urinary porphyrins

were detected and the diagnosis of subclinical porphyria cutanea tarda is biochemically unsubstantiated. Latent porphyria cutanea tarda is a possibility, however, but this can be diagnosed only with thin-layer chromatographic analysis of urinary porphyrins, where an unusual profile is found including uroporphyrin, 7C00H, 5C00H, and sometimes 6C00H porphyrins alongside the normal coproporphyrin, while the total porphyrin levels are not raised.^{4,5} Alternatively, some reports describe a decreased activity of the enzyme uroporphyrinogen decarboxylase in the red cells of patients with latent familial porphyria cutanea tarda.^{6,7}

We feel, therefore, that the suggestion of an association between familial porphyria cutanea tarda and beta-thalassaemia trait in these two patients is extremely interesting but cannot be justified until the above sophisticated analyses have been carried out and their results fully reported.

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The anaesthetist and the pain clinic

SIR,—I was most surprised to read in the article by Dr J W Lloyd (9 August, p 432) on the anaesthetist and the pain clinic that "tolerance to drugs, particularly the opiates, develops rapidly, and not uncommonly these patients need doses such as 120 mg of morphine every two hours. . . ." Has Dr Lloyd never read the many, many articles from the various hospices over the past few years on this very subject, repeatedly showing it to be a myth that tolerance and habituation occur if pain is properly managed? I would point him to Saunders¹ and Twycross,² to say nothing of my own modest experience³ with 71 patients suffering from terminal malignant disease. Of these, 46 required diamorphine at some stage in their illness, but 35 never needed more than 10 mg every four hours and only one needed 80 mg three hourly for a short time. None became habituated and many went home on another, much milder analgesic, if any.

I was also most amazed to read that Dr Lloyd classed morphine and diamorphine among drugs used only for non-ambulant patients. Almost all our patients were ambulant until a few days before death (and if they were not it was often for reasons other than their malignant disease) and we certainly did not withhold the powerful analgesics from patients who were ambulant. One man had been hospitalised for some time (and in bed) with severe pain from spinal metastases from a colonic carcinoma. We stabilised him on 80 mg of diamorphine every three hours and on that dose he was able to get up and dressed for