in 1989, by the end of 1991 half of all senior registrars were accredited, one third of them having been in the grade for over six years. A freeze on recruitment of senior registrars was imposed for at least two years,[5] thus ruining the career prospects of dozens of registrars trained in the specialty.[6]

As medical staffing budgets are finite any increase in the number of career registrars and senior registrars uses up money that would otherwise be available for expanding the number of consultants. Also, given a finite pool of doctors, increasing the numbers of consultants requires shorter, better training and reductions in numbers of the juniors.

Achieving a Balance has not failed—it has not yet been tried. JPAC may even be worsening the problems of staffing that it was established to solve. What is needed is the urgent introduction of single tier training schemes of shortened duration with wastage rates of around 10%. The numbers in these training schemes must be balanced with realistic estimates of the growth in the numbers of consultants, which should be increased and funded centrally by government.

The grim alternative is that in a few years many more specialties will be in the position of thoracic medicine and more junior doctors will spend even longer in the training grades.

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1 Department of Health and Social Security, Joint Consultants Committee, Chairmen of Regional Health Authorities. *Hospital medical staffing: achieving a balance.* London: DHSS, 1986.
2 Department of Health and Social Security, Joint Consultants Committee, Chairmen of Regional Health Authorities. *Hospital medical staffing: achieving a balance—plan for action.* London: DHSS, 1987.
3 Department of Health. *Joint Planning Advisory Committee—definite quotas for career registrars.* London: DoH, 1990. (EL(90)P47).
4 Department of Health. *Annual surgery of hospital medical and dental staff.* London: DoH, 1987-90.
5 Department of Health. *Joint planning of senior registrars in nuclear medicine and thoracic medicine.* London: DoH, 1992. (EL(92)40.)
6 Dilworth P, Howes T, Restrick L, Iredale M, Meecham-Jones J, Sanderson M. Respiratory medicine: the casualties. *BMJ* 1992;**305**:646.

Liver failure induced by paracetamol

Avoidable deaths still occur

About 160 people in England and Wales die each year from liver failure after an overdose of paracetamol,[1] although this official figure may underestimate the true annual mortality as many cases of liver failure may not be attributed to a suicidal overdose to alleviate bereaved relatives' distress. Why is the mortality from this commonly used analgesic so high 25 years after hepatotoxicity was first observed?[2,3]

Much has been learnt since then about how paracetamol damages the liver.[4] In therapeutic doses (up to 4 g a day) paracetamol undergoes glucuronidation and sulphation in the liver with only a small amount being metabolised by cytochromes[5] to the toxic metabolite *N*-acetyl-*p*-benzoquinone imine, which is inactivated by hepatic glutathione. In overdose the production of *N*-acetyl-*p*-benzoquinone imine overwhelms cellular glutathione, leading to widespread cellular damage, principally due to covalent binding of the toxic metabolite to thiol groups on cysteine residues of intracellular proteins (for example, in mitochondria). Thiol oxidation, lipid peroxidation, and activation of hepatic macrophages also occur.[4,6]

Susceptibility to the toxic effects of paracetamol taken in overdose differs between people, which may explain why some patients survive having taken large amounts of paracetamol while others die having taken only a few tablets more than the eight tablets (4 g) a day recommended by the manufacturers.[7] The best described causes of this enhanced susceptibility are chronic ingestion of alcohol[8,9] and anticonvulsant drugs,[10] but genetic factors may also play a part.[11] Although an increased susceptibility to hepatotoxicity may be contributory, the main reason for the continuing high mortality from paracetamol overdose is that many patients still present to medical care too late after ingestion for an antidote to be given according to standard guidelines.[12]

Intravenous acetylcysteine remains the antidote of choice in Britain for patients presenting to medical care early enough; oral methionine, another precursor of hepatic glutathione, is probably inferior to acetylcysteine as vomiting is common after overdose and metabolism to glutathione may be impaired by increasing liver dysfunction. Until recently acetylcysteine was not recommended for use more than 15 hours after overdose, but there is now evidence that it can safely be given to patients up to 24 hours after ingestion[13] and perhaps even later than this.[14,15] Acetylcysteine also seems to improve survival in established fulminant hepatic failure,[16] perhaps by reversing some of the adverse haemodynamic changes that occur at that time.[17] Patients at increased risk of hepatotoxicity (particularly those taking anticonvulsants) who present after taking an overdose of paracetamol should be considered for treatment with acetylcysteine even if the blood paracetamol concentration is below that at which treatment is usually started; the exact threshold at which acetylcysteine should be given in such cases is, however, unknown.

In a patient presenting late or after a particularly large overdose recognition of the onset of liver failure is crucial. Although the prothrombin time remains the best and most readily available measure of liver function in such cases, arterial acidosis (pH $< 7{\cdot}30$) and renal failure also indicate an adverse prognosis.[18] If liver function is deteriorating hypoglycaemia should be avoided, prophylaxis against gastric bleeding started, and central venous pressure maintained with colloid. Careful monitoring for the development of respiratory failure and cerebral oedema is also important. If pronounced coagulopathy, acidosis, or encephalopathy develops transfer to a specialist centre should be considered so that intensive care directed at the liver can be given and the patient considered for liver transplantation.

Despite such intensive care, including the use of "late" acetylcysteine and intracranial pressure monitoring (which helps in the early detection of intracranial hypertension), the mortality of patients with paracetamol induced fulminant hepatic failure in specialist centres continues to be over 40%—deaths are mainly due to cerebral oedema, hypotension, and overwhelming sepsis. Orthotopic liver transplantation has now been performed in several cases,[19] but its widespread use is likely to be restricted by the problems of postoperative sepsis, perioperative cerebral oedema, psychological assessment, and availability of donors.

Progress in reducing the number of deaths from paracetamol overdose may come only from preventing rather than treating fulminant hepatic failure. Increased public awareness of the dangers of exceeding the recommended dose of paracetamol might help, although this could paradoxically

encourage more people to take an overdose. It should, however, reduce the likelihood of an accidental overdose being taken from severe pain and increase the chance that if a patient's family knows of the overdose they will encourage him or her to seek prompt medical advice.

The pharmaceutical industry is in a pivotal position to address the problem of the continuing high mortality from paracetamol overdose as the addition of an antidote, such as methionine, to all available preparations might prevent every death that currently occurs. At present paracetamol-methionine combinations are costly, little publicised, and rarely prescribed. Adding methionine to all preparations of paracetamol might increase prices and therefore reduce sales. Another solution might be to develop non-hepatotoxic derivatives of paracetamol. It will indeed be tragic if the mortality from paracetamol overdose over the next quarter of a century proves to be as high as that of the last.

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1 Office of Population Censuses and Surveys. *Mortality statistics: cause. Review of the registrar general on deaths by cause, sex and age, in England and Wales.* London: HMSO, 1989. (Series DH2 No 15.)
2 Davidson DGD, Eastham WN. Acute liver necrosis following overdose of paracetamol. *BMJ* 1966;ii:497-9.
3 Thomson JS, Prescott LF. Liver damage and impaired glucose tolerance after paracetamol overdosage. *BMJ* 1966;ii:506-7.
4 Nelson SD. Molecular mechanisms of the hepatotoxicity caused by acetaminophen. *Semin Liver Dis* 1990;**10**:267-78.
5 Raucy JL, Lasker JM, Lieber CS, Black M. Acetaminophen activation by human liver cytochromes P450IIE1 and P450IA2. *Arch Biochem Biophys* 1989;**271**:270-83.
6 Laskin DL. Nonparenchymal cells and hepatotoxicity. *Semin Liver Dis* 1990;**10**:293-304.
7 Prescott LF. Effects of non-narcotic analgesics on the liver. *Drugs* 1986;**32**:129-47.
8 Lauterburg BH, Velez ME. Glutathione deficiency in alcoholics: risk factor for paracetamol hepatotoxicity. *Gut* 1988;**29**:1153-7.
9 Bray GP, Mowat C, Muir DF, Tredger JM, Williams R. The effect of chronic alcohol intake on prognosis and outcome in paracetamol overdose. *Hum Exp Toxicol* 1991;**10**:435-8.
10 Bray GP, Harrison PM, O'Grady JG, Tredger JM, Williams R. Long-term anticonvulsant therapy worsens outcome in paracetamol-induced fulminant hepatic failure. *Hum Exp Toxicol* 1992;**11**: 265-70.
11 De Morais SMF, Uetrecht JP, Wells PG. Decreased glucuronidation and increased bioactivation of acetaminophen in Gilbert's syndrome. *Gastroenterology* 1992;**102**:577-86.
12 Read RB, Tredger JM, Williams R. Analysis of factors responsible for continuing mortality after paracetamol overdose. *Hum Toxicol* 1986;5:201-6.
13 Parker D, White JP, Paton D, Routledge PA. Safety of late acetylcysteine treatment in paracetamol poisoning. *Hum Exp Toxicol* 1990;**9**:25-7.
14 Smilkstein MJ, Knapp GL, Kulig KW, Rumack BH. Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose. Analysis of the national multicenter study (1976 to 1985). *N Engl J Med* 1988;**319**:1557-62.
15 Harrison PM, Keays R, Bray GP, Alexander GJM, Williams R. Improved outcome of paracetamol-induced fulminant hepatic failure by late administration of acetylcysteine. *Lancet* 1990;**335**: 1572-3.
16 Keays R, Harrison PM, Wendon JA, Forbes A, Gore C, Alexander GJM, *et al.* Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. *BMJ* 1991;**303**:1026-9.
17 Harrison PM, Wendon JA, Gimson AES, Alexander GJM, Williams R. Improvement by acetylcysteine of haemodynamics and oxygen transport in fulminant hepatic failure. *N Engl J Med* 1991;**304**:1852-7.
18 O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology* 1989;**97**:439-45.
19 O'Grady JG, Wendon J, Tan KC, Potter D, Cottam S, Cohen AT, *et al.* Liver transplantation after paracetamol overdose. *BMJ* 1991;**303**:221-3.

Endometriosis

Should not be treated just because it's there

Endometriosis is a fascinating example of how a new diagnostic technique has transformed the understanding of a disease. Because the laparoscope has enabled easy, safe, detailed, and repeatable visualisation of the pelvis we now know that endometriosis has various manifestations and may even be present in otherwise normal peritoneum. Recent reports have argued that the presence of ectopic endometrium may be physiological and should be considered to be pathological only if associated with symptoms or signs of progression and tissue damage.[1,2]

Endometriotic implants probably evolve from active to inactive disease, and these stages are recognisable visually.[3] Histological techniques can show whether an endometriotic deposit is active and infiltrating the surrounding tissue or is superficial and inactive.[4] The pathogenesis of the disease has always been controversial, but considerable circumstantial evidence exists to support the suggestion that it is due to implantation of endometrium that has been refluxed down the fallopian tube at menstruation.[5] It is logical to hypothesise that the implantation of refluxed endometrium will be more likely to occur with increased exposure to menstruation: women now experience over 450 menstruations during their reproductive lifetime rather than the 30 to 50 that would be expected without contraception and with long periods of lactation. Changes in social habits, which increase exposure of the pelvis to menstruum, and a new diagnostic technique may therefore have combined to create an increase in the incidence of endometriosis.

The true prevalence of the visual finding of endometriosis cannot be determined at present because such studies require random operative intervention and are therefore unethical. Vessey *et al* report an increasing incidence with age, which peaks at about 6 per 1000 woman years between 40 and 44 (p 182).[6] They also show a protective effect of pregnancy and current use of the contraceptive pill. These data agree with those of Mahmood and Templeton[7] and support the hypothesis that the incidence of the disease is related to exposure to menstruation. While an individual endometriotic implant may change with time, no evidence exists that the disease will inevitably disappear. In the three studies that have reported the natural course of the disease in placebo arms of trials of medical treatment the disease progressed in about half the patients.[8-10] In the other half the disease either remained the same, improved, or disappeared. Increased disease was not necessarily symptomatic; predicting in which patients the disease would get worse was not possible.

Endometriosis should therefore not be treated simply because it is there. This is further supported by evidence that medical treatment works only temporarily, with the disease recurring once stimulation by ovarian steroids returns.[11] Endometriosis is more common in subfertile women and women with pelvic pain,[7] and logically these should be the two main indications for treatment. Unfortunately, none of the published randomised trials have shown that medical treatment improves fertility.[12] No justification therefore exists for treating subfertile women with contraceptive drugs, and the endometriosis should be considered to be coincidental unless it has caused tubal and ovarian damage that requires repair. There are no randomised studies of the efficacy of surgical ablation of endometriosis either at laparotomy or at laparoscopy on future fertility. Until this efficacy has been shown surgery cannot be recommended.

Currently, therefore, the only clear recommendation for treatment is in symptomatic patients. Classically, endometriosis is associated with cyclical pelvic pain and dyspareunia. Signs include the presence of a pelvic mass,