Methods and results

All patients had ingested paracetamol within the preceding 18 hours. Daily routine liver function tests and serum ferritins were performed and liver biopsy was obtained on the fourth or fifth day or when the prothrombin ratio was normal if that was later. One pathologist assessed biopsies blind and graded them as showing mild, moderate, or severe changes as described elsewhere.³ The patients were placed into three groups according to conventional liver function tests. Group 1 (eight females and one male): no liver damage. Serum aspartate aminotransferase (SGOT) within normal range (4–20 IU). Liver biopsy grading showed eight with mild and one with moderate damage. Group 2 (five females and three males): moderate damage. SGOT rose but did not exceed 400 IU. Biopsy gradings showed one with mild and seven with moderate damage. Group 3 (eight females): severe damage. SGOT rose higher than 400 IU. Biopsy grading showed eight with severe damage. The groups did not differ with regard to time between ingestion of paracetamol and admission to hospital. Serum ferritin was measured by immunoradiometric assay as described by Addison *et al*,⁴ and values above 6000 µg/l were not measured quantitatively. Reference values were established in healthy laboratory and medical staff. In 12 males the range was 32–240 µg/l (mean 102 µg/l). In 16 females the range was 17–158 µg/l (mean 53 µg/l).

Serum ferritin levels rose steadily and reached a peak on the third or fourth day in all groups (see table). The differences between the groups on the third day were statistically significant (groups 1–2 $P < 0.025$; groups 2–3 $P < 0.001$).

Mean serum ferritin levels (µg/l) in patients studied ($\pm$ SE of mean). Transaminase values are shown in parentheses (IU)

	Day 1	Day 2	Day 3	Day 4
Group 1	92 $\pm$ 24 (14 $\pm$ 1)	138 $\pm$ 49 (12 $\pm$ 1)	213 $\pm$ 72 (11 $\pm$ 1)	171 $\pm$ 44 (12 $\pm$ 1)
Group 2	339 $\pm$ 109 (33 $\pm$ 12)	569 $\pm$ 212 (50 $\pm$ 14)	779 $\pm$ 213 (81 $\pm$ 33)	881 $\pm$ 361 (41 $\pm$ 10)
Group 3	367 $\pm$ 95 (632 $\pm$ 458)	1652 $\pm$ 491 (869 $\pm$ 447)	5168 $\pm$ 623 (693 $\pm$ 150)	4013 $\pm$ 1229 (860 $\pm$ 314)

Group 1. By the third day only three patients had attained levels outside our reference values but eight had levels that had significantly increased from the initial value (mean percentage increase 166 $\pm$ 63 SE of mean).

Group 2. By the third day six patients had elevated levels and the mean percentage increase was 359 $\pm$ 196.

Group 3. All patients had vastly increased ferritin by the third day, six exceeding 6000 µg/l, and the lowest value being 1070 µg/l. The mean percentage increase was 1745 $\pm$ 483.

The serum transaminase levels also showed a marked difference on the third day between the groups (groups 1–2 $P < 0.05$; groups 2–3 $P < 0.005$) but levels peaked inconsistently between patients. In five patients the serum ferritin rose above normal before the SGOT, and in a further nine the rise occurred on the same day. Only two patients had elevated SGOT levels and ferritins which remained within our reference values. There was no overall correlation between ferritin and transaminase levels on the third day ($r = 0.369$; $P > 0.10$), but when the ferritin changes were expressed as a percentage of the initial values, a definite correlation emerged ($r = 0.491$; $P < 0.05$).

The results of the liver biopsy gradings show excellent agreement with the groupings, the main feature being that all patients in group 1 had mild pathological changes despite normal transaminases, and levels exceeding 400 IU always indicated severe liver damage.

Discussion

Liver damage following paracetamol overdose is practically inevitable though conventional liver function tests may be normal. We have shown that serum ferritin levels in acute hepatocellular damage, when the onset of the insult was known, correlate closely with pathological changes and are more sensitive than transaminase estimations. Since serum ferritin in health has been shown to have neither diurnal variation nor any marked daily fluctuation,⁵ any increase would suggest liver damage. We suggest that further studies should be undertaken into serum ferritin levels in patients at risk from hepatocellular damage—for example, drug trials—and that such research may help to elucidate controversial topics such as halothane hepatitis.

We thank Professor A L Latner and the Department of Clinical Biochemistry for transaminase estimations and Dr A J Watson and Dr M Lesna for pathological help. We acknowledge grants from the Medical Research Council and from the Scientific and Research Committee, University Hospitals of Newcastle upon Tyne.

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Hypoglycaemia in children undergoing adenotonsillectomy

Preoperative hypoglycaemia in children is well recognised. Bevan and Burn¹ found that 30% of children starved for operation had blood glucose concentrations of less than 3.33 mmol/l (60 mg/100 ml) at induction of anaesthesia.

Case report

A previously healthy 5-year-old girl was admitted for routine adenotonsillectomy. After surgery there was slight haemorrhage from the adenoid bed, which was recutted uneventfully in theatre. Subsequently, in spite of no further blood loss, no hypotension, and a steady pulse rate, she became progressively paler with cold extremities and did not respond to painful stimuli. Blood was transfused, and after 30 ml she had a generalised convulsion. At this point no glucose was found in the blood. She responded to intravenous dextrose treatment, and two days later was discharged in good health.

After this case, 32 consecutive children admitted for tonsillectomy or adenoidectomy, or both, aged from 3 to 11 were studied. Their blood glucose levels were estimated immediately on return from theatre by low-reading Dextrostix (see table), interpolating when necessary. A reading between 2.50 mmol/l (45 mg/100 ml) and 5.00 mmol/l (90 mg/100 ml) was taken as 3.61 mmol/l (65 mg/100 ml). This technique gives an excellent correlation with true blood glucose levels obtained by quantitative methods.²

Blood glucose values in 32 children after adenotonsillectomy

Blood-glucose (Dextrostix) (mmol/l)	..	1.39	2.50	3.61	5.00
No of children	..	4	12	3	13

Conversion: SI to traditional units—Glucose: 1 mmol/l $\approx$ 18 mg/100 ml.

By conventional criteria (< 2.78 mmol/l (50 mg/100 ml)) half these patients were hypoglycaemic. Even by Cornblath and Schwartz's³ criteria (< 2.22 mmol/l (40 mg/100 ml)), four patients (12.5%) were hypoglycaemic. Age did not appear to influence greatly the incidence of hypoglycaemia.

Discussion

Hitherto, common practice has been to give children undergoing adenotonsillectomy fluids only after bedtime on the evening before operation and nothing by mouth after 8 am for an afternoon operating session or after midnight for a morning session. Thus periods of starvation of six to 20 hours occur. By custom, patients have been starved before general anaesthesia to reduce the risk of vomiting and aspiration of gastric contents. Recently Thomas showed that this was no more likely to occur if children drank milk up to four hours before operation than if they were starved for eight hours.⁴ In Thomas's study no hypoglycaemia occurred in the first group. In the second group 15% had blood glucose levels below 2.22 mmol/l (40 mg/100 ml).

There is no constant relation between the level of blood glucose and the occurrence of hypoglycaemic symptoms. Thus fits, with consequent brain damage, spasticity, and mental deficiency, may occur without warning in an asymptomatic patient. In animal studies levels of blood glucose below 1.11 mmol/l (20 mg/100 ml) for two hours cause ischaemic cell change affecting neurones in the neocortex,

hippocampus, and cerebellum. A similar distribution is found after cerebral hypoxia or oligaemia. Hypoglycaemia has several secondary biochemical effects, one of the most dangerous being hyperkalaemia, which may lead, as it did in this patient, to electrocardiographic changes indicating hyperkalaemic damage. This may lead to ventricular fibrillation, but was fortunately reversed by intravenous calcium gluconate and rectal sodium polystyrene sulphonate (Resonium A) on this occasion. It is not unreasonable to suppose that some of the 15 to 20 children who die each year after adenotonsillectomy die from the effects of unrecognised hypoglycaemia.

A review of hospital admission procedures for children undergoing adenotonsillectomy is urgently needed. Operation times for children should be known well in advance so that they may be fed at least up to four hours before operation. Further trial should be given to using metoclopramide to allow children to drink up to one hour before anaesthesia,⁵ a distinct advantage for morning lists and day cases.

I thank Mr R J Sellick for permission to report this case, and Dr R D Jones and Dr C G D Brook for help and encouragement.

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Non-bacterial thrombotic endocarditis in early cancer

In some 90% of cases non-bacterial thrombotic endocarditis (NBTE) as a complication of cancer does not occur until metastases are widespread.^{1 2} Our experience of two patients who died of unsuspected NBTE when the small associated tumour had not metastasised beyond adjacent lymph nodes impressed on us the clinical significance of what is usually regarded as an essentially pathological diagnosis.

Case reports

Case 1—A woman aged 58 was admitted with chest pain and haemoptysis after six weeks' warfarin treatment for deep vein thrombosis of the left leg. She had a prothrombin ratio of 1.5, developed mental confusion and left hemiparesis, and had raised fibrin degradation products in serum and a platelet count of $90 \times 10^9/l$ ($90\,000/mm^3$). Heparin was given. Her mental state deteriorated and she developed progressive pulmonary infarction. She died on day 27. The necropsy findings were adenocarcinoma of body of pancreas 2 cm in diameter; adjacent lymph nodes enlarged and infiltrated by tumour; friable vegetations on mitral valve and lying free in left ventricular cavity (see fig); right renal and both common iliac veins thrombosed; and infarcts of lungs, brain, and right kidney.

Case 2—A man aged 40 was admitted with haemoptysis after three months' dyspnoea and calf pains. He smoked 40 cigarettes a day. Hodgkin's disease had been treated five years previously by radiotherapy and was now presumed inactive, though a new chest radiograph showed enlarged right hilum. Bilateral deep vein thrombosis was diagnosed and warfarin treatment started. There was steady proximal extension of thrombosis, with three major pulmonary infarctions. Diagnosis of disseminated intravascular coagulation on day 8 prompted change to heparin infusion, but 72 hours later he died of anterolateral myocardial infarction. Necropsy showed minute papillary adenocarcinoma of right upper lobe bronchus, involving hilar lymph nodes; no evidence of Hodgkin's disease; large verrucous vegetations on mitral valve; and occlusion of anterior descending branch, left coronary artery. Heart, lungs, and kidneys were extensively infarcted.

Non-bacterial thrombotic endocarditis in early cancer.

Comment

Although presenting with the familiar features of deep vein thrombosis of the leg, each case pursued an atypical course. The thrombosis progressed, causing repeated pulmonary embolism, and was associated not only with disseminated intravascular coagulation but also with episodes that suggested recurrent systemic embolism. Underlying neoplasia was suspected, and in case 2 all but proved. Nevertheless, the investigations necessary for a conclusive diagnosis were prevented by deterioration which, in retrospect, must be attributed largely to NBTE.

In some cases of NBTE due to non-malignant disease and in the 10% of cancer patients for whom, like these two, resection of the tumour is possible, death might be averted if the valvular lesion could be identified in life. Despite its well documented pathology, however, and the firm place it has gained among the complications of cancer, NBTE remains almost exclusively a necropsy diagnosis. This may be because one, or even two, of the three components accepted as being essential for diagnosis—an appropriate underlying disease, a cardiac murmur, and multiple systemic embolism³—are absent from the clinical picture. New murmurs arise in no more than 20% of patients and the more amenable to surgery the underlying tumour the less likely it is to be found by the simpler investigations.

We therefore propose the following revised criteria for diagnosing NBTE: (a) venous thrombosis accompanied by features suggesting systemic as well as pulmonary infarction; (b) progression despite anticoagulant treatment; (c) either no apparent origin for the systemic emboli or else a cardiac murmur in the presence of persistently negative blood culture. If a presumptive diagnosis could be made with these criteria, developing a non-invasive technique to confirm it would enable corrective surgery to be considered for any patient in whom disseminated malignancy or other irreversible disease had been excluded with reasonable certainty.

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