16.7% of a cohort of 253 patients followed up over 10 years.²

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Cystoscopy has little value in children

EDITOR,—Fritz H Schröder does not emphasise that his editorial on microscopic haematuria relates to adult and not paediatric practice. There is little point in children with haematuria undergoing cystoscopy, yet each year I see several children who have been investigated in urology departments and, after cystoscopy has given a negative result, are referred for a paediatric medical assessment. It would have been helpful if the editorial had emphasised this.

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Is rarely significant if asymptomatic

EDITOR,—Fritz H Schröder's editorial on microscopic haematuria seems unduly alarmist.¹ He quotes a prevalence of 12% of life threatening conditions in men and 34% in women over 50 with haematuria. However, the prevalence of serious disease depends on how the haematuria comes to light. In a paper from the Mayo Clinic Mohr *et al* found "serious" urological disease (including calculi) in 2.0% of patients with asymptomatic haematuria compared with 1.2% of controls.² The prevalence of urothelial tumours and renal carcinomas was 0.5% in the asymptomatic haematuria group (zero in the controls). These were men over 34 and women over 54 living in Rochester, Minnesota, undergoing routine urine screening.

The much higher figures quoted by Schröder must include patients who have urinary symptoms or signs. In the absence of such symptoms or signs it is arguable whether asymptomatic haematuria with less than nine red blood cells per high power field justifies investigation. In a paper from Chicago the estimated cost of diagnosing one case of renal or urothelial carcinoma in patients with asymptomatic haematuria was \$75 000-\$86 000.³

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Dipsticks may pick up haemoglobinuria

EDITOR,—Fritz H Schröder provides a logical set of practical guidelines for the investigation of microscopic haematuria.¹ Because his algorithm starts from a dipstick analysis, it is important to remember that a positive dipstick result is not synonymous with haematuria. The commonest explanation for a positive result with no red cells in

the urinary sediment is haemoglobinuria. This is much more rare than haematuria, but recognising haemoglobinuria is important because it signals, rather than renal disease, intravascular haemolysis. This in turn is the final common pathway of red cell destruction in different conditions.² Haemoglobinuria can be acute and massive, and therefore unlikely to be confused with haematuria, in haemolytic anaemias associated with glucose 6-phosphate dehydrogenase deficiency, and in rare cases of malaria ("blackwater fever") and septicemia (caused by *Clostridium welchii*); but it can be more insidious in certain forms of autoimmune haemolytic anaemia and in paroxysmal nocturnal haemoglobinuria.

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Prevalence in young men underestimated

EDITOR,—Fritz H Schröder's fine editorial and algorithm¹ is no less welcome if I cavil at his underestimate of the problem in those aged under 40 years. In the *BMJ* 10 years ago, Froom *et al* showed that about a third of fit young men in the Israeli air force had microscopic haematuria when examined over 15 years²: the sort of cumulative incidence that is not disclosed by prevalence studies.

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Paternal treatment for sterility and neonatal neuroblastoma

EDITOR,—Robaire and Hales have discussed the possible effects of paternal exposure to chemicals before conception.¹ We report a case of neuroblastoma diagnosed as stage IVS at birth (with manifestations in the skin and liver accompanied by lumboaortic adenopathy) in a male infant born in France whose father had been treated for sterility.

Metaiodobenzylguanidine scans yielded negative results, and N-myc oncogene was not amplified. The first two courses of chemotherapy with vincristine and cyclophosphamide according to the NB90 protocol of the French Society for Paediatric Oncology led to a good partial remission. This was followed by recurrence in the brain and massive pulmonary metastases, which did not respond to treatment with etoposide and carboplatin. The child died of respiratory failure at 3 months. Necropsy was not performed.

The father, aged 29, had been diagnosed as having hypogonadotrophic hypogonadism. He had been treated for seven years, until the third month of the pregnancy, with alternating human chorionic gonadotrophin, human menopausal gonadotrophin, androgens, and luteinising hormone releasing hormone. A few months before the pregnancy modest spermatogenesis had been noted. No other paternal or maternal treatments could be identified, and the parents had not been exposed to other recognised toxic compounds.

Recently, neuroectodermal tumours have been reported in children whose mothers had been

treated for infertility—in particular, after the use of drugs to induce ovulation.^{2,3} Other cases of tumours and a case of intestinal fibromatosis of the newborn have also been described after treatment with human gonadotrophins or oral contraceptives or after induction of ovulation. Gamete intrafallopian transfer has been associated with retroperitoneal haemangiolymphangioma in one case, and in vitro fertilisation with congenital malformations.⁴ Treatments for sterility affect germinal cells; therefore their role in the occurrence of genetic modifications that might play a part in the development of tumours cannot be excluded. The role of paternal occupational exposure—whether to hydrocarbons, paints, or radiation—in the aetiology of childhood cancer is still unresolved.

To our knowledge, no publication has addressed the issue of childhood cancer and medical treatment of the father. In our case the infant had a neuroectodermal tumour. As a carcinogenic mechanism has been considered to be plausible with regard to maternal exposure, a similar mechanism linking the treatment of paternal sterility and childhood cancer should not be excluded. Thonneau *et al* estimated that in 39% of infertile couples both partners have reduced fertility.⁵ It would therefore be worth investigating, in the cases already reported, whether the father had also received any fertility treatment.

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Treating hypertension after stroke

EDITOR,—In their editorial on treating hypertension after stroke,¹ Janice E O'Connell and Christopher S Gray refer to the use of sublingual nifedipine, citing an editorial in the *Lancet*,² which in turn refers to the work of Angeli *et al*.³ Sublingual nifedipine is often prescribed in severe hypertension of various aetiologies. The fact that it works, however, has nothing to do with it being sublingual.⁴ O'Connell and Gray allude to this by suggesting nasogastric administration as an alternative route, and, crucially, in Angeli's study the patients were instructed to swallow their saliva after placing a perforated nifedipine capsule under their tongue.⁵ Since therapeutic amounts of nifedipine are absorbed only after the drug is swallowed the capsules should be bitten to release the

contents and then swallowed as a glass of water is drunk.⁴ If swallowing is impaired, nasogastric administration of the capsule's contents is indeed an alternative, albeit less accurate.

Rather than sublingual nifedipine being prescribed, it would be clearer and more accurate to prescribe nifedipine for oral administration, with additional instructions that the patient should bite the capsule before swallowing it while drinking a glass of water.

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Reye's syndrome

EDITOR,—Maria Casteels-Van Daele and Ephrem Eggermont propose that Reye's syndrome is associated not with aspirin but with antiemetics given for the profuse vomiting which characterises this disorder and that antiemetic toxicity is often misclassified as Reye's syndrome.¹ As evidence they cite a paper describing two patients with classic extrapyramidal symptoms of antiemetic toxicity. Since these have been known for decades, it is unlikely that "better recognition" of these side effects could explain the decline of reported Reye's syndrome in the United States and the United Kingdom.

The authors criticise the North American case-control studies for recording only the drugs given before the onset of vomiting. They question whether this reflects the onset of Reye's syndrome itself. The onset is indeed hard to time precisely, but there is histological and ultrastructural evidence that Reye's syndrome is well established shortly after the onset of vomiting, before consciousness becomes impaired.²

Ironically, the early American case-control studies were affected of temporal precedence bias caused by analysing medications given both before and after the onset of vomiting.³ In later studies, including one funded by the aspirin industry, a detailed definition of day of onset was used; it included both vomiting and neurological symptoms. Temporal precedence bias was avoided by analysing only onset exposures before onset.⁴ No further criticisms of the timing of exposure to drugs have been published.

Casteels-Van Daele and Eggermont state that only drugs given before vomiting were registered in the second year of the Ohio study. Nevertheless data on phenothiazine ingestion throughout the illness were published. Although there was a significant excess among cases, only 19% had received an antiemetic compared with 100% exposed to aspirin. In the British study the corresponding figures were 14% and 59%. Thus if antiemetics do have a role in the pathogenesis of Reye's syndrome it must be substantially smaller than that of aspirin.

The authors further argue that the subjects in the case-control studies had a heterogeneity of conditions, including inherited metabolic disorders. Children with those inherited metabolic disorders that cause a Reye-like illness usually present in the first two years of life with an encephalopathy precipitated by a variety of viral infections. By contrast, Reye's syndrome in the United States in the 1970s and 80s occurred epidemically in association with influenza and epidemically in association with chickenpox; patients had a median age of 8-9 years.

The problem of heterogeneity was addressed in the British study, which used a clinicopathological scoring system. Patients who scored highly satisfied all the criteria of the case definition and resembled clinically those recruited to the American studies. A significant correlation was found between increasing score and aspirin exposure, suggesting that there was indeed a "subset" effect.

Therefore, though Casteels-Van Daele and Eggermont correctly state that Reye's syndrome is a heterogeneous condition, there is evidence for the existence of a subset which is clinically and epidemiologically distinct and nearly always associated with exposure to aspirin. Not only have the numbers of reported cases in the United States and the British Isles declined since the aspirin warnings, but also the epidemiological and clinical pattern has changed. The median age has fallen dramatically; furthermore, the virologically confirmed cases associated with influenza and varicella have selectively declined in the British series since 1986.⁵

Better diagnosis of inherited metabolic disorders has probably also contributed to the fall in the number of cases of Reye's syndrome reported, although there is still a need for better recognition of those disorders that cause Reye-like illnesses. There is no evidence for an aetiological role for antiemetics.

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Atherosclerotic disease and cognitive decline

EDITOR,—Monique M B Breteler and colleagues describe an association between the clinical manifestations of atherosclerotic disease and cognitive decline in elderly people. They conclude that atherosclerotic disease may account for considerable cognitive impairment and suggest it is time to study whether population wide atherosclerotic risk factor intervention can prevent such cognitive decline.¹

The assumption made is that the potentially modifiable atherosclerotic process is the major determinant of the observed cognitive impairment. This may be so for "multi-infarct" dementia, but in many patients cognitive impairment will be due to Alzheimer's disease. As with atherosclerosis, this condition probably evolves from a complex interaction of genetic and environmental factors but is unlikely to respond to conventional risk factor modification. However, one common pathogenic mechanism may link these apparently distinct entities.

The e4 allele of apolipoprotein E has been independently linked with both atherosclerosis and Alzheimer's disease. Carriage of the e4 allele is associated with increased risk of coronary heart disease² and peripheral atherosclerosis,³ clinical features used in the study as surrogate markers of the extent of cerebrovascular disease. The influence of apolipoprotein E4 is likely to be mediated through effects on plasma lipids as this

isoform contributes to higher plasma low density lipoprotein concentrations than the wild-type E3, although apolipoprotein E may also regulate smooth muscle proliferation and differentiation.

Apolipoprotein E is also involved in brain lipid metabolism, and regeneration after injury to the peripheral and central nervous system. The e4 allele frequency in patients with Alzheimer's disease is reported as 0.40-0.50 compared with around 0.12 in control populations. In addition, apolipoprotein E accumulates in the amyloid plaques and neurofibrillary tangles found in this condition, with apolipoprotein E4 showing particular avidity.^{4,5}

Thus the apolipoprotein E gene and its protein product may mediate two major mechanisms contributing to cognitive decline in the elderly. While the vascular component potentially related to apolipoprotein E4 may be influenced by targeting conventional risk factors for vascular disease as proposed by the authors, this strategy is unlikely to yield major preservation in cognitive function since the non-atherogenic expression of apolipoprotein E4 in this condition is currently not modifiable. However, intervention at the genetic and molecular level is worth further investigation as this may exclude both mechanisms and confer a dual benefit in apolipoprotein E related cognitive attrition.

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Autografts of peripheral blood stem cells

EDITOR,—Autografts of peripheral blood stem cells offer additional advantages to those outlined by Tessa L Holyoake and Ian M Franklin.¹ At the moment, peripheral blood stem cells need to be harvested in a large oncology centre with the proper equipment and skill. However, the mobilisation before the harvesting, the intensive chemotherapy followed by reinfusion, and the supportive care may be provided locally in a district general hospital. Most such hospitals have consultant haematologists and nurses with considerable skill in looking after patients with severe pancytopenia for short periods; this experience comes from their management of patients with acute leukaemia.

The patient may need to visit the main oncology centre only as a day case or for an overnight stay. This type of shared care between a major centre and the local hospital offers several advantages. Patients should have most of their treatment locally, and this should be attractive to both patients and their relatives. Most purchasing authorities prefer treatment to be given locally. The cost of inpatient care in a district general hospital should be considerably less than that in a