disorders of autonomic sensation, such as nausea^{2 9}; psychoneuroses, phobias, and depression^{2 5}; and disorders of factors under neurohumoral control, such as blood pressure^{2 8} and bronchial airflow. Placebos will not work if the disease is hyperacute (for example, cardiac arrest), or when vital functions degenerate (for example, in severe metabolic acidosis). Also, the placebo effect usually fails in unremitting disease, such as hereditary syndromes.

Adjuvant placebo treatment is useful in some neuroses and mild depression and may be useful in some chronic non-cancer pain syndromes and in hypersensitivity or hyper-reactivity conditions in which psychic factors play a part (for example, dermatitis and bronchial asthma). Adjuvant placebo seems unlikely to affect the course of cancer. Could the placebo effect be boosted long term? Prolonged administration of opioids in mice inhibits the expression of cell surface markers on T lymphocytes in a dose related manner.¹⁸ This suggests an impairment of immune function, which may outweigh the advantage of a sustained placebo effect.

What about combining placebo treatment with unorthodox techniques such as acupuncture, hypnosis, and homoeopathy? These are likely to potentiate any placebo effect only if they work through an independent mechanism. Hypnosis and acupuncture may not depend on endorphins,¹⁹ but more information is needed. Even greater is the need to determine the placebo component of medicines—both traditional and conventional. The extent to which homoeopathy works through the placebo effect is unresolved, as discussed elsewhere in this issue (p 103).²⁰ Another study in this week's journal reports that an impressive number of cancer patients experienced benefit such as increased optimism from complementary treatments (p 86).²¹ Interestingly, because a reduction in anxiety is a marker of placebo action, patients in this study who used complementary treatments were more anxious than those who did not.

Insights have come from recent studies of the placebo effect, but there is no easy way around the poor specificity

and predictability of placebo treatment. Moreover, the self regulating nature of the placebo mechanism may limit the treatment gain. Nevertheless, in appropriate patients, doctors might consider giving a placebo when active treatment is both costly and likely to confer only marginal or transient benefit.

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Microscopic haematuria

Requires investigation

Gross haematuria is obvious to the patient and is usually followed up, appropriately, by a complete urological work up. The much commoner microscopic haematuria, however, may not always receive the attention that it deserves. Dealing with this symptom adequately in the general practitioner's surgery requires a substantial body of knowledge. Recent developments warrant a re-examination of this topic.

Microscopic haematuria is rare before the age of 50 (occurring in fewer than one in 100 people of this age); after 50 the prevalence rises sharply and varies from 2% to 18%^{1 2} (with some of this variation explained by different definitions). The commonly used dipstick test gives a yes or no answer to the question of whether microscopic haematuria is present and semiquantitative information at the same time. Comparing its results with those of standard microscopic evaluation of urinary sediments, one representative study found a sensitivity of 100% and a

specificity of 60%.³ The relatively high frequency of false positive results of dipstick tests may be due to the technique's detection of normal numbers of red cells ($1-2 \times 10^{12}/l$ urine). The consensus is that if the result of a dipstick test is positive then the urinary sediment should be examined; if the result of a dipstick test is negative no further investigation is needed.

The figure gives an algorithm of recommended diagnostic tests for patients with haematuria. Several explanations exist for some of the variations in the prevalence of microscopic haematuria in different populations. A dipstick test may yield a positive result in the very concentrated early morning urine whereas it may give a negative result during the day after fluid intake. Several other artefacts, especially the contamination of urine with menstrual blood or sexual trauma in men and women, must be considered. Laville *et al* evaluated risk factors in 8200 workers in the metallurgical and chemical industries

Algorithm of diagnostic tests recommended for microscopic haematuria

and found that the following conditions conferred a significantly increased relative risk of microscopic haematuria: age above 40, female sex, arterial hypertension, smoking, the use of non-steroidal anti-inflammatory drugs, a history of urological disease, and employment in the chemical industry.⁴ It may be specific to this population group that, of 222 subjects studied, 90.5% had glomerular haematuria as defined by the presence of dysmorphic erythrocytes.

Confirm, investigate, retest if negative

A "normal" upper limit for microscopic haematuria has yet to be agreed. Recommendations vary between 2 and 5 erythrocytes/high power field. Messing *et al* found no correlation between the number of erythrocytes and the number of times haematuria was present and the seriousness of its possible cause.² Mariani *et al* found that in none of 1000 consecutive patients with a serious underlying cause for their haematuria were fewer than 3 erythrocytes present per high power field. The recommendation is that any haematuria should be re-evaluated once or twice for confirmation. Once microscopic haematuria has been reliably shown the patient should be investigated unless the finding can be explained. If the results of investigations are negative, testing for haematuria should be repeated twice at intervals of six months. Occult cancer will show within a year.

A diagnosis of haematuria, whether gross or microscopic, requires extensive investigation to exclude any serious underlying condition. Treatment with anticoagulants is not an excuse to avoid further investigation—such treatment more often provokes haematuria from pre-existing lesions than causes it *de novo*.

The chance of detecting a nephrological or urological

condition varies strongly with the risk factors discussed above. In men and women over 50, pathological explanations will be found for haematuria in up to four fifths of cases. Further investigations for haematuria uncover life threatening conditions in between 12% and 34% of patients. The risk of such conditions is lower in younger patients and is lower in women than men.

Several examinations of the urinary sediment should follow a positive result of a dipstick test. If white cells are present then urinary culture is mandatory. Recommended laboratory studies should include cytological examination of urine. This should be followed by ultrasonographic examination of the kidneys and bladder—a recommendation that is based on a recent decision analysis by Corwin and Silverstein.⁵ Their analysis clearly showed that ultrasonography is as sensitive as intravenous urography and is more cost effective. Unfortunately, the accuracy of ultrasonography depends very much on the operator so unless a high quality examination can be guaranteed intravenous urography may still be the study of choice. A plain film of the abdomen should also be obtained, mainly to rule out urinary calculi.

Glomerular or non-glomerular?

If no renal explanation is found cystoscopy should follow. The procedure can be performed with a flexible instrument in outpatients and is much less traumatic than previously.

If no explanation for the haematuria is found with the steps outlined so far, a phase contrast or Coulter counter analysis of the excreted erythrocytes should be carried out to determine whether the haematuria is glomerular or non-glomerular. (Erythrocytes that have passed through the glomerular membrane are dysmorphic and smaller than normal erythrocytes.)

Phase contrast microscopy and Coulter counter analysis detect such cells very accurately.⁶ Dysmorphic erythrocytes, especially if associated with substantial proteinuria, suggest a renal origin for the haematuria. The work up should then include a more extensive history and laboratory studies (which may include renal biopsy). If the haematuria is not of glomerular origin then intravenous urography may be needed. If a definite diagnosis cannot be made investigations should be repeated whenever gross haematuria occurs or within four to six months. Renal angiography, computed tomography, or biopsy is indicated only under very specific circumstances.

The commonest causes of glomerular haematuria are IgA nephropathy followed by the other glomerulonephritides. Among 1000 patients with haematuria the common causes of non-glomerular haematuria were inflammatory conditions of the urethra and prostate (usually trigonitis) (377 cases), benign prostatic hyperplasia (165), cystitis (73), transitional carcinoma of the bladder (65), and stones in the renal pelvis or ureter (34).¹ Altogether 80 patients had some form of cancer. In a screening study of men over 50, pathological conditions were found in 31 of 44 men who had haematuria at least once on serial testing. One third of the 44 men had either cancer of the urinary tract or other conditions requiring immediate treatment.²

Every case of microscopic haematuria should therefore be evaluated. The simultaneous use of anticoagulants is no longer a satisfactory explanation. Separating glomerular from non-glomerular haematuria with Coulter counter or phase contrast analysis of the urinary sediment can facilitate diagnosis, and these analyses should be used

often. If the results of a single work up are inconclusive and microscopic haematuria persists then the diagnostic tests should be repeated in due course.

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Growing up with asthma

The two thirds with milder symptoms should grow out of asthma

See papers on p 90 and p 95

Childhood asthma has been regarded as relatively benign and a condition that children often "grow out of." Recently, however, investigators have reported higher prevalence of asthma in children^{1 2} and more frequent persistence of childhood asthma into adult life.³ Hence further studies on factors predicting remission or persistence of childhood asthma, and the development of adult asthma, are welcomed.

Two papers in this week's journal describe outcomes of asthma in cohorts of Australian children. Both longitudinal studies began in the 1960s and both followed up children recruited at age 7 until their 30s. One might therefore expect the findings of the two studies to be similar. Nevertheless, Jenkins *et al* conclude that "children with asthma reported by their parents were more likely than not to be free of symptoms as adults" (p 90)⁴ while Oswald *et al* conclude that "many children do not grow out of asthma" (p 95).⁵ How could similar studies in similar populations come to seemingly opposite conclusions?

Jenkins *et al* followed up a birth cohort of 8700 7 year old Tasmanian children whose parents had originally completed a questionnaire inquiring about a history of wheezing and asthma, recent wheeze, frequency of episodes, age at onset, presence of hayfever, and smoking. All children were assessed by spirometry. A follow up at 29-32 years, 1000 of those with parent reported asthma or wheezing were selected, together with 1000 others; 87% were located, and 75% provided information on their current respiratory status.

Four major conclusions can be drawn from this study. Firstly, a high proportion of asthmatic children become symptom free. The symptoms of fewer than one in three asthmatic children persisted into the fourth decade. Secondly, asthma in adults can be partially predicted from childhood asthma, especially from those features reflecting severity of the childhood disease. Those with childhood asthma were 2.5 times more likely to have adult asthma than those with no such history. In those with persistent disease, risk factors included female sex, onset after age 2, more than 10 attacks throughout childhood, lower peak flow rates in childhood, and parental asthma.

Thirdly, atopy is a major determinant of the outcome, with personal and parental histories of atopy being more commonly associated with frequent, current asthma in adulthood. Fourthly, new asthma in adulthood is not uncommon. One in nine children not reported as having asthma at age 7 developed asthma by age 30. Female sex, maternal hay fever, and lower lung function at age 7 were important risk factors for this. The most impressive abnormality of lung function in children who developed

asthma in adulthood was a lower mid-expiratory flow, suggesting that small airway disease is predictive of adult asthma.

In contrast, the emphasis of Oswald *et al*'s paper is that most childhood asthma persists. This report comes from Melbourne children who were recruited in the 1960s and reviewed at age 35. Methodological differences explain the different findings. The cohort was selected from the population of 7 year olds, but when reviewed at age 10 the cohort was "enriched" with children with more severe asthma (asthma with an age of onset below 3 years, with persistent symptoms, and either chest wall deformity or low lung function at age 10). These characteristics might be expected to predict more persistent asthma, and the finding that 70% of those with severe asthma at age 10 had persistent asthma at 35 is therefore not surprising. Others have reported similarly higher levels of symptoms persisting in people who had attended asthma clinics when children.⁶ But even among the Melbourne subjects with severe childhood asthma, 10% were fully symptom free as adults and 15% had only minimal symptoms. Jonsson and Boe similarly reported that up to a half of children admitted to hospital with asthma were symptom free as adults.⁷

If the Melbourne sample with wheezing, wheezy bronchitis, or asthma at age 7 is examined before the enriched subsample was added it is apparent that only 20% of subjects had persistent adult asthma likely to be clinically important. Of those with "wheezy bronchitis," only a third had any symptoms at 35. This is consistent with "growing out of" mild asthma or wheezing, and the frequent persistence of more severe asthma. Interestingly, among Melbourne children with mild asthma, atopy was not a prognostic factor. This finding differs not only from that of the Tasmanian study, but also from other studies in Australia,⁸ New Zealand,⁹ Scandinavia,¹⁰ and Britain.¹¹ Atopy was very common in the Melbourne cohort (99% in those with more severe disease), which makes the effect of atopy more difficult to determine. Prognosis of childhood asthma in the Netherlands, however, was likewise apparently not influenced by the presence of atopic disease.^{12 13}

Other risk factors for persistent asthma in adults include airway hyperresponsiveness in childhood,¹² but the present reports do not address this. Most studies show that persistent asthma is more likely in females. The likelihood of a low forced expiratory volume at one second in adulthood is related to the degree of abnormality of forced expiratory volume in childhood.^{14 15}

Neither of these Australian papers addresses the impact of treatment on "natural" course. The favourable outcome