and greatly inhibit atherogenesis. Interactions in vivo between iron and low density lipoprotein are not well defined. The apparent lack of increased atherosclerosis in haemochromatosis may simply mean that modification of low density lipoprotein catalysed by iron is maximal or nearly maximal at a low level of excess iron.

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Control for haemotological variables

EDITOR,—In their editorial on iron and coronary heart disease M J Burt and colleagues draw attention to the associations between coronary heart disease, increased iron stores, and raised serum ferritin concentrations.[1] They suggest potential mechanisms, including the production of free radicals and the promotion by iron of oxidation of low density lipoprotein. Other factors may also contribute.

In 1971 we started a prospective study of risk factors for coronary heart disease; so far we have recruited 915 healthy men, predominantly middle aged executives (mean (SD) age at first 45·5 (8·1) years). Of these, 41 have developed manifest coronary heart disease (of whom 16 have died). We recently compared the values of risk factors at the first visit in these men with those in the remaining men, who constitute a control group who have remained free of manifest vascular disease. In addition to showing the expected differences in cigarette smoking, lipid and lipoprotein concentrations, and blood pressure, the men who subsequently developed coronary heart disease showed several differences in haematological variables at their first visit; their mean haemoglobin concentration, packed cell volume, and leucocyte count were all significantly increased (table). These differences have been found in other prospective studies.[2,3]

Mean (SD) haematological variables at first visit in controls who remained free of manifest cardiovascular disease (n=16)

		Coronary heart disease	
	Controls	All cases	Died
Haemoglobin (g/l)	146 (10)	150 (13) p<0·05	154 (11) p<0·01
Packed cell volume	0·43 (0·03)	0·44 (0·04) p<0·05	0·45 (0·03) p<0·05
White cell count (10^9/l)	6·02 (1·80)	7·29 (2·33) p<0·01	7·36 (2·19) p<0·01

Increased blood viscosity associated with a relative polycythaemia and reduced coronary blood flow might lead to an increased risk of coronary heart disease, and increases in the haemoglobin concentration and packed cell volume could contribute to this. Though an increased packed cell volume might be an adaptation to poor aerobic capacity consequent on pre-existing subclinical ischaemia, controlling for increases in the haemoglobin concentration and red cell count may be necessary if the role of increased iron stores and ferritin concentrations in the risk of coronary heart disease is to be clarified.

Burt and colleagues derive support for the importance of high serum iron stores in the risk of coronary heart disease from the correlation between rates of this disease and of iron deficiency in different countries. Such associations should be interpreted with caution. South Asians in Britain have considerably higher rates of coronary heart disease than white people,[4] but we have found them to have reduced iron and ferritin concentrations, packed cell volumes, and haemoglobin concentrations.[5]

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Iron linked to immune activation

EDITOR,—M J Burt and colleagues discussed the role of iron in the pathogenesis of atherosclerosis and ischaemic heart disease.[1] Iron may have a role in the production of free radicals, which may explain why a raised serum ferritin concentration is associated with an increased risk of acute myocardial infarction. However, the question remains whether increased dietary iron directly increases susceptibility to coronary heart disease.

Various studies suggest that activated immune cells play a part in the pathogenesis of coronary heart disease and in changes in iron metabolism. Increased neopterin concentrations were reported in patients with atherosclerosis,[2] indicating activated cellular immunity; this finding supports the view that cytotoxic products of activated immune cells, such as reactive oxygen metabolites, have a role in tissue injury.

An association was also found between increased neopterin concentrations and changes in iron metabolism in distinct groups of patients suffering from chronic inflammatory diseases, higher neopterin concentrations being associated with decreased serum iron concentrations but increased ferritin concentrations.[3] In vitro, iron was found to interfere with the activation status of macrophages.[4] Taken together, these findings provide an alternative explanation for the results of Salonen *et al* discussed in the editorial—namely, that chronic activation of the immune system is the underlying abnormality that triggers coronary heart disease and that increased ferritin concentrations simply result from chronically activated cellular immunity.[3]

From recent data it even seems that neopterin itself could contribute to tissue damage, since neopterin enhances effects mediated by cytotoxic substances like hydrogen peroxide or hypochlorous acid at physiological pH.[5] In summary, activated macrophages rather than increased availability of iron are likely to play a part in the pathogenesis of coronary heart disease. This conclusion would also be in line with the observation that subjects homozygous or heterozygous for haematochromatosis do not experience high rates of coronary heart disease.[1]

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Management of pneumothorax

EDITOR,—We are pleased that our guidelines on the management of spontaneous pneumothorax[1] have stimulated debate.[2] We entirely agree with the comments made by J A Haggie,[2] and by A J Ireland and A J Dorward[2] about the dangers of a trocar-drain assembly. These assemblies are, however, already in wide use. Though we agree that they are potentially dangerous instruments, we emphasise in our guidelines that blunt dissection with forceps or a scalpel and making a wide tract through the intercostal muscles down to and through the parietal pleura are essential. We emphasise that the sharp metal point of a trocar may be lethal if inserted forcibly and that the assembly should simply slide in.

We appreciate that there are minor differences between our guidelines and those on advanced trauma life support, but this probably reflects the differences between emergency intercostal drainage after trauma and elective drainage of a spontaneous pneumothorax. Our guidelines will be updated regularly, and other points that have been raised will be incorporated into new versions.

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Kidney granuloma in Whipple's disease

EDITOR,—A J Archimandritis and M S Weetch report a case of granulomatous interstitial nephritis in Crohn's disease;[1] this is a rare complication of the disease. We recently saw a case which suggests that granulomatous renal disease may complicate the course of another inflammatory bowel disease, Whipple's disease.

A 53 year old man was admitted to hospital because of longstanding diarrhoea and a recent increase in serum creatinine concentration. He had had ankylosing arthritis for several years. He did not have a history of either apparent infection or exposure to toxic or allergenic substances. On admission his temperature was 37·2°C and blood pressure 140/90 mm Hg. His peripheral lymph nodes were not swollen, and the liver and spleen were not palpable. No rash was noted. There was no hilar adenopathy or abnormal shadows in a chest *x* ray film. The optic fundi were normal, and examination of the eyes with a slit lamp disclosed no abnormalities.

Serum creatinine concentration was 190 μmol/l, creatine clearance 55 ml/min, and 24 hour urinary protein excretion 0·4 g, and there was microscopic haematuria. Results of liver function tests were

normal. Haemoglobin concentration was 85 g/l and the erythrocyte sedimentation rate was 30 mm in the first hour. Serum concentrations of electrolytes, including calcium, were within normal limits, and angiotensin converting enzyme activity was normal. Results of tests for complement component (C3, C4), antinuclear antibodies, rheumatoid factor, antineutrophil cytoplasm antibodies, and paraprotein were negative. A tuberculin test also yielded negative results. Other investigations showed the presence of a malabsorption syndrome with steatorrhea. A jejunal biopsy specimen showed a pattern typical of Whipple's disease with the presence in the mucosa of numerous macrophages that were positive on periodic acid Schiff and Gram staining.

Renal biopsy showed tubulointerstitial nephritis with many granulomatous formations; there was diffuse infiltration of interstitial cells and fibrosis with tubular degeneration. There was no central caseation, and no acid fast bacilli were seen on Ziehl-Neelsen staining. Immunofluorescence yielded unremarkable findings.

Treatment with doxycycline was started. His diarrhoea resolved and his weight increased concurrently. His renal impairment, however, remained stable.

Although Whipple's disease is a systemic condition that can cause granulomas in other organs, only one previous case of well documented granulomatous interstitial nephritis has been reported.[2] We believe that we ruled out other causes of granulomatous interstitial nephritis in our patient and that a link between the nephropathy and Whipple's disease is probable. Crohn's disease and Whipple's disease should probably be added to the list of aetiologic factors in granulomatous interstitial nephritis already cited.[3]

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Activated charcoal for chloroquine poisoning

EDITOR,—Of the three patients reported on in the grand round on chloroquine poisoning, two received 50 g of activated charcoal after gastric lavage and recovered without complications; the third was dead on arrival at hospital.[1] The authors did not discuss the role of activated charcoal in acute chloroquine poisoning.

We have shown that activated charcoal effectively prevents (by up to 95-99%) absorption of the fraction of ingested chloroquine dose that is in the stomach when charcoal is given (table).[2]

Effect of activated charcoal (25 g within five minutes of 500 mg chloroquine phosphate) on absorption of chloroquine in healthy volunteers. Values are means (SE)

	Control (n=6)	Charcoal (n=6)
Plasma chloroquine:		
Peak concentration (nmol/l)	124 (11)	<3·5*
Area under curve (nmol h/l)	7 270 (825)	62 (46)*
Whole blood chloroquine:		
Peak concentration (nmol/l)	996 (54)	<9·4*
Area under curve (nmol h/l)	77 470 (3200)	114 (64)*

*p<0·001.

As discussed in the grand round, death from chloroquine poisoning may be rapid without treatment; this is partly due to the rapid absorption of oral chloroquine. There is thus little time for therapeutic measures such as gastric lavage or emesis after administration of ipecacuanha. Moreover, these procedures are not particularly effective[3] and may, by delaying the administration of activated charcoal, allow absorption of chloroquine to continue. In addition, potential complications of gastric lavage include cardiac arrhythmias (chloroquine is cardiotoxic).

We believe that not using lavage or ipecacuanha but instead proceeding directly to the administration of charcoal (at least 50 g) is the best option in acute chloroquine poisoning. Repeated administration of activated charcoal, however, is not likely to enhance elimination of chloroquine if it has been already absorbed and distributed into tissues.[4] Activated charcoal should be kept readily available in all places where chloroquine is frequently used and should be given to all patients who present with overdose without delay—even at home or before transportation to hospital.

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Sex differences among recipients of benzodiazepines

EDITOR,—Fransje W van der Waals and colleagues report the trend in general practice in the Netherlands to prescribe benzodiazepines more commonly to women than men.[1] In a population based survey in the province of East Flanders, Belgium, Blondeel found a similar sex difference.[2] For this survey a sample of 1455 people aged 18 and over was randomly selected from a database of inhabitants. By means of a semistructured interview, information was collected on the prevalence, frequency, and duration of use of benzodiazepines. Altogether 18·7% of all participants were using one or several benzodiazepines daily at the time of the survey.

The proportion of users increased with age, and in all age groups a much higher prevalence was found among women than men (table). Several other sociodemographic factors were related to the use of benzodiazepines: people who were at higher risk more commonly had a low level of education, lived alone or with one other person, were unemployed, had more physical complaints, and showed more psychological dysfunction. When a logistic regression analysis was carried out, however, sex and education were no longer significant predictors of use. When factors such as age, employment, whether the person lived alone or with others, and physical complaints were considered, being female was not a factor in explaining use of benzodiazepines.

In an attempt to explain the sex difference that they found van der Waals and colleagues asked doctors to complete a registration form for each consultation. In cases in which benzodiazepine treatment was prescribed a legitimate reason for prescription was cited on this form less commonly for female than for male patients.

Numbers (percentages) of men and women using benzodiazepines by age (n=1455)

Age (years)	Men	Women
18-44	20 (5·5)	39 (10·8)
45-64	36 (18·7)	74 (30·2)
≥65	32 (27·6)	79 (45·4)
Total	88 (13·0)	192 (24·6)

A one year follow up study that we conducted in a sample of long term users of benzodiazepines, in which we also interviewed the prescribers, yielded different results.[3] The doctors gave a valid reason for treatment with the same frequency in both sexes. Yet their reports showed little conformity with patients' views. Both parties agreed that during the most recent consultation in which a prescription was given, no communication had taken place about benzodiazepines and related complaints. Contrary to the finding of van der Waals and colleagues, a higher proportion of men than women in our sample said that they had not discussed their problems with the doctor when receiving their first or last prescription.

This discrepancy might partly be due to the methods used in both studies, since neither study used direct observation of the consultation. We think that direct observation of consultations would give a more accurate view of the process that leads to a major sex difference among recipients of benzodiazepines.

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Tobacco advertising

A tricky business

EDITOR,—An advertisement for Zestril (lisinopril) appears on the back cover of the clinical research edition of the *BMJ* published on 28 August. The photograph in the advertisement depicts an apparently happy group of people who have been successfully treated with Zestril for either hypertension or congestive heart failure. However, one of the "patients" is shown smoking a pipe. Am I to infer from this advertisement that if patients take Zestril to improve their condition there is no need for them to modify their smoking practices and, further, that the benefits of Zestril are enhanced by smoking?

I appreciate that advertising is a tricky business and that the attitude of the British government to tobacco advertising (both direct and indirect) is not helpful, but a more enlightened outlook exists in the Republic of Ireland. Article 15(1)(a) of the Tobacco Products (Control of Advertising, Sponsorship and Sales Promotion) Regulations 1991 states that reference to or representation of tobacco products or smoking utensils shall not be included