Disorders, and Pain in the Neck. These are free and can be sent in bulk to general practitioners and hospital doctors or individually to patients. Special booklets for the parents and teachers of children with juvenile arthritis, *When Your Child Has Arthritis* and *When A Young Person Has Arthritis*, have also been produced.

Other booklets—*Your Home and Your Rheumatism, Marriage, Sex and Arthritis*, and *Are You Sitting Comfortably?*—are available at a modest cost. All booklets and a publication list can be obtained from the Arthritis and Rheumatism Council, 41 Eagle Street, London WC1R 4AR.

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Medicine in the Third World

SIR,—Professor J K G Webb's paper (14 April, p 1141) was most stimulating. I have recently returned from west Africa after two years in a rural mission hospital and have been reflecting on the worth of this enterprise. There seem to have been three main benefits. Firstly, the obvious benefits to me in broadening my experience of life and medicine.

Secondly, several hundred patients benefited directly from having been seen and treated by a doctor. Most of this work was curative, and often the results were dramatic despite limited resources and laboratory facilities. The major cost was not that of drugs, materials, or overheads, but of paying me. In fact since I was funded from the UK the care received was subsidised by my funding organisation. The overall cost benefit ratio was still impressive in comparison with the "first world." This reflects more on Third World deprivation than on "first world" inefficiency.

The third benefit was to the whole population. Here I believe I served as a lure. European and American trained doctors have a considerable reputation, and patients are drawn to them from great distances—often to the detriment of local clinics and hospitals. A positive side was that our hospital was able to run nurse and midwife training schools where the standards attained were adequate and, more importantly, appropriate. Without the stream of committed, mainly foreign, doctors to the hospital these schools would be threatened, and I suspect that my main contribution was this indirect support to the schools. This may encourage the deprofessionalisation of medicine, but the long term benefits will outweigh the care dispensed by quality conscious doctors.

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What carbohydrate foods should diabetics eat?

SIR,—Dr J I Mann attempts to explain the beneficial effect of cooked dried beans in terms of delayed digestion, fibre that forms gels, particle size, and integrity of structure of the food (7 April, p 1025). To the list of possible explanations should be added the effects of lectins, which are haemagglutinating proteins present in most plant products and especially prominent in legumes.¹ Some lectins are resistant to cooking and digestion

and may appear in active form in the systemic bloodstream after feeding.² Kidney bean lectin binds to intestinal epithelium and interferes with the absorption of glucose and in higher concentrations causes gut damage that is occasionally manifest as severe gastroenteritis in incautious folk who cook their beans inadequately.³

Most relevant in this context is the insulin mimicking effect of certain lectins.⁴ Wheat germ lectin binds to the insulin receptors of adipocytes and is as effective as insulin itself in enhancing glucose transport and inhibiting adenylate cyclase. A substantial effect occurs at lectin concentrations as low as 4.0 nmol/l. At such low concentrations wheat germ lectin also enhances the binding of insulin to its receptors—an effect noted by Dr Mann as resulting from a high carbohydrate diet. Although biochemists have known these findings for over 10 years,^{5,6} no physician seems yet to have tried the therapeutic effect of deliberate lectin administration, perhaps because of the fearsome reputation of some lectins as poisons.⁷ I have ingested the jackbean lectin concanavalin A many times experimentally and live to tell the tale; lectins are not as frightening as they may seem and should be investigated in diabetic therapy.

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Drug induced Parkinson's disease

SIR,—I want to make one important amendment to Dr J E C Hern's algorithm for the elucidation of tremor (7 April, p 1072). He suggests that if parkinsonian tremor is present and the patient is not taking phenothiazines, haloperidol, or tetrabenazine, then the patient should be treated for Parkinson's disease. This is an unnecessarily limited inquiry and will lead to some cases of drug induced parkinsonism being missed. We found four cases of occult drug induced parkinsonism,¹ and have added several more in the past two years. These were patients who presented with parkinsonism and in whom it appeared that no drug was responsible, but further detailed inquiry showed that they had been taking a drug capable of causing parkinsonian features.

Additionally, we have recently studied 48 cases of drug induced parkinsonism and found that while most lost their parkinsonian features between six weeks and three months a few retained these features much longer. One 88 year old lady became totally free of parkinsonian features only after nine months. She would have been caught in Dr Hern's algorithm and treated for parkinsonism—no doubt with excellent results.

Drug induced parkinsonism is much commoner (especially in the elderly) than most people have been led to believe. It is necessary to inquire minutely into all recent drug treatment before diagnosing idiopathic parkinsonism and in doubtful cases a careful "drug holiday" should be arranged at intervals of three months up to at least one year from starting levodopa or other antiparkinsonian treatment.

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¹ Murdoch PS, Williamson J. A danger in making the diagnosis of Parkinson's disease. *Lancet* 1982;ii:1212-3.

Fractures and hypercalciuria: two markers of severe dependence in alcoholics

SIR,—We have read the contrasting data of Dr R D Johnson and others (4 February, p 365) and Lindsell *et al* (28 August-4 September 1982, p 597) about the presence of fractures on chest radiographs as an indicator of alcoholism in patients with liver disease. Dr Johnson and others are probably right that the differences between surveys may reflect the different populations studied.

Many patients with alcoholic liver disease have only mild if any alcohol dependence.^{1,2} We work in a wine producing area where many heavy wine drinkers develop liver disease without major social, psychological, or behavioural problems. Our findings are that the presence of fractures is related only to the severity of alcohol dependence. We have found a similar relationship with urinary calcium excretion.

We studied 106 patients aged between 22 and 73 years (mean 43.8) admitted to the department of internal medicine and the alcohol treatment unit between 1982 and 1984 with a history of alcohol consumption of at least 160 g (5.6 oz) a day for 10 years or more. A history of alcohol consumption and inquiry of any trauma or fractures were elicited by one of the doctors using a standardised interview schedule. Dependence was assessed by an alcohol dependence questionnaire devised according to the guidelines of a World Health Committee.³ A total of 53% of alcoholics had no or only mild dependence, while 47% were classified as severely dependent. A control group consisted of 150 patients matched for age and sex and referred with various diseases not related to alcohol. Fractures were more common in alcoholics (61 patients, 58%) than in controls (11 patients, 7%). Limb and rib fractures were the most common (31 patients, 29%; and 29 patients, 27%, respectively). Rib fractures were multiple in 24% and bilateral in 9% of alcoholics. Skull, nasal septum, pelvis, and clavicular fractures were less common (11 patients, 10%). Severely dependent alcoholics showed a higher incidence of fractures compared with those with mild dependence (39 patients, 78%, compared with 12 patients, 22%). No significant difference in age, duration of drinking, serum γ -glutamyl transpeptidase or mean corpuscular volume was found between the groups, but severely dependent alcoholics showed a slight decrease in serum calcium (2.25 ± 0.11 mmol/l (9 ± 0.44 mg/100 ml) versus 2.4 ± 0.13 mmol/l (9.6 ± 0.52 mg/100 ml); $p = 0.029$).

We decided to study the renal handling of calcium in our patients. Fractional urinary excretion of calcium, calculated as the ratio of calcium clearance to creatinine clearance, and fasting urine calcium to urine creatinine ratio were measured within 48 hours of admission. Severely dependent alcoholics showed increased fractional urinary excretion of calcium compared with those with mild dependence (1.387 ± 0.502 versus

0.602±0.289; $p < 0.0001$) and with controls. Three fifths of severely dependent alcoholics and a quarter of those with mild dependence had a fasting urine calcium to urine creatinine ratio exceeding the upper normal limit of 0.12. There was an impressive correlation between fractures and hypercalciuria.

The increased urinary calcium excretion probably has no important relation to the fractures. These seem rather to be secondary to injury. The hypercalciuria in alcoholics, however, seems to be a useful indicator of the alcohol dependence syndrome. We conclude that the presence of fractures has limited use in diagnosing alcoholism. The presence of fractures, especially if multiple, and the hypercalciuria may be of value in estimating the severity of dependence in individual alcoholics.

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¹ Wodak AD, Saunders JB, Ewusi-Mensah I, Davis M, Williams R. Severity of alcohol dependence in patients with alcoholic liver disease. *Br Med J* 1983;287:1420-2.

² Jellinek EM. *The disease concept of alcoholism*. New Haven: Hillhouse Press, 1960:36-41.

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Haemoperfusion in acute intermittent porphyria

SIR,—Dr A C Y Laiwah and others (10 December, 1746) presented their experience with charcoal haemoperfusion and haemodialysis in patients with acute intermittent porphyria. The acute hepatic porphyrias (acute intermittent porphyria, variegata porphyria, and hereditary coproporphyria) are dangerous conditions and each possible new treatment is a valuable contribution.

Last year we performed 21 haemoperfusions in three patients with hepatic porphyria.¹ One with acute intermittent porphyria was treated by single haemoperfusion and we describe this case.

In May 1979 a 35 year old woman on no drugs suffered an acute attack of severe abdominal pain with vomiting. This recurred in July 1979 and subsequently after taking barbiturates, and in November 1979 after taking barbiturates and tilidinium chloride she had a severe attack accompanied by a hypertensive crisis. Acute intermittent porphyria was diagnosed based on increased concentrations of aminolaevulinic acid, porphobilinogen, and porphyrins in her urine.^{2,3} This was confirmed by measuring the activity of uroporphyrinogen I synthase in erythrocytes (94 pmol uroporphyrin/mg protein/30 min/37°C, normal 150.0; SD 30).⁴ Between 1980 and 1983 she had four acute attacks with abdominal symptoms and hypertension. These were treated with glucose, high doses of β -blockers, chlorpromazine, and intensive care.

Her most recent attack (March 1983) was treated by single haemoperfusion lasting six hours using a Hemosorb A-2 column and Amberlite XAD-2 sorbent coated with a 1% (weight) poly (2-hydroxyethyl methacrylate).⁵ During haemoperfusion a 32% decrease in total plasma porphyrins (determined by direct

spectrofluorometry^{6,7}) was noted. This was due to a decrease in porphyrinogens (60%) with the level of preformed porphyrins remaining unchanged.⁷ A total of 617 nmol of uroporphyrin, 41 nmol of coproporphyrin, and 28 nmol of the remaining polycarboxyl-porphyrins⁸ were desorbed from the column. Urinary excretion was 4005 nmol of uroporphyrin/20 h, 437 nmol of coproporphyrin, 307.2 μ mol of porphobilinogen, and 486.5 μ mol of δ -aminolaevulinic acid before haemoperfusion, and 2208 nmol/20 h, 322 nmol, 287.7 μ mol, and 391.9 μ mol respectively after.

After haemoperfusion the abdominal pains disappeared and her mood improved. It is possible that a factor responsible for the clinical picture—other than porphobilinogen, δ -aminolaevulinic acid, and porphyrins—is eliminated by haemoperfusion.

No definite conclusions can be drawn from a single case but we believe that resin haemoperfusion contributed to the recovery of this patient. Our results differ from those of Dr Laiwah and others. This may be due to the different sorbent used, or to individual variation in the disease.

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¹ Grabecki J, Haduch T, Urbanowicz H. Die Einfachen Bestimmungsmethoden der delta-Aminolävulin-säure im Harn. *Int Arch Gewerbepath Gewerbehyg* 1967;23:226-32.

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⁷ Day RS, de Salamanca RE, Eales L. Quantitation of red cell porphyrins by fluorescence scanning after thin-layer chromatography. *Clin Chim Acta* 1978;89:25-33.

Risks of radioiodine treatment of thyrotoxicosis

SIR,—I want to add a postscript to my leading article (17 December, p 1821) as two helpful studies have just been published.

Holm reports on 4557 patients treated with radioiodine in 1951-75 at the Radiumhemmet in Stockholm followed up to death or to the end of 1976,¹ and Hoffman reports on 1005 women treated with radioiodine and 2141 treated by surgery at the Mayo Clinic from 1946-64 followed up to death or to the end of 1978.² Both reports are summarised in the table: they show no significant excess of any cancer or leukaemia.

Incidence of cancer and leukaemia in 4557 Swedish patients treated with radioiodine and in 3146 patients treated at the Mayo Clinic with radioiodine at thyroidectomy

Malignancy	Sweden		Mayo Clinic (radioiodine)		Mayo Clinic (surgery)	
	Observed deaths	Expected deaths	Observed deaths	Expected deaths	Observed deaths	Expected deaths
Thyroid cancer	4	3.8	3	0.8	1	2.2
Leukaemia	10	10.2	4	3.2	10	6.7
All cancers and leukaemias	398	395.6	105	129.8	247	285.9

The Mayo Clinic report is particularly valuable since surgical patients have also been followed up and the follow up is from 14 to 32 years.

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¹ Holm LE. Malignant disease following Iodine-131 therapy in Sweden. In: Boice JB, Fraumeni JF, eds. *Radiation carcinogenesis: epidemiology and biological significance*. New York: Raven Press, 1984:263-71.

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Postmarketing surveillance of adverse drug reactions

SIR,—Professor Michael Rawlins in his leading article on postmarketing surveillance makes a plea for large numbers of subjects and control groups (24 March, p 879). Unfortunately his statistics are sufficiently misleading to warrant comment.

The numbers needed in a particular study depend on three main factors¹: the background incidence of a reaction in the general population; the magnitude of the drug's effect; and the required probability that a drug's adverse effect if present will be detected.

Professor Rawlins states that 10 000 patients and 10 000 controls will be sufficient to detect with 95% confidence those events occurring in one in 3000 patients. This is so only if there is, as is rarely the case, zero background incidence—that is, a new clinical entity.¹⁻³ Even then the 95% degree of certainty relates to the chance of having at least one such unique event occurring in the 10 000 patients. To be 95% certain of having at least two such unique events the drug induced incidence would need to increase to the order of one in 2000, and for three to one in 1500, etc.

Notice that the control group is of no importance. There are practical considerations which are important. We are dependent on the uniquely affected patient being thoroughly examined by a doctor. He in turn must be motivated enough to identify and describe in detail the unique event to a researcher sufficiently knowledgeable to appreciate it. If the unique condition (such as sclerosing peritonitis with praxolol) was reported as "fibrous abdominal adhesions"—not unlikely with a new entity—even the 95% chance of detecting the one in 3000 incident once is lost.

What if the event is not clinically unique? Suppose a new drug caused diabetes mellitus in one in 3000 patients and diabetes had an incidence of 1% in the population under investigation. To be 95% certain of detecting the increase due to the drug we need two million patients with the same number of controls.¹ If the incidence of, say, impotence was 10% in the population to be 95% certain of detecting a one in 3000 drug induced