mm/h but none had antibodies to native DNA (normal <30%, Farr assay) or extractable nuclear antigen. Six of the seven patients were slow acetylators, in contrast to nineteen of the thirty-two symptom-free ANA-positive controls. The lupus patients also had a greater incidence of high titre ANA. LCA, as measured by a microcytotoxic assay at a 1:2 serum dilution,[1] were present with similar frequency and levels in both groups. All symptoms in the lupus group resolved within 6 months of withdrawal of hydralazine, and this improvement was accompanied by at least a two-fold reduction in ANA titre.

LYMPHOCYTOTOXIC ANTIBODIES IN HYDRALAZINE-INDUCED LUPUS

Group	Acetylator phenotype*	ANA titre (⩾1/640)	LCA index† ⩾2·0
Symptom-free (n=40)	13R, 19S	4	13
Lupus (n=7)	1R, 6S	6	4

* Determined using oral sulphamethazine.[7] R (rapid) >77% and S (slow) <70% of acetylated sulphamethazine in a 5–6 h urine collection after calculated dose of drug. Only 32 of symptom-free patients were tested.
† LCA index is graded 1–8 : (1) <20% cells killed (normal); (2) 20–40%; (4) 40–60%; (6) 60–80%; (8) 80–100%. Abnormal lymphocytotoxicity = index ⩾2·0. Means were 3·95 (symptom-free) and 4·25 (lupus syndrome).

The higher titre of ANA was not paralleled by a higher LCA index in the lupus group despite the fact that all but one were slow acetylators. The assay used by Bluestein et al. and by us detects predominantly IgM, complement-dependent, cold-reactive antibodies which react with both B and T cells.[2] We cannot be certain whether these antibodies are of direct pathogenetic relevance, or, as has been recently demonstrated in CNS lupus[3] and in abortion in SLE,[4] a marker for a group of antibodies only some of which react with tissue antigens. The demonstration of an autoantibody with antinuclear and functional lymphocytotoxic reactivity in both SLE[5] and mixed connective tissue disease[6] emphasises the complexity of these antibodies.

Although LCA have now been described in two forms of drug-induced lupus, the data do not permit any conclusion about which (if any) autoantibody is of more importance in the origin and persistence of the disease.

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CAUTION WITH SELENIUM REPLACEMENT

SIR,—I read with interest your Oct. 27 editorial on a selenium-deficiency cardiomyopathy (Keshan disease) in children; however, you should have been more cautious about sodium selenite prophylaxis. Even benign drugs can have long-term toxicity. Dimethylselenide, which is produced in the liver after a significantly large exposure to inorganic selenium, is an acute respiratory-tract irritant, and chronic low-dose exposure shifts hepatic production away from the more innocuous trimethylselonium ion in favour of dimethylselenide.[1] We recently reported necropsy findings on a selenium refiner who had marked accumulation of selenium in his lungs associated with diffuse non-caseating granulomas.[2] It appears that dimethylselenide produces not only acute respiratory-tract symptoms, known as the "rose cold", but also a chronic granulomatous hypersensitivity lung disease. Widespread use of sodium selenite may produce clinically evident disease.

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HEPATIC ANGIOSARCOMA ASSOCIATED WITH ANDROGENIC-ANABOLIC STEROIDS

SIR,—Dr Falk and his colleagues (Nov. 24, p. 1120) have demonstrated the importance of careful documentation of previous drug therapy and thus uncovered an association between hepatic angiosarcoma (HAS) and androgenic-anabolic steroids. Case 2 had been treated with isoniazid, a substituted hydrazine, for two years before steroid therapy. Although isoniazid has never been implicated in HAS, another substituted hydrazine, phenelzine, has been associated with HAS in a single case.[3] In view of Toth's studies[4,5] demonstrating the angiosarcomatous properties of substituted hydrazines, pretreatment with isoniazid in case 2 may have had a permissive role in the development of HAS. We suggest that ingestion of hydrazine compounds (e.g., phenelzine, isoniazid, procarbazine, and hydralazine) be added to the information sought from patients with HAS.

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EFFECT, ON SERUM LIPID LEVELS OF ω-3 FATTY ACIDS, OF INGESTING FISH-OIL CONCENTRATE

SIR,—Mr Reed (Oct. 6, p. 739) discusses dietary measures to increase the concentration of ω-3 eicosapentaenoic acid (EPA) in blood so as to reduce the incidence of thrombotic disorders. He suggests that the intake of 1 g of EPA daily (10 g of cod liver oil) might be sufficient. In continuation of earlier work[6,7] we studied the influence on blood lipid and lipoprotein levels and on the fatty acid composition of serum lipids, of ingesting various amounts of EPA.

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DISTRIBUTION (%) OF FATTY ACIDS IN SERUM LIPIDS IN VOLUNTEERS BEFORE AND DURING FISH-OIL INGESTION

Serum lipids	ω-3 daily intake											
	0 g			2 g			4 g			8 g		
	CE	TG	Lec	CE	TG	Lec	CE	TG	Lec	CE	TG	Lec
Linoleic acid	59	19	28	57	22	25	51	17	22	49	19	21
Arachidonic acid	5	1	8	7	2	9	7	1	9	7	1	9
Eicosapentaenoic acid	0	0	0	3	1	2	5	3	5	8	6	7
Docosahexaenoic acid	0	0	3	1	3	5	1	6	7	1	10	8

Five groups of ten healthy non-fish-eating volunteers ingested 0, 1, 2, 4, or 8 g of a fish oil concentrate daily for four weeks. The preparation contained 81% of ω-3 docosahexaenoic acid (DHA).

Blood-samples were taken weekly—the first before the trial and the last two weeks after the volunteers had finished ω-3 consumption. The influence on total cholesterol and on HDL cholesterol was not significant at any level of intake of ω-3 fatty acids; however, fasting triglyceride and very-low-density lipoprotein levels fell significantly (up to 30%) in the group ingesting 8 g of fish oil daily.

The ω-3 fatty acid concentrations reached steady levels in cholesterol esters, in triglycerides, and in lecithins after two weeks of ω-3 intake, the levels being more or less proportional to the amounts ingested daily.

As the table shows, the increase in ω-3 fatty acids is mostly at the expense of linoleic acid, while the arachidonic acid percentage remains fairly constant. Two weeks after the experiment levels of ω-3 fatty acids had fallen to low values, so a regular intake would be necessary to assure a permanently increased level.

Reed's remark about how little we know of DHA is underlined by the mysteriously low level of this fatty acid in cholesterol esters in contrast to the high levels in triglycerides and lecithins.

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PRIMIDONE-INDUCED "URÆMIC FLAP"

SIR,—We have seen a case of primidone toxicity presenting with a severe flapping tremor, resembling uræmic encephalopathy, and with drowsiness and cerebellar signs. The patient had moderate renal insufficiency.

A 61-year-old woman was admitted with a 1 month history of drowsiness, slurred speech, and tremor of the hands. 2 years previously renal insufficiency probably due to chronic glomerulonephritis had been diagnosed. She had been an epileptic for 20 years and was taking primidone 250 mg three times a day. The patient was also on frusemide, hydralazine, methyldopa, and cimetidine (for a hæmatemesis 6 weeks previously).

The patient was drowsy but not clinically acidotic. She was normotensive but in biventricular failure. No pericardial rub was audible. She had a flapping tremor, generalised hypotonicity with depressed reflexes, absent ankle jerks bilaterally, and ataxia and cerebellar signs, especially on the left. Biochemical findings confirmed poor renal function (urea 27·3 mmol/l [164 mg/dl], creatinine 497 μmol/l [5·5 mg/dl], creatinine clearance 8 ml/min). Renal tomography revealed bilateral smooth small kidneys.

The neurological signs seemed out of keeping with the degree of renal failure, and a drug-induced mechanism was postulated. Primidone and cimetidine were stopped and the patient was treated with fluid restriction while her diuretic and antihypertensive drugs were continued. Blood levels of primidone and phenobarbitone (a metabolite) were above the therapeutic range at first (see table).

SERUM PHENOBARBITONE, PRIMIDONE, AND CREATININE
CONCENTRATIONS

—	Day after drug withdrawal				Therapeutic range
	1	2	3	6	
Phenobarbitone (μmol/l)	304	172	159	163	65–172
Primidone (μmol/l)	106	133	55	9	23–55
Serum-creatinine (μmol/l)	479	470	491	497	..

SI conversions: phenobarbitone 1 μmol/l=23 μg/dl; primidone 1 μmol/l=21 μg/dl; creatinine 100 μmol/l=1·1 mg/dl.

The tremor, drowsiness, and cerebellar signs began to improve 5 days after withdrawal of primidone and cimetidine, during which time neither serum-creatinine (table) nor blood urea had changed. There were no abnormal neurological signs 10 days after admission except for a mild intention tremor. An EEG done at this time showed a generalised arrhythmia.

The patient's spontaneous recovery and renal-function studies point to a drug-induced mechanism rather than renal failure as the explanation for the neurological findings.

Cimetidine can cause headache and irritability, confusion, diplopia, vertigo, dysarthria, and visual hallucinations,[1-3] but a flapping tremor has not been described. Primidone in excessive dosage, may cause numerous central-nervous-system side-effects, including sedation, vertigo, dizziness, ataxia, diplopia, and nystagmus.[4] Primidone is converted to two active metabolites, phenobarbitone and phenylethylmalonamide (PEMA). In animals primidone and PEMA seem to be detoxified via renal excretion.[5] 20% of the drug is excreted unchanged in the urine.[6] Primidone, rather than its metabolites, seems to be the likely cause of the neurological signs because clinical recovery coincided with a fall in primidone levels while phenobarbitone levels were still in the upper limit of the therapeutic range. This observation accords with the studies of Kappy et al.[7]

We agree with Bennett et al.[8] that the dose of primidone should be decreased in renal failure and suggest that blood

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