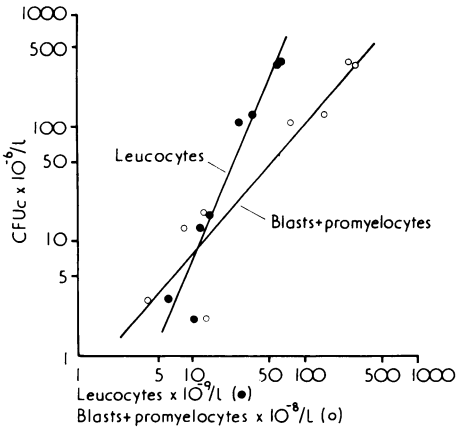
effect vitiates the linearity of the relationship between CFUc and blast cell numbers in treated patients. We have, however, had the opportunity to study a 53-year-old woman with Ph[1]-chromosome-positive CGL whose clinical course after diagnosis was atypical. Despite adequate initial treatment with busulphan her spleen remained very large. Blast cells seldom disappeared completely from her blood and she continued to need blood transfusion. For these reasons splenectomy was performed seven months after diagnosis. The spleen weighed 2·75 kg. Thereafter the need for blood was reduced but the percentage of blast cells gradually rose. Some control of leucocyte numbers was achieved first with cyclophosphamide and later with hydroxyurea. In the last six months of her life blast-cell numbers rose steeply and the disease was refractory to busulphan, to hydroxyurea, and to a variety of other drugs used in combination. She died 31 months after diagnosis. Blood CFUc numbers were assayed on eight occasions during the first two years of her disease. Standard agar culture techniques were used.[1 5] The relation between CFUc numbers and those of total leucocytes and immature leucocytes (blasts plus promyelocytes, predominantly the former) is shown in the figure.



Relation of CFUc to total and immature leucocyte counts.

In this patient there was a clear relation between CFUc and total leucocyte numbers. This observation accords with reports cited above and suggests that such a relationship throughout the chronic phase of CGL is the rule rather than the exception. Our additional finding of a relation between CFUc and immature leucocyte numbers adds support to the contention of Dr Barrett and his colleagues that there is a close relation between the CFUc and the myeloblast. But since these cells are present in the blood in a ratio of about 1:100 (see figure) one can scarcely draw the inference that they must be morphologically similar. Such data as are available on the morphology of the normal human CFUc suggest that they are not.[6]

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Alternatives to medicine

SIR,—Minerva (11 June, p 1539) refers to alternative careers to dentistry and wonders whether there is an organisation that gives details of alternative careers to medicine but in the medical field. There is in fact a booklet called *Alternatives to Medicine*, by Dr John C Thurman, a careers adviser at the University of East Anglia, which gives very useful information indeed about alternative careers to medicine and covers all the important careers in the paramedical field. It is obtainable from Yare Valley Publishers, Robin Hill, 20 Bluebell Road, Norwich NR4 7LF, price 80p including postage.

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Beta-blockers and lipid metabolism

SIR,—In a recent letter (16 April, p 1033), Dr S P Deacon discussed the possibility that long-term treatment with β-adrenergic blocking agents may influence lipid metabolism. Although the acute administration of these drugs seems to lower the levels of free fatty acids,[1 2] the effect of long-term administration may well be different. In fact Tanaka *et al*[3] found that propranolol initially lowered plasma free fatty acids, whereas increased levels were found after 7-8 weeks of treatment. Furthermore, postheparin lipolytic activity, as a reflection of blood triglyceride elimination capacity was lowered. This effect was reversed 10 days after withdrawal of the drug. Such an effect of a β-adrenergic blocking drug is in contrast to what may be expected on a theoretical basis, since adipose tissue lipoprotein lipase activity usually increases under conditions where the mobilisation of lipids from the fat cells is lowered. In addition, Tanaka *et al*[3] found a change in the distribution of the plasma lipids in the different lipoproteins. Total lipids in very low density lipoprotein (VLDL) increased but decreased in low-density lipoprotein (LDL) as well as in high-density lipoprotein (HDL). Furthermore, apo-HDL decreased. This finding indeed suggests the need for further studies since a low HDL concentration has been implicated as a risk factor for coronary heart disease.[4]

Fasting blood triglycerides before and after 3 months' treatment with metoprolol

	Before	1 month placebo	3 months' metoprolol
Triglycerides (mmol)	1·42 ± 0·71	1·41 ± 0·73	1·27 ± 0·70

Means ± SD; n = 9.
No significant differences between any group.

We have recently had the opportunity to study nine male patients with moderate hypertension treated with the cardioselective β-blocker metoprolol. The patients were investigated under controlled metabolic ward conditions before treatment, after one month with placebo, and after three months on metoprolol. The dose varied between 50 and 150 mg tid. The plasma triglycerides at these three occasions are shown in table I. In contrast to Waal-Manning[5] we found no change in the fasting blood triglyceride levels with metoprolol. This discrepancy may be explained by the fact that our studies were performed under controlled conditions while Waal-Manning's study was performed on an ambulatory basis and possibly included diabetic patients. Also, the possibility that the increase in blood triglycerides noted in Waal-Manning's study may be due to an increased body weight cannot be ruled out, since this information was not reported in her paper. In addition, in our study[6] no effect of metoprolol on blood triglyceride levels was found when measured postprandially in the upright position before and following physical exercise (bicycle ergometer).

In conclusion, it seems that metoprolol does not increase blood triglyceride levels. Similar findings have been reported with another cardioselective β-blocking agent, practolol, by Ghosh *et al*.[7] However, in view of the recent results of Tanaka *et al*[3] discussed above more careful investigations on the blood-triglyceride-removing capacity as well as the lipids in different lipoprotein moieties are warranted.

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Psychotropic drugs and road accidents

SIR,—All practising doctors must share the concern expressed by Dr D C G Skegg and his colleagues on the use of medicines in general practice (18 June, p 1561) over the possible dangers of side effects occurring with psychotropic drugs as a cause of road accidents. Indeed, this possibility is now so well recognised that it is common practice to warn patients about it and to suggest that they do not venture on to the roads during the first few days of therapy until it can be determined whether drowsiness or other side effects may intervene.

There is, of course, another possibility. In untreated cases the patient's judgment may also be impaired by the illness itself. Thus retardation, both mental and physical, and suicidal tendencies in untreated depressed patients must interfere very considerably with their ability to drive a motor vehicle or indeed to avoid one should they be pedestrians. The anxious or phobic patient also is not likely to drive competently, particularly in crowded urban traffic.

It must also be remembered that the majority of patients taking psychotropic drugs do not in fact suffer from side effects that are likely to interfere with driving ability. Thus in a large number of trials conducted by our group in general practice the incidence of drowsiness with chlordiazepoxide amounted to 15% (compared with 6% with placebo) and with amitriptyline to 11%.[1]

As with practically every drug tested, there are always conflicting reports concerning efficacy. However, over the 20 years or more that psychotropic drugs have been available to us there have been many hundreds if not thousands of papers recording their effective-

ness in properly conducted double-blind comparisons with placebo. Such reports vastly outnumber reports showing no such differences.

May I conclude, Sir, by asserting that the hazards of treatment with psychotropic drugs are far outweighed by the hazards of leaving untreated those illnesses for which they are indicated.

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Takayasu's disease and giant cell arteritis—a single disease?

SIR,—We would dispute the statement made in a recent leading article (12 March, p 667) that Takayasu's disease can be distinguished clinically and pathologically from giant cell arteritis. We describe a patient who presents features common to both which highlight our contention that they are not separate entities but form components of a continuous spectrum of inflammatory arterial disease.

In 1971 a 55-year-old woman developed aching and weakness of the shoulders, hips, and thighs which was worst on rising in the morning and was relieved by activity. Her general practitioner diagnosed rheumatoid arthritis and treated her with steroids. She developed severe back pain due to osteoporotic vertebral collapse, and the steroids were stopped. One year later she again complained of aching and weakness of the limb girdle muscles. The ESR was 30 mm in the first hour. A diagnosis of polymyalgia rheumatica was made, and steroids were restarted. Once again there was dramatic clinical improvement, but following a further episode of back pain they were discontinued. The ESR rose to between 70 and 120 mm in the first hour and her symptoms recurred but were partially relieved by indomethacin. She developed a microcytic, hypochromic anaemia which did not respond to iron supplements and for which she required transfusion.

She was admitted to this hospital in December 1976 with a six-month history of increasing malaise, anorexia, and tiredness. For four months she had noticed constant tingling in all the fingers of both hands and, increasingly, pain in both shoulders and arms, worse on exertion and relieved by rest. By the time of admission she was unable to do even light housework. On examination she was apyrexial and anaemic, her hands were cold and white, and no axillary, brachial, or radial pulses could be felt in either arm. There was a loud right subclavian bruit. All other pulses were normal. Blood pressure (popliteal artery) was 200/90 mm Hg. Investigations showed haemoglobin 10·7 g dl, normochromic, normocytic red cells. The ESR was 83 mm in the first hour. The bone marrow was of normal cellularity, iron stores were plentiful, and erythropoiesis was normoblastic. Serum iron 4·5 μmol/l, iron binding capacity 31·5 μmol/l. The alkaline phosphatase was normal. the Wassermann reaction and rheumatoid and antinuclear factors were negative. There was a diffuse elevation of α_2 and γ globulins, IgG raised, 17·75 g/l, IgA and IgM normal. Thyroid function was normal. Spinal *x*-rays showed generalised osteoporosis and collapse of D4, 7, and 8. On arch aortography stenoses of both subclavian arteries involving the origin of the vertebral arteries were seen. The aorta and all its other large branches were examined and found to be normal. The patient was treated with prednisolone, 100 mg on alternate days. Her tiredness and malaise improved and five weeks later the ESR had fallen to 29 mm in the first hour and the haemoglobin had risen to 12·9 g/dl, but the symptoms of upper limb claudication persisted unchanged.

The clinical and pathological overlap between polymyalgia rheumatica and temporal arteritis is such that they are now usually accepted as manifestations of one condition, polymyalgia arteritica or giant cell arteritis.[1] Similar overlap occurs between giant cell arteritis and Takayasu's disease. Our patient's illness illustrates the systemic disturbances which may preceed and accompany the specific features of arterial insufficiency, the anaemia, the high ESR, and the response to steroids common to both. That giant cell arteritis may cause large vessel occlusion and an aortic arch syndrome identical to that of Takayasu's disease is well documented.[2] A female preponderance is common to both[2] and both may burn themselves out. Far from being pathologically distinct their microscopic morphology is said to be indistinguishable.[1] A panarteritis with giant cell formation occurs in both and may affect both large and medium sized vessels.[3] The sole remaining distinction, that of age, has not prevented Takayasu's disease being diagnosed in the elderly.[3]

We feel that an unnecessary distinction is being made and that a single disease entity exists which presents as a variety of symptom complexes whose incidence may vary with age. Hall has suggested the name "idiopathic arteritis" for what he calls the "Unholy Trinity" of cranial arteritis, polymyalgia rheumatica, and Takayasu's disease.[4]

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Diagnosing familial hypercholesterolaemia in childhood

SIR,—Dr J V Leonard and his colleagues (18 June, p 1566) provide very interesting data on serum cholesterol and low density lipoprotein (LDL) cholesterol levels in children for the diagnosis of familial hypercholesterolaemia (FH). They conclude that when the total serum cholesterol concentration is in the range of 6·5-7·0 mmol/l (250-270 mg/100 ml) the diagnosis of FH cannot be made or excluded with complete confidence. They make the point that alternative methods of diagnosing FH are needed and suggest that the abnormality of the LDL receptor sites[1] on cells might provide the basis for a test with greater discriminating capacity than the determination of total serum cholesterol or LDL cholesterol.

We would like to draw the authors' attention to our report published in the *BMJ* in 1975.[2] We investigated 16 members of the family of a patient heterozygous for FH by measuring the regulation of 3-hydroxy-3-methylglutaryl coenzyme-A reductase (HMG CoA reductase) activity (which probably depends on an intact LDL receptor) in freshly prepared leucocytes preincubated in delipidated serum and then transferred to medium containing complete serum. In normal subjects there was almost complete suppression of enzyme activity on transfer of the cells to medium containing complete serum; patients heterozygous for FH showed only partial suppression. Ten members of the family were aged 16 years or under (see table). We found that four children of the family showed failure of normal regulation of HMG CoA reductase activity and in only one of these children was the serum cholesterol level unequivocally raised. We assume that failure of regulation of HMG CoA reductase is close to the genetic defect and is a diagnostic marker for the disease in this kindred.

We would, however, offer a word of caution in that we have subsequently found one member of a kindred heterozygous for FH with massive tendon xanthomata and premature myocardial infarction who shows no abnormality in the regulation of HMG CoA reductase,[3] suggesting heterogeneity in this condition.

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Regulation of HMG CoA reductase activity in leucocytes in members of family of patient heterozygous for FH

Sex	Age (years)	Serum cholesterol (mmol l)	Serum triglycerides (mmol/l)	HMG CoA reductase activity (nmol mevalonate/g protein in 15 min)	
				Delipidated fetal calf serum	Complete fetal calf serum
F	16	4·29	0·81	30·0	Not detectable
F	14	5·46	0·81	36·0	2·7
F	10	3·51	0·73	31·1	Not detectable
F	8	3·38	0·66	42·5	Not detectable
M	10	5·20	1·45	47·0	Not detectable
F	8	4·68	1·28	41·0	Not detectable
M	10	5·46	1·03	53·5	47·2*
M	3	5·72	1·49	57·1	32·1*
F	8	5·38	1·49	59·2	38·1*
F	6	7·80	1·01	55·4	40·0*

*Failure of normal regulation.
Conversion: SI to traditional units—Cholesterol: 1 nmol/l ≈ 38·7 mg 100 ml. Triglycerides: 1 nmol/l ≈ 88·6 mg/100 ml.

Phenothiazine resistance

SIR,—It has been my experience over some years that there is a small number of patients suffering from acute schizophrenia whose condition appears to be resistant to treatment with phenothiazines and thioxanthines. Much larger than normal doses of the drugs can be given without any effect on the psychosis. In such cases my practice has been to give a short course of electric convulsion therapy (ECT), usually 3-4 treatments, which seems to break down the resistance, thus making the patient's condition sensitive to the phenothiazines. They