for them at a rate of around £250 per week. No mention is made of the dialysis of the solitary parent and the care of children involved if this ceases.

The third fault is an ethical one, that if a treatment is available (and we have plenty of evidence that the public at large want to support this sort of treatment in machine and kidney donation), then the decision should not be in the hands of administrators or social scientists or even the Department of Health and Social Security, but be put very firmly before the relatives of the patients and the public. Regular dialysis was helped in Britain by public pressure, and if the social policy makers concentrated their efforts in getting the public to increase the falling 4.9% of the gross national product directed towards health the need for selection would go and we could concentrate on efficiency.

No mention is made of the responsibility of society to care for patients, whatever their income or potential for productivity. Part of our social concern in this country is to continue and to be seen to care for those who can no longer add to its financial wealth. If this is not the case then such cost-benefit analyses should be directed towards the geriatric population and those with severe deformities.

The authors mention nothing of the advantages that large-scale dialysis programmes have brought to research in the prevention of renal disease, bone disease, and hypertension. Finally, the weakest part of the article is its exclusion of transplantation. We now have as many patients transplanted, living active and productive lives, as we have patients on home dialysis. A unit in our own region has reached the situation where the dialysis unit's work load has been reduced in the past two years by one-half because of the activity of successful transplantation.

Costly compassion never was approved of by those who "held the bag," but if you stop caring with the skills that you have, true poverty will have begun.—We are, etc.,

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Medical Education and the Pharmaceutical Industry

SIR,—The Department of Health has requested members of the pharmaceutical industry to reduce their promotional expenditure from 13.8% to 10% of turnover. The industry has a well-founded and creditable reputation for giving support to educational activities, including the indirect support of reputable and valuable medical journals through the placement of advertising material. Naturally each company will wish to decide for itself where economies are to be made, but I plead that they be selective and bear in mind the advantages to the whole profession of continuing to advertise in journals of true educational value.—I am, etc.,

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Potential of Warfarin by Co-trimoxazole

SIR,—Drs. D. B. Barnett and B. W. Hancock (15 March, p. 608) describe a patient resistant to anticoagulant treatment with warfarin. During the warfarin treatment the patient received co-trimoxazole for nine days, which caused a considerable increase in plasma warfarin level and a decrease in prothrombin index. The authors suggest that co-trimoxazole inhibits warfarin metabolism.

This interesting observation seems to confirm our finding of co-trimoxazole as an inhibitor of drug metabolism in man. In six patients receiving co-trimoxazole we found an increase in diphenylhydantoin (DPH) half life from 12.8 ± 4.3 hours to 19.2 ± 3.9 hours and a decrease in metabolic clearance rate from 41.3 ± 13.4 ml/min to 30.1 ± 10.1 ml/min ($P < 0.001$).¹ We have further studied the influence on DPH metabolism of a number of sulphonamides. In usual therapeutic doses sulphaphenazole, sulphadiazine, and sulphamethizole also inhibited the metabolism of DPH, while sulphadimethoxine, sulphamethoxypyridazine, and sulphamethoxidiazine did not affect the half life and metabolic clearance rate of DPH.² The biotransformation of other drugs metabolized in the liver microsomal enzyme system, such as tolbutamide and warfarin, has also been found to be inhibited by sulphaphenazole, sulphamethizole, and sulphadiazine.³⁻⁵

It is well known that sulphonamides increase the effect of coumarin anticoagulants, and this effect is generally thought to be explained by a depression of the intestinal bacterial flora producing vitamin K. However, the data of Drs. Barnett and Hancock and our own previous studies suggest that inhibition of coumarin metabolism caused by some sulphonamides might be the primary explanation of the hypoprothrombin-aemic effect of these clinically important drug interactions.—We are, etc.,

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¹ Skovsted, L., et al., *Drug Interactions*, ed. P. L. Morselli, S. Garattini, and S. N. Cohen, p. 81. New York, Raven Press, 1974.

² Hansen, J. M., et al., *Svenska Epilepsia*, 1974, Suppl. 2, p. 23.

³ Christensen, L. K., Hansen, J. M., and Kristensen, M., *Lancet*, 1963, 2, 1298.

⁴ Kristensen, M., and Christensen, L. K., *Acta Diabetologica Latina*, 1969, 6, Suppl. 1, p. 116.

⁵ Siersbæk-Nielsen, K., et al., *Clinical Pharmacology and Therapeutics*, 1973, 14, 148.

⁶ Lumholtz, B., et al., *Clinical Pharmacology and Therapeutics*. In press.

SIR,—We were interested to note the raised plasma warfarin level accompanied by increased prothrombin time in a patient who was also receiving co-trimoxazole, reported by Drs. D. B. Barnett and B. W. Hancock (15 March, p. 608). We have seen a potentiation of the action of warfarin probably due to this combination in seven patients. In two of these who were studied more fully, however, a fall in total serum warfarin (warfarin plus metabolites) was observed. This would be consistent with

the displacement by sulphamethoxazole of some of the protein-bound warfarin, thus increasing both its intrinsic action and its rate of metabolism and excretion.

In-vitro studies, however, using therapeutic concentrations of the drugs, showed an increase of free warfarin from 20.6% to 23.4%. We felt that such a small increase was unlikely to account for the increased hypoprothrombin-aemic effect. The suggestion by the above authors that co-trimoxazole inhibits the metabolism of warfarin, presumably made after noting an increase in hydroxylated metabolites separated by chromatography, may therefore be the explanation.

Whatever the reason, the concurrent administration of co-trimoxazole to at least some patients already stabilized on warfarin may lead to an increase in prothrombin time.

Our full results will be published on completion.—We are, etc.,

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Racial Differences in Leucocyte Count

SIR,—We read with great interest the paper by Drs. Barbara J. Bain and J. M. England (8 February, p. 306) about sex difference in the neutrophil count. It raises the question: What is "normal range" in most biological investigations, especially when comparing populations from very different parts of the world? We would like to enlarge on a point which Drs. Bain and England mention—racial differences in leucocyte count. As they point out, Shaper and Lewis and others,¹⁻⁴ particularly in East Africa, have shown that African patients, more often when living in a traditional manner, show a strong neutropenia.

We have observed the same phenomenon in West Africa.⁵ The entire adult populations of three rural communities of the Bamako region (Mali Republic) were examined in March 1973. A capillary puncture was performed by means of the Unopette system to reduce the errors of manipulation as much as possible. The total leucocyte count was made in a Nageotte glass cell by a single observer under field conditions. The differential count was made on the basis of 100 cells stained with May-Grünwald and Giemsa. The table compares our findings with those from other African populations and with Wintrobe's American norms.⁶

Seemingly leucopenia due to neutropenia is a constant feature in Africans. Over 5% of our subjects had a neutrophil count lower than $1 \times 10^9/l$ ($1000/mm^3$).⁵ A genetic origin for this phenomenon has not been established.^{7,8} We have discussed elsewhere⁵ some environmental factors, such as malaria infestation or leucokinetic patterns, that might explain it. The well-known "tropical hypereosinophilia" is commonly observed, especially in Malians. The highly prevalent helminthiasis like schistosomiasis and onchocerciasis certainly play a causative role in eosinophilia. Nevertheless, its precise causes remain unknown.^{4,7} The low monocyte count common in African populations seems to confirm the positive correlation between neutrophil and monocyte counts seen by Drs. Bain and England.

This brief analysis could be developed in more detail, but our aim is simply to draw attention to the important geographical differences in leucocyte count. Since patients

Mean Total and Differential Leucocyte Counts in Some African Populations Compared with Wintrobe's Norms

Source	Subjects (No.)	Total Leucocytes ($\times 10^9/l$)	Neutrophils ($\times 10^9/l$)	Lymphocytes ($\times 10^9/l$)	Eosinophils ($\times 10^9/l$)	Monocytes ($\times 10^9/l$)
Kampala, Hawgood ¹	Outpatients (88)	5.30 (2.80-9.20)*	2.25 (0.80-5.05)*	2.20 (1.15-3.85)*	0.56	0.27
Nairobi, Kasili <i>et al.</i> ²	Blood donors (152)	5.00 (2.00-10.70)†	2.11 (0.36-5.62)†	2.43 (0.81-5.45)†	0.33 (0.2-1.1)†	—
Lusaka, Ezeilo ³	Blood donors (133)	5.16 (2.60-7.70)†	1.94	2.67	0.45	—
Kampala, Shaper and Lewis ⁴	Blood donors (250)	5.10 (1.90-8.30)*	1.96 (3.20-3.60)*	2.10 (0.74-3.56)*	0.72 (0.2-2.6)*	0.25 (0.0-0.55)*
Bamako, Rougemont <i>et al.</i> ⁵	Unselected adults (555)	5.51 $\pm$ 1.80‡	2.33 $\pm$ 1.37‡	2.47 $\pm$ 0.99‡	0.83 $\pm$ 0.74‡	0.19 $\pm$ 0.20‡
U.S.A., Wintrobe ⁶	Medical students (105)	7.78 $\pm$ 1.46‡	4.30 $\pm$ 1.21‡	2.71 $\pm$ 0.61‡	0.23 $\pm$ 0.17‡	0.50 $\pm$ 0.18‡

*95% confidence limits.

†Range.

‡Mean $\pm$ S.D.Conversion: SI to Traditional Units—W.B.C.: $1 \times 10^9/l = 1000/mm^3$.

from African countries are not rare in Europe this matter seems to be of some practical interest.—We are, etc.,

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Effects of Exertion on Hormone Secretion

SIR,—Strenuous exercise increases plasma renin activity (P.R.A.) to a degree that depends upon the intensity and type of the exercise.¹ We have reported the changes in plasma cortisol and testosterone levels in a group of Finnish sportsmen (30-40 years old) and one 58-year-old Greek who all ran a non-competitive marathon in 210-285 min over the classical course in Athens (29 June 1974, p. 726). As these data suggested a correlation between physical fitness and changes in hormone profiles we investigated whether P.R.A. had undergone similar changes.

The results for P.R.A. obtained by radio-immunoassay² and for plasma osmolality

obtained with a Fiske osmometer are shown in the table. The P.R.A. control values, taken in the upright position, were slightly higher at 1200 hr than at 1600 hr, in accordance with the circadian rhythm of P.R.A.³ After the run P.R.A. increased highly significantly ($P < 0.0005$) except in the fittest participant (no. 12), who ran the marathon in only 180 min and arrived at the finish in exceptionally good condition. Plasma osmolality increased highly significantly after the run ($P < 0.005$). A similar increase of P.R.A. has been found in 22 skiers after a 70-km cross-country ski race.⁴

We believe that the increase in P.R.A. in response to such severe exercise reflects a meaningful reaction tending to restore the balance of body fluids and electrolytes by renin-angiotensin-stimulated release of aldosterone. The lack of rise of P.R.A. in the fittest subject may be due to his larger blood volume, resulting in a smaller reduction of the circulating blood, and to a variety of adaptive adjustments resulting in a lesser degree of sympathetic discharge during strenuous exercise than in the other runners.—We are, etc.,

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Participant No.	Control Samples		After Marathon at approx. 1600 hr
	1200 hr	1600 hr	
<i>Plasma renin activity (ng ml⁻¹h⁻¹)</i>			
1-11	0.89 ± 0.18 (S.E.M.)	0.66 ± 0.11	5.75 ± 0.74 (S.E.M.)
12	1.09	N.D.	1.18
14 (Greek)	N.D.	0.19	4.41
<i>Plasma osmolality (mmol/kg H₂O)</i>			
1-11	285.1 ± 12.5 (S.E.M.)	300.0 ± 3.4 (S.E.M.)	314 ± 1.8 (S.E.M.)
12	305	—	312
14 (Greek)	N.D.	—	320

N.D., = not detected

Rubella in Pregnancy: a Difficult Diagnosis

SIR,—When it can be proved that a woman has been infected by rubella virus in early pregnancy it is usual to recommend termination. We wish to report a case in which it was difficult to make a clinical decision for or against this measure.

The patient had a rubella haemagglutination inhibition (H.A.I.) titre of less than 1/16 in 1973 when in her second pregnancy. In this locality more than 90% of women with such a finding are considered susceptible to infection since they respond serologically to rubella vaccination. She presented again in January 1975 in the 10th week of her third pregnancy, with a history of close and continuous contact with rubella (her own daughter) five weeks previously. Unfortunately there was no recorded evidence that she had been immunized after her second pregnancy. Her rubella H.A.I. titre was 1/32 and the complement fixation (C.F.) titre was 1/10. Identical results were obtained two weeks later. These low titres did not appear to be consistent with recent infection. Nevertheless, she was apparently susceptible at the beginning of this pregnancy (as judged by the 1973 sample), had been in close contact with rubella in the early weeks, and at the 10th week did have measurable antibodies. It seemed possible, therefore, that she had contracted the disease in early pregnancy. Termination was advised. This was performed at the 14th week using a combination of intravenous prostaglandin E₂ and oxytocin. The patient made an uneventful recovery.

The serum collected in 1973 was retested in parallel with a sample taken before termination. The H.A.I. titre of the earlier specimen was confirmed as less than 1/16 and the antibody level of the last serum collected in the pregnancy was again 1/32. Tests for neutralizing antibody and for rubella-specific IgM and IgA were not performed. The fetus and placenta were tested in Vero and RK₁₃ tissue cultures. Rubella virus was not recovered.

This confusing clinical problem re-emphasizes the need for puerperal immunization of "susceptible" women. This may be overlooked very easily when a patient is discharged early in the post-partum period, as happened in this case. It must be appreciated that a laboratory handling large numbers of antenatal sera each week selects women most likely to benefit from post-partum immunization only by employing a screening dilution of serum that will discriminate between those who are "certainly immune" and those who are "likely to be susceptible." Women whose antibody titres lie close to the borderline are reported as susceptible. A few women have low antibody levels and have recordable H.A.I. titres of less than 1/16 but are in fact immune.

In retrospect it seems likely that a non-infected pregnancy was terminated, but we are unable to explain with certainty the rising titre between 1973 and 1975. Such changes are not caused by other infections or by pregnancy. It is possible that the patient was immunized by her family doctor after her second pregnancy (she changed doctors at this time and there was some confusion about postnatal care). The results could be due to slight variations in samples collected from an immune individual with very low levels of antibody (possibly boosted by close contact with her daughter's uninvestigated illness) or from a subclinical infection occurring between the second and third pregnancies.

Different interpretations of the laboratory results in this situation caused considerable difficulty. We should be interested to know