confirmed the figure of 23 hours for nurses employed by general practitioners and have found that attached nurses are almost all contracted to work 40 hours a week, though not all for the same practice.

Although the term is attractive, we should be careful in our use of "nurse practitioner," which in the USA at least is conferred only after a rigorous training lasting nine months on average. This includes the basic informational skills of clinical history taking, physical examination, and the use of the problem-orientated record. Nothing of the kind exists in Britain so far as I know and I believe that it is unfair and dangerous to involve community nurses in first-contact encounters without such a training. It is also misleading to give them a title which suggests that they have received it.

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¹ Reedy, B L C, Philips, P R, and Newell, D J, *British Medical Journal*, 1976, 2, 1304.

Intrauterine fetal transfusion

SIR,—When the papers by Palmer and Gordon¹ and Robertson *et al.*,² both critical of the improvement in survival rates with intrauterine transfusion (IUT) in severe Rh isoimmunisation, appeared in the same issue of the *British Journal of Obstetrics and Gynaecology* I resisted the impulse to formulate a rebuttal. However, when the *BMJ*, in which Liley's original and epoch-making work was published in 1963, publishes a leading article (16 April, p 990) echoing their scepticism I am compelled to report to you our own experience with IUT, which is diametrically opposed to that of the above authors.

The Winnipeg Rh Laboratory is responsible for the management of pregnant isoimmunised women from a population of one million and receives referrals of severely affected patients from as far away as Thunder Bay, Ontario; Omaha, Nebraska; and Calgary, Alberta. Both amniotic fluid spectrophotometry and fetal intraperitoneal transfusions are carried out using Liley's original method of measurement and technique with no modification whatever. Accuracy of amniotic fluid spectrophotometry is based on serial amniotic fluid examinations and does carry with it a certain degree of unavoidable error.

Of 212 isoimmunised women whose final amniotic fluid examinations fell into zone I (of Liley) the reading was life-threateningly inaccurate in 3 (1.4%); of 437 in zone II in 16 (3.7%); and of 279 in zone III in 2 (0.7%). I must report that of the 252 fetuses on which we have carried out 596 fetal transfusions, 4 (1.6%), all survivors, were negative for the antigen to which their mother was isoimmunised (3 Rh(D), 1 Kell).

Our experience with survival rates after IUT (see table) and the overall lowering of perinatal mortality from isoimmunisation has

been much better than that reported by the above authors. Early initial fetal transfusion, although survival rates are less, carries with it a very real chance of survival even when carried out as early as 21½ to 23 weeks' gestation. For the 11½ years ending 30 April 1977 our overall survival rates ranged as follows: 69% (of 110 fetuses transfused) when IUT was initiated after 26 weeks, 67% (of 52) when IUT was initiated between 24 and 26 weeks, 64% (of 25) between 23 and 24 weeks, and 42% (of 26) between 21½ and 23 weeks' gestation. Although 42% may seem a very poor survival rate, it represents 11 babies who would not have survived without the procedure. Our experience would indicate that, although there is a risk to the procedure for the fetus, it is acceptable, being 5.4% overall in the past 7½ years (10% for the first, 3% for subsequent IUTs).

In our single experience with plasmapheresis (46 l removed in 11 weeks) the procedure did not prevent the need for IUT. The fetus had ascites in utero but survived. Certainly once IUT becomes necessary plasmapheresis should not be continued since the Rh-negative donor red cells transfused will be unaffected by maternal Rh antibody.

Further proof of the effectiveness of IUT must be related to perinatal mortality from isoimmunisation. Modern methods of management, of which IUT is the most important, have reduced perinatal mortality from isoimmunisation from 14.3% to 1.5% in the past decade.

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¹ Palmer, A, and Gordon, R R, *British Journal of Obstetrics and Gynaecology*, 1976, 83, 688.

² Robertson, E G, *et al*, *British Journal of Obstetrics and Gynaecology*, 1976, 83, 694.

Plasma exchange in severe rhesus disease

SIR,—We read with great interest the article on continuous flow plasmapheresis in the management of severe rhesus disease by Dr J Graham-Pole and others (7 May, p 1185).

At these hospitals research has been continuing along independent but parallel lines to those indicated in the article. The present state of practice in our unit is amply illustrated by the following case report.

A 30-year-old patient with a history of severe rhesus disease has recently been successfully delivered of a live infant at the Coombe Hospital. She had previously lost a pregnancy at 26 weeks' gestation from hydrops fetalis and had been delivered of a baby at 36 weeks which required three exchange transfusions and four "top-ups." Maternal plasma exchange was used in this case as an alternative to fetal intrauterine transfusion. Treatment was started at eight weeks' gestation, which was the earliest notification of the pregnancy. Nine litres per week were exchanged with fresh plasma, a total of 237 l of plasma being exchanged in 79 procedures. On two separate occasions, however, it was found that the antibody levels

were showing an increase and the plasma exchange was increased to 15 l.

The first amniocentesis at 18 weeks showed the optical density ($\Delta 450$ nm) to be in the mid-zone (Liley¹) and below Whitfield's action line.^{2,3} This indicated a moderately severely affected fetus, but, as can be seen from the table, as the pregnancy progressed the further six monitoring amniocenteses showed no deterioration in the fetal haemolytic condition.

Results of amniocentesis

Gestation (weeks)	Optical density ($\Delta 450$ nm)	Prediction zone (Liley)	Lecithin: Sphingomyelin ratio
18	0.185	Mid-zone	1.0
24	0.13	Mid-zone	1.22
36	0.107	Mid-zone	1.55
28	0.065	Mid-zone	1.56
31+	0.09	Mid-zone	1.82
33+	0.014	Lower zone	1.83
35+	0.01	Lower zone	2.26

The patient went into spontaneous labour at 36 weeks following an exchange transfusion but not in association with any intrauterine manipulation. Caesarean section was carried out as monitoring showed fetal distress, and a live male weighing 2550 g was delivered. This baby had a cord haemoglobin of 108% and a plasma total bilirubin level of 34 μ mol/l (2 mg/100 ml). One exchange transfusion and one "top-up" were required subsequently.

It therefore appears that with a well-motivated patient and doctor (for the procedure is very time-consuming) and where a good blood transfusion service is available plasma exchange of mother's blood provides an excellent alternative to intrauterine transfusion in the management of severe rhesus haemolytic disease. As the haemolytic process starts early in pregnancy, however, we recommend that treatment should commence when pregnancy is first diagnosed; the use of β -subunit human chorionic gonadotrophin assay may be necessary to ensure this.

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¹ Liley, A W, *American Journal of Obstetrics and Gynecology*, 1961, 82, 1359.

² Whitfield, C R, *et al*, *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1970, 77, 791.

³ Whitfield, C R, *American Journal of Obstetrics and Gynecology*, 1970, 108, 1239.

Ulcerogenic action of azapropazone

SIR,—The report of Dr P R Powell-Jackson (7 May, p 1193) of the occurrence of gastric ulceration in a patient undergoing treatment with both anticoagulants and azapropazone prompts me to draw your attention to observations made in this department in which a comparison of the ulcerogenic action of azapropazone, phenylbutazone, and oxyphenbutazone was made.¹

The actions of anti-inflammatory drugs on

Fetal transfusions, Manitoba, 1 January 1964-30 April 1977

Period	Fetal transfusions	Fetuses transfused	Total survivors	Hydrops transfused	Hydropic survivors	Traumatic deaths	Traumatic risk per IUT
First 2 years	86	40	12 (30%)	14 (35%)	1 (7%)	15 (38%)	17.5%
Second 4 years	232	104	62 (60%)	24 (23%)	8 (33%)	20 (19%)	8.6%
Last 7½ years	278	108	75 (70%)	32 (30%)	15 (47%)	15 (14%)	5.4%
Total	596	252	149 (59%)	70 (28%)	24 (34%)	50 (20%)	8.4%

lysosomes are of interest since lysosomal enzymes are involved in the acute inflammatory reaction.² In previous observations we have found that the actions of some anti-inflammatory aromatic acids and anti-inflammatory steroids are concentration-dependent.^{3,4} The anti-inflammatory activity of steroids has been related to their stabilising action on lysosomes.⁵ It was therefore of interest to investigate the effect of concentration of the non-steroidal anti-inflammatory drugs azapropazone, oxyphenbutazone, and phenylbutazone on lysosomes. The gastrointestinal ulcerogenic action of anti-inflammatory drugs may result, in part at all events, from lysosomal damage consequent on high local concentration of these compounds, such as may be achieved after oral administration. We have shown that this may result in the intracellular release of acid hydrolases such as cathepsins, with consequent damage to surrounding tissues.³

In experiments on isolated lysosomes we have consistently shown a biphasic effect of azapropazone, oxyphenbutazone, and phenylbutazone on the release of acid hydrolases. The equilibrium concentrations which are attained under normal therapeutic conditions stabilise lysosomes, and this property may be a significant factor in their anti-inflammatory action.¹ However, at higher concentrations, such as may be attained locally in the gastrointestinal tract, lysis of lysosomes with liberation of powerful proteolytic enzymes has been demonstrated. The effect of phenylbutazone was very much more powerful than that of the other drugs.

Phenylbutazone was shown to have a much more powerful ulcerogenic action than azapropazone in experimental animals (rats, rabbits), though the latter drug was not devoid of action in high concentrations such as those which may be released locally after oral administration of therapeutic doses. Both drugs were demonstrated to be capable of producing ulcers in the pyloric region, with which lysosomal damage was correlated, while duodenal ulceration was induced by phenylbutazone but not by azapropazone. Using the quantitative index of ulcerogenic effect proposed by Münchow⁶ as a measure of the severity of ulceration azapropazone was less than one-quarter and one-half as strongly ulcerogenic as phenylbutazone and flufenamic acid respectively. Its effect was approximately equal to that of mefenamic acid. The therapeutic ratio between ulcerogenicity ED_{50} and anti-inflammatory ED_{50} was 2.2-2.5 for azapropazone, 1.0 for phenylbutazone, 2.0-2.5 for mefenamic acid, and 1.2 for flufenamic acid and indomethacin. Evidence of liberation of lysosomal enzymes in the tissues was histochemically demonstrable in subulcerogenic doses, thus raising the possibility that these drugs may induce a preulcerogenic state in concentrations insufficient to produce ulcers.

Thus our results have shown that even in the absence of anticoagulants azapropazone has ulcerogenic potential, though admittedly much less than that of phenylbutazone. The importance of Dr Powell-Jackson's observations is that an enhanced ulcerogenic activity of azapropazone is demonstrable in the case of patients concurrently treated with warfarin and is presumed to be due to an interaction between the drug and warfarin analogous to that which takes place with phenylbutazone. No studies appear to have been carried out on the interaction between azapropazone and warfarin. However, azapropazone has no

significant effect on normal prothrombin time, and does not enhance the effect of nicoumalone. The mechanism of the ulcerogenic action of azapropazone in patients on anticoagulants is clearly worthy of further investigation, but the conclusions to be derived from our experimental work is that ulcerogenesis can occur with this drug even in the absence of anticoagulants, though it is far less likely than with phenylbutazone.

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¹ Lewis, D A, Capstick, R B, and Ancill, R J, *Journal of Pharmacy and Pharmacology*, 1971, **23**, 931.

² Weissman, G, *Annual Review of Medicine*, 1967, **18**, 97.

³ Lewis, D A, *Journal of Pharmacy and Pharmacology*, 1970, **22**, 909.

⁴ Lewis D A, Symons, A M, and Ancill, R J, *Journal of Pharmacy and Pharmacology*, 1970, **22**, 902.

⁵ Weissman, G, and Dingle, J T, *Experimental Cell Research*, 1961, **25**, 207.

⁶ Münchow, O, *Arzneimittel-Forschung*, 1954, **4**, 341.

Interferons and rabies

SIR,—During the past 24 months, if my arithmetic does not play me false, we have seen four deaths from rabies in Britain—and this in spite of intensive care units and devoted attention, where it was possible to do so, by our medical and paramedical staff.

At the close of last year a scientist from this famous establishment was pulled through a most serious viral infection (Ebola fever), against which we have as yet no protective prophylactic vaccine, by interferon (IF) and specific serotherapy plus, of course, expert medical attention as noted above in the case of the rabies patients. It would seem, therefore, that an opportune moment has arrived to have a supply of IF (or possibly an IF inducer) stocked and ready available for treatment of the next rabies patient at some national designated centre. Is this not worth a trial, I wonder, in view of the 100% failure rates recorded so far in this country since I qualified in 1946?

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Lithium carbonate in schizoaffective states

SIR,—I have now used lithium carbonate in many manic-depressive states for 12 years, having talked personally with Cade, on a visit to Australia, about its value and the two deaths from overdosage. For a long time blood lithium concentrations were not available, but no trouble occurred with small doses, which one lowered if hand tremor or gastric upset occurred. Nobody can now doubt its value when working at the bedside, but recently I have also been seeing a very interesting phenomenon when lithium carbonate is used, often alone or together with the phenothiazines, to control recurrent schizoaffective breakdowns.

Patients are sent to me for consultation in deep depression filled to the brim with phenothiazines but with no delusions. Their illness had often started with an attack of

apparent schizophrenic excitement with delusions and hallucinations. These had been damped down and over-damped down, by phenothiazines and the patient became depressed, anergic, and often sent to a back ward of a mental hospital as a deteriorating schizophrenic, to be kept on phenothiazines indefinitely and looked after by a junior registrar.

One only has to reduce the dosage of phenothiazines greatly and give lithium for the patient to recover, and in many cases there are no more attacks of schizophrenic excitement. Any further depression on lithium in these patients can be dealt with by the addition of antidepressant drugs. Nothing would induce me to continue to torture such patients by double-blind sampling them; most have had so much suffering already. But from clinical observation it seems that lithium carbonate may be found as helpful as the phenothiazines in what one must, I suppose, call "schizoaffective" states. I sincerely hope it will be tried "anecdotally" at the bedside by psychiatrists and by general practitioners, who are taking over so much of our present psychiatric treatment now it has become so physical and simple to give.

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Endocrine versus cytotoxic treatment in advanced breast cancer

SIR,—In concluding that cytotoxic therapy is the treatment of choice for premenopausal women with locally recurrent or metastatic breast cancer Dr J Priestman and his colleagues (14 May, p 1248) are not making a fair comparison. They match ovarian ablation alone, a manoeuvre of known limited effectiveness, against repeated cycles of powerful cytotoxic drugs. They appear to ignore completely the great palliative value of simple radiotherapeutic techniques, which may be added to endocrine treatments but cannot be applied while continuing with chemotherapy.

A more realistic study would be the comparison of cytotoxic and non-cytotoxic policies, the latter to include not only ovarian ablation but also radiotherapy, non-virilising androgens, and corticosteroids given as required.

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Vitamin D "resistance" and bioavailability of calciferol tablets

SIR,—The suggestion by Dr C R Paterson that calcitonin may increase vitamin D requirement in hypoparathyroidism (9 April, p 952) is interesting, but the documentation of a subnormal response to treatment in the reported case is inadequate.

It has been shown on several occasions¹⁻³ that the ergocalciferol tablets available in the United Kingdom are most unsatisfactory because they contain substantially more than the stated quantity when new,³ are subject to unpredictable deterioration and loss of strength when old,⁴ and are sometimes very poorly absorbed.² In current jargon, the bioavailability of calciferol tablets BP is unpredictable and sometimes very low.

Problems related to the quality of the vitamin D preparation used are by far the commonest