compared with 2·52±1·01 nmol/l on VIP treatment; $p<0·01$, Student's paired t test). We have observed a similar increase in plasma noradrenaline after VIP infusion in normal subjects.

We believe that the small and statistically insignificant difference in plasma adrenaline seen between our two treatment groups cannot explain the degree of bronchodilatation produced by VIP. In no case were the levels of adrenaline outside the normal physiological range obtained for the resting or recumbent position. Furthermore, there was no correlation in individual subjects between the degree of bronchodilatation produced and plasma adrenaline concentration. Despite a rise in the level of noradrenaline with VIP, which presumably reflects reflex sympathetic activation, there is no evidence that this catecholamine can cause bronchodilatation, as determined by studies with noradrenaline infusions in man.[4]

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INHALED STEROIDS AND DYSPHONIA

SIR,—Your Feb 18 editorial contains an error of fact. The study by Williams et al[5] conclusively showed that the changes are reversible, not irreversible: "After discontinuation of the inhaled steroid the laryngeal appearances and the voice invariably returned to normal, although this sometimes took months".

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⁂We thank Dr Dash, Dr Pover, and others for pointing out this bad mistake. "Reversible" was, of course, the word we supplied to our printers.—ED. L.

IgE CONTENT OF COMMERCIAL INTRAVENOUS IgG PREPARATIONS

SIR,—Many IgG products for intravenous use are available. Their biochemical properties, antibody titres, and protein composition, particularly for single Ig classes and IgG subclasses, have been analysed,[6,7] but the IgE content has not been reported. Using an IgG preparation ('Endobulin') in children with primary hypogammaglobulinaemia, we observed the appearance of circulating IgE after infusion. When we assayed[8] the IgE content in several batches we consistently found significant IgE levels (106–356 kU/l). IgE were also detected in other intravenous IgG preparations (see table).

The physiological role of IgE is not completely understood but IgE is involved in some allergic reactions. Immediate or anaphylactoid reactions sometimes follow intravenous IgG infusion,[9] though the mechanism responsible remains unclear. Complement-activating IgG aggregates seem primarily involved, even though the anticomplementary activity of the products is not related to the incidence of side effects.[9] Antibody production against immunogenic substances such as IgA; vasoactive contaminants, such as prekallikrein activator and/or kallikrein; and microbial contaminants, such as pyrogens, have also been considered.[9] However, none of these hypotheses explains the higher incidence of reactions in hypogammaglobulinaemic patients.[9] Perhaps basophils and mast cells in these patients, who cannot synthesise IgE and IgG_4, have high avidity for these antibodies. Infusion of these immunoglobulins followed by binding to free receptors might trigger the release of vasoactive substances and cause anaphylactoid symptoms, provided that primed cells come into contact with specific antigen.

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AVERAGE IgE CONCENTRATIONS IN INTRAVENOUS IMMUNOGLOBULIN PREPARATIONS

Product	Method of preparation	Ig concentration	
		IgG (mg/ml)	IgE (kU/l)
'Endobulin'	Treatment with polyethyleneglycol	50	216
'Sandoglobulin'	pH 4 treatment with traces of pepsin	30	70
'Rhodiglobin'	Plasmin degradation	50	319
'Veinoglobuline'	Plasmin degradation	50	259

METHOTREXATE IN LIEU OF RAZOXANE FOR INCAPACITATING PSORIASIS

SIR,—Razoxane (ICRF 159) is an antimitotic agent that is highly effective in the treatment of severe psoriasis and psoriatic arthropathy.[10] The manufacturers have found, however, that 7 out of 3000–4000 patients treated with razoxane for psoriasis and, as adjuvant therapy, for colorectal cancer in clinical trials have acquired acute myeloid leukaemia (AML) and that cutaneous basal cell or squamous cell carcinomas have developed in 6 patients. The expected annual incidence of AML in the UK is about 3 per 100 000. A possible association between razoxane therapy and the development of AML in cancer patients was suggested in 1981.[11] Although a causal relationship between razoxane and leukaemia and cutaneous carcinoma has not been proved, the UK licensing authority has suspended all clinical trials with this drug (J. D. Fitzgerald, personal communication). Thus, dermatologists must now choose an alternative therapy for patients with severely incapacitating psoriasis.

This prompted us to review data on the carcinogenicity of methotrexate, an appropriate therapeutic alternative to razoxane. Methotrexate has both immunosuppressive and cytotoxic properties and has been used successfully to treat severe psoriasis for over 25 years. There is very good clinical evidence to suggest that methotrexate causes no significant increase in either cutaneous or internal malignancies in man.

Methotrexate prevents the formation of thymidylic acid, a nucleotide found in DNA, by inhibiting dihydrofolate reductase.[12] It thus prevents DNA synthesis but does not alter existing DNA. Methotrexate is negative in the Ames test,[13] and studies in laboratory animals have found that it is not carcinogenic.[14–16] Three large retrospective studies in psoriasis patients on long-term methotrexate revealed no increase in the incidence of cutaneous or systemic malignancies.[17–19]

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Potentially serious and sometimes fatal hepatic, pulmonary, and haemotopoietic complications may occur when methotrexate is used to treat psoriasis.[17] Infrequent serious and sometimes fatal complications may also occur as a result of the liver biopsies which are necessary in the management of patients on methotrexate. However, these complications are in large measure preventable,[20] and in our experience the incidence of fatal complications due to methotrexate therapy is low.

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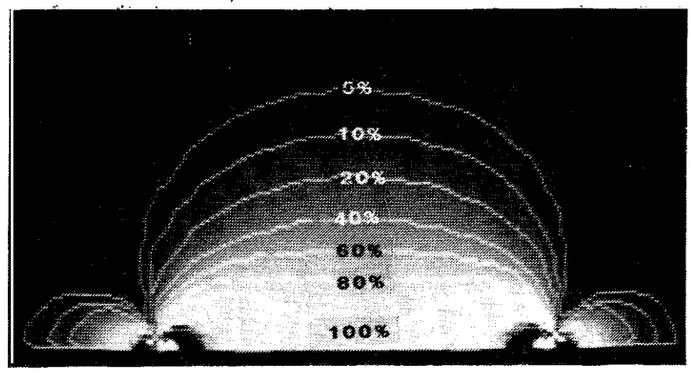
SURFACE COIL NMR SPECTROSCOPY OF BRAIN

SIR,—Pettegrew et al[1] calculated a theoretical volume of brain tissue from which signals might be detected by surface coil phosphorus (^{31}P) nuclear magnetic resonance (NMR) spectroscopy. These calculations were based on studies of newborn infants[2] and an adult.[3] Pettegrew et al concluded that, with the coil placed over the temple,[3] as much as 96% of the signal could come from extracerebral sources in an adult and 68% in a child (when we repeated this calculation for a child we obtained a figure of 86%). We[2] placed the coil immediately above the ear, and Pettegrew et al calculated that for this position up to 54% of the signal could have come from outside the brain. Haase et al[4] ask for more details of our methods, which we provide here together with an explanation of why we think that little, if any, of our signal came from outside the brain.

We normally used a 7·4 cm diameter surface coil made from a single turn of copper wire 0·3 cm diameter and separated from the skin by 0·25 cm of polytetrafluorethylene. The pulse duration was usually 100 μs and the flip angle at the centre of the coil was between 90° and 100°. An angle of about 180° might have been preferable for cerebral localisation, but possibly at the expense of a reduced signal-to-noise ratio. Field profiling was used, but measurements with phantoms suggest that this procedure was unlikely to have excluded any extracerebral signal. The pulse interval was usually 2·256 s, although we have made observations with intervals from 0·506 s to 20·256 s in an attempt to estimate saturation factors for the various peaks. We agree about the importance of saturation, especially since the relaxation time of the phosphomonoester peak is exceptionally long.

To apply the method of Pettegrew et al to our experimental conditions, we measured the distance from the skin to the inner skull table at the site of the centre of the coil on computerised tomography scans from ten infants born at 28 to 41 (median 36) weeks of gestation and aged 2 days to 18 weeks (median 1 week). This distance was 0·43±0·11 SD cm, in contrast to 0·74±0·25 cm found by Pettegrew et al for children. Using our value and Pettegrew's model for surface coil response (uniform signal from inside a right cone with radius and height equal to the coil radius; zero signal from outside the cone) and taking into account the distance from the coil plane to the skin (0·40 cm) we calculate that 34% (not 54%) of the signal could theoretically have been extracerebral. However, the assumptions made by Pettegrew et al are less accurate than in the description of surface coil response provided by Ackerman et al.[5] The figure illustrates the spatial variation of coil sensitivity derived from this description. Assuming a uniform concentration of ^{31}P within all the tissue, and making suitable geometrical assumptions about skull shape, we calculate from this model that only 20–25% of our signal could have come from extracerebral sources.[6]



Spatial variation in sensitivity for single turn surface coil in plane through coil centre and parallel to static field, for flip angle $\phi = 90°$ at coil centre.

Sensitivity is highest in brightest regions. Isosensitive contours from 5% to 100% of value at coil centre are shown. Sensitivity is proportional to $B_{1xy} \sin \phi$ where B_{1xy} is the component of radiofrequency field B_1 perpendicular to static field. This three-dimensional function is not symmetrical about the coil axis. The signal from any point is concentration of ^{31}P multiplied by sensitivity at that point; the total signal from coil, given in text, is sum of contributions from all points in tissue.

But the concentration of ^{31}P is not uniform. Bone contains no mobile ^{31}P and cannot have contributed to our spectra. Furthermore our post mortem dissection of the scalp of a baby showed that very little muscle was to be found under the coil; and in studies of a baby with propionicacidaemia whose cerebral metabolism was severely deranged no signals from ATP or phosphocreatine were detected in the brain spectra, whereas large signals were present in spectra from peripheral muscles.

We conclude that essentially all our signals must have come from the brain.

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TUNNELS DO NOT PROTECT AGAINST VENOUS-CATHETER-RELATED SEPSIS

SIR,—Dr Keohane and colleagues (Dec 17, p 1388) define catheter sepsis on the basis of a laboratory report of "significant growth of organisms from catheter tip". Qualitative tip culture should not be used as the sole criterion to define catheter sepsis. The lack of concomitant blood cultures makes these data difficult to interpret. Positive tip cultures were said to be more common in untunnelled than in tunnelled catheters, this difference being abolished once a specialised nutrition nurse started looking after the catheters. However, analysis of the "before nurse" data (table II) shows that the frequency of tip-positive culture was not significantly greater for the untunnelled catheters (11/25) than for the tunnelled catheters (6/26) ($p > 0·1$ by χ^2 test). The difference is significant in the series as a whole because of the addition of the 2 new septic untunnelled catheters in the "after nurse" series. Even this difference, between all untunnelled and all tunnelled catheters, is of doubtful significance because application of Yates' correction gives a χ^2 value of 3·25 ($p > 0·05$).

We have been unable to reduce catheter sepsis by tunnelling central venous catheters. In two consecutive series of 73 untunnelled and 35 tunnelled total parenteral nutrition (TPN) catheters, the sepsis rates were 12% and 9%, respectively. Although not randomised, both groups were treated on the same protocol by the same nurses and physicians.