that this is due to competition by circulating immune complexes, but there are many possibilities, which might of course have to be analysed in vitro.

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- ¹ Normann, S J, *Journal of the Reticuloendothelial Society*, 1973, 13, 47.
² Drivas, G, Uldall, P R, and Wardle, E N, *British Medical Journal*, 1975, 3, 743.

Aplastic anaemia and hair dye

SIR,—Following the recent report by Drs P J Toghill and R G Wilcox (28 February, p 502) we would like to recount a similar case in this hospital

The patient was a 54-year-old housewife who developed aplastic anaemia of undetermined aetiology. As in the case reported, she had been using a new hair dye prior to this. This contained *para*-toluene diamine sulphate. She showed no response to prednisolone or oxymetholone, being maintained by blood and platelet transfusions. Five months later she remains well and is taking ethamsylate 500 mg four times daily.

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Exchange transfusion in prevention of iron overload

SIR,—Your leading article (1 November, p 244) entitled "Blood transfusion and iron overload" states that children suffering from chronic aplastic anaemia or homozygous thalassaemia requiring frequent blood transfusions usually die during adolescence or early adult life and treatment must be directed to preventing iron accumulation by all available means. I wish to report a method of exchange blood transfusion which I have found to be successful in this regard.

Case 1—A boy aged 16 had required frequent blood transfusions since infancy to sustain life. He was suffering from a haemoglobinopathy and showed the full syndrome of haemochromatosis with involvement of skin, bone marrow, liver, heart, pancreas, kidneys, and testes. The serum iron was 54 $\mu\text{mol/l}$ (300 $\mu\text{g}/100\text{ ml}$), with 100% saturation of iron-binding protein. A series of 14 exchange blood transfusions were given at intervals of 2-3 months. Two direct blood transfusion pumps were used simultaneously to take blood from a femoral vein and give blood into the other femoral vein from 6-8 consecutive donors.¹ There was marked clinical improvement and serum iron fell to 35 $\mu\text{mol/l}$ (195 $\mu\text{g}/100\text{ ml}$), with 55% saturation of the iron-binding protein. He died suddenly after a transfusion in February 1963.

Case 2—A woman aged 40 suffering from aplastic anaemia and paroxysmal nocturnal haemoglobinuria received, over a period of 12 years, 131 regular blood transfusions. Her skin became pigmented and she showed an increased amount of iron in the bone marrow, liver, and kidneys. In October 1958 her serum iron was 47 $\mu\text{mol/l}$ (260 $\mu\text{g}/100\text{ ml}$), with 98% saturation of the iron-binding protein. Regular exchange blood transfusions, given by the direct method using two donors, were then started. As a result of this treatment her clinical condition improved and by December 1967 the serum iron was reduced to 11 $\mu\text{mol/l}$ (64 $\mu\text{g}/100\text{ ml}$), with 26% saturation of iron-binding protein. During the period of 10 years until the patient's death in February 1969 from a subarachnoid haemorrhage she received 94 exchange transfusions. With

exchange transfusions her haemoglobin level ranged from 6 to 13.4 g/dl compared with 4.3-7.6 g/dl during the period of non-exchange transfusions. Post-mortem histological examination showed increased fibrosis of the liver with moderate deposition of haemosiderin. There was no excess iron in the bone marrow or kidney.

It is concluded that the exchange transfusions given in these two cases were beneficial because abnormal red cells were removed and replaced by normal erythrocytes with normal cell life span and normal haemoglobin.

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- ¹ McLean, J A, and Luke, H A, *British Medical Journal*, 1967, 4, 78.

Carcinoma-in-situ of cervix in sisters

SIR,—May I support Mr S Bender's suggestion of investigating sisters in patients with an intraepithelial carcinoma of the cervix (28 February, p 502)? In 1959¹ I reported the simultaneous cytological diagnosis of cervical cancer in three sisters, the third of whom we "waylaid" while she was visiting her other two sisters, then in hospital. All these three women are still alive and well. In over 25 years' experience in my department we have at least six other examples of preinvasive carcinoma of the cervix and clinical carcinoma of the cervix in sisters and we have at least 12 examples of the same in mother and daughter.

As Mr Bender states, there are no cancer families in which the cervix has been the organ affected, but, knowing what we now know about the epidemiology of this disease, it appears to be a case of "like mother, like daughter."

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- ¹ Way, S, Hetherington, J, and Galloway, D C, *Lancet*, 1959, 2, 890.

Immunological findings in multiple sclerosis

SIR,—The study reported by Dr G Lamoureux and others (24 January, p 183) is interesting with regard to the broad spectrum of tests performed. Unfortunately, the number of patients with multiple sclerosis (MS) investigated (23) was small and because of the criteria applied for selection (young adults with a remitting course and a CSF IgG value exceeding 0.035 g/l) the conclusions drawn apply only to a particular group of MS patients.¹

We have attempted to obtain detailed information from all patients with MS in a defined area of Lower Saxony² concerning the incidence of the following childhood infections: measles, mumps, rubella, varicella, poliomyelitis, fifth disease, herpes zoster, herpes simplex, exanthema subitum, rickettsioses, scarlet fever, encephalitis, meningitis, and hepatitis. Two control groups consisted of 53 patients with disc lesions or psychiatric illnesses in the same area and 17 relatives or friends of the MS patients who had lived with or close to them during childhood and were not more than three years older or younger.

No statistically significant difference was found between the three groups in the incidence of any infections with the single exception of fifth disease, of which eight

members of the first control group but none of those of the other two groups had a history. These results are in contrast to those of Dr Lamoureux and his colleagues, though the small number of their cases makes the interpretation difficult.

As MS is a disease common enough in northern Europe (prevalence about 50 per 100 000 inhabitants) it is possible to include as many patients and controls in a study as the level of significance requires. Conclusions should be drawn with caution from studies in which a small number of highly selected patients are investigated.

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- ¹ Olsen, J E, et al, *Journal of Neurological Sciences*, 1976, 27, 233.
² Firnhaber, W, *Vorkommen der Multiplen Sklerose und epidemiologische Aspekte in einem umschriebenen Gebiet Südniedersachsens*. Göttingen, Habil.-Schrift, 1969.

Failure of phenobarbitone to prevent febrile convulsions

SIR,—I was brought up on the conventional teaching that phenobarbitone was the most useful single drug for treating most cases of epilepsy in children, a statement that regrettably continues still to be repeated in books and review articles. Experience gradually led me to the exactly opposite conclusion—that phenobarbitone was worse than useless for this purpose. Worse not only because does one seldom come across a child whose fits have been benefited by it but also because so often the child's behaviour deteriorates noticeably (He's become so irritable, say the parents).

Hard evidence to disprove the effectiveness of an anticonvulsant drug is never easy to obtain or collect. Greatly to be welcomed, therefore, is the evidence that Dr J Z Hackmatt and his co-workers from Glasgow (6 March, p 559) have provided to counter the widely held notion that phenobarbitone is effective in one context at least—the prevention of febrile fits.

If phenobarbitone ceased altogether to be regarded as a drug for treating children with fits would there be anything but gain?

DOUGLAS GAIRDNER

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Hazards of ergotamine tartrate

SIR,—Experience in the headache clinic at this hospital lends support to the note of caution sounded by Drs F C Rose and Marcia Wilkinson (28 February, p 525). I have seen many instances of the characteristic nausea and headache, present all day and every day and relieved briefly only by further ergotamine. These symptoms are due both to ergot toxicity and to the invariably coexistent tension (muscle contraction) headache; they are similar to the migraine that the patient has had in the past but are distinguished by the fact that uncomplicated migraine almost never occurs continuously every day. This complex picture is important because it is a sign not only of ergot toxicity but also of habituation.¹

The only treatment that succeeds is to admit the patient to hospital, to provide short-term sedation, and to wean him or her totally from ergot. Spectacular remission of headache occurs after one or two early rebound headaches in the first few days after withdrawal.

Drs Rose and Wilkinson are right to point out that ergotamine habituation can occur on doses of 1 mg or more per day. The drug manufacturers should be urged to modify their present recommendations for the treatment of migraine, which mostly advise up to six doses (6-12 mg depending on the preparation) per 24 h and up to 12 doses (12-24 mg) per week. In our experience if 1 mg, repeated if necessary after $\frac{1}{4}$ - $\frac{1}{2}$ h, is ineffective then ergot should be abandoned for that particular attack; analgesics will provide some degree of relief—certainly sufficient to make a severe pain tolerable.

Recognising these difficulties, we find that the correct use of ergotamine, often by suppository, is still highly effective in between 50 and 60% of our patients with migraine. It should not be discarded because of the relatively uncommon examples of habituation. The unpleasant acute dyskinesia² which complicates the use of metoclopramide and the phenothiazines in a minority of patients serves to remind us that no treatment is without hazard and that, to be successful, therapy must be carefully tailored to the individual.

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¹ Foster, J B, in *Modern Topics in Migraine*, ed J Pearce, p 143. London, Heinemann, 1975.

² De Silva, K L, Muller, P J, and Pearce, J, *Practitioner*, 1973, 211, 316.

Ibuprofen hydrochloride and terbutaline in asthma

SIR,—We have read with interest the article by Dr B Arner and Mr P O Magnusson (10 January, p 72). In our department we likewise have performed a comparative study of the bronchodilating effects of ibuprofen and terbutaline (in our study they were in inhalation form.² We did not observe any difference of importance between the two compounds. Ibuprofen was more effective weight for weight, but in equipotent doses the onset, duration, and peak of the effects of the two compounds were identical. We find that the same conclusion must be drawn from the study of Dr Arner and Mr Magnusson, but this is not quite apparent from their article.

The authors at first tested 2 mg of ibuprofen (generating 1.36 mg of terbutaline after hydrolysis) against 5 mg of terbutaline. These doses seemed to be equipotent. There was no significant difference in the onset, duration, or peak of their effects. In the discussion it is concluded from this, that "ibuprofen hydrochloride thus seems to produce a bronchodilating effect that is more than three times that of terbutaline sulphate." This conclusion seems to be unreasonable. The bronchodilating effect is the same, but the dose, weight for weight, of ibuprofen is one-third of that of terbutaline. The difference is obvious. Later the authors doubled the dose of ibuprofen (4 mg) without changing the dosage of terbutaline and demonstrated a clearly significant difference in favour of ibuprofen. We do not find this comparison to have any relevance since the doses used were clearly not equipotent.

The conclusion from the results of the study must be that the highly lipophilic compound ibuprofen is more effective per unit of weight, probably because of a higher absorption rate. Apart from this the two compounds are identical in their effects.

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¹ Poulsen, S S, and Petersen, B N, *Scandinavian Journal of Respiratory Disease*. In press.

Neuroblastoma in infancy

SIR,—We were interested to read the comment of Professor G M Besser and Dr W J Jeffcoate (21 February, p 448) that neuroblastoma of infancy is a highly malignant tumour and that treatment is almost uniformly fatal. In our experience and that of many other centres the reverse is true.

Young infants more commonly present with localised tumours, which may be partially resected and treated with postoperative radiotherapy, than do older children (in whom metastases to bone are frequently present at the time of diagnosis). In addition there is the group of young infants, originally described by D'Angio *et al*¹ in whom the primary tumour, which is usually in the adrenal gland, metastasizes to the liver, skin, and occasionally bone marrow but *not* bone; these infants have an excellent prognosis and require only minimal treatment, or sometimes no treatment at all, to initiate regression of disease.

In our own series the disease-free survival rate for infants under one year of age at diagnosis is 60%, while that for the older child is only 13%. In older children disease-free survival is usually associated with known good prognostic factors such as tumour in the thorax² or a partially differentiated ganglioneuroblastoma. In all forms of neuroblastoma the most important diagnostic and prognostic test is the serial estimation of urinary levels of vanillylmandelic acid before and after treatment.³

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¹ D'Angio, G J, Evans, A E, and Koop, C E, *Lancet*, 1971, 1, 1046.

² Filler, R M, *et al*, *Journal of Pediatric Surgery*, 1972, 7, 136.

³ Bond, J V, *Archives of Disease in Childhood*, 1975, 50, 691.

Antibiotics for kicks

SIR,—While we all know that some young people recklessly consume quantities of amphetamines and other drugs, it came as a surprise to me to learn from one of my patients that he is in the habit of taking 15-20 antibiotic tablets, plus a glass of beer, for the sensation of euphoria that the combination gives him.

My patient informs me that as a seaman he is able to obtain drugs from doctors all over the world, trading on an infected finger or some such. He hoards the penicillin or tetracycline tablets and takes them when he feels he would like to sample the effect. As it happened on his reception into prison he was

found to have "black tongue". This condition has cleared up since his confinement to prison prevented further antibiotic self-medication.

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Alpha-chain disease cured with antibiotics

SIR,—Dr J Rogè and others (25 October, p 225) report a case of heavy-chain disease of alpha type in complete remission after treatment with tetracycline and oleandomycin. We have observed a patient with μ -chain disease who had a remission of clinical and laboratory signs of the disease after treatment with ampicillin and tetracycline.

The patient suffered from generalised lymphadenopathy, hepatosplenomegaly, and severe anaemia; μ -chain protein was detected in the serum by chromatographic and immunological methods. Her clinical state remained unchanged for about 18 months after the onset of symptoms.

In January 1974 the patient was admitted to this clinic with symptoms of a bronchopulmonary infection. She was treated with ampicillin (total 13 g) and tetracycline (20 g) by mouth. From this moment the patient, to our surprise, improved steadily and reached a complete remission. The haemoglobin level went up from 9.2 g/dl to 14.0 g/dl, the enlargement of the mediastinal lymph nodes showed a regression to normal size, and μ -chain protein could no longer be detected in the serum. The splenohepatomegaly also subsided completely.

We would like to stress the following points with regard to the significance of μ -chain protein and antibiotic therapy in this patient. Histologically the lymph nodes showed signs of heavy inflammation and deposits of periodic acid-Schiff-positive protein within the germinal centres. It was suggested by the pathologist (Professor K Lennert, Kiel) that toxoplasmosis and syphilis should be considered. Serologically, however, these diagnoses could not be confirmed. From the clinical findings this patient shows some similarities to cases with the chronic, pluri-potential, immunoproliferative disorder of Westerhausen and Oehlert.¹ The patients reported by these authors, however, had paraproteinaemia of IgM or IgA type and were treated with cytostatic agents or radiotherapy.

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¹ Westerhausen, M, and Oehlert, W, *Deutsche medizinische Wochenschrift*, 1972, 97, 1407.

C3 inactivator and hypocomplementaemia in a "healthy" woman

SIR,—Dr Anita Karstorp's report (28 February, p 501) of the female patient with arthralgia and a circulating C3 inactivator (the term "C3 activator" is a synonym for activated factor B of the alternative complement pathway) is hardly the first report of this phenomenon in an apparently healthy person, as she claims. Dr R H R White and I in 1973¹ reported three patients with partial lipodystrophy, two of whom were in complete