available to manufacturers, and those attributing agranulocytosis to mianserin were passed to me with the consent of the CSM. Some described agranulocytosis that might have been attributable to the drug. Most were from hospitals rather than general practice, and in many cases there was no possibility that adequate inquiries into recent drug histories could have been conducted. The clue to this was the fact that the date of diagnosis of alleged "mianserin agranulocytosis" and the date of the report to the CSM were so close that there could have been no time for discussion with the general practitioner concerned. Such discussion is essential to exclude more likely causes such as treatment with co-trimoxazole.

Withdrawal of use in the elderly could lead to substitution of more dangerous drugs. None of 60 patients who attempted suicide with mianserin alone and 4 of 169 who used amitriptyline alone died. (Combinations with other drugs such as paracetamol accounted for 2 other deaths in each group.) No patient who had taken mianserin had required intensive care compared with 56 who survived amitriptyline overdose. Since these 56 were derived from about half of the patients receiving the drug during only one month, there could, if all were switched to the more dangerous drug, be more than 400 such admissions and perhaps 20 deaths each year.

It is unfortunate that the CSM's remit does not extend to consideration of drug use in overdosage, which must surely be an essential aspect of the management of acute depressive illness. Is it not time for this defect in the 20-year-old Medicines Act of 1968, which precludes a balanced assessment of the risks and benefits, to be put right?

Drug Safety Research Unit,
North Croft House,
Winchester Road,
Botley, Southampton SO3 2BX W. H. W. INMAN

SUBCUTANEOUS ERYTHROPOIETIN

SIR,—Recombinant human erythropoietin has been evaluated extensively in both dialysis and pre-dialysis with anaemia of chronic renal failure. Professor Bommer and colleagues' letter (Aug 13, p 406) suggest that the ideal subcutaneous dose has been found. Ortho Pharmaceutical Corporation and our European Cilag companies have an intensive programme under way to evaluate changeover doses from intravenous to subcutaneous administration. While we agree with the general conclusions drawn by Bommer et al, we would emphasise that evaluation of best frequency of dosing for the subcutaneous route and the risk of increased immunogenicity has not been completed. Regulatory bodies in Europe and the United States are aware of these trials. Neither Ortho nor Cilag advises the administration of this drug subcutaneously until the evaluation is complete. We expect to have full data on hundreds of patients available soon.

Cilag AG,
CH-8201 Schaffhausen, Switzerland KENNETH J. BOUGHTON

Ortho Pharmaceutical Corporation,
Raritan, New Jersey, USA ROBERT I. ABELS
SETH A. RUDNICK

REYE'S SYNDROME AND ASPIRIN

SIR,—An 11-year-old boy attended with a history of upper airway infection. He was treated with aspirin and 2 days later had vomiting and altered consciousness. On the day of admission he was drowsy and he deteriorated within a few hours. Reye's syndrome was diagnosed on Centers for Disease Control criteria.[1] After 4 days of grade IV coma the boy recovered slowly and the only handicap was diminished vision in the left eye. His identical twin brother had the same respiratory illness and was treated with the same dosage of aspirin but Reye's syndrome did not develop. The above case of Reye's syndrome was the first reported to the Italian Ministry of Health[2] since legislation in December, 1987, made compulsory the reporting of any adverse reaction to drugs. A relation with the administration of salicylates during the antecedent illness was postulated.

This experience suggests the involvement of additional factors in Reye's syndrome because the identical twins (checked by study of histocompatibility antigens) presumably had the same respiratory illness and were treated with the same drug at the same dosage, yet the disease developed in only one. A role for aspirin in the pathogenesis of Reye's syndrome has been discussed.[3] The illness in our patient and its absence in his twin brother show how little we know about this syndrome, which is surely a multifactorial disease.

Paediatric Department,
Ospedale Predabissi,
20077 Vizzolo Predabissi, Italy A. ANDREOLI
G. BONORA
L. LUCIANI
L. PERLETTI

1. Centers for Disease Control. Reye's syndrome, United States. *MMWR* 1981, **34:** 244.
2. Editorial L'acido acetilsalicilico concausa della sindrome di Reye?. *Il Med Ital* 1988, no 19: 21.
3. Orlowski JP, Gillis J, Kilham HA. A catch in the Reye. *Pediatrics* 1987, **80:** 638–42.

PROGESTERONE FOR PREMENSTRUAL EXACERBATIONS OF ASTHMA

SIR,—Dr Beynon and colleagues (Aug 13, p 370) report the successful treatment of premenstrual exacerbations of asthma with intramuscular progesterone. In 1953 Greene and I described 5 women similarly treated,[1] and 2 of these women (plus 2 with premenstrual epilepsy and 2 with premenstrual migraine) were the first diagnosed premenstrual syndrome (PMS) cases to be treated successfully with intramuscular progesterone.[2] It was these 6 cases and my own progesterone-treated PMS migraine that instigated my lifelong interest in PMS. The term "premenstrual syndrome" was proposed to emphasise that both somatic and psychological symptoms may recur in the premenstruum. 6 years ago an 18-year-old student and a 42-year-old housewife were referred to the PMS clinic at University College Hospital, London. They had both had more than twenty hospital admissions for acute asthma before an alert nurse noted the premenstrual timing. Both responded to progesterone.[3]

A survey of 1095 women with PMS treated in 1982 with progesterone included 13 women with asthma, who also had fewer symptoms characteristic of premenstrual tension.[3] Oral contraceptives will not improve asthma control, for progestagens lower the blood progesterone level. 1 woman had symptoms continuing until the second day of her period. Perhaps she had only scanty menstruation on the first and second day, for premenstrual exacerbations ease with the onset of the full menstrual flow. The scanty flow occurs during the physiological premenstruum, although chronologically it is during menstruation itself.

Since the isolation of human progesterone receptors in 1980,[4] the mechanism of action of progesterone has emerged, and recent work suggests that the fault in PMS lies with the progesterone receptors. Among the many sites of progesterone receptors are the nasopharyngeal passages and lungs, where they may be responsible for premenstrual exacerbations of rhinitis, sinusitis, sore throat, and asthma. In rats and guineapigs the receptivity of progesterone receptors is decreased in the presence of noradrenergenic agents.[5] Also after the first dose of progesterone the receptors become hyposensitive and require a pharmacological, rather than a physiological, dose of progesterone to stimulate them;[6] this would account for the high dose of intramuscular progesterone required.

It is unlikely that there are any specific reports of progesterone in the treatment of asthma, for most studies deal collectively with the one hundred and fifty presenting symptoms of PMS and it is unlikely that "asthma" would appear in the classification.

100 Harley Street,
London W1 KATHARINA DALTON

1. Greene R, Dalton K. The premenstrual syndrome. *Br Med J* 1953; **1:** 1007-10.
2. Dalton K. Discussion on the premenstrual syndrome. *Proc R Soc Med* 1955, 48, **5:** 337–47.
3. Dalton K. The premenstrual syndrome and progesterone therapy, 2nd ed. London. William Heinemann Medical Books, 1984; **79:** 253–62.
4. Jacobs BR, Suchocki S, Smith RG. Evidence of human ovarian progesterone receptor. *Am J Obstet Gynecol* 1980; 138, **3:** 332–36.
5. Nock B. Noradrenergic regulation of progestin receptors: new findings, new questions. In: Reproduction: a behavioral and neuroendocrine perspective. *Ann NY Acad Sci* 1986; **474:** 415–22.
6. Blaustein JD. Steroid receptors and hormone action in the brain. In: Reproduction: a behavioral and neuroendocrine perspective. *Ann NY Acad Sci* 1986, **474:** 400–14.