findings except that the frequency observed is lower than previously reported. We consider the elevated IgE concentration as a non-specific expression of the inflammatory process in the skin, as has been discussed in other skin diseases.^{4,5}

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- ¹ Tan, R S H, *et al*, *British Journal of Dermatology*, 1974, **91**, 607.
² Zachariae, H, *et al*, *Acta Dermatovenereologica*, 1975, **55**, 466.
³ MacKie, R, *et al*, *British Journal of Dermatology*, 1976, **94**, 173.
⁴ Arbesman, C E, *et al*, *Archives of Dermatology*, 1974, **110**, 378.
⁵ Bruns, G R, and Ablin, R J, *Archives of Dermatology*, 1977, **113**, 1461.

Maternal pethidine and neonatal depression

SIR,—We are grateful to Dr M Rosen and his colleagues (18 February, p 438) for a more complete description of the methods used in their trial of naloxone in neonates (23 July 1977, p 229). Following their censure we have earnestly endeavoured to give their paper a "proper" reading, but we feel that their letter fails to answer the points which we previously raised.

Our main concern was that a relatively new drug was used in this trial on babies who appeared to be perfectly healthy and that a large dose was administered in a situation in which pethidine antagonists would not normally have been considered. We wholeheartedly support their view that no drug should be given without a clinical indication and this is especially true in neonates. In their letter they mention that naloxone was not given routinely to babies included in the trial but only to those who had a clinical problem associated with pethidine used in labour. We are unable to find an explanation of exactly what this problem was. The criteria mentioned by the authors in their paper seem only to emphasise what fine fettle the babies were in at birth and it is difficult to envisage what problem occurred in the first 60 s of life that necessitated the use of naloxone. Furthermore, the authors persistently refer to the subjects of the trial as "healthy mature neonates." It seems to us of fundamental importance that normal babies should not be exposed to the unnecessary risks associated with trials of new drugs. That drug effects may be more clearly demonstrated in healthy babies is hardly a justification for such conduct, for the effects of prematurity, asphyxia, and birth trauma should be excluded by subjecting the results of a large trial to conventional statistical analysis.

Their trial failed to show how naloxone acts in the clinical situations in which pethidine antagonists are conventionally employed. It would be unethical to use a placebo in such instances, but most paediatricians have used nalorphine and levallorphan quite successfully for years, and this was why we suggested that a trial comparing naloxone with the older antagonists would have given more meaningful results. What effect a drug has on adults or anaesthetists may be irrelevant to the neonate and is certainly not a justification for dismissing the conventional antagonists out of hand. Similarly, substances innocuous in the adult may be toxic to the newborn and one need only quote bilirubin and oxygen to illustrate the point. On what grounds Dr Rosen and his colleagues abandoned use of conventional pethidine antagon-

ists "years" ago is uncertain. A safe and well-established drug should be superseded by a newer one only after scientific proof of superior efficacy or safety.

At the present time we question whether there is sufficient evidence to justify widespread use of naloxone. For the most part significant pethidine depression is easy to diagnose and, in our experience, responds well to nalorphine. We have had very few problems with the older antagonists. If pethidine toxicity is in doubt—for example, if asphyxia has also occurred—and if further depression would be deleterious then we use intravenous naloxone as a diagnostic aid. With these restrictions we use the newer drug rarely but have been impressed with its performance.

Pethidine antagonists have a small role to play in neonatal medicine, but at times they may be life saving. Their widespread use for trivial depression will put an unacceptably high number of healthy babies at risk. All drugs have side effects and any talk of safety of a drug after animal testing and small clinical trials is spurious. Unless we learn our lessons from thalidomide and practolol avoidable iatrogenesis will continue to occur. Practolol was widely prescribed in conditions in which its selectivity was completely unnecessary. It would be a pity if naloxone succumbed to the same fate.

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Cimetidine and serum prolactin

SIR,—Firstly, we thank Dr M C Bateson (18 March, p 718) very much for pointing out the error in the calculation of the mean value of our observations on serum prolactin reported earlier (18 February, p 409); however, the corrected mean value lies well within the normal limit and hence does not alter our conclusions. We sincerely regret this unintentional error and offer our apology to readers for the confusion it might have created.

Secondly, the suggestion by Dr W L Burland and others (18 March, p 717) of involvement of the dopaminergic receptors in the hypothalamus (prolactin-inhibiting factor, PIF) in cimetidine-induced hyperprolactinaemia in healthy male subjects is a provocative hypothesis. It may be relevant to mention that certain non-phenothiazinic antihistaminics (H₁-receptor antagonists), meclozine and tripeleminamine, stimulate prolactin secretion.¹ Meclozine is a piperazine derivative and tripeleminamine an ethylenediamine; it may be postulated that H₁-receptors and dopaminergic receptors have some structural or stereochemical similarities and it could even be true for H₂-receptors as well. Of course, cimetidine is an amidazoline derivative with a cyanoguanidine group attached to the side-chain. Receptors, in the present state of our knowledge, are, however, pharmacological concepts engraved in a philosophical mosaic.

Prolactin was the first hormone shown to be predominantly under the control of hypothalamic PIF but, though unelucidated yet, a prolactin-releasing factor (PRF), probably a polypeptide dependent on serotonin as the intrahypothalamic neurotransmitter, has also been proposed.² Balance between PIF and PRF could be the final regulating mechanism of prolactin secretion and release; in view of this the effect of cimetidine on both factors needs to be examined.

Thirdly, circulating prolactin has normally a circadian rhythm and levels rise during the early part of the night; it may also be secreted during stress.³ The time of collection of blood samples and the stress factor, though of minor importance, might deserve some consideration. Further study on these lines is in progress.

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- ¹ Williams, R R, *Lancet*, 1976, **1**, 996.
² Mortimer, C H, and Besser, G M, in *Recent Advances in Medicine—17*, ed D N Baron *et al*, p 441. London and Edinburgh, Churchill Livingstone, 1977.
³ Besser, G M, and Thorner, M O, in *Advanced Medicine Symposium—11*, ed A F Lant, p 225. Tunbridge Wells, Pitman Medical, 1975.

Subarachnoid haemorrhage in patients over 59

SIR,—I refer to Dr B V Martindale and Mr J Garfield's article (25 February, p 465) and subsequent correspondence (25 March, p 783).

There is no particular mystique about the age of 60. In an aging population many of our citizens lead active, useful lives for a further one or two decades and an arbitrary age limit imposes a check on both thought and effort. Each patient should be considered according to the clinical condition.

In a personal series of 694 patients with cerebral aneurysms and angiomas presenting with subarachnoid haemorrhage, 75 were aged 60 or over (mean age 62.6 years); 42 of these were operated upon (craniotomy for 40) and nine died within three months. Thirty-three (mean age 63.9 years) were not operated on and 10 of these were dead within three months. Survivors of both groups were followed up for an average of 6.3 years. In the operated series the quality of life was distinctly improved compared with the unoperated.

Factors other than arbitrary age are more important in selection of patients—for example, coma, multiple ruptures, hypertension. It is hoped that these and other considerations will be presented soon in a prospective study of over 900 personal cases of spontaneous subarachnoid haemorrhage seen during a period of 17 years.

Finally, in the context of the above and with reference to the article by Stewart *et al*¹ on neurosurgery in the older patient (over the age of 65), I do not think the resources available for neurosurgery are being used unwisely.

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- ¹ Stewart, I, Shephard, R H, and Millac, P, *Postgraduate Medical Journal*, 1975, **51**, 453.

Typhoid and its serology

SIR,—Your leading article (18 February, p 389) states that "serology plays a minor part in the diagnosis of enteric fever." May I mention an outbreak¹ in which serology was very helpful?

Knowing of two cases of paratyphoid fever, apparently unrelated, a practitioner submitted blood from four persons ill for a few days. Within four hours a presumptive diagnosis of paratyphoid infection was made in three cases,