non-crying babies. Hutt⁷ describes parallels. High pulse rates have been found in withdrawn psychotic patients.⁸

While preparing a paper on adolescent suicide attempts in this health district over 12 months I noted that, with a few exceptions, both the mothers' memory and medical records indicated that the 40 teenagers were non-crying babies. I had hoped to entitle the presentation "The unheard cry growing up."

Although, as Dunn surmises,² parents and babies are allowed time to adjust and early reactions are certainly not exclusively all-important for future emotional development, awareness of "silent" infant protest is important. We can then deal with causative factors and learn to contain also the anxiety or aggression arising therefrom.

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¹ Klaus M, Kennell J. *Maternal infant bonding*. St Louis: Mosby, 1976:74-81.

² Ciba Foundation Symposium 33. *Parent infant interaction*. Oxford: Association of Scientific Publishers, 1975:137-48, 155-68, 201, 241-60.

³ Ainsworth M, Bell SM. *Child Dev* 1972;43:1171-90.

⁴ Klaus M, Kennell J. *Maternal infant bonding*. St Louis: Mosby, 1976:38-97.

⁵ Dunn J. *Distress and comfort*. London: Fontana, 1977:90-7.

⁶ Sander L, Rexford E, Shapiro T. *Infant psychiatry*. Yale University Press, 1976:63.

⁷ Hutt S, Lenard H, Precht H. *Advances in child development and behaviour*. New York: Academic Press, 1969:127-67.

⁸ Venables P. *Research in psychophysiology*. London: Wiley, 1975:282

Common napkin rashes

SIR,—The most common napkin area eruption is an irritant frictional contact dermatitis primarily affecting the convexities and with groin sparing. It is correctly referred to as irritant napkin dermatitis but unfortunately is still sometimes called ammoniacal dermatitis, as Dr H B Valman does (21 June, p 1525).

Irritant napkin dermatitis, which is uncommon in the first month of life, may present as erythema, papulovesicles, or erosions. Certainly ammoniacal dermatitis occurs and is usually the erosive type of irritant dermatitis and one can smell the ammonia, but irritant dermatitis is usually not ammoniacal. Indeed, the affected skin and napkin pH is acid in some of these infants. It has been suggested that, in occasional cases, urinary ammonia may play a secondary role in aggravating already damaged skin but that by itself it does not initiate a dermatitis.¹

Regarding nappy liners, the popular fabric and paper ones increase the chance of frictional irritation and may cause a W-shaped dermatitis² but use of pure Terylene nappy liners is safe.³

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¹ Leyden JJ, Katz S, Stewart R, Kligman AM. *Arch Dermatol* 1977;113:1678-80.

² Larrègue M, Gallet P, Rat JP, Bressieux JM. *Dermatologica* 1975;151:104-12.

³ Verbov J. *Practitioner* 1978;220:779-84.

Sleep disturbance in the young child

SIR,—The review of sleep disturbance in the young child by Dr M C O Bax (10 May, p 1177) is a nice example of an excellent article by the wrong author. The subject is,

as he admits, one which concerns the whole family, so that however far the paediatrician moves into the community he will never be the appropriate professional involved. Nearly all of these problems are brought to the health visitor and the general practitioner, who will of necessity remain the experts in this field.

The only British papers in the very limited literature on the subject are from general practice^{1 2} and were not referred to. The text of the article, incidentally, did not refer to the first two references. But it was a pleasure to read such a thoughtful paper. Even Professor Court's committee might agree that, however essential paediatricians are in childhood illness, minor behavioural disturbances of infancy are the province of the present primary team.

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¹ Seiler ER. *Practitioner* 1972;208:271-6.

² Aylett MJ. *Update* 1977;14:367-72.

* * * We regret that the first two references were not cited in the text of Dr Bax's article. They should have been included in the first sentence of the second paragraph.—ED, *BMJ*.

Beta-blockers in the treatment of myocardial infarction

SIR,—In his recent letter (19 April, p 1088) Professor Geoffrey Rose, commenting on the study by Dr R G Wilcox and others (29 March, p 885), made the important point that confidence limits should be reported in any "negative" trial. We have calculated the approximate 90% confidence limits for 18 clinical trials of beta-blockers in myocardial infarction for which we could obtain the necessary data, including the study by Dr Wilcox and his colleagues. Our results are shown in the figure. Wherever possible total mortality has been used, but in some trials only cardiac mortality was available. It can be seen that 14 of the 18 encompass within their 90% confidence intervals a potential 50% reduction in mortality. However, all but two studies^{1 2} fail to exclude the possibility of

an increase in mortality on treatment, thus demonstrating their inadequate size.

For reasons of visual clarity, our statistical methods are approximate; but we would emphasise that more precise methods do not affect the pertinent issue. Further details concerning the methods and also the full list of references will gladly be supplied on request.

Presentation of information in this way should not only caution us (as Professor Rose points out) against premature dismissal of potentially useful agents, but also stimulate us to ask if certain groups of patients are responding to treatment while others are not.

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¹ Multicentre International Study. *Br Med J* 1975; iii:735-40.

² Snow PJD. *Lancet* 1965;ii:551-3.

Retroperitoneal fibrosis associated with atenolol

SIR,—The letter of Dr M J Gavin and others (17 May, p 1227) commenting on the report of retroperitoneal fibrosis in a person taking atenolol by Mr J N Johnson and Mr J B McFarland (22 March, p 864) itself deserves comment.

Firstly, an erythrocyte sedimentation rate (ESR) of 24 mm in one hour in November 1975 can scarcely be considered to be raised compared with a value of 106 mm in July 1979. Such a minor elevation would be appropriate, for example, to any minor infection. The reason for measuring the ESR is unfortunately not given, but presumably it was done at a time when the patient felt temporarily unwell, as with a minor infection. Marked elevation of the ESR is, of course, common in both drug-induced and idiopathic retroperitoneal fibrosis.¹

Secondly, it is said that two expert patholo-

Effect of beta-blockers on postinfarction mortality: difference in mortality rates (shown by thick vertical lines) with 90% confidence limits expressed as a percentage of observed control rate in 18 controlled trials. O=oxprenolol; P=propranolol; AI=alprenolol; At=atenolol; Pr=practolol.

gists stated that "the appearances are those of idiopathic retroperitoneal fibrosis. The histological appearances of practolol peritonitis are different..." This is not the appropriate comparison. The patient obviously had fibrosis in the retroperitoneal space and not the peritoneal cavity. The point is that idiopathic and drug-related (for example, methysergide) retroperitoneal fibrosis present the same histological picture.¹

Oxprenolol is also listed in reports of the Committee on Safety of Medicines as being ingested by patients developing sclerosing peritonitis or retroperitoneal fibrosis; this does not necessarily imply a causal relationship or that other drugs were not also being taken. Practolol, atenolol, and oxprenolol have thus been associated with fibrosing syndromes. A comparison of the structure of these beta-blockers with that of those which have not been so associated is therefore of interest.

The majority of beta-blockers contain an unsaturated six carbon ring with two side chains. The ring and one side chain, R, is common to metoprolol, atenolol, practolol, propranolol, and some other beta-blockers. R is $-\text{OCH}_2\text{CH}(\text{OH})\text{CH}_2\text{NHCH}(\text{CH}_3)_2$. Acebutalol contains this side chain and an additional ring substituent ortho to it.

The problems with practolol therefore presumably arose because of the unique structure of the second side chain. Practolol, atenolol, metoprolol, and acebutalol are substituted para to the first side chain, R, and oxprenolol ortho. Side chain sizes of the three drugs mentioned in relation to fibrosing syndromes are 58, 57, and 58 daltons for practolol, oxprenolol, and atenolol respectively. They all contain a double bond and would possess a somewhat similar electron cloud configuration. The side chains of practolol and atenolol are essentially identical—that is, acetamide (NH_2COCH_3)—with attachment to the ring via the nitrogen atom in the former case and the methyl carbon in the latter.

Oxprenolol has a side chain of similar size ($-\text{OCH}_2\text{CH}=\text{CH}_2$), also with a double bond.

On the other hand, metoprolol has a side chain of 59 daltons but no double bond and acebutalol a more bulky side chain of 86 daltons. Propranolol is a double ring structure.

The three beta-blockers under consideration therefore show a high degree of similarity in structure and further reports of their association with fibrosing syndromes will be of interest.

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¹ Graham JR, et al. *N Engl J Med* 1966;274:359-68.

Repeat exposure to Althesin

SIR,—For the past 18 months our department has offered a service to anaesthetists in the Avon area and surrounding districts in investigating the immunological basis of

hypersensitivity reactions to anaesthetic drugs. We are increasingly concerned about the number of such reactions which follow repeat exposure to Althesin (alphaxalone and alphadolone acetate). Routine investigations include immunological analysis of serial blood samples for consumption and conversion of the C3 and C4 complement components.

Of 22 patients with clinical signs of hypersensitivity to Althesin subsequently confirmed by laboratory investigation, 17 had received the drug on at least one previous occasion, while five had no known previous exposure. Nine of these 17 patients had severe clinical reactions, involving cardiovascular collapse; and, of these, eight had already received Althesin within the previous two months. Of the five who reacted on first exposure, only one had severe symptoms. The majority of our patients were receiving anaesthesia for minor gynaecological or orthopaedic procedures, and all were otherwise fit with no apparent haematological or immunological abnormality.

At present we do not have figures to show the frequency of uneventful anaesthesia following either first or repeat exposure to Althesin in the Avon area, but our results so far indicate that there is a greater possibility of hypersensitivity reactions in patients who are re-exposed to Althesin.

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Acute renal failure

SIR,—The leading article on acute renal failure (7 June, p 1333) raises important issues in relation to diagnostic screening and dialysis timing. Expert overview of uraemic patients is to be endorsed. An interested nephrologist reviewing "uraemic" biochemistry reports from his area laboratory daily enables timely advice to be given and permits realistic planning of acute renal services.

In the Sunderland area (population 400 000) this practice reveals 1200-1500 patients annually with a blood urea of 15 mmol/l (90 mg/100 ml) or more. The dominant causes are myocardial infarction 12%, stroke 8.7%, cardiac failure 9.8%, diabetes 10%, gastrointestinal tract and hepatic pathology 12.5%. From 50 to 60 cases of severe acute renal failure (blood urea ≥ 30 mmol/l (181 mg/100 ml) are diagnosed annually. There is rarely diagnostic difficulty affecting management of the uraemia, 78% being the result of hypovolaemia with or without sepsis.

Serum protein changes receive little comment, although an earlier review¹ did discuss the possible role of albumin infusion in preventing acute renal failure. In this area 72% of patients with severe acute renal failure are hypoalbuminaemic at the time of diagnosis. The effect of albumin on intrarenal haemodynamics still requires clarification. Nephrologists are all familiar with the dramatic effects of a small albumin load in an apparently diuretic-resistant nephrotic patient.

The problem of timing dialysis is raised and mention made of a urea level of 30 mmol/l. For the past two decades there has been little impact on the high mortality in acute renal failure despite "prophylactic daily dialysis." While patients who have chronic renal failure

seem to tolerate uraemia, an ongoing study in this unit suggests that those with acute renal failure are better if kept non-uraemic. This entails continuous haemodialysis or combined haemodialysis and peritoneal dialysis, treatment being continued until diuresis occurs, maintaining a blood urea level between 0 and 10 mmol/l (up to 60 mg/100 ml).

Preliminary results demonstrate that survival, well being, taste and appetite, haemoglobin levels, and resolution of infection and wounds are improved compared with those treated by short daily or alternate-day dialysis. This would suggest that if volume replacement and ionotropic drugs fail dialysis should be instituted at an earlier stage than has generally been recommended.

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¹ Anonymous. *Br Med J* 1980;280:2-3.

Distalgesic poisoning—cause for concern

SIR,—The tragic circumstances whereby individuals die as a result of poisoning, either accidental or deliberate, is bound to bring calls that the causative agent be removed from temptation. On the other hand, where that causative agent is a useful and safe medicinal product when correctly used the clamour for product withdrawal or reclassification has to be balanced against the scientific and clinical arguments for and against. At the present time, so far as dextropropoxyphene is concerned such an impartial review has yet to appear in the literature. The present authors are working with this objective. However, we would comment on some of the issues raised by Drs R J Young and A A H Lawson (12 April, p 1045).

The majority of the people who die from any drug overdose do so outside hospital.¹ The authors fail to mention this and subsequently appear to distort the mortality due to Distalgesic overdose in their paper. The death rate in all poisonings of 0.76% represents mortality in hospitals only.² This is compared with mortality in the community and hospital for Distalgesic (12.7%). The authors continue by calculating that 53.4% of the patients admitted after January 1976 were in a high-risk category (31/58). However, they then calculate the mortality from this group of 31 patients, but include the five deaths outside hospital in which Distalgesic was implicated. Further errors are made when the authors calculate the "potential death rate" (whatever this means). The five deaths occurring outside the hospital are again added, to provide an inflated figure of 60%.

Oral dextropropoxyphene undergoes extensive first-pass metabolism.³ Consequently changes would be expected to occur in the pharmacokinetics of the drug in patients with alcoholic liver disease. Six of the eight deaths attributed to Distalgesic in the paper by Drs Young and Lawson were in recognised alcoholics. We suggest, therefore, that the amount of unmetabolised drug reaching the systemic blood circulation and subsequently the central nervous system after an oral dose would be much higher in patients with