findings suggest that glycyrrhizic acid mimics this as well as other actions of aldosterone.

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¹ Davanzo, J P, Crossfield, N C, and Swingle, W W, *Endocrinology*, 1958, **63**, 825.

² Horton, R, and Biglieri, E G, *Journal of Clinical Endocrinology*, 1962, **22**, 1187.

Dermatitis from cosmetics

SIR,—Every practising dermatologist must welcome your timely leading article (24 September, p 782) on this difficult problem, but I think there are two additional aspects which should be stressed if the problem is to lessen.

It may seem trite but it would be invaluable for the Dermatologists Subcommittee of the Central Committee for Hospital Medical Services to point out to manufacturers that, perfumes apart, the commonest allergens in cosmetics are lanolin, ethylenediamine, used as a stabiliser, and parabens, used as preservatives, and that substitutes for these should be found.

Conversely, and quite the reverse of enforced American law, there is still no requirement in Britain or the EEC for a list of contents to appear on each cosmetic package, though it was quite clearly stated by the relevant EEC committee many years ago that it would seem to be imminent. How can any doctor advise his cosmetic-allergic patient to change to a new preparation, even if "hypoallergic," when he has no more knowledge than she if this is going to make the situation better or worse?

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Erythema nodosum and oral contraceptives

SIR,—We were most interested in the case report of Dr S Bombardieri and others (11 June, p 1509) describing erythema nodosum associated with pregnancy and oral contraceptives, as we have recently investigated a woman who developed erythema nodosum while taking Minilyn (ethinylloestradiol 50 µg, with lynoestrenol 2.5 mg). There has been a previous report of erythema nodosum occurring with this preparation; the pill taken by Bombardieri's patient also contained ethinylloestradiol. We wish to emphasise the need for caution before attributing erythema nodosum to oral contraceptives.

A 26-year-old woman who had been taking Minilyn for three years was admitted with erythema nodosum of the lower limbs. This developed one week after she had been given Cephalax for a sore throat. When she was admitted both drugs were withheld and the lesions subsided within a week. Later the Minilyn was restarted; the erythema nodosum returned within three days and then subsided after withdrawal of the drug. This sequence was repeated the following week. Her WBC was $14 \times 10^9/l$ with a neutrophilia, the ESR

was 40 mm per hour, and she had a mild normochromic anaemia. The following investigations gave normal results: chest x-ray, ECG, urea and electrolytes, nose and throat swab, 24-hour urinary calcium, Kveim and Paul-Bunnell tests, brucella and yersinia antibody titres. The ASO titre never exceeded 200 international units. She had never had BCG and she was Mantoux-negative.

The patient was then challenged with four types of coded capsules supplied by Organon Laboratories Ltd. She took one of the specially formulated preparations each day for two weeks and then took no tablets for the next two weeks. This sequence was then repeated with each of the preparations in turn. Two weeks after finishing this programme she took Minilyn again for two weeks. No further lesions developed in response to the capsules—which were a placebo, Minilyn, Lynoral (ethinylloestradiol), and Exluton (lynnoestrenol), respectively. There was no reaction to the final Minilyn challenge nor was there any variation detected in the weekly measurements of T cell lymphocytes measured throughout the period.

We conclude that this patient's erythema nodosum could not be attributed to her contraceptive pill despite the three apparent responses to Minilyn challenge. But it is of course possible that repeated challenges with Minilyn over a long period resulted in desensitisation and a lack of further response.

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Hexachlorophane—yes or no?

SIR,—I would like to comment on your leading article (5 February, p 337) and subsequent correspondence—in particular, the comments of Drs M D Young and Glenda Treadway (2 April, p 904) involving an article of which I was coauthor.¹ Specifically, I do not agree with their implication that our study supports the safety of hexachlorophane. In our study the number of subjects not hexachlorophane-bathed was 18, a limitation which makes it difficult to show a statistically significant difference unfavourable to hexachlorophane. Nevertheless, we did show that hexachlorophane was present in brain tissue in four of six infants bathed in it at birth and in one of two infants whose mothers were prepared with it just prior to delivery. As we pointed out, both of the two subjects bathed in hexachlorophane who did not show tissue levels survived long enough to have eliminated it from their systems even though in one lesions were still present.

Premature babies absorb more hexachlorophane from a given exposure, but infants in our study showed more lesions as their birth weight increased, and lesions were seen in mature infants. We would interpret this as indicating that in man as in rats the period of maximum myelination of the central nervous system coincides with the period of maximum susceptibility.² Thus, data based on follow-up of prematures may not be a reliable indication of the effects in full-term infants.

In regard to the safety of hexachlorophane when used less than three times, the manufacturer's directions suggest that repeated use is necessary for effectiveness, and further that

rinsing is not effective in removing it from the skin: "Cumulative antibacterial action develops with repeated use. This antibacterial residue is resistant to removal by many solvents, soaps, and detergents for several days."³

There are other studies which show that other, more malignant, organisms colonise the newborn if, in fact, hexachlorophane bathing does eliminate *Staphylococcus epidermidis*.⁴⁻⁶ In many cases, the appearance of minor staphylococcal skin lesions is merely postponed until the baby has left the hospital.⁷ It is problematical whether this is good or bad. On the one hand, older babies may tolerate these infections better; on the other, the IgG immunity derived from the mother begins to decline and may lower their resistance. At any rate, most staphylococcal skin infections are minor and of no practical consequence.

In summary, hexachlorophane is absorbed from the intact skin of the newborn, both premature and full term.⁸⁻¹³ Vacuolisation of the central nervous system can be found in the brains of infants so bathed¹⁴⁻¹⁶ in our study associated with tissue levels of hexachlorophane.

Discontinuance of hexachlorophane bathing has not increased perinatal mortality.¹⁷ It seems to me that the hazard is proved. Other methods of preventing staphylococcal infection are available and should be pursued.

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¹ Gowdy, J M, and Ulsamer, A G, *American Journal of Diseases of Children*, 1976, **130**, 247.

² Kimbrough, R D, *Archives of Environmental Health*, 1971, **23**, 119.

³ Physicians' Desk Reference 31st edn, p 1721. Oradell, New Jersey, 1977.

⁴ Light, J J, et al, *New England Journal of Medicine*, 1968, **278**, 1243.

⁵ Farfar, J O, Gould, J C, and Maccabe, A F, *Lancet*, 1968, **2**, 177.

⁶ Stratford, B C, *Medical Journal of Australia*, 1963, **50**, 308.

⁷ Ferenczi, E, Pomoth, R, and Kende, E, *Oruosi Hetilap*, 1967, **108**, 12.

⁸ Curley, A, *Lancet*, 1971, **2**, 296.

⁹ Corner, B D, et al, *British Medical Journal*, 1977, **1**, 636.

¹⁰ McQueen, E G, and Ferry, D G, *Lancet*, 1971, **1**, 637.

¹¹ Plueckhahn, V D, *Medical Journal of Australia*, 1973, **1**, 93.

¹² Cunningham, M D, and Tsoulos, N G, *Pediatric Research*, 1972, **46**, 431.

¹³ Alder, B D, et al, *Lancet*, 1972, **2**, 384.

¹⁴ Schuman, R M, Leech, R W, Alvord, E G, Jr, *Pediatrics*, 1974, **54**, 689.

¹⁵ Schuman, R M, Leech, R W, and Alvord, E G, Jr, *Archives of Neurology*, 1975, **32**, 320.

¹⁶ Plueckhahn, V D, and Collins, R B, *Medical Journal of Australia*, 1976, **1**, 815.

¹⁷ Gordon, R R, *British Medical Journal*, 1977, **2**, 705.

Indomethacin in pleurisy

SIR,—I wish to comment on the use of indomethacin as an analgesic for patients with pleurisy. I can find no previous reference to this, although the value of the drug in acute pericarditis has been reported.¹

During the past eight months 21 hospital inpatients with pleurisy were given indomethacin for relief of their chest pain. Two had tuberculous pleural effusions, three had pulmonary infarcts, and the remainder had pleurisy with pneumonia. The dose was 25 mg two or three times a day and in some cases 50 mg at night. All patients expressed satisfaction with the relief of pain and they were able to cough and breathe deeply with little or no discomfort. The drug had to be stopped in two patients because of side effects: one had a haematemesis and the other severe nausea.

Chest pain in pleurisy is not well controlled by simple analgesics such as paracetamol or

aspirin, while opiates and their derivatives cause unwanted central nervous depression. Indomethacin seems to provide effective analgesia without making the patient drowsy, and based on this limited experience I strongly recommend it for this purpose. Other similar drugs which combine analgesic and anti-inflammatory properties might prove to be equally effective.

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¹ McGinn, J T, Rosati, M, and McGinn, T G, *New York State Journal of Medicine*, 1970, **70**, 1783.

Quality v quantity in children

SIR,—In your leading article on "Birth weight" (9 July, p 79) you state that obstetricians, paediatricians, and mothers "are increasingly concerned about the quality rather than the quantity of children." I have always considered this overworked phrase to be the rather silly and empty-headed catch cry of women's lib and the Family Planning Association, but when it comes from the *BMJ* it gives me pause and makes me wonder if my judgment was too peremptory.

Could you please explain for your less enlightened readers exactly what you mean? I can understand that if one has £x to spend one could choose one Rolls-Royce rather than five cheaper cars (*pace* British Leyland), but when it comes to human beings how is the fashionable two-child family of higher quality than a six-child one? Or, if parents have two high-quality children and then unpatriotically add a few more, does the quality of the original fortunate siblings gradually decline? I cannot see how in human affairs quality and quantity are mutually exclusive—unless one has the temerity to observe that, in general, the poor have more children than the rich.

There ought by now to be experimental evidence to show that the offspring in modern two-child families are of higher quality than those of the less pessimistic prewar days. To my simple observation the proof of your proposition is completely lacking; but its frequent restatement does harm to the confidence of parents and even to the nation itself.

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. In this context quality implies lack of defects; the change in attitudes has come from a realisation that perinatal morbidity is just as important as perinatal mortality and that there is no profit in preserving the lives of very small infants unless they grow up free of gross physical or mental handicap.—Ed, *BMJ*.

Fatal chlormethiazole poisoning in chronic alcoholics

SIR,—I should like to reply to Dr M M Glatt's letter (22 October, p 1088), in which he misquotes the opening statement of my report (3 September, p 614), and to suggest, with respect, that he himself misses the point.

Nowhere in the report is it stated that chlormethiazole is an antidepressant, although condensation of the paper into a short report may have led to some loss of clarity. The opening statement was: "Chlormethiazole edisylate (Heminevrin) is a sedative, hypnotic,

and anticonvulsant drug widely used in the treatment of depression." A depressed patient may need treatment with a sedative or hypnotic drug in addition to any antidepressant therapy.

The manufacturers (Astra Chemicals Ltd) state that it is a drug of low toxicity.¹ This may have led some general practitioners to believe that a patient who is depressed and has suicidal tendencies may come to little harm if an overdose of the drug is taken. The drug is packaged in bottles of 100 tablets and the pharmaceutical chemists to whom I have spoken say that in their experience this is the quantity in which the drug is usually prescribed. In two of the fatal cases I described a bottle which had contained 100 tablets of chlormethiazole was found near the body of the deceased.

The point of my report was to show that chlormethiazole is potentially dangerous, especially when taken with alcohol. It is surely logical to conclude that this is not a drug which a general practitioner may safely prescribe for someone who is depressed, has suicidal tendencies, and above all is an alcoholic. Chlormethiazole is a useful drug for the treatment of withdrawal symptoms in alcoholics in hospital *under strict supervision*. This is not the situation with which my report dealt.

A fifth case of chlormethiazole poisoning has recently occurred in the Bedford area, but the results of the analysis arrived too late for inclusion in the report.

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¹ *Data Sheet Compendium*. London, Association of British Pharmaceutical Industry, 1977.

Outpatient chemotherapy for breast cancer

SIR,—In their recent paper on chemotherapy for carcinoma of the breast (22 October, p 1064) Drs J H Goldie and L A Price have shown that an excellent response can be obtained by giving the drugs on only one day in every three weeks. Unfortunately their regimen necessitates admission to hospital and this alone may deter doctors in very busy district hospitals where the use of hospital beds is under severe pressure from using it.

The major reason that the patients need admission is for the infusion of the methotrexate. This, however, could be given as a single intravenous injection together with the other drugs. The therapeutic blood level would last only about 4 h as opposed to 16 h by infusion, but it is unlikely that this change would make a marked difference to the tumour response rate. Thus the regimen could be changed to giving intravenously vincristine 1 mg/m², cyclophosphamide 600 mg/m², 5-fluorouracil 500 mg/m², and methotrexate 100 mg/m² on one occasion every three weeks; 30 mg of folinic acid should be taken by mouth 18 h later. Alternatively the methotrexate could be given by mouth—50 mg at the time of the injection and 50 mg 6 h later. This would give longer-lasting therapeutic blood levels. The folinic acid rescue would also need to be extended, possibly by giving a further 30 mg at 24 h. This scheme would require a very dependable patient.

If the advantages of such chemotherapy for breast cancer, with its good response rate and low morbidity, are to be offered to patients

throughout the country, then it must be easy to administer on an outpatient basis. The above modified regimens would fulfil these requirements.

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Blood for antenatal tests

SIR,—An increasing number of serological and other tests are now required during antenatal care. Each test, except that for haemoglobin estimation, calls for 10 ml of clotted blood. Would a lesser quantity—say, 2 ml—be feasible? It should then be possible to perform all the tests from 8 or 9 ml of clotted blood collected in a single container using one 10-ml syringe, leaving the few remaining drops for the haemoglobin estimation.

The saving in time, space, containers, and syringes would be considerable.

L G HULL

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Association of autoimmune diseases with HLA-B8

SIR,—I was very interested to read the report by Dr B Hazleman and others (15 October, p 989) on their findings of HLA-B8 in 54% of their patients with polymyalgia rheumatica (PMR) and giant-cell arteritis.

Of the other suspected autoimmune diseases associated with B8 which they mention, chronic active hepatitis has not been associated with PMR, whereas a mild cholestatic hepatic dysfunction, described by different authors in recent years,¹⁻⁵ seems to be common in patients with PMR. However, the nature of the underlying hepatic lesion has not been well understood.

In our study⁶ of the 37 patients with PMR in whom it was measured, 23 (62%) had elevated activity of serum alkaline phosphatase (AP), mainly of hepatic origin, and bromsulphalein retention was abnormal in six out of 13 patients (46%). Fine-needle liver biopsy of the liver was performed on six patients, four of whom had elevated AP levels of hepatic origin. Three of the four patients for whom liver smears were stained for AP activity had an increased activity in their bile canaliculi that corresponded to a rise in the serum concentration of AP. In one of these three patients staining with naphthylamidase showed that the bile canaliculi had a calibre wider than normal and had irregular and granular walls. A partial reversal of these changes was shown in a second biopsy performed 10 days after corticosteroid therapy had been given. Mild fatty degeneration of the liver cells was seen in two other patients, whereas a patient with normal serum AP activity also had normal liver cells and bile canaliculi. The pathological structural changes observed in the wall of the bile canaliculi in one patient and the increased AP activity in this same patient and in two others may be evidence of a subclinical hepatic disease of variable severity associated with PMR. The increased number of lymphocytes and plasma cells observed in half of the biopsy specimens points to an immunological pathogenesis of this hepatic lesion.

In their report Dr Hazleman and his colleagues also refer to the prevalence of HLA-A10 and B8 in Hodgkin's disease shown in