women who received daily doses of corticosteroids equivalent to 2–30 mg. of prednisone that there was no correlation between corticosteroid dosage and urinary oestrogen excretion. It seems a little unwise, therefore, to argue, on the basis of a single estimation, that the reduction of the dose of corticosteroid in Dr. Driscoll's patient was responsible for the rise of the oestriol excretion to a normal value. What does the associated fall in pregnanediol excretion reflect?

We would suggest that a controlled study of the many aspects of corticosteroid therapy in pregnancy is necessary and that in the meantime it would be wrong to read too much into reports of isolated cases.—We are, etc.,

R. E. OAKLEY.
J. QUARRIE.

Department of Chemical Pathology,
University of Leeds,
Yorks.

REFERENCES

- Oakey, R. E., and Stutch, S. R., *J. Endocr.*, 1967, 38, xxiii.
- Scommegna, A., Nedoss, B. R., and Chatteraj, S. C., *Obstet. and Gynec.*, 1968, 31, 526.
- Brown, J. B., Beischer, N. A., and Smith, M. A., *J. Obstet. Gynaec. Brit. Cwllth*, 1968, 75, 819.

Disodium Cromoglycate in Bronchial Asthma

SIR,—In the article by Dr. D. G. Robertson and others (1 March, p. 552) on disodium cromoglycate in bronchial asthma I am taken to task for criticizing the claims that have been made for this drug on the grounds that the degree of improvement obtained from it has been too small to be worth while in most cases. I did in fact express the view¹ that the "statistically significant" degree of superiority of disodium cromoglycate over a placebo²⁻⁴ was unlikely to be of clinical value, except in an occasional case. In rebutting my criticism Dr. Robertson and his colleagues stated that "a very marked symptomatic improvement" was recorded in the nine patients who benefited from disodium cromoglycate, but if one looks closely at their Table I, in which the total symptom scores are recorded, it will be seen that this claim has little substance.

According to their scoring system a patient would require to record 126 points fewer on disodium cromoglycate than on placebo in order to show consistent improvement, for seven days and seven nights, from the middle of the "severe" grade (8 points) for breathlessness+tightness+ wheeze to the middle of the "moderate" grade (5 points) for these symptoms. I would agree that an improvement of this order could be regarded as modest but useful. When one looks at the relevant column in Table I, however, it can be seen that this degree of superiority was achieved by disodium cromoglycate in only two patients (Cases 9 and 10). In one patient (Case 2) a similar margin was recorded in favour of placebo, but the authors claim extenuating circumstances for this aberrant result. In another patient (Case 7) there was no difference. In four of the remaining seven patients the degree of superiority of disodium cromoglycate over placebo amounted to 7 points (Case 1), 4 points (Case 3), 3 points (Case 5), and 9 points (Case 11). Even if one takes the best of those four results (Case 11) the degree of superiority was equivalent only to the

difference between "moderate" and "severe" breathlessness, tightness, and wheeze on one single day or one single night per week. To claim "very marked symptomatic improvement" from disodium cromoglycate for those four patients is surely to debase the meaning of words. In the remaining three patients the degree of superiority (43, 36, and 31 points) was equivalent to a modest symptomatic improvement on three to five days or nights per week. In terms of breathlessness, tightness, and wheeze the results would thus be more appropriately interpreted as follows:

Disodium cromoglycate markedly superior to placebo ...	2
Disodium cromoglycate marginally superior to placebo ...	3
Placebo markedly superior to disodium cromoglycate ...	1
No difference ...	5
Total ...	11

The results in a few of these cases can admittedly be made to look a little more favourable to disodium cromoglycate if the scores for cough and inhaler usage are included in the analysis, but the basic conclusions, as shown above, remain the same.

Dr. Robertson and his colleagues claim a "highly significant" difference in favour of disodium cromoglycate in terms of morning and evening peak expiratory flow measurements, but mention that the results of the other physiological tests "varied." It would perhaps have been wiser for them to have made more extensive use, in a larger series of patients, of these "more elaborate" tests and of the forced expiratory volume before assuming that these investigations were less reliable than peak expiratory flow in assessing the response of disodium cromoglycate.

For the past 18 months I seem to have been the only correspondent to the weekly medical journals who has offered any serious criticism of the spate of articles in favour of disodium cromoglycate. The pressure on medical practitioners to prescribe this drug is now intense, and I think it is time that some of the more experienced chest physicians looked critically at the evidence for and against it, and either wrote in support of my view that disodium cromoglycate is of only marginal value in the treatment of bronchial asthma, or told me that the criticism I have made of all the clinical trials, apart from that reported by Kidner *et al.*,⁵ are unfounded.—I am, etc.,

IAN W. B. GRANT.

Respiratory Diseases Unit,
Northern General Hospital,
Edinburgh 5.

REFERENCES

- Grant, I. W. B., *Lancet*, 1968, 2, 282.
- Howell, J. B. L., Altounyan, R. E. C., *Lancet*, 1967, 2, 539.
- Smith, J. M., Devey, G. F., *Brit. med. J.*, 1968, 2, 340.
- Moran, F., Bankier, J. D. H., Boyd, G., *Lancet*, 1968, 2, 137.
- Kidner, P. H., Meisner, P., Pride, N. B., Pearson, R. S. B., *Lancet*, 1968, 2, 655.

Contamination of Disinfectants

SIR,—The observation of Dr. G. A. J. Ayliffe and others that hexachlorophane detergent creams which are used for hand-washing can become contaminated with Gram-negative bacteria (22 February, p. 505) prompts me to report similar findings.

Sixteen dispensers of a detergent cream containing 3% hexachlorophane which were examined were all contaminated. In contrast with the findings of Dr. Ayliffe and his colleagues, the organisms most commonly isolated were *Candida* spp., which were present in 13 dispensers, in three of which they were accompanied by *Klebsiella* spp. In the remaining three, *Klebsiella* spp. were present alone. *Klebsiella* spp. were also isolated from the necks of four stock bottles, two of which were unused, and *Candida* spp. were isolated from the necks of two others. Samples of the cream taken from the bottles without touching the sides were sterile. A notice on stock bottles from one manufacturer warned that dispensers should be rinsed in 70% alcohol before refilling, but the dispensers themselves bore no warning. Moreover, I suspect that disinfection by this method may not be adequate, as some dispensers have narrow nozzles in which organisms might prove inaccessible.

It seems unwise to rely on the self-disinfecting properties of the fluid in the dispenser, for resistant organisms have already been found in working solutions of cetrimide,¹ chlorhexidine,² Savlon,³ and the phenolic disinfectant Printol.³ I suggest that a heat process is the only safe method of sterilizing bottles which are to be refilled with a disinfectant solution. An alternative to sterilization would be the provision of disposable bottles.

A possible source of infection equally as dangerous as the hexachlorophane cream was also discovered here when two samples of oily cream, B.P., which was used as an emollient after hand-washing, were found to be contaminated. One contained *Pseudomonas aeruginosa*, and the other *Staphylococcus aureus* and *Escherichia coli*. This hand cream is no longer used in this hospital.—I am, etc.,

N. A. SIMMONS.

Department of Pathology,
Chase Farm Hospital,
Enfield, Middlesex.

REFERENCES

- Lowbury, E. J. L., *Brit. J. industr. Med.*, 1951, 8, 22.
- Burdon, D. W., and Whitby, J. L., *Brit. med. J.*, 1967, 2, 153.
- Simmons, N. A., and Gardner, D. A., submitted for publication.

Pregnancy Prurigo

SIR,—Having read your leading article on pregnancy prurigo (15 February, p. 397), I would like to question on two counts the validity of using progestins in this condition.

Firstly, in view of the vast quantities of progesterone already being produced in pregnancy, it must be open to question whether they have any worthwhile effect in this condition when given therapeutically. Secondly, norethisterone is probably one of the worst examples you could have given. It was first mooted in 1958 that progestins, when given in pregnancy, may cause virilization of the female foetus.

Jacobson¹ found virilization in 18% of female infants whose mothers had received norethisterone for several weeks. Some of the mothers themselves complained of androgenic side-effects, such as acne and hoarseness.

In my limited experience of this condition I have found treatment may well be necessary for several weeks, and therefore the giving of norethisterone could certainly cause virilization. Other progestins, including ethisterone, have been incriminated, though

some such as 17 α -hydroxyprogesterone 17-n-paprate and norethynodrel have been shown to be free of these unfortunate side-effects.

I would have thought that progestins are best avoided in the treatment of pregnancy prurigo, and the simpler measures that you advocated are best adhered to.—I am, etc.,

J. E. A. ONI-ORISAN.

Obstetric Unit,
Stobhill General Hospital,
Glasgow N.1.

REFERENCE

- ¹ Jacobson, B. D., *Amer. J. Obstet. Gynec.*, 1962, 84, 962.

Avulsion of the Upper Limb

SIR,—Reading Mr. J. A. Barclay's letter (15 February, p. 444) reminded me of an incident in *Leaves from the Life of a Country Doctor* by Dr. Clement Gunn,¹ who practised in the Scottish border town of Peebles around the turn of the century. The incident occurred in 1890 and was recorded in Dr. Gunn's diary as follows:

"I was driving to an urgent maternity case some distance away, when I encountered a gig coming from the opposite direction, driven at a furious pace. Its driver at once pulled up, and signed to my man to do likewise. 'We're juist seeking you, Doctor!' shouted the newcomer; 'Tam here has got his airm aff i' the threshing-mill!' 'His arm off! Surely not!' I ejaculated, with a hasty glance at the lad of fifteen sitting beside him, wrapped in a shepherd's plaid. To my amazement the boy shouted indignantly: 'No aff, dae ye say? I'll sune show ye!' 'Here it's!'—and with that he held up in one hand his other arm, completely severed close to the shoulder, and brandished it in our faces. . . .

"I bade them drive on to Peebles and call in another doctor; and promising to return as soon as possible, hastened on with all speed. All went well with mother and child, and in less time than I had ventured to hope for, I was amputating Tom's splintered bone at the shoulder-joint, a fellow-practitioner having administered the anaesthetic. After two hours' rest we had the lad conveyed home in a cab, surrounded by hot bottles; early next day I drove out to visit him, filled with apprehension lest the combined effects of shock, exposure, and delay should have ended in a fatal collapse during the night. The first object which met my eyes on entering the farmhouse was the redoubtable Tom, sitting up and supping a big bowl of porridge with every appearance of satisfaction! The wound healed rapidly, and in a short time the lad was up and out-of-doors again, wrapped in his plaid, laughing and joking as usual."—I am, etc.,

J. MURRAY DRENNAN.

Edinburgh 4.

REFERENCE

- ¹ *Leaves from the Life of a Country Doctor*, C. B. Gunn, p. 86, edited by R. Crockett, 1935. Edinburgh, Moray Press.

Admissions to Hospital Due to Drugs

SIR,—We read with interest Dr. Natalie Hurwitz's survey (1 March, p. 539) of admissions to hospital due to drugs, in which 25 of the 1,268 (2%) patients occupying 230 beds over 52 weeks were admitted.

In comparison, analysis of admissions to 25 general medical beds at the Luton and Dunstable Hospital during 1966 showed that 85 of 1,786 patients (1.4%) were admitted entirely because of an adverse drug reaction (excluding attempted suicide). But in comparing hospital admissions from different centres allowance must be made for the bed/population ratio, which in our own hospital is very low (1.7 acute beds per 1,000 population). This produces a heavy demand upon beds, and referral to and acceptance by the hospital of all patients is highly critical, probably resulting in a lower incidence of admissions from drug reaction, since the less severe cases remain at home under the care of their family doctors.

In discussing measures for preventing drug reactions Dr. Hurwitz states that pre-

vious reactions to drugs should warn the physician of the need for special care. No practical advice is given, however, as to how best to bring such previous information to the notice of the physician. Our own policy is based on the liberal use of red-lettered, sticky-backed sensitivity discs for all patients who produce an adverse reaction to any drug. The disc is placed prominently on the patient's notes and on the outside of the containing envelope folder. It is also our practice to attach a disc to the discharge letter to the general practitioner when a patient leaves hospital having experienced an adverse reaction to a drug.—We are, etc.,

T. PARKINSON.
A. H. KNIGHT.

Luton and Dunstable Hospital,
Luton, Beds.

Maternal Rh-immunization

SIR,—May I comment on the most interesting paper by Dr. W. Q. Ascari and others (15 February, p. 399) with regard to their conclusions as to the effect of ABO incompatible foetal erythrocytes upon maternal immunization to the Rh(D) antigen.

The studies which they quote,¹⁻³ do in fact show a decrease in the incidence of maternal immunization to D where there has been an ABO incompatible mating, whatever the maternal ABO group, with the single exception of Donohue and Wake's¹ mating AB $\times$ A or B. Taking the matings where the mother is not group O, the absence of any statistical difference between the observed and expected frequencies in part reflects the relatively small numbers of individuals within these matings.

TABLE I.—ABO Mating Types Where Mother Immunized to Rh(D) by Previous Pregnancy

		Mother				Total
		O	A	B	AB	
Father	O	555	329	99	21	904
	A	157	241	51	11	460
	B	75	45	28	6	154
	AB	5	13	0	3	21
Total	..	792	628	178	41	1,639

TABLE II.—Comparison between Expected and Observed Frequencies of Maternal D-immunization in ABO Incompatible Matings

Investi- gators	No. of Families	A $\times$ O		B $\times$ O		A $\times$ B		B $\times$ A		AB $\times$ A or B	
		exp	obs	exp	obs	exp	obs	exp	obs	exp	obs
Hopkins ..	1,639	287	157	95	75	58	51	58	45	21	13
		-45%		-21%		-12%		-23%		-38%	
All four series	6,476	943	555	239	164	179	136	185	151	82	58
		-41%		-31%		-21%		-22%		-29%	

In studying the effects of husband's Rh phenotype and of saline anti-D upon Rh(D) immunization and haemolytic disease of the newborn,⁴ I obtained figures for the ABO groups of 1,639 women and their husbands (Table I). The gene frequencies for this region are: o 0.7308, a 0.1977, b 0.0715. In Table II I give my figures for the ABO incompatible matings (husband ABO incompatible with his wife) in the same form as Table III of Dr. Ascari and colleagues, and also add my figures to the series of Donohue and Wake,¹ of Cohen,² and of Reepmaker,³ to give totals for all four series. Table III combines these into "O" and "non-O" mothers.

All four series show a decrease in the incidence of immunization to D among both

group O and non-group O mothers, although the decrease is considerably greater among the

TABLE III.—Table II Condensed to "O" and "Non-O" Mothers

Investi- gators	No. of Families	A $\times$ O and B $\times$ O		A $\times$ B, B $\times$ A AB $\times$ A or B	
		exp	obs	exp	obs
Hopkins	1,639	382	232	137	109
		-39%		-20%	
All four series	6,476	1,182	719	446	345
		-39%		-23%	

former. In either case, the possibility that the majority of incidents of maternal immunization were caused by ABO-compatible foetuses has not been excluded. Most of the group A and B fathers would be of genotypes AO and BO, and from the mating types here considered there would arise many foetuses which were ABO compatible with the mother. The only mating in which foetal-maternal ABO incompatibility is assured is AB $\times$ O, and it is interesting to note that in my series there are only five such matings, against 26 expected.

From all of these figures, it follows that ABO incompatibility does give at least partial

protection from maternal immunization to the Rh(D) antigen. In this context Murray⁴ has estimated 90% protection by maternal anti-A, 55% protection by maternal anti-B.—I am, etc.,

D. F. HOPKINS.

Glasgow and West of Scotland
Blood Transfusion Service,
Law Hospital,
Carlisle,
Lanark.

REFERENCES

- Donohue, W. L., and Wake, E. J., *Canad. med. Ass. J.*, 1964, 90, 1.
- Cohen, B. H., *Amer. J. hum. Genet.*, 1960, 12, 180.
- Reepmaker, J., *Thesis, Leyden*, 1955, cited *Brit. med. J.*, 1969, 1, 399.
- Hopkins, D. F., *Vox Sang.*, 1969, in press.
- Murray, S., Knox, E. G., and Walker, W., *Vox Sang.*, 1965, 10, 6.