able to concentrate their resources on these very high risk infants.—I am, etc.,

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Hammersmith Hospital,
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¹ Cross, K. W., *Lancet*, 1973, 2, 954.

SIR,—Your leading article, "Respiratory Distress Syndrome in the Newborn" (23 November, p. 428), outlines some of the problems facing clinicians dealing with pre-term labour and delivery. The use of a constant distending pressure (C.D.P.) in the airway has made the management of the idiopathic respiratory distress syndrome less empirical, and your plea for centres in each N.H.S. area fully equipped to deal with premature labour and with facilities for proper neonatal care should not be taken lightly.

It is therefore a contradiction to hope, as you do in your last sentence, for a quick and easy way of applying C.D.P. to be available at any maternity hospital. The progress that has been made in this branch of medicine is the tribute to the high degree of medical and nursing skills, with the help of complex apparatus, that is available only at the few prenatal centres that have so far been established. Your hope that the same results could be obtained with methods not requiring this degree of expertise is a false one and can lead only to further expensive pieces of equipment collecting dust in the cupboards and nurseries because they are "difficult to set up and adjust."

What is really expensive is the experienced personnel, and their concentration into the regional centres you rightly suggest establishing is the only way further fallacies and fancies in management will be exposed and progress continued.—I am, etc.,

ANDREW WILKINSON

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Oxford

SIR,—I read with interest your very succinct leading article (23 November, p. 428) on this subject. Having studied the encouraging results of the use of the Gregory box and in an effort to simplify this kind of treatment I designed and built a new box while working at the Jenny Lind Hospital in Norwich in 1972.

The box, made of Perspex, is similar in appearance to a small "iron lung" in which a constant negative pressure is maintained to obtain an identical effect on the baby's chest wall to that of the positive pressure Gregory box but leaving the baby's head free for access for infusions, aspiration, and intubation as necessary. It was interesting that shortly afterwards a German firm was demonstrating a similar negative pressure box, identical in principle to my design but more elaborate, complicated, and expensive. As far as I know the only English equivalent is rather cumbersome, adapted from an incubator the whole of which is evacuated to the required negative pressure.

Does anyone use a negative pressure box now or have they been found to be unsuccessful? If not, perhaps we should be thinking of developing the idea further and turning the prototype into a production model. If anyone is interested I should be

only too pleased to show them the box and to hear their suggestions.—I am, etc.,

WILLIAM BEVINGTON

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SIR,—It was disappointing that your leading article (23 November, p. 428) made no reference to the excellent work of Barrie.^{1,2} His method of applying continuous positive airway pressure has been adopted in our unit with great success. Nothing could be simpler than the adaptation of a plastic freezer bag for the purpose. We have now used this technique successfully for the past eight months and our Gregory box is discarded. Junior housemen quickly learn to set it up and the nursing staff find continued observations and monitoring straightforward. In our experience there has been a dramatic improvement in the prognosis of hyaline membrane disease since its introduction and we would recommend other paediatricians to try it.—I am, etc.,

C. E. M. JONES

St Mary's General Hospital,
Portsmouth

¹ Barrie, H., *Lancet*, 1972, 1, 776.
² Barrie, H., *Lancet*, 1973, 2, 851.

Oral Contraception and Increased Formation of High Molecular Weight Derivatives of Fibrinogen

SIR,—An increased formation of soluble fibrin in patients taking oral contraceptives was reported by L. O. Pilgeram and others (31 August, p. 556). They found that contraceptive medication induced a greater uptake of ¹⁴C-glycine ethyl ester into a fibrinogen derivative. This seems to correspond with earlier observations of Alkjaersig *et al.*,¹ who noted a chromatographic shift of the fibrinogen peak towards higher molecular weight fibrinogen derivatives. Recent experiments in our laboratory, using a modified agarose gel filtration technique, confirm these results and provide more quantitative information about the induction of intravascular fibrin formation by treatment with oestrogen-containing oral contraceptives.

Seven healthy women aged from 17 to 35 years were examined before and during a four- to 12-week period of treatment with an oral contraceptive containing norgestrel 0.25 mg and ethinyloestradiol 0.05 mg. Citrated plasma taken on days 24 to 26 of the anovulatory menstrual cycles was chromatographed on a Biogel-A-5m-column (25×2.3 cm). Fibrinogen-related material in the eluates was titrated manually with the staphylococcal clumping test² and the mean concentrations before and during contraceptive treatment calculated for each fraction. These concentrations are shown in the table and graphically represented in the figure.

The results show (1) an unchanged elution position of the quantitatively increased fibrinogen (compare with Alkjaersig *et al.*¹); (2) increased amounts of high molecular weight derivatives in the early fractions, forming a shoulder in the ascending part of the fibrinogen peak; and (3) the elution position of the main fraction of high molecular weight derivatives in the position calculated for the fibrinogen-fibrin-dimer. Mathematical processing of the data suggests that the polymers represent 5.6% of the

Concentrations of Fibrinogen-related Material before (n = 6) and during (n = 7) Contraceptive Treatment

Fraction No.	Mean Concentrations (mg/100 ml ± S.D.)	
	Before Treatment	During Treatment
16	0 ± 0	0 ± 0
17	0.02 ± 0.01	0.04 ± 0.03
18	0.05 ± 0.01	0.14 ± 0.13
19	0.11 ± 0.06	0.27 ± 0.56
20	0.19 ± 0.13	0.59 ± 0.24
21	0.37 ± 0.24	1.08 ± 0.33
22	0.77 ± 0.43	2.52 ± 1.46
23	4.25 ± 2.88	10.74 ± 8.07
24	11.65 ± 12.45	29.76 ± 13.36
25	23.89 ± 14.07	45.12 ± 2.005
26	61.23 ± 30.21	80.64 ± 26.88
27	86.61 ± 47.30	107.54 ± 60.10
28	85.12 ± 46.06	115.20 ± 55.34
29	69.44 ± 24.66	111.36 ± 56.87
30	53.01 ± 28.67	72.96 ± 63.45
31	38.83 ± 34.63	38.25 ± 20.82
32	18.29 ± 7.55	21.12 ± 15.72

A. Fibrinogen-related material measured by staphylococcal clumping test before (—) and during (x—x—x) contraceptive treatment. B. High molecular weight material calculated as the difference of the areas under the original curves in A.

total amount of the fibrinogen peak. This would correspond to a monomer concentration of 2.3%, assuming that a 1:1 complex of fibrinogen and fibrin monomers is formed.—We are, etc.,

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J. BEBBER
J. VAN DE LOO

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West Germany

¹ Alkjaersig, N., Fletcher, A. P., and Burstein, R., *Thrombosis et Diathesis Haemorrhagica*, 1971, Suppl. no. 49, p. 125.

² Asbeck, F., Lechler, E., and van de Loo, J., in *Fourth Congress International Society on Thrombosis and Haemostasis*, 1973, abstr. p. 287.

Normal Short Children

SIR,—Your leading article (9 November, p. 308) discusses the admirable Newcastle study¹ but does not mention an earlier paper² on this topic. It reported from Bristol that in a group of short children the search for physical causes had drawn an almost complete blank; growth hormone levels were found to be normal. This finding has now been confirmed from Newcastle. It is contrary to the finding of Powell *et al.*,³ which you cite, that "severe emotional deprivation with reversible failure of growth hormone

release has been recognized as an important cause of growth failure."

The Bristol report showed that stunting of physical growth is commonly associated with a low and/or inappropriate intake of food over a long period (starvation in the midst of plenty). It went on to suggest that this reflects impaired family relationships, especially between the child and his mother. The thorough and systematic Newcastle study of growth retardation, which you deservedly review in some detail, clearly demonstrates how rare is asymptomatic organic disease and how common is a defective home environment.

There is therefore a combination of stunted physical growth, deficient food intake, and impaired family relationships. In this context to call them "normal short children" is illogical. To do so is likely to block attempts by parents or doctors to understand and help affected children to attain, both physically and mentally, their true potential stature.—We are, etc.,

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D. RUSSELL DAVIS

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- 1 Lacey, K. A., and Parkin, J. M., *Lancet*, 1974, 1, 42.
- 2 Apley, J., et al., *Proceedings of the Royal Society of Medicine*, 1971, 64, 135.
- 3 Powell, G. F., Brasel, J. A., and Blizard, R. M., *New England Journal of Medicine*, 1967, 276, 1271.

Pseudomonas Septicaemia Following Superficial Colonization

SIR,—Recently my colleagues and I reported (23 November, p. 440) four patients with leukaemia or lymphoma, neutropenia, and apparently trivial infections of the skin or conjunctiva from which *Pseudomonas aeruginosa* was isolated. All four later developed septicaemia and the same organism was isolated from cultures of peripheral blood: three patients died. It was suggested that the isolation of pseudomonads from apparently localized lesions in patients with compromised antibacterial defences is an indication for systemic antibiotic therapy. Since that communication was submitted for publication two further instances have been observed of colonization by pseudomonads in neutropenic patients. In each case, septicaemia due to the same organism rapidly ensued.

Case 5.—An 8-year-old boy with acute promyelocytic leukaemia became neutropenic (neutrophils 100/ μ l) during initial chemotherapy with doxorubicin and cytarabine. Though he was febrile on admission, repeated swabs and blood cultures disclosed no pathogens. When he developed pharyngitis attributed to the antileukaemic drugs a throat swab grew *Ps. aeruginosa*. Three days later his pyrexia increased and the same organism was isolated from blood cultures. Because the bacteriological findings on the throat swab were already known, treatment with gentamicin and carbenicillin was begun when the blood cultures were taken and he improved rapidly with these antibiotics supplemented by granulocyte transfusions.

Case 6.—A 17-year-old youth with acute undifferentiated leukaemia in relapse was treated intensively with doxorubicin and cytarabine and his peripheral blood neutrophil count fell to 10/ μ l. *Ps. aeruginosa* was isolated from routine swabs taken from the axillary and inguinal skin; no cutaneous lesion was present at either site. Two days later he became febrile and unwell and *Ps. aeruginosa* was isolated from blood cultures. Gentamicin and carbenicillin were begun at the time of blood culture and granulocyte transfusions were given, and the patient recovered.

Knowledge that pseudomonads have previously been isolated from an inappropriate site, such as the pharynx in case 5, should affect the initial choice of antibiotics for a subsequent febrile episode in a neutropenic patient. In case 6 the occurrence of septicaemia after a positive skin swab but in the absence of any cutaneous lesion suggests that the mere presence of *Ps. aeruginosa* on the skin of a neutropenic patient may be an indication for systemic antibiotic therapy as well as the local use of antiseptics. Isolation of pseudomonads from a cutaneous lesion, however minor, is an even stronger indication for systemic treatment.—I am, etc.,

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Prevention of Exercise-induced Asthma by Indoramin

SIR,—I write on behalf of Professor S. Bianco and others in reply to the letters from Dr. K. N. V. Palmer and his colleagues (16 November, p. 409) and from Dr. S. Godfrey (23 November, p. 469).

We are, of course, aware of Dr. Palmer's interest in the possible applications of alpha-adrenoceptor blockade in asthmatic patients and look forward to seeing his data on the effects of these drugs on response to beta-adrenergic agonists. We published¹ some casual observations on this subject in relation to the action of thymoxamine. It would seem that Dr. Palmer's more extensive data may be clinically important. I may say at this point that six of our patients remarked upon the improvement in symptoms after dosage with indoramin.

Dr. Godfrey's letter deals specifically with our article (5 October, p. 18). He gives an alternative interpretation of the data which we published, taking exception to the use of the word "prevent" in describing the effects of indoramin on the response to exercise in patients with exercise-induced asthma (E.I.A.). Clearly his criticism has substance, since the general shape of the response in time, in terms of specific airways conductance (SGaw) and FEV₁, is broadly similar after administration of the drug to that before. This is a direct result of the initial bronchodilatation which occurs after indoramin and can be interpreted to indicate that the drug is not preventing the unusual response at all. I suspect that larger doses of the drug could have completely swamped the response to exercise but this possibility does not affect the general line of this argument. We were most careful not to claim that our observations proved an abnormal activity of alpha-receptors as the cause of E.I.A. but merely that they were consistent with this hypothesis.

This is not the place to deal with the details in the contents of the third paragraph

of Dr. Godfrey's letter except to state that the random errors of estimations of SGaw and the other measurements were minimized so far as possible by replication and suitable statistical assessment of the raw data. We consider that the effect of the small increase in dose of indoramin in the one subject who was tested at two dose levels might well have been due either to a variation in absorption of the drug, which was given by mouth, or to the known variability of E.I.A. itself. We are grateful for the reference to Sly et al.,² which had escaped our notice.—I am, etc.,

F. J. PRIME

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¹ Griffin, J. P., et al., *Lancet*, 1972, 1, 1288.

² Sly, R. M., et al., *Journal of Allergy*, 1967, 40, 93.

SIR,—The observations of Dr. S. Godfrey (23 November, p. 469) on the paper by Professor S. Bianco and others (5 October, p. 18) reporting the prevention of exercise-induced asthma by indoramin deserve comment. Dr. Godfrey stated that the fall in specific airway conductance after exercise, expressed as a percentage of the post-indoramin value, ranged from 0 to 69% and in the control tests from 38 to 81% (presumably calculated from the five-minute post-exercise time point). However, it seems to us from the evidence presented by Professor Bianco and his colleagues that these post-drug conductance values in fact ranged between an increase of 25% (case 4) and a decrease of 69% (case 10). In comparison with control 10 of the patients after indoramin treatment had less exercise-induced bronchoconstriction and only in case 5 was it worse (excluding the low dose result in case 9). In fact, taking the group as a whole and examining the differences between the post-indoramin and control responses to exercise by both the paired *t* test and the Wilcoxon matched pairs signed ranks test, indoramin highly significantly reduced the degree of bronchoconstriction at all time points (see table).

While agreeing with Dr. Godfrey that the work of Professor Bianco and his colleagues might have been improved by the inclusion of placebo control and a note on the variability of the response to exercise, he is not strictly correct in stating that the authors did not provide data on the reproducibility of their tests. Inherent in their table of results are comparisons between two control values on the first day 90 minutes apart and a further pretreatment control on the second day. Despite the fact that in eight of the 11 patients the baseline conductance was lower on the second day the mean change ($\pm$ S.E. of mean) for the group of 0.33 ± 0.19 kPa⁻¹s⁻¹ was not statistically significant. There was also no difference between the control values taken at 90-minute intervals on the first day.

Mean Change ($\pm$ S.E.M.) of Specific Airway Conductance induced by Exercise expressed as % 90-minute Control or 90-minute Post-indoramin Values in 11 Patients studied by Bianco et al.

	Time after Exercise		
	Immediate	5 min	10 min
Control (untreated) group	-46.4 $\pm$ 6.9	-51.8 $\pm$ 5.3	-55.2 $\pm$ 5.9
Indoramin group	-2.5 $\pm$ 15.7	-21.7 $\pm$ 9.8	-16.5 $\pm$ 7.4
Difference (% control group)	94.6	58.1	70.1
P (paired <i>t</i> test)	0.05-0.02	0.01-0.001	<0.001
P (Wilcoxon)	0.026	0.016	0.006