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Prevention of Hyaline Membrane Disease

SIR,—In your leading article on this subject (14 April, p. 65), the recent reports of trials of corticosteroid therapy both pre- and postnatally were rightly highlighted. It was also stated that much of the rationale for these trials was derived from animal work.

At the present time perinatal care is more than ever committed to providing for the quality of life and not merely survival. However, evaluation of the animal work which stimulated the human trials, and presumably the leading article, shows little to indicate that viability was enhanced by the administration of corticosteroids. The tacit assumption that enhanced pulmonary maturation can be equated with viability in all species is far from proved. In fact, viability, the capacity to maintain life, has readily been implied from work that has shown only enhanced pulmonary maturation.

In the remarkable observations of Liggins in 1969¹ relating premature induction of labour and coincident prematurity of the lung to corticosteroid infusion, it should be noted that nine of 10 spontaneously delivered lambs were actually found dead, though with evidence of lung aeration. The tenth showed signs of respiratory distress before death. While these observations in lambs of 117-123 days' gestation clearly indicated a significant beneficial effect on lung maturation, little could be said about viability.

In fact Delemos,² in work concentrating on the mode and manner of accelerated pulmonary maturation, stated that no lamb whose birth was induced prematurely following hydrocortisone infusion survived more than 12 hours. In these experiments it was shown that when pressure-volume curves were constructed neither the volume per gramme at maximal pressure nor the percentage retained at atmospheric pressure was as great as in the full-term lambs. Whether

it is this factor or others related to the effect or lack of effect of corticosteroid on other systems which determines survival is not known. In an earlier review³ the possible detrimental effects of steroid administration to the fetus were mentioned, ranging from reduced cell number in the lungs of rabbits so treated⁴ to permanent neurological deficits in rats.⁵ Is there a price to be paid, or can catch-up growth occur?

Recent work by Alexander⁶ has shown that surviving premature lambs following corticotrophin infusion lack a response to thermal stress and moreover do not improve with age in this respect. This is the first report pertaining to the quality of survival. In the human, among recent advances in the management of the respiratory distress syndrome, Gluck⁷ has advanced his preliminary information to show that the amniotic lecithin: sphingomyelin ratio correlates well with "functional maturity" and not simply gestational age. In addition, the introduction of continuous positive airway pressure,⁸ especially when used early in the disease,⁹ has certainly provided a successful alternative form of management of the syndrome in the preterm infant, reducing mortality successively from 33% to 14.7% to 4.9%. It is clear that the management of the at-risk preterm fetus must be based on the careful assessment of several perinatal factors in each individual case.

It is the purpose of this letter to help place the conclusions drawn by others from a very significant observation in their true perspective. Indeed, the initial observation is likely to have more far-reaching implications in the physiology and pathology of the perinatal period than hyaline membrane disease.—I am, etc.,

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"Indian Colonel Syndrome"?

SIR,—During the past 13 years I have observed hypervolaemic-type hypertension with water retention and (since I started measuring them recently) elevated aldosterone levels in people born and raised in, or acclimatized while young to, the tropics.

Recently I have checked 20 such persons of both sexes in the 50-60-year age group, as nearly matched as possible, using very sophisticated gamma-camera equipment and found no renal or cardiac compromise of note, while 20 hypertensive natives of Detroit matched as nearly as possible in respect of age and physical condition all showed varying degrees of renal damage and other evidence of hypertensive-arteriosclerotic mosaic disease, or so-called A.S.C.V. mosaic disease.

Over the age of 60 there is little difference in the incidence of A.S.C.V. mosaic disease in the two groups, with the main pathology illustrated by (often unsuspected) advanced renal lesions and coronary artery compromise with left ventricular preponderance. This was unsuspected in many cases because the results of the usual tests for disease in these

areas were within normal limits. All the "tropical transplants" tested had been in a cold climate for over five years and if they were under 40 (females) or 50 (males) showed no hypertension. Twelve such persons were checked and one 10-year-old girl showed hypercholesterolaemia and a uric acid level of 9.5 mg/100 ml, which was considered to be unrelated to the environmental change.

I suspect there is a causal relationship between hyperaldosteronism and acclimatization to a sodium-leaching environment, with persistence of the hormonal conservation mechanism on transplanting to a cold climate and consequent sodium retention with its usual sequelae. One patient had a weight change overnight of up to 5 lb (2.3 kg), and this occurred every night. Radioisotope studies were entirely normal but chronic asymptomatic *Enteramoeba histolytica* infestation was found and treated successfully. No change was observed in the weight pattern. Another patient was unable to compensate so well and at present takes a daily diuretic which controls his water retention and an anti-aldosterone (Aldactazide).

Should there be any readers involved in projects dealing with these matters in a scientific way I would be happy to hear from them, as my own clinical observations and impressions lead me to the strong inclination to propose a definite syndrome of the "Indian Colonel" of the old comic stories—plethoric, irascible, hypertensive, acclimatized in youth to heavy strain on the milieu interne, and then repatriated in late middle life to a cold climate. Perhaps such a syndrome has already been described.—I am, etc.,

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Bronchospasm following Althesin Anaesthesia

SIR,—Althesin is a recently introduced steroid anaesthetic agent and as such it received considerable attention at the 5th World Congress of Anaesthesiologists in September 1972. Since then it has been taken into widespread use. While the drug has several advantages, it is beginning to become apparent that in some patients quite severe bronchospasm can complicate its use. Among others, Avery and Evans¹ reported five cases and Hester² one case of bronchospasm after Althesin. We would like to report the following case:

A 28-year-old 70-kg man was given an uneventful anaesthetic for examination of his knee. The technique used was that of thiopentone induction, intubation using succinylcholine, maintenance on intermittent positive pressure ventilation with alcuronium, and reversal of the muscle relaxant at the end of the operation with atropine and neostigmine in the usual way.

A few days later he was premedicated with papaveretum and hyoscine 75 minutes before the induction of anaesthesia for repair of the medial ligament of the knee. Induction was with Althesin 4 ml followed immediately by pancuronium 6 mg, and the patient's lungs were inflated with a nitrous oxide/oxygen mixture. Intubation after about a minute was followed by considerable bucking and coughing, which rapidly settled.

Over the next few minutes the lungs became more and more difficult to inflate. A further 2 mg of pancuronium was given with no effects and airway suction produced no secretions. Auscultation showed very poor air entry to all areas, and after

dismissing an initial tentative diagnosis of bilateral tension pneumothorax, such had been the suddenness of onset, it became obvious that one was dealing with a severe bronchospasm. This was successfully treated by inflating the lungs with considerable difficulty using a 50:50 nitrous oxide/oxygen mixture plus 1% halothane. The spasm relaxed completely over the next 20 minutes, and the operation was concluded normally with no residual damage to the patient. A further anaesthetic using a thiopentone, nitrous oxide/oxygen, halothane regimen was carried out subsequently with no problem. It is perhaps relevant to relate that, though the patient had denied anything but the most robust health before the first anaesthetic, on further questioning later he admitted to mild asthma in childhood.

Dundee and Clarke³ have asked for reports of idiosyncrasy to any anaesthetic agent to be reported to them in order to make a detailed evaluation of the extent of this problem, and this case has been so reported.—We are, etc.,

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¹ Avery, A. F., and Evans, A., *British Journal of Anaesthesia*, 1973, 45, 301.

² Hester, J. B., *British Journal of Anaesthesia*, 1973, 45, 304.

³ Dundee, J. W., and Clarke, R. S. J., *British Journal of Anaesthesia*, 1973, 45, 304.

Actinomycin D for Wilms's tumour

SIR,—My previous letter (17 February, p. 420) was intentionally provocative and I am pleased to see that it has stimulated the publication of results from Liverpool by Professor P. P. Rickham (14 April, p. 114), from Toronto by Dr. R. D. T. Jenkin (26 May, p. 485), and from Melbourne by Dr. T. F. Sandeman (26 May, p. 485). All these results are very impressive when compared with those from Birmingham, but it should be noted that they all quote three-year survival (unqualified), whereas the Birmingham results were for three-year survival *free of disease*. If one adds on children still alive at three years despite recurrence or metastases the results appear to be better. This is yet another way in which the comparison of results from different centres may be misleading. If all survivors are included regardless of the presence or absence of disease, the three-year results in the Birmingham region for the years 1965-9 for patients who received actinomycin D initially are increased from 6/29 to 9/29 (31%) and for those who did not receive actinomycin D they are increased from 7/17 to 8/17 (47%).

The results presented by my former colleague Dr. Sandeman are particularly striking, and though the groups were not contemporaneous I agree that his figures make it difficult to defend a controlled trial involving the omission of any initial chemotherapy. Nevertheless, the conflicting Birmingham results remain unexplained.

A number of correspondents have emphasized the importance of a centralized service for the treatment of Wilms's tumour so that the paediatrician, surgeon and radiotherapist can work as a team with a common policy and seeing a sufficient number of patients each year. With this I am in full agreement. It is probably a matter of greater importance than the use of chemotherapy. Though until 1970 there was no surgeon practising exclusively paediatric surgery in the Birmingham region, there were a number of sur-

geons with great experience of paediatric work. In 1965 a policy was established within the United Birmingham Hospitals whereby all children diagnosed as having Wilms's tumour were treated at one hospital by one surgeon and by one radiotherapist who also gave chemotherapy. The three-year survivals free of disease were worse prior to 1965 and the figures for 1950-64 for the whole Birmingham region are given for comparison:

Stage I	...	...	...	9/20
Stage II	...	...	...	4/15
Stage III	...	...	...	1/28
Stages IV and V	...	...	...	0/14
Stage unknown	...	...	...	2/5
Total				16/82

Thus the results for all stages were 19% compared with 28% for the years 1965-9. It so happened that actinomycin D was first used in Birmingham at about the same time as the paediatric oncological team was set up. It is difficult to be certain which factor improved the results, but I doubt if actinomycin D had any great influence. Unfortunately, though the team was set up in 1965 the majority of children with Wilms's tumour continue to be treated at other hospitals scattered throughout the region. In the years 1965-9 the three-year survival for children treated solely at the Queen Elizabeth Hospital, Birmingham, was 5/11 (45%), for those referred for radiotherapy but who had surgery elsewhere it was 5/13 (38%), and for those treated entirely at other hospitals it was 7/22 (32%).—I am, etc.,

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Drug-induced Respiratory Disorders

SIR,—In your leading article on this subject (12 May, p. 320) you mention especially aspirin, sulphonamides, and nitrofurantoin as causes of pulmonary eosinophilia—"an allergic manifestation in which eosinophilic infiltrations of the lung are accompanied by fever, cough, sputum, dyspnoea, and crepitations." We would like to add niridazole (Ambilhar) to the list of drugs that can cause severe pulmonary sensitivity reactions. Since reporting the occurrence of this syndrome in two patients treated with niridazole in 1972¹ we have seen it develop, in varying severity, in at least 10 more patients. The following case illustrates how dangerous and serious the reaction may become if ignored.

An 18-year-old farmer was admitted for treatment of *Schistosoma mansoni* infection. He was started on oral niridazole at a dose of 12.5 mg/kg daily for 12 days; on the sixth day of treatment he developed severe dyspnoea and on auscultation there were widespread crepitations over both lungs. A chest radiograph performed next day showed widespread large scattered pulmonary infiltrations (see figure). The total white blood count was 6,200/mm³ and the eosinophil count had risen from 7% to 22%. He responded rapidly to oral chlorpheniramine. Two months later (because he was still passing live eggs of *S. mansoni*) he was restarted on oral niridazole. Within one hour of having received half a tablet he developed a severe asthmatic attack. On auscultation there was severe wheezing with widespread crepitations, and a chest radiograph showed a recurrence of scattered, rounded patches