LETTERS TO THE EDITOR

The objectives of medical research

EDITOR,—Dr Marlow's interesting annotation on high frequency ventilation,¹ with its pithy epigraph, adopts a common attitude to the methodology of medical research. This holds that, to be "scientific," a study must specify a null hypothesis and then attempt, using data, to disprove it. This agrees with the writings of Karl Popper, but goes back further to the founding father of modern statistics, R A Fisher, who² wrote: "Every experiment may be said to exist only to give the facts a chance of disproving the null hypothesis."

In recent years many statisticians have come to take a much broader view of research methodology. In applied fields such as medicine, engineering, and agriculture, null hypotheses—that two treatments are equal in their effects—are often neither plausible nor interesting, and it must be remembered that the null hypothesis specifies exact equality, not merely negligible difference. Instead, the existence of some difference between the treatments is taken for granted and the study aims at establishing its size, whether it is large enough to be important, or perhaps small enough to be ignored. The calculation of confidence limits aims precisely at demarcating the range of true differences which are consistent with the data; whether or not these include zero is of secondary importance. I have referred to this type of study as "technological."³

Schwartz *et al*⁴ make a similar distinction between explanatory and pragmatic clinical trials. They point out that in the latter case the exact equivalence of two treatments is seldom plausible and it is necessary to arrive at a definite recommendation that one treatment is to be preferred to another. The type I error rate is then 100%—the null hypothesis that the treatments are equivalent is always rejected. For the same reason the type II error rate is zero. As the treatments are unlikely to be exactly equivalent (and if they are, it does not matter which is recommended), neither of these errors is of any interest; the important error is that of recommending an inferior treatment, one which they refer to as type III. This formulation has not been so widely accepted, but is well worth consideration at the design stage of a technological study.

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- 1 Marlow N. High frequency ventilation and respiratory distress syndrome: do we have an answer? *Arch Dis Child* 1998;78: F1-2.
- 2 Fisher R A. *Design of experiments* (section 8). 4th edn. Edinburgh: Oliver and Boyd, 1947.
- 3 Healy M J R. Is statistics a science? *J Roy Statist Soc A* 1978;141:385-93.
- 4 Schwartz D, Flamant R, Lelouch J. *Clinical trials*. London: Academic Press, 1980.

The neonatal thymus and antenatal steroids

EDITOR,—To investigate the effect of antenatal steroids on thymic size, we reviewed the chest x ray pictures taken in the first 36 hours of life in two groups, each of 25 infants. The first group of infants was born in 1992-3; none of

their mothers had received antenatal steroids. The second group was born in 1995-6; all of these mothers had received two doses of dexamethasone before delivery. The groups were matched for sex, birthweight (± 100 g), and gestation (± 1 week). There was no significant difference in the causes of premature delivery; the most common stated cause of premature delivery was amnionitis (six from group 1, seven from group 2), although in most cases the cause of premature delivery was unclear (12 from group 1, 14 from group 2).

In group 1 we observed thymic shadows in 16 of the chest radiographs. Mothers of group 1 infants with no thymic shadows had hypertension (4 mothers) or suspected amnionitis (5 mothers). In group 2 no radiograph showed a thymic shadow. Using χ^2 analysis, these figures gave a probability value of $p < 0.01$ for the null hypothesis that antenatal steroids do not cause thymic atrophy in the fetus. Does the neonatal thymus grow after such suppression? In six of the group 2 infants we reviewed successive chest radiographs over the first 4 weeks of life. Three infants showed a steady enlargement of the thymic shadow in relation to the cardiac outline and thoracic cavity on successive radiographs. In all infants from both groups the total white cell counts and lymphocyte counts were within the normal ranges throughout their follow up.

Thymic stroma is particularly sensitive to endogenous or exogenous steroids which induce rapid apoptosis. The volume of the thymus in older children is reduced following stressful stimuli such as infection or chemotherapy.¹⁻⁴ Birth stresses in term, but not preterm infants have been noted to cause this regression on a chest radiograph.⁴ This series of radiographs suggested that the use of antenatal steroids is a clinically significant cause of reversible thymic atrophy in the premature infant, in whom the thymus is usually particularly large and active.

We observed no sequelae to the atrophy induced by antenatal steroid. This is not surprising in view of the observation that very small thymic size in some patients with Catch 22 syndrome seems to have no relevance to their long term immunological outcome. In our series radiographic evidence of a change in thymic size was not accompanied by any measurable change in the total lymphocyte count; more subtle changes in T cell phenotype function and dynamics need to be examined. Thymic regeneration has been observed following the use of steroids in older infants.⁴ Studies using ultrasound scanning and formal T cell phenotyping are currently under way and may help determine what regulates the rate of thymic recovery. Our observation merits careful examination in neonates, as in older children and adults thymic size has been shown to influence the rate of recovery from insults including chemotherapy and radiotherapy.⁵

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- 1 Kitonyi JM. Radiological behaviour of the thymus in chest infection in the under fives. *East Afr Med J* 1995;72:81-2.
- 2 Bancalari A, Herrera A, Rodriguez MS, Pandolfi E, Cantin A. Correlations of clinical, radiologic and pathologic aspects of the thymus in newborn infants. *Rev Chil Pediatr* 1989; 60:135-42.

- 3 Bode U, Scheidt W. Change of thymic size during and following cytotoxic therapy in young patients. *Pediatr Radiol* 1988;18:20-3.
- 4 Caffey J. The Thymus. In: Caffey J, ed. *Pediatric X-Ray Diagnosis*. 7th Edn. London: Year Book Medical Publishers, 1978:510-27.
- 5 Mackall CL, Fleischer TA, Brown MR, *et al*. Age, thymopoiesis and CD4+ T-lymphocyte regeneration after intensive chemotherapy. *N Engl J Med* 1995; 332:143-9.

Immaturity related lung hypoplasia: comment on current classification in neonatal death statistics

EDITOR,—The Office for National Statistics uses an algorithm to classify neonatal deaths.¹ It is based on an hierarchical classification of causes to derive a single cause group for each death.² Cause groups include, in descending order: congenital malformations, antepartum infection, immaturity related conditions, asphyxia/anoxia/trauma, external conditions, infections, other specific conditions, sudden infant deaths, and other unclassified conditions.

In applying the algorithm, we noted a surprisingly high frequency of deaths from malformations of the respiratory system, especially lung hypoplasia. This is one of the most common findings in neonates.³ Most cases are secondary to congenital malformations or pregnancy complications that inhibit lung development.⁴ As lung hypoplasia is secondary to preterm birth or premature rupture of membranes, it may be preferable to classify an infant death due to prematurity related lung hypoplasia under immaturity related conditions, rather than congenital malformations. We looked at how the reclassification of prematurity related lung hypoplasia deaths under immaturity related conditions, instead of congenital malformations, would affect the current hierarchical classification.

A detailed investigation of all 168 neonatal death records in 1993 with a code for lung hypoplasia (ICD 9: 7845) showed that 55 of these cases (32.7%) are secondary to immaturity related conditions (having one of the "immaturity" codes in the hierarchical classification) and have no other congenital malformations; 96 cases appear as secondary to other congenital malformations; and 17 appear as isolated lung hypoplasia or associated with other conditions such as hydrops fetalis. In the Office for National Statistics algorithm the 55 immaturity related cases would be classified as congenital malformation deaths because of the lung hypoplasia 7845 code. The cause groups for 1993 show that the total number of neonatal deaths classified under congenital malformations as the single cause is 1314.¹ We conclude that a small percentage—that is, 4.2% or 55 of 1314—should preferably be classified as immaturity related conditions.

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- 1 Office for National Statistics. *Mortality statistics: Childhood, infant, and perinatal. 1993 and 1994*. Series DH3, No 27. London: The Stationery Office: 1994.
- 2 Alberman E, Botting B, Blatchely N, Twidell A. A new hierarchical classification of causes of infant deaths in England and Wales. *Arch Dis Child* 1994;70:403-9.
- 3 deMello DE, Reid LM. Respiratory tract and lungs. In: Reed GB, Calireaux AE, Cockburn F, eds. *Diseases of the fetus and the newborn. Vol 1*. London: Chapman & Hall Medical, 1995:523-61.
- 4 Lauria MR, Gonik B, Romero R. Pulmonary hypoplasia: pathogenesis, diagnosis, and antenatal prediction. *Obstet Gynaecol* 1995;86:466-75.

BOOK REVIEWS

Fetal and Neonatal Physiology. 2nd Ed. Vols 1 and 2. Richard Polin and William Fox eds. [Pp 2504 hardback]. WB Saunders Co, 1998. ISBN 0-7216-6016-9.

It is difficult to know where to start reviewing a book of 228 chapters, and some 355 contributors, all but a handful of whom come from North America, and most of whom, unsurprisingly are paediatricians. But as this work is essentially physiological, rather than about management, it will translate well into the practice of any country.

The overall layout of each chapter is good, with the potential for inconsistency that often dogs multi-author books, not a feature. And as I moved around each chapter, I was confident that I would easily find what I was seeking.

Each of the book's sections—and there are 29—deals with a particular subject, dealt with first as it affects the fetus and then the neonate; this pattern is maintained throughout. Most of the chapters contain detailed information and are well referenced.

Who would find this book useful? It is clear from the preface that many found the first edition to be a valuable source book, a fact which led to the demand for this new edition. Clearly, paediatricians and neonatologists might find it most helpful, but so will materno-fetal medicine specialists and trainees. The latter might be disappointed at some of the more obstetric chapters, but there is plenty of other material which will be helpful and relevant. Physiologists, particularly undergraduates, will also probably find much to interest them.

In an era in which books find themselves unfashionable, this text remains relevant and the editors are to be congratulated on keeping their contributors, and their references, current.

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Placental function and fetal nutrition. Frederick C Battaglia, ed. [Pp 263, hardback]. Nestlé UK Ltd, 1997. ISBN 0-7817-1406-0.

How is it that hibernating mother bears don't eat and drink, but still produce baby bears that are not growth retarded? When there is some restriction of nutrient supply to the human fetus, what are the adaptive mechanisms that are made successfully in one pregnancy and not so successfully in another? These are among the many challenging questions considered by expert contributors to this 1996 workshop on placental function and fetal nutrition. Much of the work reported is from animal studies, and species differences and developmental considerations inevitably complicate our understanding of the relation between fetal growth and placental function. However, the advent of novel techniques such as stable isotope methodology have permitted new insight into human physiology. For example, rather than the fetus being a major drain on the resources of maternal metabolism, the rate of transfer of amino acids from the mother indicate that in well nourished women the needs of the fetus ought to be supplied by very small increases in protein intake (or whole body protein breakdown).

One essential role for the placenta is to modify the maternal reproductive tract into a hospitable and nutritive environment for the developing embryo, a role for which paternal genes seem to be essential. Subsequently, placenta and fetus function as an integrated unit. The supply of some amino acids (such as branched chain) depends not only on placental transport but also on placental metabolism, and studies in sheep show that gluconeogenesis in the fetal liver increases only when placental delivery of glucose falls to a low level. The trophoblast secretes steroids and

trophic peptides that are essential for fetal growth and development, among them human growth hormone variant which may have a role in mediating the metabolic demands of pregnancy, and in preparing the breast for lactation. In conjunction with hormones, dietary constituents also have a role in the regulation of gene expression. In the hyperglycaemic diabetic mother, for example, there is a fourfold increase in messenger RNA for the glucose transporter GLUT-3, which probably has a major role in placental glucose uptake and metabolism.

Chronic oxygen deficiency restricts and modifies the pattern of fetal growth, altering fetal plasma amino acid profiles, while anabolic hormones decrease and catabolic hormones increase. Although the possibility exists that the induction of maternal hyperoxia might be an appropriate intervention for intrauterine growth retardation, its safety and effectiveness are not established. Other factors known to reduce the transport of specific amino acids include prolonged alcohol consumption, cocaine use, and excessive smoking.

There is now considerable evidence pointing to an association between poor growth in early life and the risk of age related disease in adulthood. Intrauterine growth retardation affects 4–10% of deliveries and an understanding of the metabolic perturbations underlying this heterogeneous condition may ultimately lead to the development of therapeutic strategies which will improve both short and long term outcomes. Those caring for the newborn or their mothers, and anyone intrigued by the Barker hypothesis will find that this series of scientific papers gives a fascinating overview of a burgeoning area of nutritional research.

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