LETTERS TO THE EDITOR

The objectives of medical research

EDITOR.—Dr Marlow’s interesting annotation on high frequency ventilation, with its pithy epitaph, sets 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, who 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.”

Schwartz and al. 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.

M JR HEALY
23 Colderidge Court Milton Road Harpenden AL5 5LD

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 1993–6; 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 prematurity 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 preterm 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, preeclampsia, or suspected amnionitis (5 mothers). In group 2 no radiograph showed a thymic shadow. Using χ² 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 range of their follow up.

Thymic stroma is particularly sensitive to endogenous or exogenous steroids which induce rapid apoptosis. The volume of the thymus in old age is reduced following stressful stimuli such as infection or chemotherapy. Birth stresses in term, but not preterm infants have been noted to cause this regression on a chest radiograph. This series of radiographs suggest that the use of antenatal steroids is a clinically significant cause of reversible thymic atrophy in the preterm 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 syndrome, 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 infants. Studies using ultrasound scanning and formal T cell phenotyping are currently under way and may help determine which 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.

C A MICHE
N HASSON
Department of Paediatrics, Evelina Hospital, Middlesex UB1 3HP

R TULLOH
Department of Paediatric Cardiology, Guy’s Hospital, London

1 Marlow N. High frequency ventilation and respiratory distress syndrome: do we have an answer? Arch Dis Child 1998;78: P1–2.


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

EDITOR.—The Office for National Statistics uses an algorithm to classify neonatal deaths. It is based on the importance of the classification of causes to derive a single cause group for each death. Cause groups include, in descending order: congenital malformations, antepartum infection, immaturity related conditions, asphyxia/anoxia/trauama, 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. Most cases are secondary to congenital malformations or pregnancy complications that inhibit lung development. 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, 35% of all immaturity related cases would be classified as congenital malformation deaths because of the lung hypoplasia 7485 code. The cause groups for 1993 show that the total number of neonatal death classified under congenital malformations as the single cause is 1314. We conclude that a small percentage—that is, 4.2% or 55 of 1314—should preferably be classified as immaturity related conditions.

M VRJHIEND
H DOLK
London School of Hygiene and Tropical Medicine
Keppey Street, London WC1E 7HT

BOOK REVIEWS


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 multiauthor 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.