LETTERS TO THE EDITOR

The objectives of medical research

EDITOR,—Dr Marlow’s interesting annotation on high frequency ventilation,1 with its pithy epigraph, draws our attention 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, who went 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 or small, consistent with the data; whether or not these 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 or small, consistent with the data; whether or not these

1 Marlow N. High frequency ventilation and respiratory distress syndrome: do we have an answer? Arch Dis Child 1996;78: P1–2.

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 1994–5; 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 death of the fetus 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 severe enough to require antenatal amniocentesis (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 success 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 at 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 Birth stresses in term, but not preterm infants have been noted to cause this regression on a chest radiograph.2 This series of radiographs demonstrate that the use of antenatal steroids is a clinically significant cause of reversible thymic atrophy in the pre-mature 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.3 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.4

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 gynaeologists, obstetricians 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 under graduates, will also probably find much to interest them.

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

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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 ana bolic 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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