The Fragile Balance Between Cells, Organisms and Environment

D. Tibboel and E. v. d. Voort

Introduction

Along different lines specialized units have been instituted providing intensive care for children with a large variety of bodyweight, age and disease entities. Not only the diseases treated in these units are very diverse, the same is through for the medical background of the physicians who are primary responsible for the care of these critically ill children. Due to local differences in set up pediatricians, pediatric surgeons or anesthesiologists have been appointed chairman of a specialized intensive care unit. Although new modes of treatment are continuously developed, in many instances the treatment modalities are symptomatic and as such not always based on a profound scientific basis.

Besides developments in intensive care in the last 5 to 10 years, major changes have taken place through the effort of basic scientists, elucidating basic mechanisms of cell growth, cellular differentiation and the importance of growth factors. Moreover genes responsible for certain diseases such as Duchenne muscular dystrophy, cystic fibrosis have been identified.

Intensivists can not close their eyes for the fast developments in molecular biology and we have to realize that the gain of knowledge in the basic science laboratories will have implications for our daily clinical practice.

Molecules and Cells

Today billions of US dollars are spend to unravel the human genome. As a consequence of this international collaboration genes are identified which are responsible for devastating diseases such as multicystic kidney disease, cystic fibrosis, hemophilia etc. The identification of these genes will lead to the increasing use of prenatal diagnostic procedures and as such result in real prevention and hopefully disappearance of a disease. This will inevitably lead to changes in disease patterns in the pediatric and pediatric surgical ICU's.

In the field of developmental biology, researchers are encircling basic mechanisms of cell multiplication and cell death, both important processes for normal morphogenesis and organ differentiation. Important processes such as cell-cell signalling during development, the molecular mechanisms of morphogenesis and the control of tissue differentiation by transcription factors are nowadays studied. These studies take place in animal systems which at first

D. Tibboel et al. (eds.), *Intensive Care in Childhood*

sight are far away from the human, like the zebrafish, axolotl, tadpoles, fruit fly, and to some extent in mice [1–4]. We can not close our eyes for these tremendous developments because the application of newly developed technics such as transgenic mice, in which certain genes can be blocked or overexpressed, can provide new insight into the etiology and pathogenesis of a disease. As a consequence of these developments, so called suicide genes in retrovirus mediated vectors can be of additional help in the treatment of certain forms of cancer such as brain tumors. Another example is the treatment of the respiratory manifestations of CF through transfer of the CFTR cDNA using adenovirus or liposome vectors [5]. Today neither conceptual or technological limitation will limit the progress in molecular genetics. The greatest challenge we face is not the scientific question of how to do this research, but the question of what to do with its products. Once applied in human, the reaction of the critically ill child will be sometimes unpredictable. Intensivists have to be aware of the background and side effects but are they really able to understand?

Along these lines of research, specific chromosomal locations have been identified to contain the genes for tumors like retinoblastoma, neurofibromatosis and Wilms's tumor. Tumor suppressor genes are of great importance in the normal regulation of cellular proliferation and differentiation [6].

In conjunction with the increased understanding of the normal behavior of cells, progress is made in the cellular and subcellular mechanisms involved in cell damage as occurs in different organs and endothelial cells such as occur during shock (polytrauma, burn shock) or during massive intra-operative stress (prolonged ischemia, major soft tissue injury). These are examples of non-bacterial inflammation, triggered by activation of various mediators of both humoral and cellular systems. Besides knowledge of the intracellular mechanisms resulting in the release of cytotoxic agents as part of the (normal) inflammatory response, biochemistry has provided us with increased knowledge of the membrane associated oxidases. We have to understand that there is still a limitation in our understanding of supply of oxygen in disease states, mostly because of unavailability of methods to assess organ specific cellular metabolism [7–9].

From time to time new molecules are discovered of which nitric oxide is the most exciting one of the last decade. Nitric oxide activity and changes in nitric oxide synthase is suggested to be of importance in a variety of diseases ranging from pulmonary hypertension to organ damage such as acute respiratory distress syndrome (ARDS) [10–12]. Today it is nearly impossible to make a list of accepted indications for the use of inhaled nitric oxide because the full spectrum of effects has to be elucidated in more detail improperly designed perspective randomized control trials (PRCT's).

Organisms

Following an infectious or a non-infectious insult, the body will depending on age and preceding disease state react with an inflammatory response. This in-

flammatory response can be triggered by an infectious agent but the sequence of events which is nowadays known as the systemic inflammatory response syndrome (SIRS) can be present without sepsis. It may occur following uninfected trauma, part of this has long been known as the metabolic stress response. The identification of a number of humoral factors released by cells of the host or by the invading micro-organisms, can result in an overreaction of the host which is no longer controlled anymore by natural inhibitors [13, 14].

Although the principles of management of septic shock such as meningococcal disease are well determined, the very complicated response, from a cellular point of view, impairs the widespread use of specific inhibitors of the different pathways involved such as monoclonal antibodies raised against specific cytokines or factors [15, 16]. Although the interleukin number has reached already number 13, no clinical trial has proven significant reduction in mortality. Especially identification of the tumor necrosis factor and its gene on one hand and the use of corticosteroids on the other, has attracted investigators to search for the final solution for the high mortality in septic shock both in children and adults. Acute respiratory distress syndrome (ARDS), know to occur in newborns as well, is a good example of the difficulty there is to pinpoint the crucial step in the pathogenesis of the reaction of the body to an insult. Besides measurements to maintain tissue oxygenation and adequate blood pressure, the variety of treatment modalities proposed, clearly demonstrates the lack of real understanding of the complex pathophysiological sequence of events which occur in the symptom complex called ARDS [17].

In this context old questions are reconsidered such as whether the lung should be rested or recruited. For over 15 years barotrauma has been the key feature explaining ongoing lung damage in which the high inspiratory pressures were thought to be crucial. Today this acronym is replaced more and more through volutrauma [18, 19].

One of the most exciting developments in the application of new technologies in pediatric intensive care is extracorporeal membrane oxygenation (ECMO). Although originally practiced in neonates with different disease entities, considerable doubt exists to apply ECMO in congenital diaphragmatic hernia. Following an almost religious appreciation of ECMO for 10 years now [20, 21] ECMO is only one of the treatment modalities together with high frequency oscillation with or without nitric oxide and more recently partial liquid ventilation [22, 23] enabling us to treat respiratory insufficiency.

The application of high frequency oscillation has significantly decreased the use of ECMO in case of neonatal respiratory insufficiency. In contrast there seems to be a tendency to increase the use of ECMO in non-neonatal therapy refractory respiratory insufficiency. Today no clear indications are available when and how to apply ECMO in non-neonates because prospective randomized trials are lacking and entry criteria are not well established [24].

Due to the development of perinatology birth of a child is not anymore the natural boundary when neonatologists and pediatric surgeons start to face their patient. The continuous development of fetal surgery for a variety of con-

genital anomalies, such as cystic adenomatoid malformation of the lung (CCAML), aortic valve obstruction and urinary tract obstruction, resulted in survival of a number of fetuses who would otherwise be born with an endstage disease or therapy-refractory respiratory insufficiency. It is obvious that these procedures should only be performed in a limited number of centers [25, 26]. The same holds through for the transplantation of stem cells, taking advantage of the immature and therefore highly tolerant immune system of the fetus for treatment of hereditary or metabolic diseases.

Advances in understanding the specific immunology related to organ transplant, including the concept of chimerism, will result in altered treatment schemes for immunosuppression with hopefully less secondly malignancies following organ transplant [27]. Next to this development, transplants are being performed in young children now, such as liver transplant in babies under 1 year of age in which reduction hepatectomy has resulted in a significant change in treatment [28].

Identification of the genes for insulin, growth hormone and a number of different growth factors, like insulin like growth factors (IGFs), has opened the opportunity for recombinant human DNA hormone manufacturing [29]. As such these hormones are easy obtainable and will probably find their way therapeutic agents in the critically ill. Today IGF trials started in adults have been stopped in children. The application of growth hormone as adjuvant therapy in pediatric intensive care is dependent on the proper assessment of the metabolic rate and progress in nutritional assessment in small children.

This is mainly influenced by the lack of data describing

1) steady state following an operative procedure in the immediate postoperative period;
2) a clear description of disease specific changes in resting energy expenditure (REE) and
3) difficulty of interpretation of the obtained values by indirect calorimetry due to tube leakage.

Not only hormones but DNAse is used as well. The gene for DNA-ase has been cloned now which has resulted in human recombinant DNA-ase I used as aerosol inhalation in cystic fibrosis patients [30]. This kind of developments will probably influence the morbidity and length of stay in the ICU and should be evaluated in properly designed prospective randomized trials.

Environment

The child in the ICU is prone to encounter iatrogenic side effects due to the non-natural environment. This may have a major impact not only on the span of life but on the occurrence of long term morbidity as well. In this context should be mentioned: the immature brain in the premature born infant has a high susceptibility to develop intracranial hemorrhage, the child with the short gut syndrome developing end stage liver disease through a combination of to-

tal parenteral nutrition and recurrent periods of sepsis. Moreover following a difficult intubation a child may end up with a trachea canula and repeated ENT surgery for treatment of the laryngeal problems.

People working in the intensive care unit are starting to realize that mortality is not the only outcome parameter to compare treatment results of different ICU's [31]. Morbidity at predetermined intervals following admission to the intensive care is at least as important as publishing mortality rates [32–36]. A number of scoring systems is developed which objectively enables us to judge upon new treatment modalities, such as the use of monoclonal antibodies to endotoxin, tumor necrosis factor or interleukin 1 receptor antagonists. Most neonatal intensive care units have well organized follow-up programs and people specially trained in child development and psychological assessment. Follow–up of intensive care treatment in older children, including pediatric surgical diseases, is lacking behind in this respect. Other specialists, apart from doctors, have developed new ways of measuring outcome. Consequently in a number of countries technology assessment is an integral part of evaluating treatment children admitted to the ICU [37]. The problem remains however, whether application of validated scoring system has the same significant for the individual patient as for patient groups as a whole [38]. Although applied technology and treatment results are frequently the scope of publications of intensive care physicians, this is only one part of the spectrum. The humane part is at least as important as the application of technology. We are awaiting bereavement in the ICU and the circumstances surrounding a bereavement may influence future morbidity and even mortality in surviving family members. Fortunately, in most intensive care unit guidelines are available for both physicians and nurses to cope with this part of their everyday workload in the intensive care unit, being death and the dying process [39].

Concluding Remarks

Every decade trends of treatment are changing as shown in Table 1. Intensivists, both physician and nurse, are confronted with the new possibilities of molecular genetics and are part of the process to transfer basic laboratory science into clinical practice. Consequently the intensivist is facing unknown technologies

Table 1. Trends in treatment modalities during the last decade

– The use of high frequency ventilation and optimal mode of ventilation
– Steroids and septic shock
– The role and dosage of epinephrine in treatment of septic shock
– Emergency operation in congenital diaphragmatic hernia
– Hyperventilation, hypothermia and barbiturates in increased intracranial pressure
– Intra-osseal infusions
– Indications for sodium bicarbonate
– Hemodynamic monitoring with Swan-Ganz catheters

and consequences of new findings which are now ready to be used in humans. We have to be aware not to act only as servants to scientists trying to apply new technologies, operative procedures or just thoughts to the individual patient. On the other hand, the intensivist should not be the factor hampering progress in this respect. We have to protect the balance and be aware how new treatment modalities are evaluated. Therefore we need an open mind for new thoughts and ideas but have to be protective in an attempt to do what is in the best interest for the individual child and his parents. Making a career in intensive care in childhood may include knowledge of developmental biology, technology assessment and application of new technologies to go hand in hand with a common sense to guarantee dignity of the individual patient under all circumstances.

In this way the fragile balance between cells, (micro)organisms and environment can be maintained.

References

1. Editorial: Looking to Development's Future. Science 1994;266:561–614.
2. Paigen K (1995) A Miracle Enough: the Power of Mice. Nature Med 1:215–220.
3. Culliton BJ (1995) Molecular medicine in a changing world. Nature Med 1:1.
4. Kirschner MW, Marincola E, Olmsted Teisberg E (1994) The role of biomedical research in health care reform. Science 266:49–54.
5. Crystal RG (1995) The gene as the drug. Nature Med 1:15–17.
6. Skuse GR, Ludlow JW (1995) Tumour suppressor genes in disease and therapy. Lancet 345:902–906.
7. Schlag G, Redl H, Hallström S (1991) The cell in shock: the origin of multiple organ failure. Resuscitation 21:137–180.
8. Babcock GT, Wikström M (1992) Oxygen activation and the conservation of energy in cell respiration. Nature 356:301–309.
9. Wagner PD (1995) Limitations of oxygen transport to the cell. Intensive Care Med 21:391–398.
10. Giaid A, Saleh D (1995) Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension. N Eng J Med 333:214–221.
11. Loscalzo J (1995) Editorial: Nitric Oxide and Vascular Disease. N Engl J Med 333:251–253.
12. Fink MP, Payen D (1996) The role of nitric oxide in sepsis and ARDS. Intensive Care Med 22:158–165.
13. Pittet D, Rangel-Frausto S, Li N et al. (1995) Systemic inflammatory response syndrome, sepsis, severe sepsis and septic shock: incidence, morbidities and outcomes in surgical ICU patients. Intensive Care Med 21:302–309.
14. Lamy M, Deby-Dupont G (1995) Is sepsis a mediator-inhibitor mismatch ? Intensive Care Med 21:S250-S257.
15. Parillo JE (1993) Pathogenetic mechanisms of septic shock. N Engl J Med 328:1471–1477.
16. Giroir BP (1993) Mediators of septic shock: New approaches for interrupting the endogenous inflammatory cascade. Crit Care Med 21:780–789.
17. Kollef MH, Schuster DP (1995) The acute respiratory distress syndrome. N Engl J Med 332:27–37.
18. Dreyfuss D, Saumon G (1992) Barotrauma is volutrauma, but which volume is the one responsible ? Intensive Care Med 18:139–141.

19. Dreyfuss D, Saumon G (1994) Should the lung be rested or recruited ? The Charybdis and Scylla of Ventilator Management. Am J Respir Care Med 149:1066–1068.
20. Kanto WP (1994) A decade of experience with neonatal extracorporeal membrane oxygenation. J Pediatr 124:335–347.
21. Walsh-Sukys M, Stork EK, Martin RJ (1994) Neonatal ECMO: Iron lung of the 1990's? J Pediatr 124:427–430.
22. Curtis S (1991) Perfluorocarbon-associated gas exchange: A hybrid approach to mechanical ventilation. Crit Care Med 19:600–601.
23. Shaffer TH, Wolfson MR, Clark LC (1992) Liquid Ventilation. Pediatr Pulm 14:102–109.
24. Moler FW, Palmisano J, Custer JR (1993) Extracorporeal life support for pediatric respiratory failure: Predictors of survival from 220 patients. Crit Care Med 21:1604–1611.
25. Adzick NS, Harrison MR (1994) Fetal surgical therapy. Lancet 343:897–901.
26. Luks FI (1995) Fetal surgery; New techniques have given surgeons a second chance. Br Med J 311:1449–1453.
27. Starlz TE, Todo S, Tzakis A et al. (1993) The transplantation of gastrointestinal organs. Gastroenterology 104:673–679.
28. Beath SV, Brook GD, Kelly DA et al. (1993) Successful liver transplantation in babies under 1 year. Br Med J 307:825–828.
29. Ross RJM, Rodrigues-Arnao J, Bentham J et al. (1993) The role of insulin, growth hormone and IGF-I as anabolic agents in the critically ill. Intensive Care Med 19:S54-S57.
30. Hodson ME, Shah PL (1995) DNase trials in cystic fibrosis. Eur Respir J 8:1786–1791.
31. Outcome Assessment of Pediatric Intensive Care; Principles and Applications. Gemke RJBJ, Thesis, Utrecht (1994).
32. Horbar JD, Onstad L, Wright E et al. (1993) Predicting mortality risk for infants weighing 501 to 1500 grams at birth: A national institutes of health neonatal research network report. Crit Care Med 21:12–18.
33. Bion J (1993) Outcomes in intensive care. Br Med J 307:953–954.
34. Sanderson C, Hall DMB (1995) The outcomes of neonatal intensive care. Br Med J 310:681–682.
35. Smit R (1995) Rationing: the debate we have to have. Br Med J 310:686.
36. Petros AJ, Marshall JC, van Saene HKF (1995) Should morbidity replace mortality as an endpoint for clinical trials in intensive care ? Lancet 345:369–371.
37. Franklin C (1993) Basic concepts and fundamental issues in technology assessment. Intensive Care Med 19:117–121.
38. Lemeshow S, Klar J, Teres D (1995) Outcome Prediction for Individual Intensive Care Patients: useful, misused, or abused ? Intensive Care Med 21:770–776.
39. Granger CE, George C, Shelly MP (1995) The management of bereavement on intensive care units. Intensive Care Med 21:429–436.