

Symposium: Pediatric Pulmonary Insufficiency: Nutritional Strategies for Prevention and Treatment

Chronic Pulmonary Insufficiency in Children and Its Effects on Growth and Development^{1,2}

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ABSTRACT Conditions leading to chronic pulmonary insufficiency can affect infants and children. These can lead to growth failure and delayed development. Among the most common and severe of these are bronchopulmonary dysplasia (BPD) and cystic fibrosis. In addition to the respiratory consequences of these diseases, there is ample evidence that they lead to decreased growth as a result of decreased energy intake and increased energy expenditure. Furthermore, there is evidence that infants with BPD may also have delayed development, independent of the effects of their prematurity. Enhancing the long-term outlook for these conditions may therefore require consideration of both improved pulmonary management and aggressive nutritional management to limit growth failure and potentially enhance developmental outcome. Specific micronutrient supplementation, such as antioxidant therapy, may also enhance pulmonary and nutritional status. *J. Nutr.* 131: 938S-941S, 2001.

KEY WORDS: • prematurity • nutritional supplementation • bronchopulmonary dysplasia

The links among nutrition, development and pulmonary status in children

Although researchers in pulmonary biology and nutrition tend to exist in somewhat separate worlds, there is considerable evidence that these two physiological systems are, in fact, closely interrelated. Conditions of malnutrition can cause significant effects on pulmonary function, and chronic pulmonary disease can lead to poor growth and delayed development. This symposium evaluates these interrelationships, focusing in particular on chronic lung disease of premature infants, bronchopulmonary dysplasia. Ultimately, the goal is to ensure that management of pulmonary diseases includes consideration of overall nutritional intake. Furthermore, exciting

developments suggest that specific nutrients, such as antioxidants, may be useful in affecting the course of pulmonary disease.

Effects of malnutrition on lung function

Animal models show that severe prenatal and postnatal malnutrition can have a significant effect on lung development, decreasing both lung function and lung size. Because this effect is unlikely to be readily manifested in children in most developed countries, Ong et al. (1998) used spirometry to evaluate lung function in school children in rural India. They found that lung function, when normalized for body size, was significantly related to nutritional indices in boys and girls. Lung function was also poorer in these children than in size-matched children from Britain or from Asian countries. The conclusion is that malnourished children have poor lung function. This may be related to early maldevelopment and is independent of their stature. An effect of malnutrition on respiratory muscle weakness is also possible.

Growth failure in infants and consequences for development

The link between poor growth and delayed brain development is well recognized and has been recently reviewed by Scrimshaw (1998). Although primary brain development and neurogenesis occur during the prenatal period, postnatal events include myelination of new axons, neuronal migration and formation of synaptic connections (Wauben and Wainwright 1999). Malnutrition may effect these and thus alter behavioral development.

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Deficiencies of specific nutrients may also affect neurological development postnatally. For example, iron deficiency in early childhood is well known to lead to long-standing behavioral and cognitive deficits. Iodine deficiency in childhood also has a severe effect on cognitive development (Scrimshaw 1998). Recently, considerable attention was paid to the effects of long-chain polyunsaturated fats on development. Although data are not conclusive, some evidence suggests that the addition of these to infant formulas may, for example, enhance cognitive or visual development in premature infants (Lucas 1997).

Specific condition: bronchopulmonary dysplasia (BPD)

Clinical overview. BPD was first described in 1967. Since then, it has become one of the major problems facing those who care for premature infants. BPD is the third leading cause of chronic lung disease in children and the primary cause of lung disease in infants. It has been estimated that there are at least 7000 infants with BPD in the United States at any given time. Although various definitions of BPD have been used, one practical definition is that proposed by Hansen and Corbet (1998): "respiratory sequelae in an infant who reaches 36 wk postmenstrual age but cannot be discharged from the hospital because of continued oxygen requirement or mechanical ventilatory requirement, or an infant who is discharged home on oxygen or ventilatory support."

The etiology of BPD is unknown, although it is closely related to extreme prematurity (< 26 wk), high oxygen exposure and prolonged ventilatory support. Because of the relationship with oxygen exposure and the possibility of oxidant damage to the lungs, it has been proposed that antioxidant therapy may prevent or limit its course, which is considered elsewhere (Welty 2001).

Effects on growth. Inadequate growth is a well-recognized complication of BPD. A series of studies have demonstrated both increased energy utilization and decreased energy intake in infants with BPD (Wilson and McClure 1994). An important recent suggestion is that growth failure may be an early occurrence in infants who ultimately develop BPD. DeRegnier et al. (1996) evaluated early growth in very low birthweight infants. They found that between 2 and 4 wk of age, infants with developing BPD consumed less protein and energy, accreted less arm fat and muscle and grew more slowly than similarly sized infants who did not develop BPD. After achieving full enteral intakes, similar rates of growth were seen, but catch-up growth did not occur. These data supported the idea that early growth failure contributes to long-term problems in infants with BPD.

Other studies showed that poor growth often continues in infants with BPD, even after hospital discharge. Estimates of growth failure range from 30% to 67% during the initial postdischarge period (Johnson et al. 1998). Of note is the suggestion of a previous study that growth failure was less in infants with BPD who were receiving oxygen at home than in those not receiving home oxygen (Chye 1995). If confirmed, this finding may imply that adequate tissue oxygenation may ameliorate some growth limitation in infants with BPD.

Medications utilized to treat infants with BPD may also affect growth. The most important of these are corticosteroids. Short- and long-term steroid administration is a common feature of management of infants with BPD. Gibson et al. (1993) reported that knee-ankle growth, which is usually approximately 0.5 mm/d in premature infants, was reduced to zero after 9 d of dexamethasone therapy, and did not return to predicted values until 30 d after treatment was stopped.

Leitch et al. (1999) recently showed that although, as expected, growth was severely impaired in infants with BPD during dexamethasone treatment compared to a nontreatment phase, this difference could not be related to differences in energy expenditure or energy intake. This finding suggests that dexamethasone alters the composition of weight gain by increasing fat and decreasing protein accretion relative to growth when dexamethasone is not administered.

Effects on development. Lifschitz et al. (1987) reported a 68% incidence of suspected or confirmed abnormal neurodevelopmental problems in infants with BPD who were followed postdischarge. Singer et al. (1997) reported a prospective, longitudinal study of very low birth weight (VLBW) and term infants to 3 y of age. BPD was shown to be an independent predictor of poorer motor outcome at 3 y of age. After adjustment for cofounders, a 10- to 12-point lower PDI was shown in BPD infants compared with other VLBW infants without BPD.

This study confirms findings by others including Northway (1990), Vohr (1991) and Robertson (1992), whose studies in the aggregate found neuromuscular problems, poorer development and smaller head circumference in infants with BPD.

In contrast to some of these earlier studies, the Singer et al. (1997) study did not identify differences in mental outcome related to BPD once data were adjusted for race, social class, birthweight and neurological risk score (a summary score of specific neurological outcomes such as periventricular leukomalacia). This result may primarily relate to the overriding effect of neurological risk score on mental outcome. Nonetheless, it is likely that the combination of lower socioeconomic status and prematurity and BPD led to a high risk for lowered mental outcome.

Giacoia et al. (1997) evaluated a small group of children with BPD compared with groups of VLBW and full-term infants at school age. They did not find any differences in verbal or performance IQ in comparing the BPD infants with other preterm infants, but did find that the infants with BPD had lower scores than full-term infants.

There is also concern that BPD may affect development of visual functioning, independent of the existence of retinopathy of prematurity. However, in a long-term follow-up study, Harvey et al. (1997) did not find evidence of abnormalities of grating acuity or visual-field development defects in children with BPD who did not have significant neurological problems or retinopathy. They did report lowered recognition acuity at 3 y of age in BPD infants, but this may have been related to cognitive differences.

Nutritional management of infants with BPD. The need for fluid restriction often leads to premature infants' having lower-than-optimal energy intakes. For example, Wilson et al. (1991) showed that actual energy intakes were far below optimal intakes throughout the first 8 wk of life in small infants who developed BPD.

Evidence of an increased energy requirement in infants with BPD comes from a series of studies using indirect calorimetry in babies with BPD. As reviewed by Wilson and McClure (1994), these studies all show an increase in energy expenditure in infants with BPD compared with controls. Differences of 15–25 kcal · kg⁻¹ · d⁻¹ are frequently reported. These studies are discussed in detail elsewhere in this journal by Denne (2001). However, significant methodological questions regarding these studies persist and the exact level of increased energy intake required by infants with BPD remains uncertain.

Fewtrell et al. (1997) randomized 60 oxygen-dependent 28-d-old preterm infants to either a 24 cal/oz (812 kcal/L)

formula fed at $180 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ or a 30 cal/oz formula fed at $145 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$. The infants fed the 30 cal/oz (1014 kcal/L) formula had a slightly greater energy intake ($9 \text{ kcal} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$) because the feeding volume was not readily maintained in the lower density-intake group. No differences between groups in growth or respiratory outcome were seen. Further studies using higher intake volumes and more concentrated formulas would be useful to evaluate the benefits to various caloric-density formulas.

A second approach to nutritional management of BPD involves altering the composition of formula to increase the fat intake relative to the carbohydrate intake. This has the potential benefit of decreasing carbon dioxide production and the respiratory quotient in infants with chronic lung disease. This approach was effective in a short-term study by Periera et al. (1994). In contrast, however, although Chessex et al. (1995) also found higher carbon dioxide production associated with high fat intakes, they did not find any rise in oxygen consumption, but did find an increase in the transcutaneously measured partial pressure of oxygen in the blood. Longer-term studies of these and other nutritional strategies to treat BPD are ongoing, as described elsewhere in this issue by Atkinson (2001).

Even after hospital discharge, infants with BPD are at risk for ongoing growth failure. Reports have indicated very high rates of growth failure after hospital discharge. This poor growth is probably caused by the infants' ongoing increased energy utilization (Kurzner et al. 1988). In addition to increased energy expenditure, other factors contributing to this growth failure may be poor oral feeding skills and tolerance, and recurrent infections and hospitalizations. Reliance on high caloric-density feedings postdischarge may not entirely resolve these issues without close nutritional supervision (Johnson et al. 1998). Singer et al. (1996) reported that postdischarge, infants with BPD spent less time sucking and took in less formula per feeding than infants without BPD, whereas this difference was not observed in comparing other VLBW infants with full-term infants. Of particular interest was their observation that symptoms of maternal depression or anxiety may have led to less prompting by some mothers of their infant to feed.

Specific condition: cystic fibrosis (CF)

Overview. CF affects approximately 30,000 Americans. Approximately one third of patients with CF are below the 5th percentile of weight for age. CF represents a good example of the bilateral relationship between pulmonary function and nutritional status. Whereas nutritional deficiency can lead to poor lung growth and increased infection, poor pulmonary function also causes increased energy utilization and growth failure. Therefore, management of these patients, as with others with chronic lung disease, requires a combination of pulmonary and nutritional management.

Nutritional requirements of children with CF. A link between malnutrition in children with CF and worsening pulmonary status has long been known and is well described (Borowitz 1996). Modern body composition techniques have furthered our understanding of this relationship. Thomson et al. (1995) used total body potassium (TBK) counting to show that deterioration in pulmonary function can be predicted by changes in body cell mass identified by TBK measurement. Of note was that this relationship was more apparent than the relationship between z -scores for height or weight and pulmonary function. The authors suggest that subtle deterioration in

nutritional status is related to deterioration in pulmonary status in children moderately affected by CF.

An increased resting energy expenditure was previously identified in children with CF. Zemel et al. (1996) demonstrated this difference in prepubertal children with mild respiratory disease. However, in their study, the level of resting energy expenditure was not associated with a decline in pulmonary status over a 3-y period. Rather, markers of nutritional status, such as percentage ideal body weight, were predictive of changes in pulmonary function over time. Fat-free mass and height were predictors of resting energy expenditure.

Macro- and micronutrient deficiencies and their effects on pulmonary function in CF patients. Protein-energy malnutrition (PEM) may develop in children with CF. In addition to its other consequences, PEM may lead to increased susceptibility to infections and further clinical deterioration (Rappaz and Roulet 1997).

Micronutrient deficiencies may also occur in CF patients as a result of their pancreatic insufficiency. Deficiencies of vitamins A and E, as well as minerals including zinc and magnesium, may be present when either intake or nutrient absorption is inadequate. These deficiencies may also affect lung status either directly or via an increased susceptibility to infections. Although vitamin A supplementation is widely used for children with CF, mineral requirements and intake levels for CF patients remain to be determined.

Other conditions

Asthma and growth. The effect of diet in determining the etiology and clinical severity of asthma is unknown. There are epidemiological data to suggest that antioxidants, magnesium, and fat consumption may have important roles in the severity of asthmatic symptoms. However, the relative importance of these individual nutrients is unclear. Interventional studies are beginning to help clarify the importance of diet in patients with asthma, and early studies suggest that antioxidants in particular may be beneficial (Fogarty and Britton 2000). However, there are too few data to draw conclusions at this time regarding antioxidant supplementation and asthma (Smit 1999).

A recent study showed that prepubertal males with mild to moderate asthma had a higher metabolic rate per unit fat-free mass than did nonasthmatic males (Maffei 1998). This is compensated for by increased energy intake. However, further data are needed regarding energy metabolism in asthmatic children before conclusions can be reached regarding nutritional supplementation.

The effects of the widespread use of inhaled corticosteroids (ICs) on growth in asthmatic children have caused concern. In one retrospective study (Van Bever 1999), adult height was assessed in young adult asthmatics who were treated with ICs during childhood and compared to asthmatic patients who were never treated with ICs during childhood. Mean adult height was the same in subjects who took ICs during childhood as compared to that of subjects who had never received ICs. However, subjects who took ICs during childhood showed a statistically significant lower value of adult height minus target height than that of subjects who never received ICs. Patients on ICs during childhood who had ever been hospitalized for asthma showed a lower value for adult height minus target height than those who took ICs but were never hospitalized. The authors concluded that, although adult height was the same in young adults who were treated with ICs during childhood compared to those who were not, their findings suggested mild growth retardation in patients who took ICs

during childhood. They noted that this finding may have been related partly to disease severity rather than the IC use.

In a short-term study Heuck et al. (1998) showed a significant decrease in short-term (4-wk) growth velocity among children treated twice daily with oral budesonide compared with children who received the same total daily dose administered once in the morning. The implications of this study are controversial (Brook 1998), but suggest that further investigation is needed on the short- and long-term effects of oral corticosteroids, as well as their optimal dosing regimen (Inoue 1999).

Congenital lung malformations. Numerous congenital lung malformations exist, which can lead to chronic pulmonary insufficiency and mimic the finding of premature infants with BPD. Among the most common and severe is congenital diaphragmatic hernia (CDH). This condition has an incidence of between 1 in 2000 and 1 in 10,000 live births. Because of the prenatal herniation, the lung volume on the affected side is small and there is frequently marked pulmonary hypertension. In addition to supportive care, management frequently involves the use of cardiopulmonary bypass, referred to as extracorporeal membrane oxygenation (ECMO). Although the benefits of this approach are controversial, there is little doubt that most survivors of CDH and ECMO are left with substantial chronic lung disease. Furthermore, many have feeding difficulties, including dysmotility with reflux and poor oral feeding (Hansen et al. 1998).

There are few follow-up data on these infants. However, several recent studies showed that development abnormalities and severe nutritional problems persist in these infants. For example, Bernbaum et al. (1995) reported that among ECMO survivors, those with CDH had slower growth and more feeding and developmental problems than those who required ECMO for other problems. Further evaluation of these relationships is required, but there a substantial possibility exists of a link between nutritional inadequacies in CDH patients and their persistent developmental problems.

LITERATURE CITED

- Atkinson, S. (2001) Special nutritional needs of infants for prevention of and recovery from bronchopulmonary dysplasia. *J. Nutr.* 131: 942S-946S.
- Bernbaum, J., Schwartz, I. P., Gerdes, M., D'Agostino, J. A., Coburn, C. E. & Polin, R. A. (1995) Survivors of extracorporeal membrane oxygenation at 1 year of age: the relationship of primary diagnosis with health and neurodevelopmental sequelae. *Pediatrics* 96: 907-913.
- Borowitz, D. (1996) The interrelationship of nutrition and pulmonary function in patients with cystic fibrosis. *Curr. Opin. Pulm. Med.* 2: 457-461.
- Brook, C.G.D. (1998) Short stature never killed anybody. *J. Pediatr.* 133: 591-592.
- Chessex, P., Belanger, S., Piedboeuf, B. & Pineault, M. (1995) Influence of energy substrate on respiratory gas exchange during conventional mechanical ventilation of preterm infants. *J. Pediatr.* 126: 619-624.
- Chye, J. K. & Gray, P. H. (1995) Rehospitalization and growth of infants with bronchopulmonary dysplasia: a matched control study. *J. Paediatr. Child. Health* 31: 105-111.
- Denne, S. (2001) Energy expenditure in infants with pulmonary insufficiency: is there evidence for increased energy needs? *J. Nutr.* 131: 935S-937S.
- DeRegneir, R. A., Guilbert, T. W., Mills, M. M. & Georgieff, M. K. (1996) Growth failure and altered body composition are established by one month of age in infants with bronchopulmonary dysplasia. *J. Nutr.* 126: 168-175.
- Fewtrell, M. S., Adams, C., Wilson, D. C., Cairns, P., McClure, G. & Lucas, A. (1997) Randomized trial of high nutrient density formula versus standard formula in chronic lung disease. *Acta Paediatr.* 86: 577-582.
- Fogarty, A. & Britton, J. (2000) Nutritional issues and asthma. *Curr. Opin. Pulm. Med.* 6: 86-89.
- Giacoaia, G. P., Venkataraman, P. S., West-Wilson, K. & Faulkner, M. J. (1997) Follow-up of school-age children with bronchopulmonary dysplasia. *J. Pediatr.* 130: 400-408.
- Gibson, A. T., Pearce, R. G. & Wales, J. K. (1993) Growth retardation after dexamethasone administration: assessment by knemometry. *Arch. Dis. Child.* 69: 505-509.
- Hansen, T. & Corbet, A. (1998) Chronic lung disease. In: *Avery's Diseases of the Newborn* (Tausch, W. & Ballard, R., eds.), 7th Ed., pp. 634-647, W.B. Saunders, Philadelphia, PA.
- Hansen, T., Corbet, A. & Ballard, R. A. (1998) Disorders of the chest wall and diaphragm. In: *Avery's Diseases of the Newborn* (Tausch, W. & Ballard, R., eds.), 7th Ed., pp. 685-697, W.B. Saunders, Philadelphia, PA.
- Harvey, E. M., Dobson, V. & Luna, B. (1997) Long-term grating acuity and visual-field development in preterm children who experienced bronchopulmonary dysplasia. *Dev. Med. Child. Neurol.* 39: 167-173.
- Heuck, D., Wolthers, O. D., Kollerup, G., Hansen, M. & Teisner, B. (1998) Adverse effects of inhaled budesonide (800 µg) on growth and collagen turnover in children with asthma: a double-blind comparison of once-daily versus twice-daily administration. *J. Pediatr.* 133: 608-612.
- Inoue, T., Doi, S., Takamatsu, I., Murayama, N., Kameda, M. & Toyoshima, K. (1999) Effect of long-term treatment with inhaled beclomethasone dipropionate on growth of asthmatic children. *J. Asthma* 36: 159-164.
- Johnson, D. B., Cheney, C. & Monsen, E. R. (1998) Nutrition and feeding in infants with bronchopulmonary dysplasia after initial hospital discharge: risk factors for growth failure. *J. Am. Diet. Assoc.* 98: 649-656.
- Kurzner, S. I., Garg, M., Bautista, D. B., Bader, D., Merritt, R. J., Warburton, D. & Keens, T. G. (1988) Growth failure in infants with bronchopulmonary dysplasia: nutrition and elevated resting metabolic expenditure. *Pediatrics* 81: 379-384.
- Leitch, C. A., Ahlrichs, J., Karn, C. & Denne, S. C. (1999) Energy expenditure and energy intake during dexamethasone therapy for chronic lung disease. *Pediatr. Res.* 46: 109-113.
- Lifschitz, M. H., Seilheimer, D. K., Wilson, G. S., Williamson, W. D., Thurber, S. A. & Desmond, M. M. (1987) Neurodevelopmental status of low birth weight infants with bronchopulmonary dysplasia requiring prolonged oxygen supplementation. *J. Perinatol.* 7: 127-132.
- Lucas, A. (1997) Long-chain polyunsaturated fatty acids, infant feeding, and cognitive development. In: *The Developing Brain and Behavior: The Role of Lipids in Infant Formula* (Dobbing, J., ed.), pp. 3-39, Academic Press, Toronto, Canada.
- Maffei, C., Chiocca, E., Zaffanello, M., Golinelli, M., Pinelli, L. & Boner, A. L. (1998) Energy intake and energy expenditure in prepubertal males with asthma. *Eur. Respir. J.* 12:123-129.
- Northway, W. H., Moss, R. B., Carlisle, K. B., Parker, B. R., Popp, R. L., Pitlick, P. T., Eichler, I., Lamm, R. L. & Brown, B. W. (1990) Late pulmonary sequelae of bronchopulmonary dysplasia. *N. Engl. J. Med.* 323: 1793-1799.
- Ong, T. J., Mehta, A., Ogston, S. & Mukhopadhyay, S. (1998) Prediction of lung function in the inadequately nourished. *Arch. Dis. Child.* 79: 18-21.
- Pereira, G. R., Baumgart, S., Bennett, M. J., Stallings, V. A., Georgieff, M., Hamosh, M. & Ellis, L. (1994) Use of high-fat formula for premature infants with bronchopulmonary dysplasia: metabolic, pulmonary, and nutritional studies. *J. Pediatr.* 124: 605-611.
- Rappaz, I. & Roulet, M. (1997) Cystic fibrosis. In: *Bailliere's Clinical Paediatrics: Nutritional Support* (Ryan, S., ed.), Vol. 5, pp. 201-214, W.B. Saunders, London, U.K.
- Robertson, C.M.T., Etches, P. C., Goldson, E., Mildred, J. & Kyle, M. (1992) Eight year school performance, neurodevelopmental, and growth outcomes of neonates with bronchopulmonary dysplasia: a comparative study. *Pediatrics* 89: 365-372.
- Scrimshaw, N. S. (1998) Malnutrition, brain development, learning, and behavior. *Nutr. Res.* 18: 351-379.
- Singer, L., Yamashita, T., Lilien, L., Collin, M. & Baley, J. (1997) A longitudinal study of developmental outcome of infants with bronchopulmonary dysplasia and very low birth weight. *Pediatrics* 100: 987-993.
- Singer, L. T., Davillier, M., Preuss, L., Szekeley, L., Hawkins, S., Yamashita, T. & Baley, J. (1996) Feeding interactions in infants with very low birth weight and bronchopulmonary dysplasia. *J. Dev. Behav. Pediatr.* 17: 69-76.
- Smit, H. A., Grievink, L. & Tabak, C. (1999) Dietary influences on chronic obstructive lung disease and asthma: a review of the epidemiological evidence. *Proc. Nutr. Soc.* 58: 309-319.
- Thomson, M. A., Quirk, P., Swanson, C. E., Thomas, B. J., Holt, T. L., Francis, P. J. & Shepherd, R. W. (1995) Nutritional growth retardation is associated with defective lung growth in cystic fibrosis: a preventable determinant of progressive pulmonary dysfunction. *Nutrition* 11: 350-354.
- Van Bever, H. P., Desager, K. N., Lijssens, N., Weyler, J. J. & Du Caju, M. V. (1999) Does treatment of asthmatic children with inhaled corticosteroids affect their adult height? *Pediatr. Pulmonol.* 27: 369-375.
- Vohr, B. R., Coll, C. G., Lobato, C., Dea, C. & Oh, W. (1991) Neurodevelopmental and medical status of low birthweight survivors of bronchopulmonary dysplasia at 10 to 12 years of age. *Dev. Med. Child. Neurol.* 33: 690-697.
- Wauben, I.P.M. & Wainwright, P. E. (1999) The influence of neonatal nutrition on behavioral development: a critical appraisal. *Nutr. Rev.* 57: 35-44.
- Welty, S. E. (2001) Is there a role for antioxidant therapy in bronchopulmonary dysplasia? *J. Nutr.* 131: 947S-950S.
- Wilson, D. C. & McClure, G. (1994) Energy requirements in sick preterm babies. *Acta Paediatr. Suppl.* 405: 60-64.
- Wilson, D. C., McClure, G., Halliday, H. L., Reid, M. & Dodge, J. A. (1991) Nutrition and bronchopulmonary dysplasia. *Arch. Dis. Child.* 66: 37-38.
- Zemel, B. S., Kawchak, D. A., Cnaan, A., Zhao, H., Scanlin, T. F. & Stallings, V. A. (1996) Prospective evaluation of resting energy expenditure, nutritional status, pulmonary function, and genotype in children with cystic fibrosis. *Pediatr. Res.* 40: 578-586.