

HYPOCALCEMIA IN OFFICE PRACTICE

B.C. Chhapparwal
S. Thora
J. Nadkarni

Although calcium is the major mineral constituent of bone, non-skeletal calcium is of great significance. Circulating serum calcium exists in three forms; ionized or free (Ca^{++}), protein bound (mostly to albumin) and complexed with bicarbonate, phosphate and citrate. Small changes in ionized serum-calcium levels are poorly tolerated. It is responsible for initiating neuromuscular action potentials and is involved as a cofactor in many enzymatic reactions. The functions of neurones of central and peripheral nervous systems, striated, cardiac and smooth muscle cells, and endocrine and exocrine secretory cells all depend on maintenance of Ca^{++} within tight limits(1,2).

Hypocalcemia is the commonest

From the Department of Pediatrics, M.G.M. Medical College, M.Y. Hospital and Chacha Nehru Bal Chikitsalaya Awam Anusandhan Kendra, Indore.

Reprint requests: Dr. B. C. Chhapparwal, Department of Pediatrics, M.G.M. Medical College, M.Y. Hospital and Chacha Nehru Bal Chikitsalaya Awam Anusandhan Kendra, Indore 452 001.

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biochemical abnormality responsible for neonatal seizures (incidence 10-20%)(1). In intensive care units, measuring ionized serum calcium is particularly important in critically ill neonates, patients with sepsis or other cardiovascular instability, massively transfused patients and those undergoing cardiopulmonary bypass or liver transplantation(3-5). Hypocalcemia is a chemical finding, the aim is to arrive at an etiological diagnosis and planning for immediate and long term management.

Calcium Physiology

Acute changes in circulating ionized calcium concentration (Ca^{++}) affect many cell types whose function is critically linked to transmembrane calcium flux. These changes activate systems which control calcium homeostasis, *i.e.*, mainly the parathyroid glands and the vitamin D endocrine system.

Parathyroid Hormone

The parathyroid glands are formed from cells of the third and fourth pharyngeal pouches and begin to secrete parathyroid hormone (PTH) by twelfth week of gestation. The parathyroid glands are the principle regulators of extracellular ionized calcium concentration. The chief cells serve as both sensors and effectors in a feedback regulatory system that governs Ca^{++} . They sense (Ca^{++}) and, if it is too low, augment the secretion of PTH. PTH is an 84 amino acid peptide, which elevates serum Ca^{++} by promoting bone resorption, decreasing urinary calcium excretion and promoting the activation of vitamin D. The cellular response of target cells to PTH

(Fig. 1) depends on the integrity of a three part receptor in the cell membrane(6).

Vitamin D

Vitamin D (calciferol) is a lipid soluble sterol produced in the skin by the action of ultraviolet light on 7 dehydrocholesterol. The vitamin is then bound to a specific binding protein (D binding protein, DBP), and is carried to the liver where it is stored and converted to calcidiol (25 hydroxy cholecalciferol). Calcidiol has weak physiological activity but is an important precursor of the active vitamin D hormone, calcitriol (1, 25 dihydroxycholecalciferol). The circulating concentration of calcidiol reflects and individual vitamin D nutritional status, so this compound, rather than the native vitamin is assayed when vitamin D nutrition needs to be assessed.

During pregnancy calcidiol crosses the placenta, and its activation to calcitriol by the fetus provides the main source of calcitriol for the fetus. However, some calcitriol may also become available to the fetus by direct transfer of the active hormone from the maternal side through the placenta. Calcitriol is made in the cells of proximal renal tubule. Its production is stimulated by PTH, hypoglycemia and phosphate deficiency. Calcitriol promotes calcium homeostasis (Fig. 2) by enhancing calcium absorption from the proximal small intestine(7).

Pathophysiology of Hypoglycemia

The normal serum calcium concentration in children lies between 9.9 to 10.1 mg/dl, the corresponding levels for ionized calcium being 4.4 to 5.1 mg/dl. Lower values are seen in normal newborns. There are no hard and fast rules regarding the levels of ionized calcium below which symptoms might occur, but these are

generally not seen until ionized calcium falls below 2.5 to 3 mg/dl. The major clinical impact of hypoglycemia is felt in the central and peripheral nervous systems and on muscular function. In infants and young children convulsions are most common manifestation and tetany is common in older children and adults(8).

The classification of hypoglycemia, association of hypocalcemia with hypo or hypophosphatemia and indications for estimation of serum calcium levels, are summarized in *Tables I-III*, respectively.

Hypocalcemia in Newborn

During intrauterine life, the fetus acquires calcium via placental transfer that involves both active transport and passive diffusion. As a result cord blood calcium level is 1 meq/litre higher than the maternal concentration. The fetus acquires 80% of its calcium in the last trimester of pregnancy and the accretion rate averages 100-150 mg/kg/day. After birth there is a drop in calcium levels specially in 24 to 48(9).

Neonatal hypoglycemia has been classified by the time of onset. Early neonatal hypoglycemia usually occurs between 24 to 48 h of life in prematures, infants of diabetic mothers and asphyxiated infants. The etiology of this phenomenon may be related to an attenuated postnatal calcitonin surge (reported in prematures), a delayed PTH response (suggested in infants of diabetic mothers), or a combination of factors, including an increased phosphate load resulting from cellular damage of perinatal asphyxia(10). Late neonatal hypoglycemia occurs between 5 and 10 days of age. Babies with this disorder are usually full term, and not breast fed, and often the mothers are vitamin D deficient. Serum calcium is low and phosphate is elevated. Hypomagnesemia has occurred

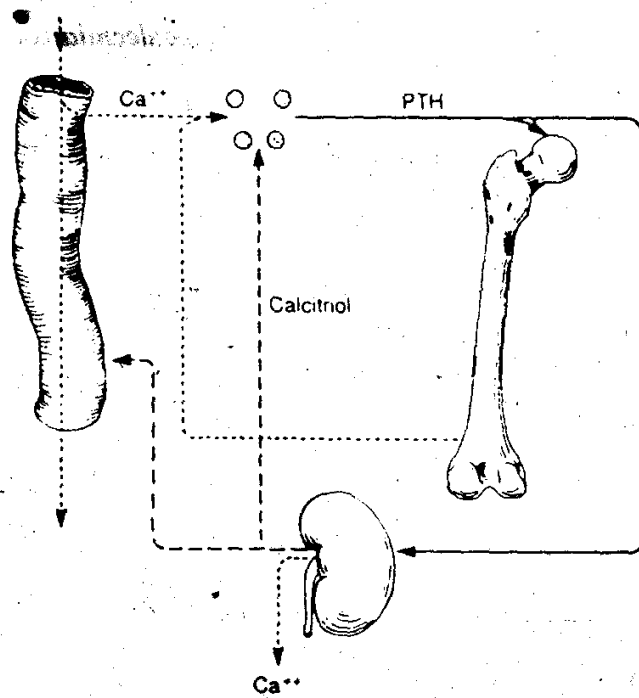


Fig. 1. The central role of parathyroid glands in calcium homeostasis. A fall in serum Ca^{++} stimulates PTH secretion. In turn this mobilizes calcium from within the body by stimulating osteoclastic bone resorption and tilts calcium balance towards positive side by reducing urinary calcium excretion and promoting calcium absorption through increased 1 hydroxylation of calcidiol.

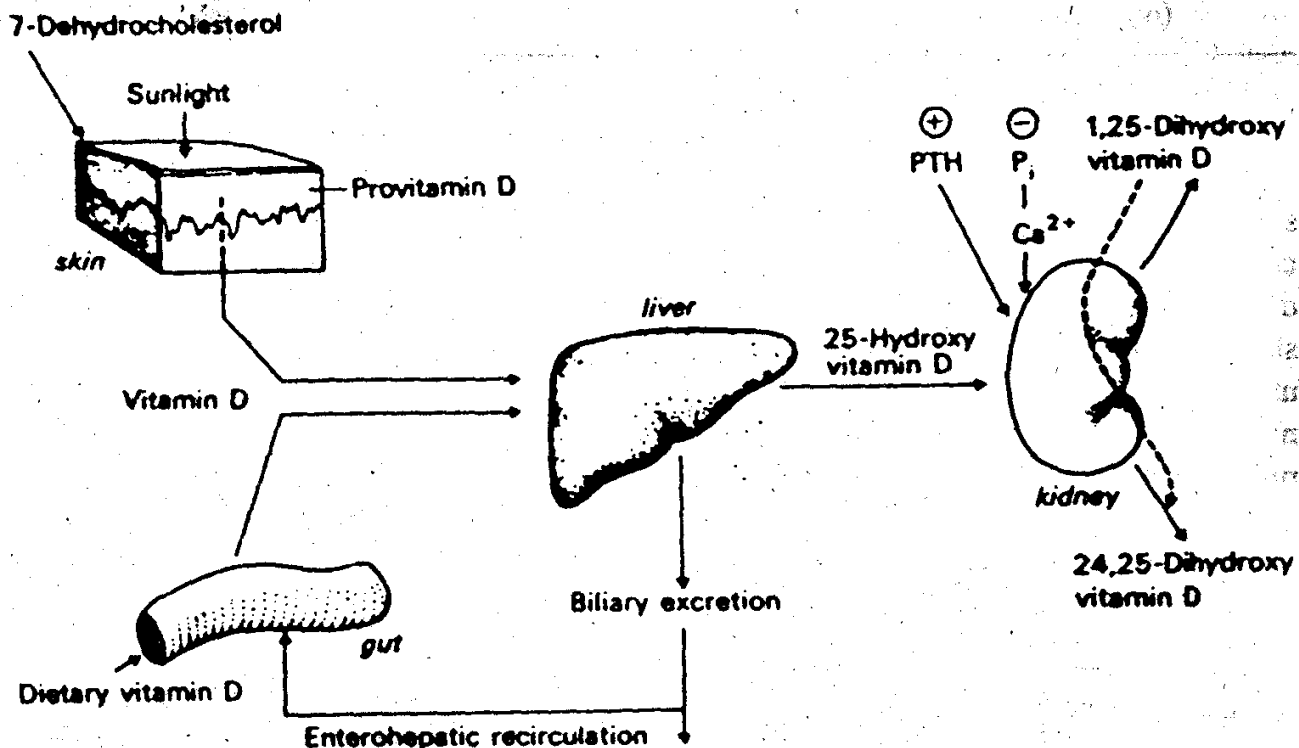


Fig. 2. The metabolic interconversions of vitamin D.

TABLE I—Classification of Hypocalcemia

I. Neonatal hypocalcemia

- (a) Early
- (b) Late—may be associated with decrease PTH levels
- (c) "Late late"—related to vitamin D deficiency
- (d) Others

Infants of mothers with diabetes, primary hyperparathyroidism, birth asphyxia.

II. Hypocalcemia of later onset or persisting beyond neonatal period

- (a) Hypoparathyroidism
 - (i) Congenital—Hypoplasia, transient, Di George syndrome
 - (ii) Acquired—Idiopathic (often familial). Polyglandular autoimmune disease, surgical, hypomagnesemia, thalassemia, Wilson's disease, surgical removal
 - (iii) Pseudohypoparathyroidism (Types I and II)
- (b) Vitamin D deficiency
- (c) Renal osteodystrophy
- (d) Magnesium deficiency
- (e) Transient hypocalcemia
 - (i) "Hungry bone" phenomenon
 - (ii) Transfusion with citrated blood
 - (iii) Phosphate load (initial therapy of leukemia)
 - (iv) Acute pancreatitis

in upto 50% of patients in some series of studies(11). Late hypocalcemia develops at several weeks to months of age and is associated with hypophosphatemia, vitamin D deficiency and poor mineralization of the skeleton. Prematures are at risk for this multifactorial syndrome. Hypocalcemia may also occur in infants of mothers with primary hyperparathyroidism. Children with this disorder usually manifest between 2 weeks to 3 months of age but may present as late as 1 year of age. The presumed etiology relates to intrauterine transfer of maternal hypercalcemia to the fetus, resulting in suppression of the parathyroid glands which persists postpartum. There is an increase in fetal morbidity and mortality

in mothers having moderate to severe primary hyperparathyroidism. Neck exploration for parathyroid adenoma during pregnancy has been advocated for this reason(12).

Clinical Features

There are no diagnostic features of hypocalcemia and many cases are asymptomatic and transient. Early symptoms in preterm babies include shallow rapid breathing with attacks of apneic spells and cyanosis. Exaggerated neuromuscular activity may manifest by jitteriness, specially in response to various stimuli, such as touch, sound and light. Twitchings may occur and infant hypocalcemia is the

TABLE II—Association of Hypocalcemia with Hypo or Hyperphosphatemia

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- I. Hypocalcemia (with hypophosphatemia)**
- (a) Vitamin D deficiently
 - (b) Inadequate phosphate intake
 - (i) Malnutrition
 - (ii) Malabsorption
 - (iii) Chronic illness
 - (c) Excessive renal loss of phosphate independent of PTH
 - (i) Intravenous saline
 - (ii) Diuretics
- II. Hypocalcemia (with hyperphosphatemia)**
- (a) Parathyroid failure
 - Congenital absence (*e.g.*, Di George syndrome, Albright syndrome)
 - (b) Chronic renal failure (uremic osteodystrophy)
 - (c) Exogenous or endogenous phosphate load
 - (i) Parental phosphate administration
 - (ii) Phosphate containing enemas
 - (iii) Use of cytotoxic drugs
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TABLE III—Indication for Estimation of Serum Calcium Levels

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- (1) Newborn with convulsion and recurrent neonatal apnea
 - (2) Renal osteodystrophy
 - (3) Vitamin D deficiency
 - (4) Latent or manifest tetany
 - (5) Aortic arch abnormalities with convulsions (Di George syndrome)
 - (6) Diarrheal dehydration with convulsion
 - (7) During cytotoxic therapy for malignancy
 - (8) Unexplained convulsions
 - (9) Hypomagnesemia
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commonest biochemical abnormality responsible for neonatal seizures. The babies remain characteristically alert and their behavior and activity is unaffected even in presence of fits as opposed to babies with hypoglycemia. The periods of muscular excitability may alternate with phases of immobility and hypotonia. Some babies may have high pitched cry. ECG

may show 2 : 1 atrioventricular block with low voltage and prolonged QT due to prolongation of ST interval(1).

Manifestations of Hypocalcemia Beyond Neonatal Period

The major signs and symptoms of hypocalcemia result from increased neuromuscular irritability. The term

"tetany" is commonly used to describe this phenomenon which can be quite variable in presentation. Tetany in an older child classically begins with perioral tingling sensations also evident in finger tips. Muscles of extremities become tense and classic carpal spasm occurs, with fingers extended, thumb adducted and wrists flexed. Laryngospasm may occur resulting in a honking sound. In infants, tremors, twitches, and brief tonic clonic seizures are more important than classic tetany. Tetany does not necessarily correlate with the ambient level of ionized calcium at the time of the attack, nor does it consistently reflect a decline in the level of ionized calcium. Other causes of tetany include, hypokalemia, hypomagnesemia and hyperkalemia. Cardiovascular effects of hypocalcemia include delaying the onset of ventricular repolarization, rendering a prolonged QT interval. This figure must be correct for heart rate, particularly in the neonatal group. The corrected interval is obtained by dividing QT by the square root of the cycle length, *i.e.*,

$$Q - T_c = \frac{Q - T}{\sqrt{R - R}} (\text{normal } 0.40 \pm 0.04).$$

This phenomenon has been widely used to confirm the suspicion of hypocalcemia when there is limited access to a clinical laboratory. The ultimate consequences of this aberration in electrical activity may be cardiac arrest or congestive heart failure(7).

Hypoparathyroidism (HP) and Pseudohypoparathyroidism (PsHP)

HP and PsHP presents with hypocalcemia and hyperphosphatemia. PTH levels are low or undetectable except in PsHP. Ectopic calcification may exist, particularly in basal ganglion and soft tissues. Of par-

ticular interest are the association between HP and T cell dysfunction. This combination is seen in the Di George syndrome in which maldevelopment of thymus and of the parathyroid gland occurs together.

The term pseudohypoparathyroidism covers several distinct conditions in which tissues show variable degree of resistance to PTH. Two distinct subtypes are recognized. The classic test for such resistance was the Ellsworth-Howard test to determine the phosphaturic response to injected PTH. In last 20 years the test has been improved by examining CAMP response to PTH instead. Injection of PTH intravenously yields a 20-40 fold rise in the urinary CAMP to creatinine ratio in normal subjects, but not more than a 2-3 fold rise in type I PsHP. Now, however, accurate assays for PTH permit the distinction between HP and PsHP on the basis of circulating immuno reactive PTH levels, low in HP and high in PsHP(13).

Type I PsHP is expressed as a failure of tissue that normally contain a PTH sensitive adenyl cyclase to generate cyclic AMP upon exposure to PTH. The best defined group of patients is that presenting with short 4th metacarpals (brachydactyly), round facies, short stature, and mental retardation (Albright's hereditary osteodystrophy); however, the physical appearance may be completely normal. Type II PsHP is very rare condition in which phosphaturic response to PTH is absent while the CAMP response remains intact(8).

Vitamin D Deficiency (Severe)

Vitamin D deficiency is especially common in infancy and the common causes are nutritional deprivation, lack of sunlight, gastrointestinal, liver disease and anticonvulsant therapy. Children with vitamin D

deficiency, manifest with recurrent respiratory infection, bone pain, myopathy and hypocalcemia. In association with signs of rickets the child may have stridor, tetany or seizures(14-16).

Uremic Osteodystrophy (UOD)

As the kidneys are the principal site of vitamin D activation, it plays an important role in regulating calcium and phosphorus metabolism. In chronic renal failure, the bony disorder occurs principally from a combination of inadequate vitamin D activation and hyperparathyroidism. The bones manifest a combination of effects or rickets and hyperparathyroid bone disease. Usual biochemical changes are hypoglycemia, hyperphosphatemia, lower calcitriol and higher PTH levels. Tetany is rare because of the combined protective effect of metabolic acidosis and hyperparathyroidism.

Hypomagnesemia

Serum magnesium level below 1.5 mg/dl causes symptoms. In newborn familial hypomagnesemia manifest with tetany and seizures at 2-4 weeks of age has secondary hypocalcemia associated. Administration of calcium is ineffective, but administration of magnesium promptly corrects both calcium and magnesium levels. The disorder is most frequently seen in boys, but it appears to be caused by an autosomal recessive gene. It also occurs in malabsorption syndromes, protein energy malnutrition(17,18), therapy with aminoglycosides and autoimmune hypoparathyroidism(19).

Hungry Bone Phenomenon

Transient hypocalcemia may occur during early treatment of rickets, because of sudden movement of circulating minerals

into the bone compartment.

Treatment of Hypocalcemia

Mild hypocalcemia may not require therapy, but any newborn with serum calcium below 7.5 mg/dl (ionized calcium less than 2.8 mg/dl) or any older child with serum calcium less than 8 to 8.5 mg/dl should be treated to prevent tetany and other symptoms. In absence of symptoms oral calcium supplement would suffice. Oral calcium glubionate is the most suitable agent for babies and young children in the dosage 115 mg elemental calcium/kg/day in 4-6 divided doses.

In older children with symptomatic hypocalcemia, oral calcium therapy is used as an adjunct during therapy for chronic hypocalcemia. For this purpose, calcium carbonate or calcium lactate is preferred to glubionate. The recommended dosage is 50 mg/kg/day.

In acute symptomatic hypocalcemia intravenous therapy is required. This should not be undertaken lightly as rapid injection can cause serious cardiac arrhythmias and calcium salts are locally toxic and lead to severe tissue burns on extravasation. The usual dose is 0.5 to 2 ml/kg/day of a 10% calcium gluconate solution slowly over a period of 5-10 min after dilution with dextrose(1).

Chronic hypocalcemia except in mildest cases, is treated by vitamin D or its metabolites. Dihydroxycholesterol, an analogue of vitamin D, has shorter half life and has until recently, been the sterol most widely used to treat hypocalcemia specially when it is due to hypoparathyroidism. Today the most active metabolite of Vitamin D, calcitriol or its analogue, 1 hydroxyvitamine D is widely used for

chronic hypocalcemia. Calcitriol does not need to pass the rate limiting renal 1 hydroxylase step in order to be active and its biological half life is much less than vitamin D, ensuring the safety of vitamin D metabolite therapy. The dosage of calcitriol in children is generally higher than in adults. It ranges from 0.1 (in small babies) to 3.0 $\mu\text{g}/\text{day}$. It is given once or twice daily until normocalcemia is attained. Oral calcium supplements are usually required(22).

In treatment of hypoparathyroidism, the dosage of vitamin D metabolites are so adjusted to maintain serum calcium levels at lower range of its normal limit to minimize hypercalciuria and the risk of urolithiasis, as the renal threshold for calcium falls in this condition. The addition of hydrochlorothiazide may also reduce hypercalciuria and can, in some cases of hypoparathyroidism, greatly reduce the need for calcium and vitamin D metabolite therapy(8). Vitamin D deficiency rickets is treated by oral massive vitamin D (600,000 I.U.) unless there is intestinal malabsorption, where it should be given parenterally. Further dose of vitamin D is individualized depending on biochemical and radiological changes. Daily requirement of vitamin D is 400 IU/day.

In uremic osteodystrophy, adequate nutrition including adequate calcium intake, should be maintained and acidosis corrected. Hyperphosphatemia is reduced by dietary restriction and the administration of phosphate binding agents. Calcium carbonate is now favoured over aluminium hydroxide for this purpose. Vitamin D or one of its metabolite is routinely given to maintain serum calcium and to improve skeletal mineralization. Now-a-days calcitriol is preferred over dihydrotachysterol for this purpose(20).

REFERENCES

1. Singh M, Neurological disorders *In: Care of the Newborn*, 3rd edn. New Delhi. Sagar Publications, 1988, pp 295-316.
2. Taylor B, Sibbald WJ, Edmonds MW, *et al.* Ionized hypocalcemia in critically ill patients with sepsis. *Can J Surg* 1978, 21: 429-433.
3. Fuhrman BP. Hypocalcemia and critical illness in children. *J Pediatr* 1989, 114: 990-991.
4. Gay TA, Buckley BM, Sealey MM, *et al.* Plasma ionized calcium monitoring during liver transplanation. *Transplantation* 1986, 41: 335-339.
5. Hysing ES, Kofstad J, Lilleaasen P, *et al.* Ionized calcium in plasma during cardiopulmonary bypass. *Scand J Clin Lab Invest* 1986, 46 (Suppl 1984): 119-123.
6. Endres DB, Villanueva R, Sharp CF, *et al.* Measurement of parathyroid hormone. *Endocrinol Metab Clin North Am* 1989, 18: 611-629.
7. Reichel H, Koeffler HP, Normal AW. The role of vitamin endocrine system in health and disease. *N Engl J Med* 1989, 320: 980-991.
8. Behrman RE. Disorders of the parathyroid glands. *In: Nelson Textbook of Pediatrics*. Eds Behrman RE, Vaughan VC, Nelson WE. Philadelphia, W.B. Saunders Company, 1987, pp 1209-1211.
9. Hillman LS, Haddad JG. Perinatal vitamin D metabolism. III. Factors influencing late gestational human serum 25 hydroxy vitamin D. *Am J Obst Gynecol* 1976, 125: 196-200.
10. Callenback JC, Sheehan MB, Abramson SJ, Hall RT. Etiological factors in rickets of very low birth weight infants. *J Pediatr* 1981, 98: 800-805.
11. Cooper LJ, Anast CS. Circulating immunoreactive parathyroid hormone

- levels in premature infants and the response to calcium therapy. *Acta Paediatr Scand* 1985, 74: 699-773.
12. Carpenter TO, Lyndon Key L. Disorders of the metabolism of calcium, phosphorus and other divalent ions. *In: Pediatric Text Book of Fluid and Electrolytes*. Ed Ichikawa Baltimore, Williams and Wilkins, 1990, pp 273-277.
 13. Hillman LS, Haddad JG. Calcium disorders. *In: Clinical Endocrinology*. Eds Health DA, Marx SJ. London, Butterworth International Medical Reviews. 1982, pp 248-276.
 14. Goodman DS. Vitamin A and retinoids in health and disease. *N Engl J Med* 1984, 310: 1023-1031.
 15. Barr DG, Forfar JO. Oral calcium loading test in infancy with particular reference to idiopathic hypercalcemia. *Br Med J* 1969, 1: 477-480.
 16. Reichel H, Koeffler HP, Norman AW. The role of vitamin D endocrine system in health and disease. *N Engl J Med* 1989, 320: 980-991.
 17. Chhapparwal BC, Mehta S, Singh SD. Magnesium levels in serum erythrocytes and urine in PCM. *Indian J Paediatr* 1971, 38: 162-166.
 18. Sarkar S, Prakesh D, Gulati S, Chauhan J. Hypomagnesemic hypocalcemia as a cause of persistent upper airway obstruction in acute bacterial tracheitis. *Indian Paediatr* 1991, 28: 806-810.
 19. Venkataraman PS, Han BK, Tsang RC, Daugherty CC. Secondary hyperparathyroidism and bone disease in infants receiving long term furosemide therapy. *Am J Dis Child* 1983, 137: 1157-1161.
 20. Lewy, JE. Nephrology: Fluids and Electrolytes. *In: Nelson's Essentials of Pediatrics*. Eds Behrman RE, Kliegman R. Philadelphia, W.B. Saunders Company, 1990, pp 574-575.

NOTES AND NEWS

III JOINT CONVENTION OF NATIONAL NEONATOLOGY FORUM

AND

INDIAN SOCIETY OF PERINATOLOGY AND REPRODUCTIVE BIOLOGY

The Department of Pediatrics, K.G's Medical College, Lucknow is hosting III Joint Convention of National Neonatology Forum and Indian Society of Perinatology and Reproductive Biology on 27th and 28th February, 1993 (C.M.E. on 26th February, 1993). The last date for registration is 15th November, 1992.

For detailed information, please contact:

Dr. P.K. Misra,
Organizing Secretary,
Professor and Head, Department of Pediatrics,
K.G's Medical College,
Lucknow.