TRANSIENT CONGENITAL PSEUDOHYPOPARATHYROIDISM TYPE II

KODAMA, Soichi

(Citation)
The Kobe journal of the medical sciences,24(4):199-210

(Issue Date)
1978-12

(Resource Type)
departmental bulletin paper

(Version)
Version of Record

(URL)
https://hdl.handle.net/20.500.14094/0100488912

Kobe J. Med. Sci. 24, 199 - 210, December 1978

TRANSIENT CONGENITAL PSEUDOHYPOPARATHYROIDISM TYPE II

Soichi KODAMA, Michindo NINOMIYA, Atsushi SEKI, Takashi SAKURAI, Yorihiko MORISHITA, Ryuzaburo YAGI and Tamotsu MATSUO

Department of Pediatrics
Kobe University School of Medicine

INDEXING WORDS

neonatal hypocalcemia; renal responsiveness to PTE; cyclic AMP in urine; phosphorus in urine

SYNOPSIS

Generalized convulsion, hypocalcemia and hyperphosphatemia were found in 10-day-old and 30-day-old newborns with breast-feeding. Normal blood concentration of 25 hydroxyvitamin D_3 and normal radiographs of bones in these patients confirmed the absence of a rickets-like disorder. Contents of parathyroid hormone were under 500 pg./ml. as well as those of 3 controls.

Studies on renal responsiveness in urinary excretion of cyclic AMP and phosphorus to parathyroid extract suggest that transient disturbance in reception of cyclic AMP signal in neonate is one of the etiologies concerning later neonatal hypocalcemia.

INTRODUCTION

Later neonatal hypocalcemia is distinguished from early form of neonatal hypocalcemia. Gardner and his co-workers[9] reported that later neonatal hypocalcemia was induced by a phosphate load when the infant was fed too much cow's milk. Practically, in breast-fed babies serum phosphorus levels are lower and calcium levels higher than in babies fed on unadapted cow's milk mixtures. However, Thomas[16] has reported that with adapted milks serum calcium and phosphorus levels were closer to the values of those

Received for publication June 1, 1978

Authors' names in Japanese: 児玉 荘一　二宮 道人　関　温　桜井　隆　森下 順彦　八木隆三郎　松尾　保

of breast-fed infants. This report suggests that concerning the etiology to later neonatal hypocalcemia, there are many different possibilities except for artificial feeding. Indeed, commercially available infant milks are almost adapted milk as far as calcium and phosphorus contents are concerned. Transient congenital idiophthic hypoparathyroidism[7] and transient delayed development of renal response in receptor to parathyroid extract[11] may probably be one of the etiologies concerned to later neonatal hypocalcemia.

Recently, we have studied the breast-fed infants suffering from tonic convulsion, with hypocalcemia and hyperphosphatemia on the 10th and the 30th day. In these patients, a marked increase in urinary excretion of cyclic AMP in response to exogenously administered parathyroid extract was found. However, no increase in urinary excretion of phosphate and in serum concentration of calcium was found. On the other hand, the homeostatis of calcium and phosphate in these patients remains normal without any treatments up to the present. These results suggest that a transient delayed development or defect in the reception of the cyclic AMP signal[5] is also one of the etiologies of later neonatal hypocalcemia.

MATERIALS AND METHODS

Materials.

Fifteen healthy mature infants were selected to determine development of renal responsiveness to parathyroid hormone. Each five of them was of 24 hours of life, 5 days and 2～4 months of age. Infants were made to fast for the first 12 hours of life, then given 5 percent of glucose solution to 24 hours of life followed by formula B every three hours.

Case I (T.S.) was a full term 2900 g female product of a spontaneous vaginal delivery after a normal pregnancy and appeared to thrive normally with breast-feeding until one month of age. At the 31th day of age, generalized tonic convulsion was noted and laboratory studies revealed a hypocalcemia with hyperphosphatemia. At the 37th day of life, she was admitted to Kobe University Hospital for further examination and treatments.

Case II (K.L.) was also a full term 2800 g female product of

a spontaneous vaginal delivery and appeared to thrive normally with breast-feeding until the 17th day of life. At the 17th day, she suffered from common cold, followed by generalized tonic convulsion and showed hypocalcemia with hyperphosphatemia. At the 20th day, she was admitted to our hospital.

Methods.

Serum calcium level was determined by the chelating method,[4] serum and urine phosphorus levels by Tausky's method.[15] Serum magnesium was determined by atomic absorption spectrophotometry. Urine creatinine level was determined by Bosnes's method.[3] Alkaline phosphatase of serum was measured by Bessey's method.[2] Cyclic AMP contents in urine were determined by Gilman's method,[10] using appropriate kit (Amersham, Buckinghamshire, England).[17] 25-OH-Vitamin D_3 contents of serum were determined by Belsey's method.[1] Serum immunoreactive parathyroid hormone was measured by radioimmunoassay, using an antibovine parathyroid hormone guinea pig antiserum (W-RD, Wellcome, Co.).[13]

Administration of parathyroid extract (PTE-Eli Lilly Com., Indianapolis) was carried out at 9～10 a.m. Five percent of glucose solution was given by mouth adlibitum and PTE at a dose of 5U/kg. was given intravenously as a single bolus. Urine specimens were collected during each two hours, before and after administration of PTE.

Urine cyclic AMP and phosphorus values were expressed in nanomoles of cyclic AMP and milligram of phosphorus excreted per milligram of creatinine respectively.

RESULTS

Renal Responsiveness to Parathyroid Extract in Newborn Period.

The results of renal responsiveness to PTE are shown in Fig. 1. Mean values of urine cyclic AMP on the first day of life were 3.9± 1.8 and 4.5 ± 2.9 nmoles/mg. creatinine (5 cases), before and after PTE administration respectively. Mean values of urine cyclic AMP on 5th day of life were 5.3± 2.2 and 18.2± 14.7 nmoles/mg. creatinine (5 cases), before and after PTE administration respectively. Mean values at 2～4 months of age were 4.5 ± 0.7 and 102.9 ± 18.3 nmoles/mg. creatinine (5 cases), before and after PTE administration respectively. Those on two adolescents were 2.6 and

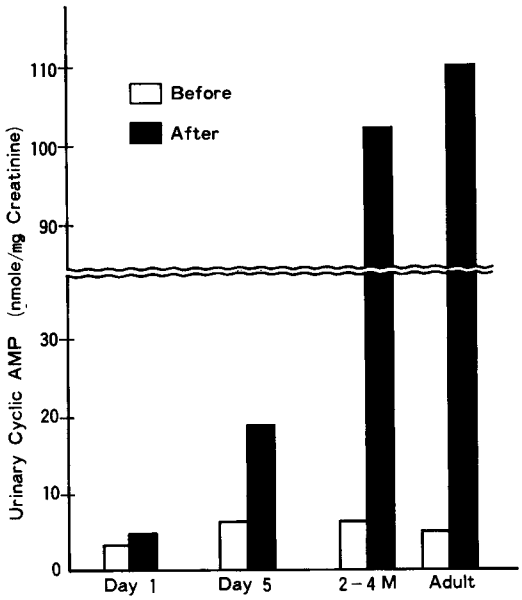

Fig. 1 Effect of parathyroid extract on urinary excretion of cyclic AMP.

108.8 nmoles/mg. creatinine before and after PTE administration. Response to PTE exhibited a marked increase at 2～4 months of age as well as adolescents. These results suggest that newborn's renal responsiveness of hormone receptor to PTE is recognized on about 5th day of life[12] and completely develops at 2～4 months of age.

The urine phosphorus values were determined as well as the urine cyclic AMP, before and after PTE administration. The results of urine phosphorus values are summarized as follows. Mean values of urine phosphorus before PTE administration were 0.06± 0.08, 0.56± 0.34, 1.60± 0.52 and 0.62 mg/mg. creatinine, on the first day of life, on the 5th day of age, at 2～4 months of age and adolescents, respectively. Those values after PTE administration were 0.05± 0.05, 1.26± 0.86, 5.13± 2.32 and 1.44 mg/mg. creatinine on the first day of life, on the 5th day of age, at 2～4 months of age and adolescents, respectively. In the excretion of urine phosphorus, infusion of PTE caused no change on the first day of life and 3-fold increase in response to PTE on the 5th day of age. These results suggest that development in the reception of cyclic AMP signal may be the same as that of hormone receptor.

Renal Responsiveness to PTE in Transient Congenital Pseudohypoparathyroidism Type II.

Laboratory data obtained on admission are shown in Table 1. There was no other abnormality except for the slight elevated values of transaminases and hypocalcemia with hyperphosphatemia in case I. Results of case II were in normal range except for slight hypoproteinemia and severe hypocalcemia. Normal blood concentration of 25 hydroxyvitamin D_3 and normal radiographs of bones in these patients confirmed the absence of a rickets-like disorder. Contents of parathyroid hormone in these patients were under 500 pg/ml. as well as those of 3 controls. In our studies, the small amount of unlabelled hormone which gives a significant decrease of B/F ratio (B/F: antibody bound (B) and free (F) hormone), was 500 pg/ml.

Table 1 Laboratory data on admission.

	Case I	Case II
Total Protein (mg/dl)	6.3	5.4
B.U.N. (mg/dl)	10.0	9.1
G.O.T. (K.U.)	42	22
G.P.T. (K.U.)	42	7
Al-phosphatase (mMU)	4.4	5.5
Ca. (mg/dl)	5.4	1.4
P. (mg/dl)	8.1	7.7
Mg. (mEq/1)	1.7	1.8
$25(OH)D_3$ (ng/ml)	35.3	24.5
Parathyroid hormone (pg/ml)	500 ↓	500 ↓
Urinalysis		
Protein	(-)	(-)
Specific aminoaciduria	(-)	(-)

Results of renal responsiveness to PTE are shown in Table 2. These patients did not show so much increased basal excretion of cyclic AMP before PTE administration and their responsiveness to PTE was recognized in the same manner as compared with that of controls in cyclic AMP excretion. On the other hand, these patients did not show decreased basal excretion of phosphorus before PTE administration but their responsiveness to PTE was not found in

Table 2 Renal responsiveness to parathyroid extract.

	Case I (40th day)		Case II (27th day)	
	before	after	before	after
Urinary cyclic AMP (nmole/mg.cr.)	6.0	38.4	3.0	39.2
Urinary phosphorus (mg/mg.cr.)	2.5	2.6	1.0	1.2
Serum Ca (mg/dl)	6.6	6.7	4.0	4.0
P (mg/dl)	8.1	8.0	9.4	9.2

phosphorus excretion, in spite of considerable amount of phosphorus intake. Serum concentration of calcium and phosphorus in patients did not change, before and after PTE administration. These results suggest that development of renal responsiveness is found in parathyroid hormone receptor, but results of phosphorus excretion show defect or delayed development in the reception of the cyclic AMP signal.

The Effect of Milk to Transient Congenital Pseudohypoparathyroidism Type II.

The composition of milk formula used for treatment is listed in Table 3. Formula B is dealt commercially in Japan. The

Table 3 Composition of milk formula used for treatment.

(/100 ml)

	S-26 (Wyeth)	Formula A	Formula B
Fat (g)	3.5	3.3	3.3
Carbohydrate (g)	7.1	9.1	9.1
Protein (g)	1.5	2.0	2.0
Lacto-albumin	0.9	2.0	1.1
Casein	0.6	/	0.9
Calcium (mg)	41.6	53	53
Phosphorus (mg)	32.8	27	45
Ca/P	1.3	2.0	1.2

composition of formula A and B is summarized as follows. Butter fat contained in both formulae is replaced by olive oil and its

concentration is 3.3 percent. The concentration of protein is 2 percent in both formulae and lacto-albumin/casein ratio is about 1.2 in formula B. On the other hand, formula A contains lacto-albumin only as a milk protein. The contents of calcium and phosphorus in 100 ml. of formula B are 53 mg. and 45 mg., respectively. Its calcium/phosphorus ratio is 1.2. Contents of those in formula A are 53 mg. and 27 mg., respectively and its ratio is 2.0, the same as that of breast milk. Formula A was prepared specially in order to reduce the content of phosphorus. As shown in Figs. 2 and 3, therapy with intravenous administration of calcium gluconate, 2g. of oral calcium lactate, 0.375 mg. of oral dihydrotachysterol and intramuscular administration of PTE was performed in case I. Although improvement of seizures was found, serum concentration of calcium and phosphorus did not change throughout the treatments. After the 64th day of age, formula B which the patient had been feeding was changed to S-26 (Wyeth), with the same treatment except PTE administration. Then, serum concentration of calcium elevated gradually. This result may be based on that restriction of phosphorus absorption from intestine elevates calcium absorption through increased product of 1.25 dihydroxyvitamin D_3.[14] Thereafter, formula A which contains less phosphorus than S-26 was used with 2 g of oral calcium lactate,

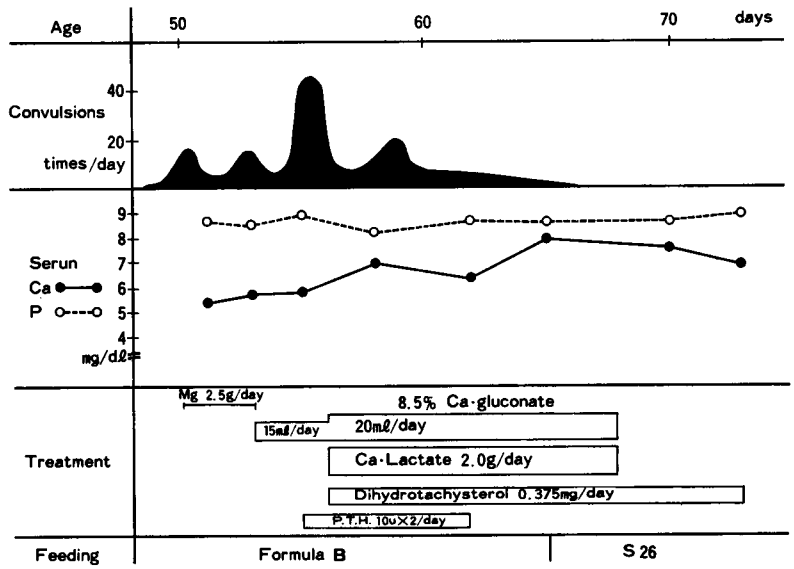

Fig. 2 The clinical course of case I.

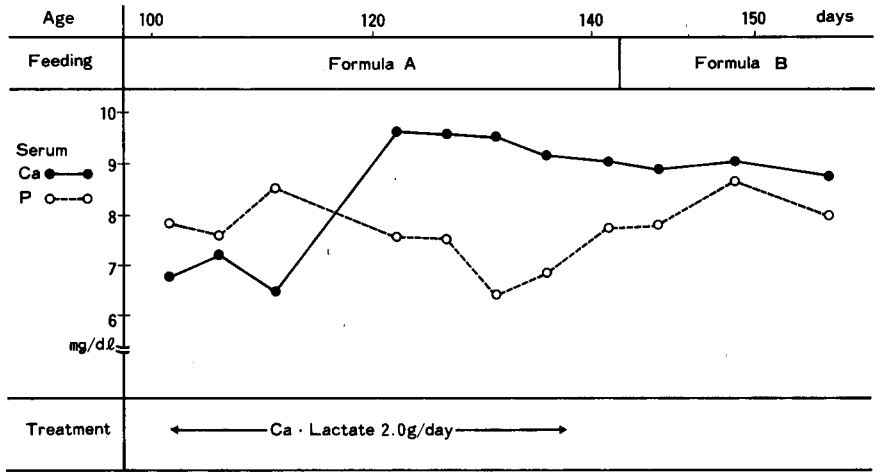

Fig. 3 The clinical course of case I.

until the 140th day of age, as shown in Fig. 3. After changing to formula A, serum concentration of calcium elevated from 6.8 mg./dl. to 9.6 mg./dl. and that of phosphorus decreased from 8.0 mg./dl. to 6.1 mg./dl. within 30 days. Changing back to formula B gave rise to reduction of serum calcium level and elevation of serum phosphorus level again. Since 10 months of age, the patient's homeostasis of calcium and phosphorus has remained normal without any treatment up to the present.

As shown in Figs. 4 and 5, in case II the same therapy was performed. However, serum concentration of calcium and phosphorus did not change until changing from formula B to A. After changing to formula A, serum calcium level elevated and phosphorus level decreased rapidly. Although the changing from formula A to B gave rise to reduction of serum calcium level and elevation of serum phosphorus level, changing back to formula A from B restored normal serum concentration of calcium and phosphorus. Since 3 months of age, serum calcium and phosphorus level has remained normal without any treatment up to the present. Both patients' renal responsiveness to PTE was found in the same manner as compared with that of controls at 10 months of age.

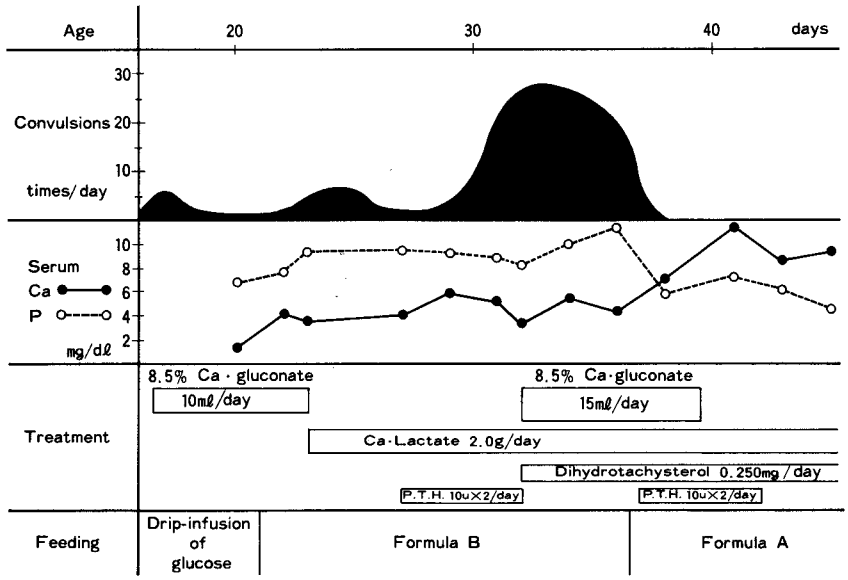

Fig. 4 The clinical course of case II.

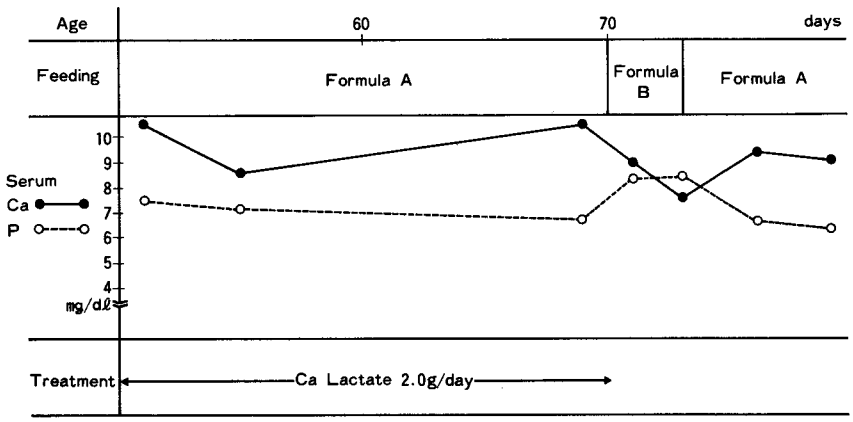

Fig. 5 The clinical course of case II.

DISCUSSION

Although radioimmunoassay for measuring parathyroid hormone has been established, it is difficult to assay small amount of

parathyroid hormone in neonate. However, Fairney[6] has reported that the concentration of parathyroid hormone in normal infants rose from 97 pg./ml. in cord blood after birth to 217 pg./ml. at 6 days of age in spite of the low concentration during several weeks in neonatal hypocalcemia and that prolonged immaturity of parathyroid function may contribute to the etiology of hypocalcemia. This report suggests that concerning the etiology of later neonatal hypocalcemia, transient disturbance of parathyroid function is also one of etiologies besides high phosphate intake due to artificial feeding.

Authors have reported the hypocalcemic infant with transient delayed development of renal response in receptor to parathyroid hormone.[11] The patient suffered from generalized convulsion on the 10th day of life, showing no other abnormality except for hypocalcemia (4.6 mg./dl.) with hyperphosphatemia (10 mg./dl.) and his renal responsiveness to PTE was not found in urine cyclic AMP and phosphorus excretion on the 20th day of life. Then, by the treatment with intramuscular administration of PTE for 10 days, convulsion and serum concentration of calcium and phosphorus were improved. After PTE administration was discontinued, his serum concentration of calcium and phosphorus remained normal. Two months later, renal responsiveness to PTE was examined again and was found the same as that of controls in excretion of cyclic AMP and phosphorus. This result suggests that transient delayed development of renal response in receptor to parathyroid hormone is one of the etiologies. The increasing GFR of neonate could in part explain the increasing cyclic AMP but would not explain the low basal level of urinary cyclic AMP in adolescent and high basal level at the 5th day of life.[12]

Renal responsiveness to PTE of the patients described here, resembles that of pseudohypoparathyroidism Type II[5] but their transient disturbance in reception of cyclic AMP signal is distinct from pseudohypoparathyroidism Type II. We would like to suggest the interpretation of transient congenital pseudohypoparathyroidism Type II due to delayed development in reception of cyclic AMP signal. In these patients, the therapeutic effect to repeated intramuscular injection of PTE for 10 days was not found as well as considerable amount of dihydrotachysterol medication was not effective. After exchanging milk for formula A, serum concentra-

tion of calcium elevated and that of phosphorus decreased in these patients. These results suggest that reduction of phosphorus intake from intestine is effective to congenital transient pseudo-hypoparathyroidism Type II.

REFERENCES

1. Belsey, R.E., Deluca, H.F., and Potts, J.T.Jr. J. Clin. Endocrinol. Metab. 1974. 38. 1046/1051. A rapid assay for 25-OH-Vitamin D_3 without preparative chromatography.
2. Bessey, O.A., Lowry, O.H., and Brosk, M.J. J. Biol. Chem. 1946. 194. 321/329. A method for rapid determination of alkaline phosphatase with five cubic millimeters of serum.
3. Bosnes, R.W., and Tausky, H.H. J. Biol. Chem. 1945. 158. 581/591. On the calorimetric determination of creatinine by Jaffe reaction.
4. Connerty, H.V., and Briggs, A.R. Am. J. Clin. Path. 1966. 45. 290/296. Determination of serum calcium by means of orthocresolphtalein complexion.
5. Drezner, M., Nelson, F.A., and Lebovitz, H.E. N. Engl. J. Med. 1973. 289. 1056/1060. Pseudohypoparathyroidism Type II: A possible defect in the reception of the cyclic AMP signal.
6. Fairney, A., Jackson, D., and Clayton, B.E. Arch. Dis. Childh. 1973. 48. 419/424. Measurement of serum parathyroid hormone, with particular reference to some infants with hypocalcemia.
7. Fanconi, A., and Prader, A. Helv. Paediat. Acta. 1967. 4. 342/359. Transient congenital idiopathic hypoprathyroidism.
8. Gardner, L.I., Mac Lachlan, E.A., Pick, W., Terry, M.L., and Butlen, A.A. Pediatrics. 1950. 5. 228/239. Etiologic factors in tetany of newly born infants.
9. Gardner, L.I. Pediatrics. 1952. 9. 534/543. Tetany and parathyroid hyperplasia in the newborn infants: Influence of dietary phosphate load.
10. Gilman, A.G. Pro. Natl. Acad. Sci. 1970. 67. 305/312. A protein binding assay for adenosine 3'5'-cyclic monophosphate.
11. Kodama, S., Sakurai, T., Seki, A., Morishita, Y., and Matsuo, T. Kobe J. Med. Sci. 1975. 21. 69/76. Etiological analysis

of neonatal hypocalcemia: Relationship with reactivity to parathyroid hormone.

12. Linareli, L.G., Bobik, J., Bobik, C. Pediatrics. 1972. 50. 14/23. Newborn urinary cyclic AMP and developmental renal responsiveness to parathyroid hormone.
13. Schopman, W., and Hackeng, W.H.L. Acta. Endocr. 1970. 63. 643/654. A radioimmunoassay for parathyroid hormone in man: I. Development of a radioimmunoassay for bovine PTH.
14. Tanaka, Y., and Deluca, H.F. Arch. Biochem. Biophys. 1973. 154. 566/574. The control of 25-hydroxyvitamin D metabolism by inorganic phosphorous.
15. Tausky, H.H., and Subbarow, Y. J. Biol. Chem. 1925. 66. 375/400. A microcalorimetric method for the determination of inorganic phosphorous.
16. Thomas, E. Oppé, and David, R. Lancet. 1968. May 18. 1045/1048. Calcium and phosphorous levels in healthy newborn infants given various type of milk.
17. Tovey, K.C., Oldham, K.G., and Whelan, J.A.M. Clin. Chim. Acta. 1974. 56. 221/234. A simple direct assay for cyclic AMP in plasma and other biological samples using an improved competitive protein binding technique.