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- Requests for reprints should be addressed to: G. Schilirò, M.D., Department of Pediatrics, V. le A. Doria, 95100 Catania (Italy).
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Acini lobular ducts
calcium pancreas morphology islets
cystic fibrosis

The Pancreas in Cystic Fibrosis: Chemical Composition and Comparative Morphology

L. E. KOPITO AND H. SHWACHMAN⁽²³⁾

Department of Clinical Nutrition, The Ina Sue Perlmutter Cystic Fibrosis Center, The Children's Hospital Medical Center, and the Department of Pediatrics, Harvard Medical School, Boston, Massachusetts, USA

G. F. VAWTER AND J. EDLOW

Department of Pathology, The Children's Hospital Medical Center and Harvard Medical School, Boston, Massachusetts, USA

Extract

Sections of pancreas from 16 individuals who died with cystic fibrosis (CF) were classified by morphometric criteria into four categories in increasing order of pancreatic involvement. The concentration of acini, islets, main ducts, lobular ducts, connective tissue, and fat was compared with control levels. The results show that in the least involved pancreases, from neonates who died under 5 months of age, acini were reduced to 33% of control levels and the following were increased: islets, to 410%; lobular ducts, to 250%; and main ducts, to 1700% of controls.

With increasing severity of the pancreatic disease the acini were

further reduced to 5% and lobular ducts to 37% of control levels, respectively. Main ducts increased by 19-fold, and fatty infiltration accounted for more than 25% of the fresh weight of the pancreas in 9 of the 16 specimens.

Comparative biochemical studies of 35 fibrocystic pancreases were quantitatively related to the severity of the pancreatic involvement as follows. Water and volatile matter, normally accounting for 80±% of the weight of the fresh pancreas, was reduced to less than 30% in the most affected organs. The concentration of zinc diminished from near normal mean levels of 193 µg Zn/g dry pancreas to 10% of this amount in the severely involved pancreases.

Elevated concentrations of calcium, amounting to over 10 times control level, were found in obstructed ductal structures. Calcium was depleted from pancreatic sections adjacent to the obstructions. The following biochemical indicators were significantly different in their mean levels in the 35 fibrocystic pancreases when compared with the 17 controls: ($P \leq 0.001$) fat, water, zinc, calcium, copper, magnesium, potassium, and sodium ($P \leq 0.01$).

Speculation

Morphometric and biochemical studies of the pancreas in cystic fibrosis are interpreted to favor an early and perhaps primary role of ductal and ductular abnormality in the pathogenesis of the pancreatic lesion. The principal basis for this suggestion lies in the demonstration of early massive enlargement of the ductular system and the consequent accumulation of viscous calcium-rich inspissated material responsible for the formation of functional ductal obstructions. Alterations in calcium concentration and binding in the pancreas and in pancreatic juice are believed to be responsible for changes in membrane permeability and the transport of water and electrolytes. The pancreatic disease process begins *in utero* and the degeneration of the pancreas progresses through life in nearly all patients with cystic fibrosis.

Cystic fibrosis accounts for nearly all young patients with pancreatic insufficiency (17). There is no known single defect to relate the various organ involvements in CF; each system presents with different degrees of affliction and with no correlation with the general severity of the disease. The onset of symptoms may vary considerably. In about 15% of our patients with CF the disease is evident at birth as a consequence of meconium ileus (7). In some patients (15–20%) no pancreatic enzyme deficiency may be detected even as late as 10 years of age (18). In these patients the pancreatic lesion may be minimal; however, progression to the end stage of fatty replacement and extensive fibrosis occurs in most patients (1).

Alterations in calcium concentration and activity have been previously associated with biochemical and biophysical changes in various exocrine secretions from patients with CF (3, 5, 6, 14, 16).

Forstner *et al.* (8), in a recent study of intestinal goblet cell mucus from patients with CF, demonstrated that calcium interacted with mucus anions resulting in significant dehydration and insolubility; conditions which might account for the formation of mucous "plugs."

The present study of the pancreas from patients who died with CF was undertaken to assess the degree of damage to this organ on the basis of morphometric and histometric observations. These were correlated with alterations in water content of the pancreas, the amount of extractable fat, and electrolyte concentrations.

SPECIMENS AND METHODS

Random sections, usually from the tail of the pancreas, weighing about 1 g, were obtained postmortem from 35 individuals who died with CF and from 17 control subjects. Of the CF group, 16 were females and 19 were males. The ages at death ranged from 15 days to 23 years; 5 were under 5 months of age. Four infants had meconium ileus. The cause of death was listed as follows: severe pulmonary infection, 12; respiratory insufficiency, 6; cardiac arrest, 5; cor pulmonale, 5; meconium ileus, 3; pneumothorax, 3; hemorrhage, 1.

Control specimens were from 5 females and 12 males aged 3 days to 13 years. Four specimens were from infants under 5 months of age. The patients in this group had the following diagnoses: leukemia, 4; tumors, 4; agammaglobulinemia, 2; auto accident, 1; asphyxia, 1; tetralogy of Fallot, 1; Wilson's disease, 1; thalassemia major, 1; congenital heart disease, 1; meningitis, 1.

A preliminary study of intrapancreatic chemical variability was undertaken to evaluate how closely a random section of pancreas

may reflect the electrolyte composition of the whole pancreas. Two whole organs were dissected longitudinally and then cut into 20 separate sections each weighing between 0.6 and 1.2 g. One pancreas was from a male patient with CF who died at 15½ years of age. This pancreas weighed 23.4 g, or less than half of the expected weight. A second pancreas from a male child who died with a congenital heart defect at age 2½ and weighed 13.2 g, within the expected weight range. This pancreas revealed no histologic or morphologic abnormalities.

The specimens were obtained within 2–8 hr after death, and were immediately frozen. Before analyses, the original, or "wet" weight of the tissue was determined. The "dry" weight was obtained after overnight desiccation and served as the basis for the quantitative determination of electrolytes by atomic absorption spectroscopy (12).

MORPHOMETRIC AND HISTOMETRIC STUDIES

Percentages of various pancreatic tissue components, including fat, connective tissue, islets, acini, acinar ducts, and main ducts, were estimated in formalin-fixed, paraffin-embedded sections stained with hematoxylin and eosin prepared from 1–3 blocks of pancreas. The microscopic images were projected at 100 times magnification through an ocular lens containing an inscribed line to graph paper. The various types of tissue crossing or touching the line were counted. Ten such observations were made on each section, starting and subsequently moving the field at random. Total values for each component were then calculated as concentration (percentage). The percentages obtained from multiple blocks were averaged.

RESULTS

Weights of the organs and age at death are summarized in Table 1. Of the 16 pancreases, 11 were within the expected weight range and 2 each, in *groups II* and *III*, were below expected weight.

Without knowledge of the chemical composition, the pancreatic

Table 1. *Weight of pancreas and age at death of 16 patients with cystic fibrosis*¹

Sex	Age, yr	Pancreas wt, g	Comments
<i>Group I</i>			
M	½	4	Meconium ileus
M	¾	4	Meconium ileus
F	½	6	
<i>Group II</i>			
M	¾	4	Meconium ileus
F	3½	15	Meconium ileus
F	5	39	Diabetes, cirrhosis
M	20	19	Pancreatic atrophy
<i>Group III</i>			
F	4	14	
F	8	30	
F	12	30	Extensive calcification, diabetes, and cirrhosis
M	14½	58	Cirrhosis
M	15½	34	
<i>Group IV</i>			
F	7½	25	
F	13	40	
F	15	62	
M	15½	45	Cirrhosis

¹ Expected pancreas mean weight (grams) at age: 1 month, 5.6; 2 months, 7.1; 5 months, 11.0; 1–2 years, 13.5; 2–4 years, 19.0; 4–6 years, 22.0; 6–12 years, 29.0; 12–14 years, 35.0; 14–16 years, 68.0; Adult, 85–120.

sections from the above 16 specimens were grouped into four categories, in increasing order of pancreatic involvement on the basis of the morphometric data shown in Table 2. The values (mean and range) for each group are expressed as percentage of controls, taken as 100%. Control levels for fatty infiltration are less than 1%. Representative photomicrographs of one pancreatic section from each group are shown in Figures 1-4.

The results indicate that even in specimens from *group I* (taken from neonates who died under 5 months of age) considerable differences are seen in the concentration of acini, lobular and main ducts, and islets. *Group II* includes a young patient who had meconium ileus and a 20-year-old male who had not been diagnosed until 4 years before death. The concentrations of acini are markedly reduced, whereas main ducts increase to 18 times of control levels. There is minimal fatty infiltration (photomicrograph, Fig. 2)

Group III specimens are characterized by very large main ducts and more extensive fatty infiltration. The concentration of acini and lobular ducts are reduced to 6% and 75% of control levels, respectively (photomicrograph, Fig. 3)

All specimens from *group IV* show markedly decreased parenchymal and lobular duct elements. The fat concentration averaged 68% (53-92%) (photomicrograph, Fig. 4)

INTRAPANCREATIC CHEMICAL VARIABILITY

The "mapping" of two whole pancreases each dissected into 20 individual sections shows a considerable range of concentration for each component (Table 3). The concentration of calcium, which ranged from 42 to 5,550 $\mu\text{g/g}$ of dry tissue, was the most variable of all of the determinations in CF. In this pancreas four adjacent segments had concentrations of 144, 5,550, 4,930, and 139 $\mu\text{g Ca/g}$

Table 2. *Morphometric classification of pancreatic sections from 16 patients with cystic fibrosis*

Group	n	% Acini	% Islets	% Lobular ducts	% Main ducts	% Connective tissue	% Fat
I Mean	(3)	33	410	250	1,700	110	1
(range)		(28-40)	(300-550)	(170-320)	(800-2,000)	(100-130)	(0-1)
II Mean	(4)	16	380	175	1,800	135	1.2
(range)		(13-20)	(150-1,000)	(50-280)	(1,300-2,600)	(110-160)	(0-4)
III Mean	(5)	6	210	75	1,900	105	26
(range)		(5-13)	(100-450)	(25-125)	(450-3,600)	(66-125)	(21-31)
IV Mean	(4)	6	190	37	450	48	68
(range)		(4-8)	(100-200)	(25-50)	(300-1,000)	(31-60)	(53-92)

¹ Group mean values are expressed as percentage of control. Control equals 100 of all observations except percentage of fat, where control value is less than 1%.

Fig. 1. *Group I*. Figures 1-4 are representative microscopic fields of cystic fibrosis pancreas. All photomicrographs are hematoxylin and eosin stained at magnification $\times 40$. There is a diffuse, fine interstitial fibrosis with mild intraductal secretion and intralobular ductular hyperplasia.

Fig. 2. *Group II*. Shows ductal secretory inspissation and acinar atrophy. Fibrosis is increased. See legend to Figure 1 for further details.

Fig. 3. *Group III*. Further reduction in exocrine parenchyma is seen with increasing perilobular adipose tissue. Acinar atrophy and fibrosis are increased. See legend to Figure 1 for further details.

Fig. 4. *Group IV*. Only intralobular ductules remain, while acinar tissue is lacking. Adipose tissue further subdivides the residual glandular structure. Islets appear highly concentrated and some are very large. See legend to Figure 1 for further details.

Table 3. *Intrapancreatic variability of electrolytes, fat, and volatile matter in two whole pancreases (based on 20 individual sections from each pancreas)*

	Dry weight as % of wet weight	Fat as % of wet weight	Concentration, $\mu\text{g/g}$ dry pancreas				Concentration, mEq/kg dry pancreas	
			Zn	Cu	Ca	Mg	Na	K
Patient with cystic fibrosis								
Arithmetic mean	45	31	42	3.0	639	108	111	33
Median	44	33	39	3.1	128	110	108	35
Range	(30-69)	(18-45)	(22-70)	(1.7-7.0)	(42-5,550)	(34-229)	(43-166)	(5-50)
SD	10	8.9 (12 obs.)	13	1.4	1578	44	35	13
Patient with congenital heart defect								
Arithmetic mean	24	5.1	150	10	250	505	345	141
Median	21	2.6	150	8.0	245	543	368	142
Range	(19-36)	(1-15)	(93-219)	(3-28)	(158-300)	(279-730)	(169-553)	(91-182)
SD	4.7	5.2 (9 obs.)	39	7.5	48	135	116	31

pancreas. The high concentrations of Ca were located in a ductal structure which was obstructed.

Selective sampling from the "tail" of the pancreas revealed much less chemical variability. For this reason only "tail-end" sections were used whenever possible.

A summary of all observations comparing mostly pancreatic tail sections of 35 patients with CF with those of 17 controls is presented in Table 4. Mean extractable fat was about 7 times higher in specimens from the CF group. The lowest fat level in a patient with CF was 2%. This patient, who was followed by us since infancy, had normal pancreatic function through life and

highly variable "sweat tests." He died at age 12 from severe pulmonary involvement. A moderate to severe water loss was observed in nearly all of the CF specimens with exception of the neonatal pancreases. The concentration of Zn and Cu were significantly lower in the CF specimens, averaging less than one-half of control values.

CF neonatal pancreases were studied separately in comparison with a group of four age-matched controls. The results, summarized in Table 5, show remarkable similarity between the two groups in the mean concentration of Cu, Mg, Na, K, and Ca. Although the absolute Zn level in these CF neonatal specimens was

not statistically significantly decreased, the ratio of Zn to ductules was less than one-fifth of controls and the ratio of Zn to ducts was about 3% of controls. None of the infant pancreases contained appreciable fat and only one CF specimen was dehydrated (55% dry weight).

Alterations in electrolyte concentrations in the specimens classified by morphometric data (Table 6) show a striking correlation with the degree of pancreatic involvement. Severe dehydration occurred in all except one specimen of groups II, III, and IV.

With the exception of Ca and Mg, a significant diminution was observed in the concentration of all electrolytes. Zinc diminished from a mean of 193 $\mu\text{g/g}$ dry pancreas in group I specimens to 106, 42, and 20 $\mu\text{g/g}$ in specimens from groups II, III, and IV, respectively.

In order to correct for the progressively larger fatty infiltration of the pancreas with the increasing severity of the pancreatic damage, fat was extracted with ethyl-ether and electrolytes were determined in the fat-free tissue. On this basis, specimens from patients of groups III and IV showed an increase in Zn levels to 62 and 57 $\mu\text{g/g}$ from previous values of 42 and 20 $\mu\text{g/g}$, respectively. However, even the corrected values were considerably below the control levels. Changes of similar magnitude were observed in other electrolytes. Calcium, the most variable of the pancreatic electrolytes, was greatly influenced by the presence or absence of

inspissated mucus in the section analyzed; the unusually elevated Ca concentrations were associated with cystically dilated ducts, whereas lower values were found in sites adjacent to the cysts. These extremes in the distribution of Ca were most evident in group II and III specimens (Table 6). The specimens with the highest calcium deposits were also recognized by histologic methods. In some patients the deposition of calcium in the pancreas could be detected by radiography. It is noteworthy that in three of four specimens of group IV subjects, Ca levels were only 22, 42, and 59 $\mu\text{g/g}$. In these sections there were few ducts and virtually no cysts.

Magnesium concentrations in the pancreatic sections varied in an erratic manner. Specimens of group IV patients had concentrations of Mg of 22, 32, 622, and 728 $\mu\text{g/g}$. Other group values were more homogeneous, particularly the specimens of group I and II.

Concentrations of sodium and potassium diminished markedly with increasing severity of the pancreatic disease, approaching levels of 10% or 15% of group I specimens and those of control values.

DISCUSSION

The unknown basic defect in cystic fibrosis causes widespread alterations in the mucus-secreting glands of the entire body (1).

Table 4. *Electrolytes, fat, and volatile matter in random sections of pancreas from 35 patients with cystic fibrosis (CF) and 17 control subjects*

	Fat as % of wet weight	Dry weight as % of wet weight	Concentration, $\mu\text{g/g}$ dry pancreas				Concentration, mEq/kg dry pancreas	
			Zn	Cu	Ca	Mg	Na	K
35 patients with CF								
Mean	28	46	77	5.0	454	248	204	89
Range	(2–57)	(14–86)	(9–248)	(0.5–22)	(27–5,550)	(22–728)	(22–655)	(11–262)
SD	18 (10 obs.)	21	73	6.1	1005	222	188	82
17 controls								
Mean	4.1	26	193	13 ¹	286	596	336	202
Range	(0.1–21) ²	(17–35)	(99–496)	(4–33)	(124–580)	(330–790)	(186–714)	(104–272)
SD	7 (8 obs.)	6	94	12	117	162	158	51
<i>P</i>	<0.001	<0.001	<0.001	<0.001	<0.001	<0.01	<0.001	<0.001

¹ Patient who died with Wilson's disease is not included (the concentration of Cu in this pancreas was 49 $\mu\text{g/g}$).

² Patient who died with agammaglobulinemia had a fatty pancreas (20.2% extractable fat).

Table 5. *Electrolytes and volatile matter in section of pancreas from five neonates with cystic fibrosis (CF) and four control subjects (age at death: under 5 months)*

	Dry weight as % of wet weight	Concentration, $\mu\text{g/g}$ dry pancreas				Concentration, mEq/kg dry pancreas	
		Zn	Cu	Ca	Mg	Na	K
5 patients with CF who died between ages of 2 and 30 weeks							
Mean	27	202	18	421	530	483	237
Range	(18–55)	(180–248)	(11–26)	(278–606)	(437–595)	(337–714)	(186–268)
SD	16	27	6	188	23	136	62
4 controls who died between ages of 3 days and 14 weeks							
Mean	29	307	15	440	639	557	228
Range	(22–35)	(157–496)	(7–25)	(382–580)	(538–755)	(342–800)	(212–261)
SD	6	142	7	94	188	237	69
P^1		0.143	0.206	0.548	0.143	0.193	0.032

¹ By Mann-Whitney "U-test."

Table 6. *Electrolytes and volatile matter in sections of pancreas from patients with cystic fibrosis grouped according to severity of pancreatic involvement by morphometric data*

Group	Dry weight as % of wet weight	Concentration, $\mu\text{g/g}$ dry pancreas				Concentration, mEq/kg dry pancreas	
		Zn	Cu	Ca	Mg	Na	K
<i>I</i> (<i>n</i> = 3)							
Mean	20	193	13.6	360	493	404	244
Range	(18–22)	(180–203)	(11–15)	(278–496)	(437–530)	(342–436)	(214–261)
SD	2	12	2.3	119	49	54	26
<i>II</i> (<i>n</i> = 4)							
Mean	48	106	8.5	506	438	371	156
Range	(22–79)	(37–184)	(2.3–22)	(98–1,300)	(340–595)	(138–755)	(96–226)
SD	25	61	9.1	546	110	218	54
<i>III</i> (<i>n</i> = 5)							
Mean	51	42	2.4	955	126	133	52
Range	(35–75)	(25–61)	(0.6–4.8)	(34–3,270)	(42–192)	(45–211)	(18–87)
SD	21	15	1.7	1548	69	72	32
<i>IV</i> (<i>n</i> = 4)							
Mean	69	20	1.8	139	351	57	18
Range	(59–83)	(9–29)	(0.9–2.7)	(27–447)	(22–728)	(22–104)	(11–26)
SD	11	8	0.8	205	596	35	8

The striking secondary changes in the pancreas are but one of the manifestations possible resulting from obstruction by inspissated secretions in the pancreatic acini and ducts.

The morphometric data in *group I* and, especially, *group II* appear to confirm the diagnostic concept of fibrosis. The rich connective tissue content of the infant pancreas normally becomes quite inconspicuous by late childhood. Fibrosis is then evident in *group III* in contrast to *group IV*, where relatively inconspicuous total concentrations of connective tissue are evident. At different stages of the pancreatic involvement there is active fibroplasia, dense heavy scar, or, finally, less conspicuous fibrosis. This suggests a considerable early, rapid, and later, slow erosion of connective tissue through the disease. The end-stage of pancreatic destruction is characterized by dehydration, liposclerosis, and calcification of intraductal concretions, similar to the sequence of events previously described by Blanc (2).

Of the electrolytes determined in this study, zinc and calcium are the most interesting from a functional point of view. Ionized calcium is one of the activators of trypsinogen, chymotrypsinogen, and lipase (4). In about 80% of patients with CF these enzymes show little or no activity (17).

Hematoxylinophilia is a well known morphologic indicator of mineral and calcium phosphates as in bone. Hematoxylinophilic ductal content was seen only in the two pancreases with the highest calcium concentration. Lack of this reaction in other segments of pancreas rich in calcium may indicate the presence of other than highly acidic phosphate bonding. For example, calcium oxalates are not hematoxylinophilic; it is more likely that this calcium is absorbed on to (neutral) protein or glycoproteins. Moreover, correlation with the morphometric data strongly indicates that calcium in pancreatic juice may be largely of duct epithelial origin, just as bicarbonates are thought to be. The excessive binding of calcium by intraductal secretions may be responsible for the formation of calcium soaps and ultimately, viscous insoluble obstructions. The depletion of Ca and Ca^{++} from tissues surrounding the inspissated material may alter membrane potentials and cause widespread changes in the physiochemical properties of the cell membrane. Rasmussen (15) suggested that the transport of water Na^+ and K^+ is governed by the degree and rate of dissociation of Ca to Ca^{++} . The significant changes in Ca^{++} binding observed in this study could, therefore, initiate the dehydration of the pancreas and induce the consequent parenchymal atrophy, fibrosis, and finally, fatty replacement.

Zinc is a constituent of a number of metalloenzymes including

carbonic anhydrase (0.3% Zn) and pancreatic carboxypeptidase A (1 gram-atom Zn/molecule) (19, 20).

Carboxypeptidase catalyzes the hydrolysis of carboxyterminal peptide bonds in proteins and peptides and also hydrolyzes esters. Carbonic anhydrase reversibly catalyzes the hydrolysis of carbon dioxide to form carbonic acid and bicarbonate (11). Although only a relatively small amount of Zn is required to activate these enzymes, a severe Zn deficiency (10) or a ductal obstruction may cause partial deactivation or immobilization of the available ionized Zn. Impaired activation of these two essential pancreatic enzymes could result in dehydration, reduced bicarbonate production, changes in pH, and reduced cleavage of proteins, conditions which have been observed in most pancreatic secretions from patients with CF. In particular, a consistent observation has been significantly reduced bicarbonate concentrations in this disease regardless of the state of nutrition of the patient or the presence of some of the proteolytic enzymes (9).

At birth and for several months later neonatal pancreases usually contain an excess of Zn, averaging about 50% higher (per unit dry weight) than observed later in life. Increased Zn stores are also found in the neonatal CF specimens; however, the depletion of pancreatic Zn in the CF specimens appears to be rapid and severe. It is possible that Zn depletion in CF begins *in utero*, although the present data fail to confirm this with statistical certainty. This suggestion is supported by a previous study of Zn in meconium (13). Specimens of meconium collected within 10 hr of birth from 65 apparently healthy neonates contained a mean concentration of 230 μg Zn/g dry meconium. Meconium from 8 infants with CF contained a mean Zn concentration of 157 $\mu\text{g/g}$. In four patients with meconium ileus the analysis was done on material removed surgically from the obstructed gut. This meconium contained, on the average, only 138 μg Zn/g, or about 60% of "normal" values.

SUMMARY

Morphometric, histometric, and biochemical data are presented for 35 pancreases obtained from subjects who died with cystic fibrosis and 17 control subjects. The biochemical changes are quantitatively related to the severity of pancreatic involvement. At different stages of the disease there is active fibroplasia, liposclerosis, calcification, and considerable dehydration. Ductal structures are obstructed with viscous, calcium-rich inspissated material, whereas sections adjacent to obstructions are depleted of calcium. The degeneration of the pancreas appears to progress through life.

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- The present address of Dr. L. E. Kopito is: Department of Nutrition, Massachusetts Institute of Technology, Cambridge, Mass.
- The present address of Dr. J. Edlow is: Department of Pathology, Mt. Sinai Hospital, New York, N. Y.
- Requests for reprints should be addressed to: H. Shwachman, The Children's Hospital, Medical Center, Boston, Mass. 02115 (USA).
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Calcitonin parathyroid hormone
calcium phosphorus, inorganic
magnesium plasma
newborn

Calcium Metabolism in Newborn Animals: The Interrelationship of Calcium, Magnesium, and Inorganic Phosphorus in Newborn Rats, Foals, Lambs, and Calves

JEAN-MICHEL GAREL⁽⁴⁸⁾ AND JEAN-PIERRE BARLET

Laboratoire de Physiologie du Developpement, Université Pierre et Marie Curie, Paris, and Physiopathologie de la Nutrition, I.N.R.A. Theix, Beaumont, France

Extract

The plasma concentrations of calcium, inorganic phosphorus, and magnesium were studied during the early postnatal period in a rodent (rats), in ruminants (lambs and calves), and in foals. Decreases in plasma calcium after birth were observed only in newborn rats and foals. In rats the postnatal fall in plasma calcium level was already evident 1 hr after cesarean section (9.20 mg/100 ml) as opposed to 11.90 mg/100 ml *in utero*) and reached a nadir within 6 hr (-4.05 mg/100 ml). Newborn foals showed a small decrease in plasma calcium (-0.73 mg/100 ml) 48 hr after birth. In the four species, plasma inorganic phosphorus increased in the days after birth; plasma magnesium levels were only slightly affected over the first week of life. In ruminants and in foals, the high plasma calcitonin levels were not always related to plasma calcium, nor with plasma inorganic phosphorus over the first week of life. Newborn calves showed at birth detectable levels of plasma parathyroid hormone, similar to those found in their mothers, with individual values ranging from 0.80-3.50 ng/ml. These re-

sults are discussed in light of the well known early neonatal hypocalcemia occurring in normal human newborns.

Speculation

The parathyroid status at birth is species dependent. In some species, it has been suggested that *in utero*, high plasma calcium levels inhibit the parathyroid function before birth, but other unknown factors may be involved in this suppression. The maturity of the renal cortex adenyl cyclase activity in the early postnatal period is also species dependent and the degree of renal immaturity is not sufficient to explain the postnatal increase in plasma inorganic phosphorus.

Hypocalcemia is well known to occur in human neonates but is strangely unreported in animals. It has been postulated that hyperphosphatemia *per se*, transient hypoparathyroidism, and/or end-organ unresponsiveness might explain the early postnatal de-