NEONATAL KIDNEY AND FLUID-ELECTROLYTES

DEVELOPMENTS IN NEPHROLOGY

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Neonatal Kidney and Fluid-Electrolytes

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edited by

JOSÉ STRAUSS, MD
Division of Pediatric Nephrology
University of Miami
School of Medicine
Miami, Florida, USA

with the assistance of

LOUISE STRAUSS, MS, MA

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DEDICATION

To the family

and

To what remains
of the three who became four
but now are no more...

"In this world of change naught which comes stays,
and naught which goes is lost." -Swetchine

FOREWORD

The purpose of this volume and Pediatric Nephrology Seminar IX from which it was created is to provide easy access to current concepts in the diagnosis and management of kidney diseases in the newborn. Complimentary to this purpose is the opportunity the Seminar structure gives me to invite those particularly interested in the subject chosen to come together, share experiences and ideas in an unhurried, unpressured atmosphere for four continuous days - an oasis for me and, I am told, also for the faculty and registrants.

This year's subject choice is an expression of my perennial interest in the kidney of the newborn. A step back to view the steps forward reveals unwittingly intertwined associations and actions which now fall into focus. When I was just beginning my pediatric nephrology training with Sol Kaplan at Downstate in Brooklyn, we discussed Bob Usher's pioneering thought that there was something wrong with the kidneys of babies with RDS. Without really knowing what needed to be done, I started looking at the kidneys of those babies. Subsequently, Dick Day who was Chairman of the Department of Pediatrics there, stopped me in the hall, and asked me to come into his office. Glowing in quiet introspection, he extolled the joy of working with one's hands, then hurried away to his laboratory. He had been the Director of the Newborn Nursery at Babies Hospital before coming to Downstate, and (as I later found out) was trying to do something with oxygen electrodes.

Not long after that, I came into contact with Stanley James who also was interested in looking at the kidneys of the newborn. Then when I became a fellow at Babies, I met William Silverman who had worked with Dick Day in the Newborn Nursery and became Director of the Nursery after Dick left. This was 1959 and Bill already was distinguished in neonatology. By chance I was sharing a lunchtime table with him in the P&S cafeteria; he introduced himself to me. I was speechless, in awe of the giant, but he said, "Call me Bill." We discussed what turned out to be common interests, and as he left the table, he made the nursery available to me for whatever studies I wanted to undertake. He became my friend and advisor. With him I started studying high protein feeding of prematures and ADH, with the help of Rose Ames. In the nursery I worked with Mrs. Parks, a Wagnerian addict who ran the nursery as though it was a favored West Point regiment. All of us respected her unwavering discipline of all.

Gradually I also became involved with Stan James, and helped set up his laboratory to measure inulin, PAH and osmolality. In the process I worked with Connie, his main assistant, Lotte Gran, Dr. Astrup's chief technician (who had brought the first Astrup machine to the US to be tested in Stan's laboratory), Karlis Adamsons, Eric Burnard and Amanda, my dedicated technologist. About that time, Sahla Daniel came (and without knowing it, began what to date has become twenty years of collaboration). We studied newborns in the delivery room in the first minutes after birth. Stan's initial interest was

perinatal asphyxia and RDS, but as we worked, we realized that so little was known about renal function in the first few hours after birth, we started studying that.

During this period, through Stan, I became acquainted with Millie Stahlman, Sidney Segal, Mary Ellen Avery, Bob Usher, Tim Oliver, and Virgin Apgar. (At one of Stan's parties over one of his unique concoctions, Virgin said to me, "You must study those babies' kidneys before birth." "Yes, one we will do that," I said. How could I not follow the suggestion of such a formidable figure?) I also frequently had exchanges with Gaby Nahas with wh I did experiments which indirectly tested the potential usefulness of THAM in neonates. Those were the final months of Rusty McIntosh's era at Babies but he still attended the lectures given by his staff and reviewed all publ cations being prepared. To my surprise, he called me to meet with him and g over an abstract I had written on the neonate, and offered constructive sug gestions which still are my guide.

Soon afterwards came my Visa expiration date and my return to Argentin Bernardo Houssay's comment that after five years in the States I could not live and work in Argentina was correct. In the interim before departing, Caldeyro-Barcia asked me to come over to Montevideo to show his group how to do the umbilical artery catheterization that Stan James had started. Besides meeting Caldeyro and exchanging ideas with him, I also met Carlos Mendez-Bauer who was in charge of the project to catheterize the babies. I saw their pioneering work of putting electrodes in babies in utero (and later found out that some of those electrodes attempted to measure tissue oxygenation).

After returning to the US, on my way to LA Childrens Hospital, I went Babies to complete details of past work with Stan. We discussed the project he was doing with piglets; he suggested that I look up George Misrahy who was in LA and developing an implantable oxygen electrode.

Once in LA, the arrangements made for my work as a nephrologist prove to be elusive. George and his associate, Tony Beran and then Lee Clark, became my main stimuli through experimental work with oxygen electrodes in the kidneys of rabbits plus studies of the electrical characteristics of amniotic membrane (with Gordon Silver) and fluids in the mother and fetuses of guinea pigs. There I also met Bill Oh, Ed Hon (whom I attempted to sway toward tissue oxygenation measurements only to make him more devoted to his fetal heart monitoring), Ted Quilligan, Paul Terasaki (with whom I did some work on neonates with congenital anomalies), Nick Assali, Jo Ann Hodgeman, Ben Kagan, Bill Tooley, June Brady, Professor McCance and Eileen Hasselmeye (both visiting in California), and many others working actively on the pro lems of the fetus and newborn.

Thus my associations reflected my shift from emphasis on clinical nephrology to the newborn. In the nursery , we started using THAM in human neonates, and with Tony and Rex Baker, developed the implantable electrode for the earlobe of neonates to measure PO_2. Bob Ward's wholehearted suppor and the extension of my collaboration with Bob Huxtable from fishing to tl nursery, made those years rewarding.

My organization of an oxygen conference held in Vancouver with the he of Sid Segal and Millie Stahlman, was the beginning of an exchange with Dietrich Lübbers and Manfred Kessler at the Max Planck Institute in Dort Germany. Through Dr. Lübbers (the designer and builder of the transcutaneo PO_2 electrode) I met the Huchs who later did such a thorough job of applyi it to the neonate in collaboration with Stan James, Gabriel Duc, and sever others. This expansion of my knowledge and perspective for oxygen study po bilities flowered in several directions. A highlight of this period was a

call from Dick Day, then at Mt. Sinai in New York City. He said he had been following my work with oxygen and wanted to come for a visit to learn about what we were doing - that he had been trying to work with oxygen electrodes in his laboratory at Downstate when I was there. The indomitable Dick Day!

In 1970 when William Cleveland, Sidney Blumenthal and Manny Papper invited me to join them in Miami, I came with the hope of eventually fulfilling my interest in the kidneys of the newborn. My first years in Miami were overwhelming in the sense that there was so much patient material, so many clinical problems and administrative details to be worked with in Pediatric Nephrology. Efforts to continue with experimental research gradually developed into a workable balance with clinical research. Included in this direction was reactivation of collaboration with Stan James and Sahla Daniel for completion of newborn studies and the beginning of new piglet studies to complete some of the hypoxia work started with Marc Rowe, now including Eduardo Bancalari, Director of Neonatology in Miami.

And so it is, that finally, we have a Seminar and volume dedicated entirely to the kidney and fluid-electrolytes of the newborn - a restatement of my involvement in and concern with questions, answers and comments about fetal and newborn stages of kidney health and sickness. The guest faculty contributors are Drs. Anita Aperia, Sahla Daniel, Jean-Pierre Guignard, Eddie Moore and William Oh. We have covered only problems related to the fetus and neonatal birth weight and maturity, and procedures to which neonates are subjected - just a beginning in an area of immense clinical importance: the kidney of the fetus and newborn.

José Strauss

CONTENTS

III FUNCTIONAL AND ORGANIC EVALUATION OF THE NEWBORN

IV NEONATAL PATHOLOGICAL SITUATIONS

ACKNOWLEDGEMENTS

The faculty and registrants of Pediatric Nephrology Seminar IX have created this volume. The uniqueness of it is the direct result of the inquisitiveness and interest generated because of this year's particular combination of people. The key element, as always, has been the exchange of ideas, the stimulation given and received in return. In practical terms, each author has been responsible for the camera-ready copy of his paper, and thus assumes complete responsibility for its content. This results in a less uniform text appearance but makes manageable my job as annual editor. Pearl Seidler and Estela Garcia must be thanked for their attention to book details. For financial support, these companies contributed this year:

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José Strauss

I

THE FETUS

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Intestinal Calcium Transport In Utero. Clinical Implications for the Newborn Infant

Eddie S. Moore, Craig B. Langman, Mahmoud Loghman-Adham and Margarita Ocampo

Michael Reese Hospital, University of Chicago Pritzker School of Medicine, Chicago, Illinois

Introduction

Calcium requirements for growth and for skeletal mineralization during fetal life and in early postnatal development are substantial. During fetal life, significant active transfer of calcium occurs from mother to fetus via the placenta.[1] At birth, the connection between mother, placenta, and infant is severed and the intestinal tract becomes the major organ of calcium acquisition for the infant. Early studies in newborn animals demonstrated increased rates of intestinal calcium absorption compared to adult animals.[2] However, recent studies of vitamin D deficient and vitamin D-replete rat pups showed that intestinal calcium transport during the first two weeks of life is not meditated by 1,25-dihydroxyvitamin D as is true for adult animals.[3] In these studies, a vitamin D-sensitive intestinal calcium transport system developed late in the suckling and in the early weanling period. In light of developmental changes taking place in the intestinal tract and the apparent lack of absolute dependence on vitamin D mediated intestinal calcium transport in the immediate postnatal period, we began studies on the ontogeny of intestinal calcium transport in utero. This paper reports the results of preliminary experiments carried out in fetal lambs.

Materials and Methods

Studies were performed on ewes and their fetuses at 90-150 days gestation. Normal gestation in sheep is 150 days; thus, these studies were performed in the last part of the second and during the third trimester of ovine pregnancy. Preparation of the ewe for cesarean section and fetal surgery was similar to that previously reported by our laboratory.[4]

Fetal intestinal Ca^{2+} absorption was studied in 4 nephrectomized fetuses with chronic hypocalcemia and in 8 sham nephrectomized normocalcemic controls. In previous studies, we reported that bilateral fetal nephrectomy (Nx) produces significant fetal hypocalcemia.[5] In both groups, a catheter was inserted into a femoral artery for blood sampling, actual or sham Nx performed, and the fetus returned to the uterus. The uterine and abdominal incisions were closed and the fetal catheter exteriorized via a subcutaneous tunnel in the flank of the ewe. The ewes were then allowed to recover. Fetal blood samples were drawn at surgery and on postoperative days, 1,3,5,8, and 10 and analyzed for pH, pCO_2, total Ca^{2+} and blood ionized Ca^{2+}.

On postoperative day 10, the fetuses were delivered and duplicate 1-2 cm segments of duodenum, jejunum, ileum, and ascending, transverse and descending colon were obtained to measure Ca^{2+} transport, adjacent 1-2

(CaBP) and Ca^{2+}ATPase (CaATPase) activity.

Active luminal to serosal Ca^{2+} transport was measured using a modifiation of the everted gut sac technique. Segments of intestine were everted and ligated at both ends. The everted sac was incubated for 30 min. in incubation media containing 50 mCi $^{45}Ca^{2+}$-labeled tracer with a final Ca^{2+} concentration of 1.0 mM. The sacs were removed from the incubation media and the mucosa digested from the serosa using 1.0 N HNO_3. An aliquot of the mucosa was counted for $^{45}Ca^{2+}$ activity and the remainder used to measure mucosal protein content. The results were expressed as μmCa^{2+} uptake/mg mucosal protein/30 minutes incubation.

CaBP was measured using chelex resin. The results were expressed as specific activity of CaBP/mg mucosal protein. CaATPase was assayed by measuring Pi release after reacting with a known quantity of ATPase. The results were expressed as μmPi/mg mucosal protein/5 minute incubation.

Significance between mean values was determined using Student's t-test and correlation coefficients were determined by the method of least squares.

Results

Table 1 shows serum total Ca^{2+} and blood ionized Ca^{2+} in controls and in Nx fetuses 10 days after surgery, the time of the transport study. Both serum total Ca^{2+} and blood ionized Ca^{2+} were significantly lower ($p<.001$; $p< .001$) than mean values in the control or sham Nx animals.

Table 2 shows the rate of $^{45}Ca^{2+}$ uptake and content of CaBP and CaATPase in fetal intestinal segments. $^{45}Ca^{2+}$ uptake, μmCa/mg mucosal protein/30 minutes incubation, was greatest in the transverse colon (65.4 ± 17.5), ascending colon (34.3 ± 6.4) and ileum (28.5 ± 5.2) respectively in the control animals. Although these values clearly are greater than that for the duodeum and descending colon, this method for measuring Ca^{2+} transport does not permit valid statistical comparison of different intestinal segments within the same group. Similarly, $^{45}Ca^{2+}$ uptake was greatest in these same segments in the nephrectomized hypocalcemic fetuses . However, there was no difference between $^{45}Ca^{2+}$ uptake in the hypocalcemic fetuses and the normocalcemic control fetuses. In both groups, $^{45}Ca^{2+}$ uptake did not correlate with fetal gestational age.

CaATPase activity, μmPi/mg mucosal protein/5 min., in the control fetuses was greatest in the jejunum (73.7 ± 15.9) and in the duodenum (59.3 ± 16.9). These two were significantly different from the ileum ($p<.001$; $p<.05$), ascending colon ($p<001$; $p<001$), transverse colon ($p<.001$; $p<01$) and descending colon ($p<.001$; $p<.01$) respectively. In the hypocalcemic fetuses, CaATPase activity was also greatest in the jejunum and the duodenum, but values in this group were not different from those in the same segments in the control group.

The distribution of fetal intestinal CaBP in control fetuses was similar to the distribution for rates of $^{45}Ca^{2+}$ uptake. CaBP was greatest in the transverse and ascending colon respectively. However, the next greatest

concentration of CaBP was in the jejunum rather than the ileum as was the case for ^{45}Ca uptake. In the control fetuses, intestinal content of CaATPase and CaBP did not correlate with fetal gestational age. Studies of CaBP were not done in the nephrectomized hypocalcemic fetuses.

Table 1. Serum total Ca^{2+} and blood ionized Ca^{2+} in normal control and in nephrectomized fetal lambs

	Initial		10 days Post Nx	
Group	Total Ca	Ca^{2+}	Total Ca	Ca^{2+}
	mg/dl		mg/dl	
Controls	12.16	5.34	11.93	5.84
n=8	± .23	± .18	± .35	± .21
Nephrectomized	12.63	5.90	7.65	3.06
n=4	± .36	± .13	± .05	± .18
	NS	NS	P<.01	P<.001

Nx-Nephrectomy. Values are mean ± SEM

Table 2. ^{45}Ca uptake, CaATPase and CaBP in intestinal segments in fetal lambs.

	Duo	Je	Il	CoA	CoT	CoD
^{45}Ca uptake	μm Ca/mg protein/30 min. x 10^{-3}					
Normal	23.2	27.5	28.5	34.3	65.4	23.5
n=8	±5.5	±4.2	±5.2	±6.4	±17.5	±3.4
Nx	—	21.5	31.7	33.6	78.3	29.8
n=4	—	±7.6	±13.6	±13.4	±32.2	±10.0
CaATPase	μm Pi/mg protein/5 min. x 10^{-2}					
Normal	59.3	73.7	24.2	12.2	25.5	22.9
	±16.9	±15.9	±7.1	±4.9	±7.8	±4.9
Nx	66.9	101.8	30.0	—	27.3	20.6
	±28.3	±9.3	±4.4	—	±12.2	±4.7
CaBP Specific Activity	% ^{45}Ca/mg protein					
Normal	—	8.13	5.66	11.24	14.82	6.26
	—	±0.83	±1.54	±1.76	±2.21	±2.67
Nx	ND	ND	ND	ND	ND	ND

Nx = Nephrectomy; Duo-Duodenum Je-Jejunum, Il-Ileum, CoA-Ascending Colon, CoT-Transverse Colon, CoD-Descending colon. Values are mean ± SEM

Discussion

The results of this study demonstrated that in fetal lambs, intestinal absorption of Ca^{2+} is present by late midgestation. In this species, the rate of intestional Ca^{2+} absorption apparently does not change throughout the remainder of gestation. These studies are the first to show intestinal Ca^{2+} absorption during fetal life. DeLorme et al. studied intestinal CaBP during the last five days of fetal life in rats.[6] Their studies demonstrated that intestinal CaBP is detected as early as day 17.5 of gestation and increased markedly during the last day of gestation (i.e., day 21). In our study, CaBP did not change with increasing fetal age, but specific kinetic studies were not performed on the last day of gestation. Additionally, CaBP was directly measured by radioimmunoassay in the studies reported by DeLorme et al.[6] However, intestinal Ca^{2+} transport was not investigated in these fetuses.

In adult animals as well as in man, active intestinal Ca^{2+} absorption is mediated by 1,25-dihydroxyvitamin D.[7,8] 1-hydroxylation of 25-hydroxy vitamin D is known to occur only in the kidney and the placenta.[9] Removal of kidney tissue uniformly results in a significant fall in circulating levels of $1,25(OH)_2D$ except in the pregnant female where the fall is not as great. Although vitamin D levels were not studied in these fetuses, marked hypocalcemia occurred following fetal nephrectomy. Despite the chronic hypocalcemia and presumed reduction in or absence of fetal $1,25(OH)_2D$, there was no difference in fetal intestinal uptake of Ca^{2+} or intestinal content of CaBP or CATPase in nephrectomized fetuses versus normocalcemic controls.

Halloran and DeLuca studied intestinal Ca^{2+} transport in the first weeks of life in rats.[3]. These studies demonstrated that intestinal Ca^{2+} transport in vitamin D deficient and vitamin D replete pups was identical at three and fourteen days postpartum. Administration of $1,25(OH)_2D$ during the first 14 days of life had no effect on intestinal Ca^{2+} transport. However, an effect of vitamin D was noted at day twenty five or later. These investigators concluded that intestinal Ca^{2+} transport during early development is not mediated by vitamin D but that a vitamin D sensitive transport system develops late in the suckling period. The results of our study in fetal lambs suggests that non-vitamin D-mediated intestinal Ca^{2+} absorption begins early in utero and then continues for the first two to three weeks of postnatal life.

Ghishan et al. used an in vivo perfusion technique to study maturation of Ca^{2+} transport in the small and large intestine in two, three, and six week old rats.[10] These studies demonstrated that the perfused combined cecum and colon segment in the weanling and adolescent rat absorbed Ca^{2+} against a concentration gradient, and the amount absorbed was significantly higher than that in the small intestine. They speculated that in growing animals, calcium absorption in the cecum and colon may play an important role in Ca^{2+} homeostasis. Batt and Schacther also demonstrated Ca^{2+} absorption in the colon of newborn rats and mice.[11] Our studies, therefore, confirm the observations of Ghishan et al. and Batt and Schacter and supports the hypothesis that cecal and colonic Ca^{2+} transport may play an important role in Ca^{2+} homeostasis during rapid growth. In our study, Ca^{2+} uptake was

greatest in the transverse and ascending colon respectively in both normocalcemic controls as well as in the chronically hypocalcemic fetuses.

Radde et al. used Ussing apparatus to study bidirectional Ca^{2+} flux in the small intestine of piglets between one and thirty five days of age.[12] They demonstrated net Ca^{2+} absorption that was greatest in the jejunum and duodenum respectively at age one to fourteen days. The colon was not studied. In this study, CaATPase activity was highest in the jejunum and ileum respectively at birth. Using the same methodology as Radde and associates, we demonstrated the highest CaATPase activity in duodenum and jejunum respectively in fetal lambs and the activity did not correlate with the rate of Ca^{2+} uptake in intestinal segments. In the studies of Radde et al., there was no attempt to correlate intestinal Ca^{2+} transport or intestinal CaATPase with vitamin D activity.[12]

The results of our preliminary studies of intestinal absorption of Ca^{2+} during fetal life extends previous observations in the neonatal period to an earlier period of development. In studies conducted in the first month of life in human infants, raising Ca^{2+} concentration in formula resulted in a significant increase in the rate of intestinal Ca^{2+} absorption.[13] Ca^{2+} acquisition via intestinal absorption in this study was similar to the rate of Ca^{2+} acquisition via the placenta in late fetal life. In human infants, circulating levels of $1,25(OH)_2D$ are low at birth.[14] Thus, the adaptation to increased dietary Ca^{2+} intake in the study by Shaw presumably was not mediated by $1,25(OH)_2D$.[13] Additional studies in human infants have demonstrated increased intestinal Ca^{2+} absorption with administration of vitamin D and 25(OH) vitamin D.[15] Thus, intestinal Ca^{2+} absorption can and does occur before maturation of the mechanism for 1-hydroxylation of vitamin D.

Since intestinal Ca^{2+} absorption in utero and in the immediate postnatal period is not mediated by $1,25(OH)_2D$, and intestinal Ca^{2+} absorption is the major route of Ca^{2+} acquisition in postnatal life, understanding nonvitamin D-mediated intestinal Ca^{2+} absorption is essential for optimal care of the newborn infant. The studies of Shaw indicate that high Ca^{2+} concentration in infant formula may be beneficial.[13] Additionally, administration of vitamin D appears to enhance intestinal vitamin D absorption in early life.[15] The prematurely born infant may have a large deficit of Ca^{2+} amounting to as much as 6-8 gms.[14] Until data from current and future studies suggest otherwise, care of these infants probably should include provision of additional Ca^{2+} in formula and administration of vitamin D in order to correct this deficit and minimize or prevent the possibility of metabolic bone disease and growth disturbance. Additional changes in feeding for the premature or LBW infant should be based on results of continuing research in this field.

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RENAL RESPONSE OF THE FETUS TO HYPOXIA

SALHA S. DANIEL, PH.D. AND L. STANLEY JAMES, M.D.

Columbia University, College of Physicians and Surgeons
Departments of Anesthesiology and Pediatrics
Division of Perinatal Medicine
New York, New York

Wide variations in urine composition and renal function are encountered during the immediate postnatal period (1,2). We proposed (2) that a possible cause for these variations was various degrees of disruption of maternal-fetal exchange leading to fetal and neonatal hypoxia (3,4). However, no correlation could be found between various aspects of renal function in the postnatal period and any clinical or biochemical evidence for an hypoxic insult (2). The infants studied all had one minute Apgar score of 7 or higher, were not acidotic and did not display blood pressure abnormalities. Despite this lack of correlation, there is considerable experimental evidence that hypoxia does influence renal function. It is possible that hypoxic insults during labor could be of such short duration or of an intermittent nature that they would not be evidenced by the clinical or acid-base status of the infants at birth (5). The purpose of the present experiment is to examine the renal response of the chronically instrumented lamb in utero to controlled hypoxia as well as acid-base and osmolar disturbances.

PROCEDURE

Surgery

Laparatomy and hysterotomy for instrumentation of the fetal lamb were performed under spinal anesthesia supplemented with sodium pentobarbital at 110-118 days gestation (term 148-150 days), as described previously (6). Polyethylene catheters were placed in the carotid artery, jugular vein and in the bladder via the urachus. In some animals, an inflatable rubber cuff (Rhodes Medical, CAL) with known capacity was placed around the umbilical cord and secured to the fetal abdominal skin. All vascular catheters were flushed daily and antibiotics were given to both the ewe and the fetus as described in earlier papers (6-8).

Experiments

Studies were conducted at least seven days post-operatively to allow for complete recovery of renal and endocrine systems. All fetuses were in good circulatory and acid-base condition prior to any experiment. At least one week was allowed between successive experiments on the same fetus. Fetal renal function was studied at 117-135 days gestation under the following conditions:

Normoxemic

1. Control
2. Metabolic acidosis - produced by intravenous infusio of 15 mEq/kg lactic acid to the fetus over a period of 90 minutes (6)
3. Metabolic alkalosis - produced by intravenous infusi of 20 mEq/kg sodium bicarbonate to the fetus over a period of 90 minutes
4. Dehydration - Results from fetuses with high plasma osmolality and low urine output (etiology unknown) but otherwise normal acid-base indices were selected (9)

Hypoxemic

1. Hypoxemia - Achieved by administration of 10% 0_2 in nitrogen to the ewe for thirty minutes (10)
2. Hypoxemia + Acidemia - Achieved by either partial occlusion for sixty minutes or repeated complete occlusion of the umbilical cord for two minutes (7&8)

The results in the hypoxemic fetal lamb were compared to those obtained in the normoxemic fetuses and also to those obtained in the neonate during the first few days of life under hypoxic conditions.

RESULTS AND DISCUSSION

In general these studies on the fetal lamb showed that although the placenta and not the kidney is the major organ of homeostasis in utero, urine composition is related to plasma composition in the well oxygenated fetus. Thus vasopressin in plasma and urine osmolality were significantly correlated in the normoxemic fetus and similarly blood pH had significant effect on Net Acid Excretion (NAE) (6&9).

During hypoxia with or without acidosis the following changes were shown to occur:

Cardiovascular

Systolic and diastolic pressures increased; this was accompanied by a fall in fetal heart rate. Recovery was associated with a return to control blood pressure and a prolonged tachycardia (7&8).

Hormonal

Hypoxemia also stimulated a number of endocrine systems as summarized in Table 1. Thus vasopressin(VP) and catecholamines (CA) increased severa fold, plasma renin activity (PRA) also rose while angiotensin II (A II) decreased with hypoxia because of a fall in angiotension converting enzyme activity. (11) Results from blood samples taken from the umbilical cord

Table 1. Effect of hypoxia on fetal plasma hormone levels

	HYPOXIA	ACIDOSIS	LABOR
VASOPRESSIN	↑↑	?	↑↑↑
CATECHOLAMINES	↑↑	?	↑↑
RENIN-ANGIOTENSIN RENIN	↑	?	↑
ANGIOTENSIN	↓		↑
ALDOSTERONE	↑	?	↑

Table 2. Fetal renal response to exogenous hormone administration

	LOW DOSE		HIGH DOSE	
	OUTPUT	CONCEN-TRATION	OUTPUT	CONCEN-TRATION
VASOPRESSIN	↓	↑	↑	↑
CATECHOLAMINES	↑	—	↓	↑
ANGIOTENSIN	—	—	—	—
ALDOSTERONE	↑	↑	↑	↑

at the time of delivery are also included. Note that labor and delivery appeared to have effects similar to stresses leading to hypoxemia and acidemia. The changes in plasma hormone levels during hypoxia appear to be related to both pHa and PaO_2 (12&13).

The effects of these hormones when given intravenously on the fetal renal function in the sheep following exogenous administration are shown in Table 2. Although the response was usually smaller than in the adult, AII appeared to be the only hormone with no effect on renal function in utero despite the fact that it has potent hypotensive effect on the fetus. Of interest was the observation that the response to VP and CA changed as the dose was increased. This is likely due to the fact that these hormones have both a direct effect on the kidney nephron and vasculature and an indirect effect through their cardiovascular action. Because renal response varies with levels of the hormones, the type and extent of the fetal response to hypoxia might depend on the degree and possibly the duration of the hypoxic episode.

Renal

In earlier studies we have shown that hypoxia with or without acidosis caused a fall in urine output and rise in osmolality and electrolyte concentration. There was a delay in the response presumably in part due to the lapse of time between the occurrence of the response and the appearance of urine in the bladder. Maximal renal response occurred in 15-30 minutes, while urine concentration but not antidiuresis lasted at least one hour after the cessation of the hypoxic episode (7&8). Despite the fall in urine output, the rise in solute and electrolyte concentration in the urine represented an actual increase in excretion. There is also a decrease in GFR which was significant only following partial occlusion of the umbilical cord.

The relationship between plasma composition (namely pHa, PaO_2, VP and osmolality), and maximal response in renal function during hypoxia are presented in Figures 1-7 and compared to those obtained in the well oxygenated fetus.

Figure 1 shows the relationship between P_{VP} and P_{OSM}, which rose with hypoxia. Although there is good linear correlation between log VP and P_{OSM} during hypoxia, the relationship is very different from that obtained in the non-hypoxic fetus (9) and suggests a different stimulus for VP release.

There is also a good linear correlation between P_{VP} AND U_{OSM} during hypoxia but again this relationship is different from the one that exists in the well oxygenated fetus (Figure 2).

A weak but significant correlation was found between pHa and U_{OSM} (Figure 3). No such correlation has been observed in the normoxic fetus. A strong correlation was found between PaO_2 and U_{OSM} suggesting that hypoxia and not acidosis may be the stimulus for urine concentration (Figure 4).

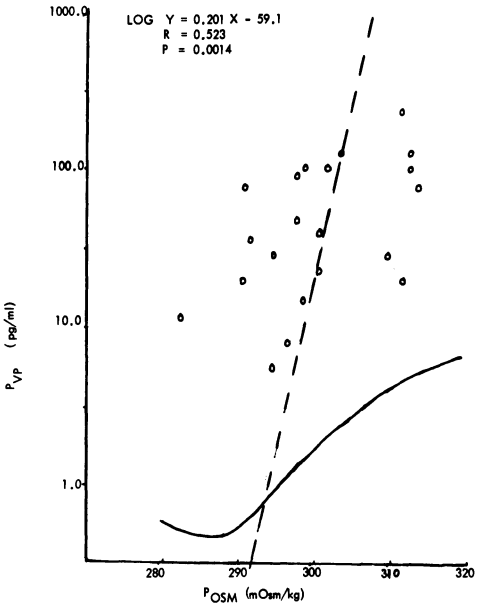

Figure 1. Relationship between plasma osmolality (P_{Osm}) and vasopressin (P_{VP}) in the hypoxic fetal lamb (dashed line and open circles). Solid curve obtained from normoxemic fetuses (9).

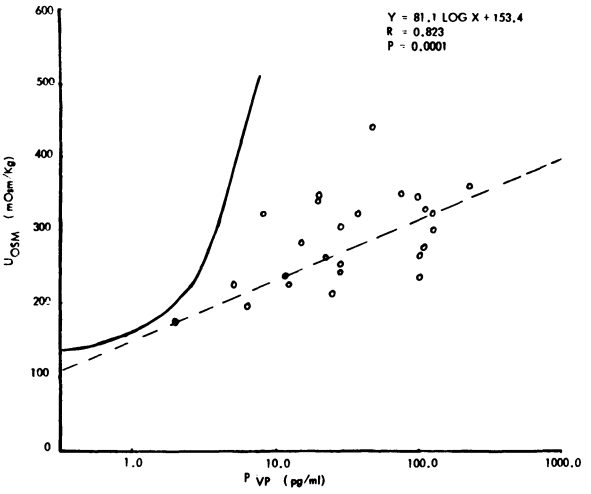

Figure 2. Relationship between plasma VP and urine osmolality (U_{Osm}) in the hypoxic fetal lamb. Symbols as in Figure 1.

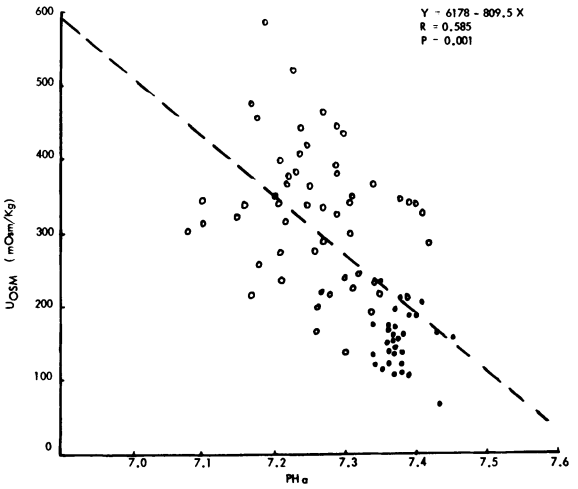

Figure 3. Relationship between pHa and urine osmolality in the fetal lamb before (●) and during hypoxia (○).

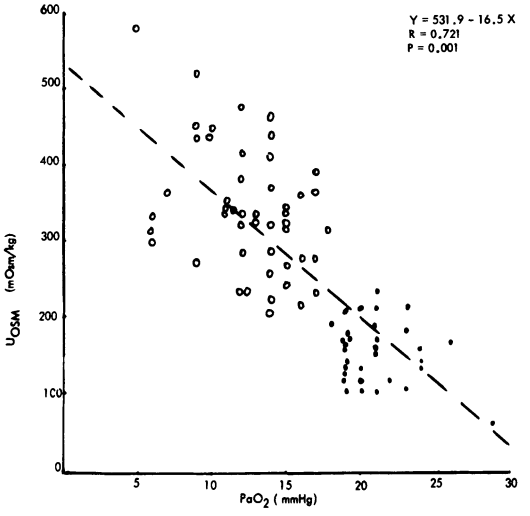

Figure 4. Relationship between PaO_2 and urine osmolality in the fetal lamb before (●) and during hypoxia (○).

Figures 5-7 show the effect of hypoxia on urine acidification process. Unlike the well oxygenated fetus, there appears to be no correlation between pHa and U_{pH}. The same is true with NAE which changed very little as pHa fell (Figure 6). It should be pointed out that since urine output fell, rate of NAE excretion actually decreased during hypoxia. Acidemia + hypoxemia caused no decrease in U_{HCO3} contrary to what was obtained following acidemia alone (Figure 7). There was an increase in urine bicarbonate concentration during hypoxia as there was with both Na and Cl.

The effects of hypoxia on renal function in the fetus and the newborn 1-3 days of age are compared in Table 3. Hypoxia was produced by administration of 10% O_2 to the ewe or neonate. Urine output fell while osmolality and Na excretion rose similarly in both. Unlike the fetus, there is no increase in urinary bicarbonate concentration in the newborn while NAE increased significantly in the neonate but not in the fetus. Preliminary results show that increased bicarbonate excretion occurs in the neonate when 5% O_2 is used instead of 10%. Thus the difference between the fetus and newborn is due mainly to degree of hypoxic stress.

Table 3. Changes in urine composition with hypoxia: Comparison between fetus and newborn

	FETUS	NEWBORN
OUTPUT (ml/Kg min)	-0.10*	-0.06*
OSM (mOsm/Kg)	+157*	+135*
Na (mEq/L)	+53.0*	+18.5*
HCO_3 (mEq/L)	+2.2*	-0.2
NAE (mEq/L)	+3.1	+15.9*
PH	+0.37*	-0.16
GFR (ml/Kg min)	-0.83	+0.21

* P 0.05

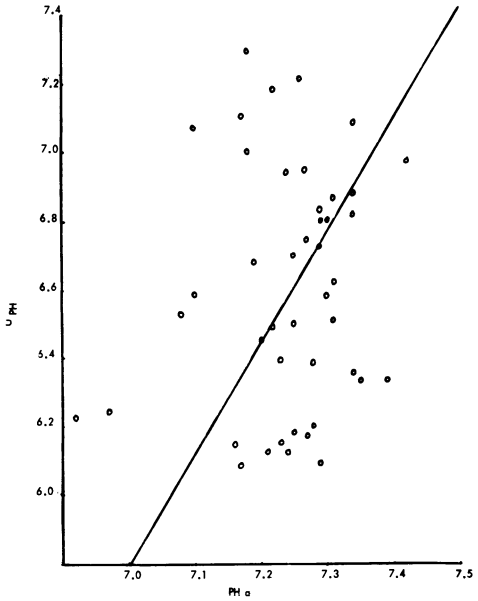

Figure 5. Relationship between pHa and urine pH (UpH) in the hypoxic fetal lamb (○). Solid line obtained from normoxemic fetuses.

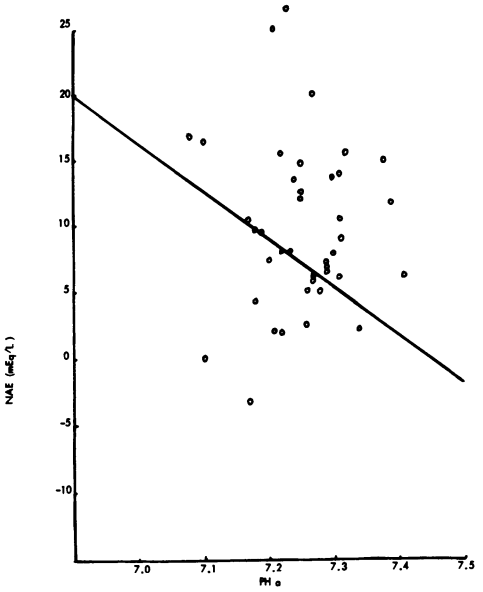

Figure 6. Relationship between pHa and net acid excretion (NAE) in hypoxic fetal lamb (○). Solid line obtained from normoxemic fetuses.

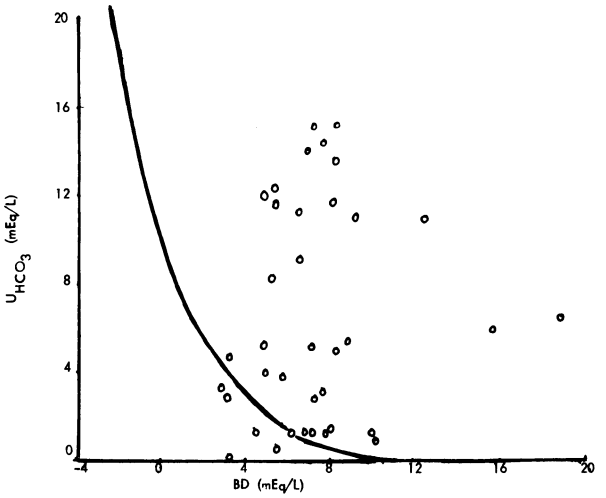

Figure 7. Relationship between base deficit (BD) and urine bicarbonate (U_{HCO_3}) in the hypoxic fetal lamb (○). Solid curve obtained from normoxemic fetuses.

CONCLUSIONS

Although neither the role of individual hormones released during hypoxia through either renal or extrarenal effects, nor the possible role of tissue hypoxia on glomerular or tubular functions are clearly established, our studies do allow the following conclusions.

1. Hypoxia in both the fetus and newborn causes an increase in urine osmolality and a decrease in urine output.

2. There is a time lag between the appearance of response to hypoxia and the occurrence of hypoxia. This explains the lack of correlation between urine composition and blood composition at birth.

3. Blood composition correlates with urine composition when maximal changes are considered.

4. The increase in urine osmolality is due mainly to an increase in electrolyte excretion including bicarbonate.

5. Because of the increase in bicarbonate excretion, the process of urine acidification, which is present in the non-hypoxic fetus, is diminished during hypoxia.

6. Although acid excretion continues in mildly hypoxic newborn, urine acidification also diminishes when the hypoxic episode is severe.

The presence of urine hyperosmolality relative to plasma during the postnatal period can be taken as a sign of occurrence and/or persistence of hypoxia. Thus kidney function is a good marker of events during the perinatal period.

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PRENATAL DIAGNOSIS OF FETAL URINARY TRACT ABNORMALITIES

A.A. BEZJIAN, M.D.

With the introduction of Real-Time Ultrasound and the improved resolution of its gray scale capabilities, certain fetal urinary tract anomalies can be diagnosed reliably by experienced sonographers. Ultrasound scanning at 18-20 weeks of gestation is indicated in any patient who has already delivered a child with a birth defect, or has a strong family history of congenital anomalies. When the disease is bilateral or is associated with outlet obstruction, oligohydramnios occurs which could be the first clue to the presence of fetal G.U. anomalies. Oligohydramnios is often suspected first by the clinician and can be documented reliably by ultrasound. When present in the second trimester without premature rupture of membranes, the outcome most often is poor (1).

NORMAL ANATOMY AND PHYSIOLOGY

The fetal kidneys can be reliably visualized by ultrasound as early as 15-16 weeks gestation as oval or round areas of echogenicity in the lumbar paraspinal regions and are best seen on transverse sections of the fetus. They should not occupy more than a third of the intra-abdominal area at any given stage of gestation (Fig. 1). An accurate assess-

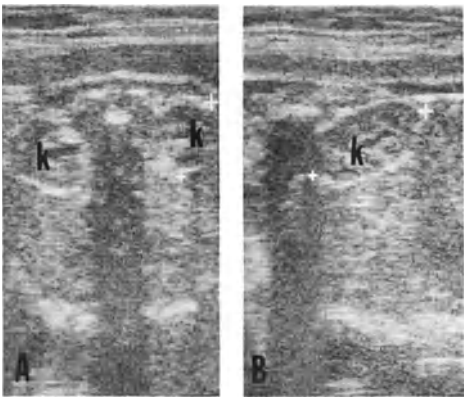

FIGURE 1. Normal fetal kidneys. A: Transverse section of the fetal abdomen showing both fetal kidneys (k) in transverse section. B: Longitudinal section of a normal fetal kidney (k).

FIGURE 2. Longitudinal section of fetal abdomen showing normally filled fetal bladder (b) in lower portion of abdomen.

ment of fetal kidney size can be made by comparing the mean kidney circumference to the abdominal circumference (KC/AC) at the level of the umbilical vein (2). Normal ureters cannot be visualized with the resolution provided with current ultrasonic equipment. The fetal bladder, when full can always be identified and its volume can be measured accurately (Fig. 2). Campbell et al (3) were able to measure the hourly fetal urinary production rate (HFUPR) at different stages of gestation by measuring the changes in the volume of the fetal bladder. More recently, other kidney function tests, i.e. glomerular filtration rate (GFR), tubular water reabsorption rate (TWR) and the effect of furesomide on fetal micturition, have been evaluated by ultrasound in normal and complicated pregnancies (4). In normal pregnancies the HFUPR increased from 2.2 ml/hr at 22 weeks of gestation to 26.3 ml/hr at 40 weeks of gestation. The fetal GFR is 2.66 ml/min at term and the percentage of TWR is 78% (4).

The external fetal genitalia can be often visualized in the third trimester if the fetus is lying in an appropiate position (Fig. 3). If the penis and scrotum are visualized, a male fetus can be predicted accurately. However it must be remembered that the labia and the clitoris of a female fetus are often hypertrophic due to maternal hormonal stimulation and this may lead to a false gender prediction. Also, lack of visualization of the male genitalia should not permit one to conclude that the fetus is a female.

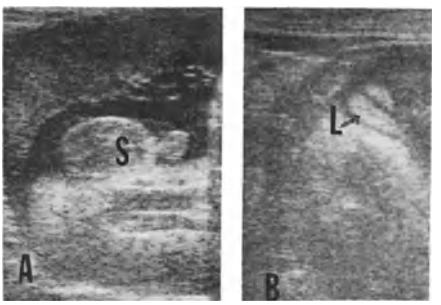

FIGURE 3. Normal fetal genitalia.
A: Fetal scrotum (S) and penis.
B: Fetal labia (L).

RENAL AGENESIS

Failure to identify fetal kidneys and bladder together with the presence of oligohydramnios must lead one to suspect fetal Potter's syndrome (5). In cases of severe oligohydramnios however, fetal organs including the kidneys are very difficult to visualize and one often resorts to the demonstration of fetal bladder to rule out renal agenesis. Failure to demonstrate the bladder however, is not pathognomonic of absent kidneys as the fetus might have voided recently. The fetal bladder must be looked for over a period of hours possibly with the injection of a diuretic (Furosemide 20 mg I.V.) to the mother. If renal function is present, the fetal bladder must be visualized within 30-60 minutes.

Frequently Potter's Syndrome is associated with other congenital anomalies, i.e. duodenal atresia and Meckel's diverticulum. These conditions can be diagnosed by ultrasound and must therefore be looked for.

RENAL DYSPLASIA

Approximately 50% of fetal abdominal masses can be attributed to a renal origin. Of these, half are related to renal dysplasia: multicystic kidneys 20% and polycystic kidneys 5%. The other renal abnormalities include hydronephrosis and Wilm's tumor 5%.

1- Cystic abnormalities of the kidneys

Fluid filled masses are clearly seen by ultrasound and hence large cystic masses in the fetal kidneys are readily diagnosed in utero. They present as multiple anechoic areas in the region of the fetal flanks and are usually unilateral. The two main pathologic conditions presenting as such are multicystic kidney disease and hydronephrosis due to uretero pelvic junction obstruction. Multiple other conditions however, can

FIGURE 4. Fetal duodenal atresia. Note 2 cystic areas (double bubble) external to normal looking kidney (k).

appear similar to unilateral cystic renal abnormalities by ultrasound. These include ovarian cysts, gastro-intestinal dilatation secondary to

obstruction, and mesenteric cysts (6). Proper delineating of the fetal kidneys is of utmost importance in differentiating renal from extra renal cysts (Fig. 4).

A- Multicystic kidneys. This is usually a unilateral condition associated with ureteral atresia and absence of a renal pelvis and calyces. Sonographically, multiple thin walled cystic masses of varying sizes are readily visualized (Fig. 5). When such a condition is diagnosed, the

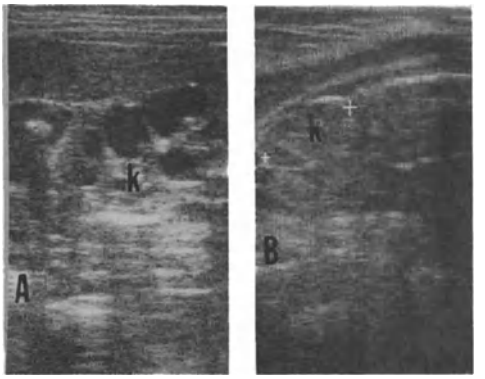

FIGURE 5. Unilateral Multicystic kidney due to ureteral atresia. A. Multicystic kidney. Note the multiple thin walled cystic masses within an enlarged kidney (k). B. Normal looking contralateral kidney (k).

status of the contra-lateral kidney must be carefully evaluated since in rare occasions the condition can be bilateral (7).

B- Unilateral hydronephrosis. This is usually due to a uretero pelvic junction obstruction or an ectopic ureterocele. A bilobed cystic mass is often seen in cases of uretero pelvic obstruction; the superior lobe representing the dilated extra renal pelvis and the inferior lobe representing the dilated extra renal pelvis (Fig. 6). Sometimes it is difficult to differentiate sonographically a multicystic kidney from unilateral obstruction.

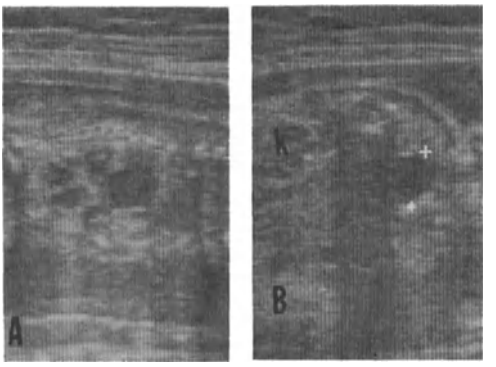

FIGURE 6. Unilateral Hydronephrosis due to ureteral obstruction. A. Longitudinal view. Note larger lower dilated extra renal pelvis and the multiple smaller intra renal calyceal dilatation. B. Transverse view showing the dilated extra renal pelvis on the right (within joysticks) and a normal kidney on the left (k).

We have recently seen several cases of mild transient hydronephrosis discovered incidentally on routine sonograms. They are usually bilateral and disappear after birth. They are most frequently observed in patients with moderate to severe hydramnios suggesting a possible relationship between the increased intra-amniotic pressure and the transient hydronephrosis (Fig. 7).

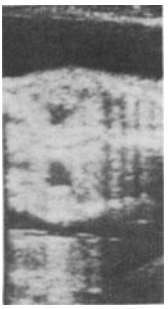

FIGURE 7. Transient bilateral hydronephrosis in patient with severe polyhydramnios. Hydronephrosis subsided post-natally.

2- Infantile polycystic kidney disease.

This is an autosomal recessive lethal condition affecting 25% of infants born to parents who are carriers. The kidneys of an affected fetus in late pregnancy are bilaterally enlarged and appear ultrasonically solid due to increased medullary echos derived from cysts too small to be visualized individually (9). We have studied one patient at risk for polycystic kidney disease. Her original sonogram at 22 weeks revealed normal sized kidneys with normal internal architecture. Repeat scan at 30 weeks revealed bilaterally enlarged kidneys with increased echogenic internal pattern. A moderate degree of oligohydramnios was also seen at that time (Fig. 8). It is our feeling that it is extremely difficult to diagnose this condition prior to 24 weeks of gestation but as the condition is lethal, an accurate diagnosis late in pregnancy is still helpful in preparing the patient for the unfortunate outcome at birth and possibly in avoiding an unnecessary surgical intervention in case of fetal distress.

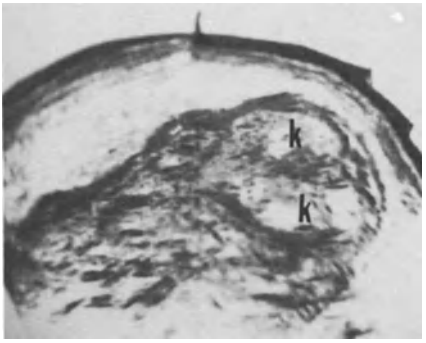

FIGURE 8. Infantile polycystic kidneys at 36 weeks gestation. Note bilaterally enlarged kidneys (k).

BLADDER OUTLET OBSTRUCTION

This leads to abnormal distension of the fetal bladder with bilateral hydroureters and hydronephrosis and oligohydramnios. Sonographically a large cystic mass (bladder) is seen in the fetal pelvis together with dilated ureters and hydronephrosis (Fig. 9). The condition when

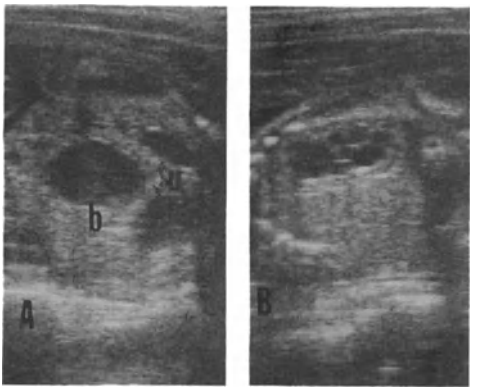

FIGURE 9. Bladder outlet obstruction due to posterior urethral valve. A. Distended urinary bladder (b) with bilateral hydroureters (u) B. Hydronephrosis in same fetus. In utero continuous fetal bladder drainage was offered to this patient but she refused.

severe and associated with fetal abdominal distension secondary to deficiency in the abdominal wall musculature (Prune-Belly Syndrome), is easily diagnosed prior to 20 weeks gestation (10). (Fig. 10). It is

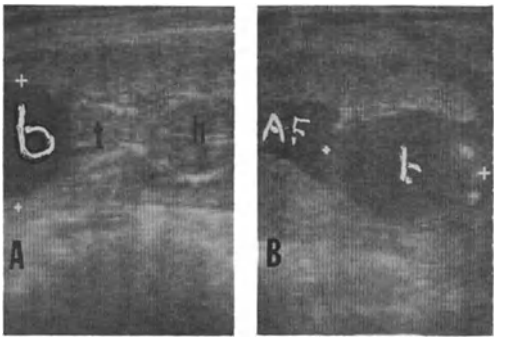

FIGURE 10. Fetal prune belly syndrome at 16 weeks gestation. A. Longitudinal section of the fetus showing fetal head (h), thorax (t) and massively dilated bladder (b). B. Transverse section of lower fetal abdomen showing the dilated bladder (b). Note the normal amniotic fluid volume (AF).

thought however, that the abdominal muscle deficiency in the prune-belly syndrome is a consequence of the urethral obstruction malformation complex (11). Recently a technique has been described for a continuous in utero drainage of an obstructed fetal bladder (12). An indwelling suprapubic catheter with a memory is placed by ultrasonic guidance into the fetal bladder allowing it to drain continuously into the amniotic cavity. This procedure however, is in its experimental stages and must only be performed at a stage II ultrasound center highly equipped and experienced in prenatal diagnosis and in in-utero surgery. Proper consent forms must be signed following extensive genetic counselling. All attempts must be made to rule out any other major congenital anomalies especially Brachial Arch Renal (BAR) syndrome. This is a lethal condition associated with multiple severe facial abnormalities and renal abnormalities including prune-belly syndrome. The decision to perform in-utero surgery must be unanimously made by the parents, the obstetrician, the geneticist, the pediatrician, the urologists and the pediatric nephrologist.

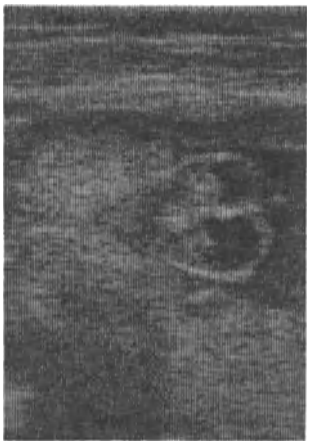

FIGURE 11. Bilateral fetal hydrocele in term fetus with descended testicles.

ABNORMAL MALE GENITALIA

Scrotal hydroceles may be readily diagnosed by ultrasound (13) and often are of no clinical consequence (Fig. 11). Ocasionally however, hydroceles might be a manifestation of generalized fetal hydrops with a rather poor prognosis.

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CONGENITAL NEPHROPATHIES

J.-P. GUIGNARD , Service de Pédiatrie, CHUV, Lausanne,Switzerland

Congenital disorders of the kidney may affect its structure and/or its function (Table I). Only cystic diseases of the kidney and congenital nephropathies diagnosed during the neonatal period will be discussed here.

Table I. Congenital nephropathies in the newborn infant

I.	Isolated malformation of renal parenchyma
	- multicystic dysplasia
	- infantile polycystic disease
	- adult polycystic disease
II.	Obstructions/malformations of renal parenchyma associated with complex malformation syndrome
	- Zellweger syndrome
	- Nail-patella syndrome
	- Ehlers-Danlos syndrome
III.	Congenital nephrotic syndrome
	- Finnish type
	- Congenital syphilis
	- Congenital toxoplasmosis
	- Congenital cytomegalovirus infection ?
	- Focal glomerulosclerosis
IV.	Bartter's syndrome
V.	Diabetes insipidus
VI.	Congenital defects diagnosed after the neonatal period

CYSTIC DISEASE OF THE KIDNEY

Renal cystic kidney disease includes a number of distinct entities (1). Two main groups will be considered : the multicystic-dysplastic disease and the polycystic kidney disease.

A. Multicystic-dysplastic disease (multicystic dysplasia): The lesion is most often unilateral, more common in males, rarely familial. The renal mass consists of a severely malformed kidney, with cysts of various size associated with primitive epithelial ducts, immature glomeruli, undifferentiated

mesenchyme and islands of cartilage. Dysplastic kidneys are nearly always associated with severe urinary tract abnormalities. Diagnosis is confirmed by urography and ultrasonography. Renal dysplasia is the most common form of cystic disease in the infant and accounts for 20 % of all urinary tract malformations. Renal dysplasia often complicates congenital lower urinary tract obstructions, and its patterns correlate with different types of obstruction in a manner suggesting causal relationships.

B. The infantile polycystic disease, characterized by dilatation of distal tubules and collecting ducts, is an autosomal recessive inherited disease. In the perinatal form, the cystic masses may be enormous. The infants are frequently still-born or succumb shortly after birth from renal failure. In the neonatal form, renal failure may develop months or sometimes years later. Hepatic involvement is minimal in the perinatal and neonatal forms, but becomes evident in the infantile and the juvenile forms of infantile polycystic disease.

C. The adult polycystic disease is increasingly recognized in neonates (2). It is transmitted by an autosomal dominant gene. Ultrasonography is the method of choice for demonstrating the renal cysts within the enlarged renal masses. Cysts may also be found in the liver, pancreas, ovary and lungs. The condition described as "glomerular cystic disease" appears to represent the early presentation of adult polycystic disease in the newborn infant (3).

CONGENITAL NEPHROPATHIES

Congenital disorders of the kidney, affecting glomerular and/or tubular function may be found in the neonate.

Congenital nephrotic syndrome (CNS): The first reported occurrence of CNS in the literature appeared in 1942 from Switzerland (4). Eight cases were observed in Finland some years later by Hallman et al. (5). Since then the majority of reported cases of CNS have come from Finland, hence the name CNS of the Finnish type (CNSF). This condition is an autosomal recessive disease predominantly observed in Finland (6). It is often associated with prematurity and fetal distress (7). The placenta is remarkably larger than normal and regularly weighs more than 25 per cent of the child birth weight (mean ratio of placenta to infant weight is 0.43 in those with CNSF, compared to 0.18 in normals (7). The proteinuria is highly selective early in the course of the disease. Edema and ascites are often present in the first postnatal week. Prerenal diagnosis is suggested by an elevation of α-fetoprotein in amniotic fluid and to a lesser extent in maternal blood (8). The disease is resistant to corticoids and immunosuppressive drugs. The clinical course is marked by severe growth retardation and recurrent life-threatening bacterial infections. Infant mortality is common, and CNSF has been invariably fatal by four years of age (6). Therapy is supportive and directed towards promoting growth

and minimizing infectious complications. Vigourous therapy of infections with appropriate antimicrobial agents is recommended rather than prophylactic antibiotic therapy. Edema control is maintained by oral diuretic therapy, which also allows a more liberal fluid and caloric intake. Renal transplantation has been successfully performed in some centers, but growth to a size sufficient for transplantation has been difficult to achieve. No recurrence of the disease in the graft has been noted so far.

Other conditions may induce congenital nephrosis : syphilis, toxoplasmosis and possibly congenital cytomegalovirus infection.

Congenital syphilis may be associated with epimembranous glomerulopathy and a nephrotic syndrome. In 8 per cent of infants with congenital syphilis, the renal disease is characterized by hematuria, proteinuria and azotemia (9). Diffuse granular deposits of IgG and the treponemal antigen have been demonstrated along glomerular capillaries. Penicillin therapy cures the disease within 2-4 weeks. Nephrosis secondary to congenital toxoplasmosis is cured by steroids and appropriate treatment of the infection. Congenital nephrosis may be associated with cytomegalovirus infection, but a causal relationship remains questionable. Focal glomerulosclerosis may represent a distinct form of primary congenital nephrotic syndrome, or be associated with CNSF. Finally, renal vein thrombosis, sometimes listed as a cause of nephrotic syndrome, is probably more a consequence than a cause of the NS.

Bartter's syndrome, described some 20 years ago, is characterized by growth retardation, polyuria, hyposthenuria, metabolic alkalosis, hypokalemia, normal blood pressure, hyperreninemia, and hyperplasia of the juxtaglomerular apparatus (10). The concentrating defect is pitressin-resistant. It may cause severe dehydration in the neonatal period. The prevalence of this syndrome, the manifestations of which may be noted as early as the first week of life, and as late as the fifth decade, is not known. Increased amounts of urinary prostaglandin E_2 have been measured, and considerable evidence supports the hypothesis that prostaglandins mediate the hyperreninemia that characterizes Bartter's syndrome (11). Administration of a prostaglandin synthetase inhibitor corrects the hyperreninemia and aldosteronism, but not the hypokalemia (12). Small dosages of prostaglandin synthetase inhibitors, along with supplemental potassium and potassium-sparing diuretics may however achieve partial correction of potassium deficiency and lower levels of plasma renin. Such a therapy can stimulate growth and development of the infants.

Nephrogenic diabetes insipidus (NDI) is transmitted via a dominant gene linked to the X chromosome, with variable penetrance in the female heterozygote. The condition is characterized by a polyhydramnios, unexplained fever or hypernatremic dehydration secondary to unrecognized polyuria. A postnatal birth-weight loss greater than 10 per cent in a normally fed infant, whose urine osmolality is below 200 mOsm/kg H_2O (specific gravity 1.005), is suspect; administration

of vasopressin fails to increase the urine concentration or decrease the polyuria. It should be remembered, however, that in a severely dehydrated infant, urine specific gravity may rise above isotonicity, without excluding the diagnosis of diabetes insipidus. Infants with NDI are usually irritable, eager to suck and show preference for water over milk. Failure to thrive and constipation are often present. Mental retardation may result from acute episodes of severe hypertonic dehydration in infancy (13). Treatment consists of the administration of adequate quantities of fluids with a low osmotic load (breast milk) (14) in order to prevent hyperpyrexia and dehydration. The use of thiazide diuretics may be helpful to decrease the polyuria (15).

Several congenital defects of transport or metabolism are diagnosed after the neonatal period, when the accumulation of toxic products, or the loss of solute has reached significant levels. Such conditions include proximal and distal tubular acidosis, hereditary fructose intolerance, Wilson disease, galactosemia, familial hypophosphatemic rickets, glycogenosis, cystinosis and cystinuria.

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HIGHLIGHTS: GENETIC ASPECTS OF GU CONGENITAL ANOMALIES AND RENAL DISEASES

H.A. Lubs, M.D.

The combination of new technologies and classical pedigree analysis offers the opportunity either to prevent certain severe forms of renal disease or to effect an early diagnosis in relatives who are at risk. Examples are given for each of the principal forms of inheritance which illustrate the diagnostic and preventive aspects of this approach (Table 1). Direct examination of family members at risk, in addition to obtaining pedigree, is critical. Although this approach may lead to early diagnosis and prevention in some families, only a minority of cases can be detected by this approach. Ultrasound screening of all pregnancies, however, which soon will likely be routine, offers a whole new approach to the early detection and prevention of severe GU disease. The possibilities for antenatal therapy as well as interruption of pregnancy should be discussed. More data concerning the early pathogenesis and fetal pathology are urgently needed to predict which cases will respond to intervention.

Table 1. Genetics and Renal Disease

Autosomal Dominant Inheritance
- adult polycystic disease
- Alport's Syndrome
- nail patella
- idiopathic Fanconi Syndrome
- medullary cystic disease
- renal tubular acidosis (distal)
- urticaria, deafness and amyloidosis
- vasopressin-resistant diabetes insipidus
- double ureters, megaloureter (?)

Autosomal Recessive Inheritance
- childhood polycystic disease
- Meckel-Gruber Syndrome
- dibasicaminoaciduria
- glucose-galactose malabsorption
- Hartnup disease
- hypercystinuria
- infantile nephrosis
- iminoglycinuria
- juvenile nephronophthisis
- nephritis and hyperprolinemia
- renal agenesis (?)
- renal glycosuria and retinorenal dysplasia

X-linked Recessive Inheritance
- Fabry's disease
- oculocerebrorenal syndrome (Lowe Syndrome)
- unilateral hydronephrosis
- vasopressin-resistant diabetes insipidus

X-linked Dominant Inheritance
- hypophosphatemic rickets
- pseudohypoparathyroidism

Multifactorial (data poor)
- ureterovesical reflux/hydroureter
- many structural anomalies

Chromosomal
- aniridia - Wilms tumor (deletion of 11p13)
- kidney is one of many anomalous organs in most severe trisomies

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DISCUSSION

José Strauss, M.D., Moderator

QUESTION: It caught my attention that your patient with Finnish type congenital nephrotic syndrome did not have cysts at birth but did have them at six months. You suggest the possibility that tubular obstruction due to proteinuria might be the cause. Is there any evidence that this is true? And if so, why don't we see more often tubular dilatation in the context of massive proteinuric states?

RESPONSE: It is not my hypothesis but it is what most of the people who deal with congenital nephrotic syndrome think. When you perform biopsies in patients at a few months of age - six months, nine months - you don't always find cystic dilatation but when you perform them much earlier in life, you don't see them at all. So probably it is an acquired lesion. Why don't we see tubular dilatation in patients with heavy proteinuria? This could be related to the fact that in the congenital nephrotic syndrome heavy proteinuria starts in utero whereas in the other conditions heavy proteinuria starts much later, in the first years of life. And it's possible that heavy proteinuria happening in utero may have a different effect on the tubule, leading to tubular dilatation after some months of life. It's only a hypothesis.

QUESTION: I would like to know if you have any ideas about what triggers the synthesis of vitamin D around the fourteenth day of life, and if the high phosphate could have any inhibitory relation to this non-secretion in the early days of life.

RESPONSE: I don't believe that there are data which at present would indicate exactly what is the triggering mechanism that induces synthesis or hydroxylation of $1,25(OH)_2D$ ($1,25\text{-}D_3$) at age 14 to 21 days. There are a couple of laboratories, including our own, that presently are looking at the appearance of receptors for parathyroid hormone in the kidney which stimulate the 1 αhydroxylation. So, it is possible that the natural event is maturation of the receptors to PTH; this occurs by age 14 to 21 days. When that is completed, the response to PTH occurs and the 1 α hydroxylation happens. Data already exist to show that the 1 α hydroxylation enzyme is present in the fetal kidney as well as in the newborn kidney in humans as well as in laboratory animals. But the net synthesis is not very high. So, it would appear that this is a receptor problem which undergoes a natural maturation. What we are trying to do is to show earlier induction of receptors by various maneuvers. A summary of the answer is that it appears that the natural developmental aspect is that receptors to PTH and perhaps to phosphate must occur before the synthesis phenomena can occur.

COMMENT-QUESTION: I'm surprised that you advised artificial insemination for autosomal dominant kind of polycystic kidney disease which does not lead to kidney failure in the vast majority until after the fourth decade of life. My question is, **for what diseases are the donors for artificial insemination screened?**

RESPONSE: First, I don't advise anything to anybody. That's a very important point about counselling. I do think that families should be informed of all the options because each family is different. In fact, one person who may have had a kidney transplant or perhaps watched his brother or father go through this and all the problems involved in this, may say: "OK, so there's a treatment. I don't want my kids to have to go through that. I would prefer to have an unaffected child even though there is good treatment now." You and I might say that or something different but each family has a different experience. One has to paint the whole picture to each family. One can include the likelihood that in the future this may be different but must not get too speculative about the therapeutic possibilities. I don't advise artificial inseminatio but I mention it as just one of about six or eight possibilities that I would discuss with a twenty-year-old or thirty-year-old man who came in and said, "I have early polycystic kidney disease. Tell me all about the future and what's going to happen with my kids because I'm deciding whether I want to have a family or not." That's the only point. Artificial insemination should be mentioned amongst the other things. Perhaps I overemphasized it because almost nobody mentions this. It still is a viabl form of treatment. In fact, amongst the exciting things in the future, given that we will know more then than we know now about the linkage of man, is the possibility that we will know that there is a cell surface antigen locus right next to the gene for autosomal dominant polycystic kidneys. We might indeed be able to use this cell surface antigen to sort out the sperm bearing the gene for this particular type of kidney disease. We are already trying this in a type of adrenal disease that happens to be right next to HLA. So, here is another whole approach to pre-selection. One can have transplantation but this costs a lot of money. The lifetime care of someone with autosomal dominant polycystic kidney disease must be in the hundreds of thousands of dollars at this point. Sorting out sperms probably would cost $50 or $100. Again, just because there is good treatment doesn't mean that some families will not take another approach. Prevention is far preferable to overloading our medical care system with people for whom we know we are going to have to spend hundreds, even thousands of dollars, not to mention the cost in human suffering. That's my own feeling, of course.

QUESTION: What diseases are screened for in the mother?

RESPONSE: This is a tender point. Usually the obstetrician, not the geneticist,does this. A family history is taken which in this case would almost certainly rule out the likelihood that one would inseminate with sperm which would be at risk of having the same gene that you were trying to prevent. Beyond that, very little. It can be a problem. If we have a carrier test in the case of autosomal recessive disorders, we try to use that. For example, **Tay Sachs. It has happened that a** child has been conceived who had Tay Sachs **when that was just** what you were trying to prevent. That's very uncommon but it can happen, particularly with autosomal recessive **disorders** where the genes in the population are quite common--one in thirty, one in forty, one in fifty--

QUESTION: When you are implanting catheters in the bladder of the fetus in the chronic fetal sheep preparation, at what age of gestation are you working and does it interfere with the development of the fetal lung?

RESPONSE: All fetuses that we catheterize are at about 100 to 110 days of gestation which is early third trimester. We insert it through the urachus, through the umbilicus. We have not specifically examined the lungs after they are born but most of these fetuses are born spontaneously and seem to develop as well as the others. Sometimes there are twins and only one is catheterized. The **catheterized twin does not seem to be any different from the uncatheterized twin so we assume that most of our acute studies do not prominently damage any** of their organs.

QUESTION: I would like to ask about the studies of hypoxia in these lambs. We are frequently called to the nursery and asked to interpret a mildly oliguric neonate who has an active looking sediment. I wonder if you have taken the opportunity to look at the sediment after you induce hypoxia in these lambs? Is that something that occurs--an active sediment following hypoxia?

RESPONSE: As far as I know probably ninety percent of the time when we do a hypoxic episode we do get a cloudy urine and proteinuria and sometimes hematuria occurs after these episodes. Our acute episodes don't last more than one hour and **the animals seem to recover within two or three hours from these episodes.**

QUESTION: You have casts and cellular debris of all types?

RESPONSE: Right. This happens about ninety percent of the time.

COMMENT: I have to give a talk on the oliguric neonate. In preparing for the talk--which is my way of letting you know I prepare for my talks, I don't just do them spontaneously--I found that **in the infants that you see in the immediate newborn period with oliguria who have suffered some perinatal asphyxia, it is controversial as to whether the oliguria is in fact related to the asphyxia or the hypoxia. What I planned to say about this is that the studies presented today support the concept that** the physiologic consequences of hypoxia or asphyxia lead to decreased urine formation and **with that you can get a very active sediment** with casts and even white cells. So, the decrease in renal tubular flow certainly will lead to a very active sediment without any necessary parenchymal damage. The hypoxia, the asphyxia can lead to the oliguria that you see in the nursery and the urinary findings will go along with that.

QUESTION: You showed a slide comparing the effect of hypoxia in fetal animals and in newborns. You also showed the effect of a slight decrease in filtration rate in hypoxic fetal animals but an increase in hypoxic newborn animals. We performed studies in newborn rabbits and have never been able to show an increase in GFR in hypoxic animals. I would like to ask, what was the level of plasma PO_2 that you induced? How severe was the hypoxemia?

RESPONSE: In the newborn we gave 10% **oxygen.** They, as you well know, will start hyperventilating at that level. We took them down to about 50% of their original PO_2. They seemed to tolerate this very well. When we took them down to less than that, then we found problems. The studies that I showed were carried out with very mild hypoxia. I should have mentioned that the change in GFR in these studies was not always consistent. In other words, in some of them there was a fall and in some, there was a rise. The mean seems to be a rise in GFR but that is not a consistent finding and it would depend on how low the PO_2 went. When the PO_2 is low, the GFR will systematically go down.

QUESTION: What do you call low? 40 mm Hg?

RESPONSE: The PO_2 in the fetal lambs at one to three days of age is between 55-70. We took them down to about 35-40 mm Hg. If you go down to 20, then you begin to see a lowering of GFR.

MODERATOR: What about the conversations that we have had in the past regarding the concept that hypoxia per se is different from the ischemia induced by compression of the umbilical cord. Could you elaborate a little bit on the results that you are getting with one procedure versus the other?

RESPONSE: The differences between ischemia and just hypoxia, especially in utero where you have the placenta still functioning, is the GFR. With ischemia there is usually lowering of GFR and sometimes a complete stoppage of urine flow. This never happens when we have just an episode of acute hypoxia, that is giving 10% oxygen to the mother. Urinary output does go down although when we did the experiments for shorter periods of time, sometimes the urine output didn't go down. So, it very much depends on the duration of hypoxia. When hypoxia, even with 10% oxygen, is prolonged, then it seems to mimic more the ischemia, **while** when we occluded the cord we always got a lowering of GFR and always a lowering of urine output. Obviously, when you cut off the placenta the whole blood distribution in the fetus is altered. The fetal kidney suffers more when it is an ischemic insult like what would happen, we think, during labor than with just giving 10% oxygen to the mother.

MODERATOR: The concept that Dr. Manfred Kessler from Germany has is that severe hypoxia is similar to ischemia. Regarding the changes induced by hypoxia, I would like to mention the studies that we did here, Dr. Rowe and our group, in piglets, with 10% oxygen in a rather simple set-up which produced a marked diuresis and natriuresis. We interpreted that as being a problem with reabsorption of sodium since there wasn't enough oxygen, presumably, to allow for the sodium pump to work.

COMMENT: As you may recall from the data we presented at the International meeting last year and the workshop in New York, we, too, have done studies with partial cord occlusion looking at some concentrating mechanisms but I think it would be difficult in studies in utero to separate hypoxia from ischemia because if you look at renal blood flow to the fetal kidney, it may or may not fall with hypoxia induced by decreasing oxygen delivered to the mother. Certainly, as has been pointed out here, renal blood

flow will fall with partial cord compression. But, in some animals, when the mother's oxygen supply is reduced through mechanisms unknown to me, there is either a net reduction in total blood flow to the fetal kidney or a redistribution of the intrarenal blood flow from the outer cortex to the inner cortex, depending upon where it was in the beginning. So I think it would be extremely difficult to separate, at least in intrauterine life, the different effects, if any, between hypoxia and ischemia.

MODERATOR: Do you think that there are differences? You imply that there may not be any.

RESPONSE: I would like to think that there are differences but I don't think that in the laboratory it's going to be simple or easy to demonstrate them.

QUESTION: I was interested in the statement that 1,25-D_3 is not important even in the first few postnatal weeks. Could you comment on some of the recent clinical studies showing that maybe the treatment for early postnatal hypocalcemia with 1,25-D_3 did seem to be effective.

RESPONSE: I apologize for offending you by saying that...I didn't use the words "not important". One of the things about going out and giving talks, I always say,"this you can quote me on". I also say,"if you say this I'll deny it on a hundred Bibles of all faiths" - I didn't mean that it wasn't important. What I think I was trying to get over with that statement is that in the first two to three weeks of life, gastrointestinal absorption of calcium appears not to be mediated by the 1,25-D_3 metabolite. That's different from saying that 1,25 dihydroxyvitamin D_3 is not important. I think that in terms of metabolic bone disease 1,25-D_3 acting with calcium and whatever else goes on in the bone,helps to have the assimilation of calcium or hydroxyapatite into bone. That's different from the supply of calcium obtained from the digestive tract and delivered to bone. Yes, there have been clinical reports of high 1,25-D_3 levels in low birth weight infants who yet have had metabolic bone disease or even overt rickets. The interpretation, at least by the group in St. Louis,was that this represented a calcium deficiency and by giving calcium to these infants, the bone disease corrected. Yet, others reported a baby with high 1,25-D_3 levels where they also had bone disease. What we were saying was that in the low birth weight infant in the first two to three weeks of life, we were recommending a higher intake of calcium and old fashioned parent vitamin D.

COMMENT: What I was referring to was this. Haven't there been studies showing that in hypocalcemia, especially of prematures, you can raise the serum calcium level in the first few days of life with 1,25-D_3 seemingly more rapidly than with nothing or with other vitamin D metabolites, suggesting that 1,25-D_3, even in the first few days of life, may increase gut absorption? Or do you feel that you are increasing it by increasing bone mobilization of calcium?

RESPONSE: You are correct. There are reports demonstrating that 1,25-D_3 in the first few days of life will raise serum calcium in the low birth weight infant. There are reports showing that giving calcium in a higher

dose--as I was recommending--will raise serum calcium in the first few days of life. There are reports indicating that 1,200 units of parent vitamin D will raise serum calcium in the first few days of life. There are reports that giving 25-D_3 will raise calcium in the first few days of life. So, clearly, that's like all the rest of medicine. The data are conflicting and what is best for the infant is the question because giving high loads of calcium by mouth may in fact help to precipitate necrotizing enterocolitis. I don't know that but that certainly would have to be considered. So, what should be done for the low birth weight infant in the first three weeks of life when there is not metabolic bone disease? I don't know, but it seems rational to me to give more calcium than we have been giving yet not give it by the ton, and give a minimum amount of vitamin D.

QUESTION: As you stated, you don't know whether 1,25-D_3 increases the serum calcium by gut absorption or not. From your data it would appear that in the first few days of life 1,25-D_3 wouldn't do anything to gut absorption.

RESPONSE: The bulk of the data suggest that, during the first few days of life, 1,25-D_3 does promote increased calcium absorption. In my opinion, giving 1,25-D_3 over several days may in fact induce receptor maturation and cause an effect in the gut. Look at the curves. There is not an immediate response. However, I would be afraid to give 1,25-D_3 because I think you can get toxicity. That's why I recommend the other course.

QUESTION: In low birth weight infants, do you think that the route of calcium administration is important? Does enteral vs parenteral calcium supply alter calcium excretion in any way? My second question, since most of the low birth weight infants weighing less than 1,250 grams are not fed the first week of life, would you think that we should supply more calcium than we do and what would be your recommendation? The last question is, do you think that hypoxemia alters the calcium and vitamin D metabolism in these infants in any way? Do you think the 25 hydroxylation is impaired in these infants?

RESPONSE: The last question first. We are in a program which is concerned with the effect of various disturbances such as acid base on divalent mineral metabolism. To the extent that hypoxia can be associated with acidosis, I can tell you that acidosis decreases the 1 α hydroxylation; acidosis, however, increases intestinal absorption of calcium in the growing rat and puppy. The human infant who is acidotic may in fact have increased calcium absorption in the intestinal tract and, therefore, decreased fecal excretion. The other question: does it matter whether you supply calcium enterally or parenterally? I think it would be difficult to provide enough calcium parenterally during the first three weeks of life - particularly the first week of life. What I would suggest on a practical basis is that instead of waiting seven days, perhaps giving calcium by mouth earlier to the 1,200 or so gramer down the road may be of benefit to that infant in preventing metabolic bone disease. The last question: when do you routinely give these infants vitamin D and in what form? The recommendation that a member of our team and a vitamin D expert makes is that vitamin D--the old fashioned one that we all learned about--should be given whenever the infant

is started on oral feeding. So, if you are starting at 3-4 days, then 400 units of D would be given as a minimum to the less than 1,500 grams low birth weight infant.

MODERATOR: What about the old problems that were created when babies were getting the large doses of vitamin D in the British Empire? How do you see that developing? I have discussed that subject recently and I see more and more people using vitamin D in the premies or in the babies with low birth weight for gestational age.

RESPONSE: It is difficult to sort that out because as I read back through the literature as we entered into our studies of this problem, use of large doses of vitamin D in England was started at a period when there may or may not have been increasing amounts of the 1,25-D_3 being produced by the newborn kidney. That would be necessary for the vitamin's hypercalcemic effect. I think that the reason why at our place we have settled on suggesting not using 1,25-D_3 is because of the possibility that toxicity may result from this. That's why we feel that--as we understand this quite complicated and confusing subject--giving a minimum amount of vitamin D and a little bit more than the calcium that we have been giving, may be the optimal way of arriving at a calcium balance that's best without inducing hypercalcemia.

COMMENT-QUESTION: First a comment on the difference between hypoxia and ischemia. It's been shown in the myocardium that there is a distinct difference in the effect on the myocardium of hypoxia versus ischemia. With ischemia there is no substrate delivered to the tissues, no glucose, no anything and this will have a much more severe effect. Presumably the same occurs with the kidney. Now, a question concerning some of the data presented on receptor site in the gut. Did the researchers look at all areas of the gut or just the duodenum and jejunum (which they have mostly studied)? If there is in fact receptor site activity present in the distal part of the gut, it may explain why one cannot find any effect from 1,25-D_3 when given in the first week or so of life.

RESPONSE: The answer is exactly as you stated. They did not look at all segments of the intestines. If you have done any receptor work you know why. It's a lot of work! It is a disappointment since our findings - and incidentally there is a study in newborn rats using a flow through system where the calcium was perfused through the segment in which the greatest amount of absorption of calcium occurred. It was called the combined cecum-jejunum. So the distal intestine during early development--at least in the third trimester and the newborn period--appears to be where most calcium is absorbed. It's disappointing that there are no data yet on receptor maturation and so forth there.

QUESTION: On the topic of vitamin D, one of the things that we often have problems with, as was alluded to earlier, is: a lot of really tiny babies who are on prolonged respirator therapy are fed parenterally over the course of the first several weeks of life. In order to avoid vitamin A toxicity with multivitamin preparations that are currently available, you have to give suboptimal amounts of vitamin D. These amounts are in the range of 50-100 units/day if you're giving the usual amounts of fluid and in order to avoid vitamin A toxicity. Do you have

any suggestions as to what to do? Most of the vitamin D preparations are enteral preparations, not parenteral.

RESPONSE: Could you state the question again?

QUESTION: We've got a child that's on prolonged respirator therapy on parenteral nutrition. The vitamin D that we're able to give with the usual nutritional preparation is only about 50 international units a day. If you give more than that, you will give toxic amounts of vitamin A because the preparation is made up as a standard preparation that you have to put into your parenteral nutrition. Since the vitamin D that's currently available is enteral - you have to give it orally- you can't give it IV. Do you have any suggestions about what to do to meet your 400 international units a day recommendation?

QUESTION: One of the problems that you run into if you're giving the babies the fairly large amounts of calcium that you recommended (in the range of 150 mg/kg/day) is getting the amount of phosphorus they need into these kids, particularly, again, if they are on parenteral nutrition. What some groups have been doing is to alternate high calcium with high phosphorus bottles of total parenteral nutrition. Is that what you all are doing? Do you have any other solution for trying to get the high doses of anions and vitamin D in?

RESPONSE: We don't have a solution and we presently have a protocol approved and we are looking at this particular problem. In another six to eight months we hope to have some preliminary data.

MODERATOR: You ask for permission from the mother?

RESPONSE: Yes.

QUESTION: One of the things not addressed that I would be interested in regarding the geneticists approach to counselling,is: what do you do with males with hypospadias depending on whether they are first degree or third degree?

RESPONSE: First, of course, we take a family history. Most of the time this is a sporadic problem. Occasionally one will see a lesser degree of the same problem in the father. Basically, are you talking about recurrence? I'm not quite sure what your question is. Are you talking about management or recurrence in future cases?

QUESTION: One question obviously relates to the management of the baby at that point in time. Do you make any difference in recommendations as far as working up the rest of the GU tract? The second question is: what do you suggest to the family as far as recurrence in other male siblings of the child?

RESPONSE: First,you've got to find out if this is the only problem, of course. Generally, the recurrence is very low. There is a slight recurrence. If you are talking about the very severe types of hypospadias, then obviously the sex may be in doubt and you will need to pull out all the stops and find out everything you can about the child. You need perhaps to do chromosome studies; you may need at least at some point to take a look at the gonads. You need to do all the examinations

you can. Ultrasound I'm sure would be increasingly helpful here in the future. But, then, you've got to sit down and think what you most likely have in the way of an entity and go on from there. It is a very complicated problem. The main thing you are concerned about, of course, is whether you have a child who is at risk for adrenal insufficiency in any way. Other than that, you can take your time for solving the problems.

QUESTION: First, **have you** studied the effects of 1,25 dihydroxy-D_3 on the inverted model loops of the fetus? Second, did you look at the levels of 1,25-D_3 in your two groups? You didn't show the data on that. Finally, just to make the record straight **, in the British study the vitamin D was given to infants and children, not only infants.**

RESPONSE: Putting 1,25-D_3 in the intestinal segments, we have not done it yet. The vitamin D levels did fall. The 1,25-D_3 did but the 24,25-D_3 levels did not. This is not the first time it was shown. In England in 1980, at the vitamin D workshop, it was reported that in three fetuses there was a fall in 1,25-D_3 with bilateral nephrectomy.

QUESTION: Does the drop in level after bilateral nephrectomy mean the fetus was synthesizing 1,25-D_3?

RESPONSE: It would take too long to answer that. That would be the case except that most studies show that circulating basal levels are not detectable at all or, if at all, are very low. It is quite confusing. I have an explanation for that - like I have an explanation for everything else...

MODERATOR: On that positive note we shall adjourn. Thanks to the panel and participants in general for their contributions.

II

LOW BIRTH WEIGHT INFANTS

Strauss, J. (ed.) Neonatal kidney and fluid-electrolytes

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FLUID AND ELECTROLYTE MANAGEMENT IN LOW BIRTH WEIGHT INFANTS

William Oh, M.D.

In this presentation, I will discuss 1) the physiologic basis for the formulation of fluid and electrolyte therapy in low birth weight (LBW) infants, 2) some practical aspects in initiating fluid therapy during the first day of life in the LBW infants, 3) describe the system for the monitoring of fluid and electrolyte balance in the first week of life, and 4) the potential complications of inappropriate fluid and electrolyte management in LBW infants, particularly those with respiratory distress syndrome.

PHYSIOLOGIC CHARACTERISTICS IN LOW BIRTH WEIGHT INFANTS WITH REFERENCE TO FLUID THERAPY

One of the unique physiologic characteristics that might influence fluid and electrolyte management in LBW infants is the composition of their body fluid at birth and its subsequent redistribution during the first week of life. Infants who are born prematurely, for instance, at 30 weeks of gestation, have high body water content (80-85% of the total body weight) and a large portion of this fluid is confined to the extracellular space (1). Within the first week of life, the body water content decreases by approximately 10% and this reduction (which is removed from the body) is primarily from the extracellular compartment (2) (Table 1). More recently, Stonestreet, et al. (3) have shown that

Table 1. Redistribution of Body Fluid in Low Birth Weight Infants During the First Week of Life (Mean Gestation=30 weeks, Birth Weight 1500 grams).

BODY FLUID (% BODY WEIGHT)	FETAL*	NEONATAL** (6 DAYS OLD)
TOTAL	83	73
EXTRACELLULAR	53	39
INTRACELLULAR	30	34

*Friis-Hansen, B.: Pediatrics 47:264, 1971.
**Kagan, B., et al.: Am. J. Clin. Nutr. 25:1153, 1972.

excess fluid and sodium intake during the first week of life may influence the pattern of redistribution of the body fluid during this period of time. In that study the protocol was designed in such a manner that the LBW infants will receive two different amounts of fluid therapy during a five day period: One group receiving in excess of 160 ml/kg/d (high intake group) and another, less than 130 ml/kg/d (low intake group). The results showed that the group of infants who received high fluid intake had expanded extracellular fluid compartment while in those who received the more conservative fluid treatment, the extracellular fluid compartment contracts by 10%. These changes were observed in spite of the appropriate changes in renal functions in these two groups of infants, i.e., those who received high fluid intake had an increase in free water clearance and urine output. In spite of these adaptive renal changes, the infants had expanded extracellular fluid representing fluid retention (Table 2).

Another important variable that would influence the fluid therapy in low birth weight infants is the ability of the kidney to compensate for excessive or inadequate fluid intake. Previous works by Calcagno, et al. (4) have shown that comparing to adult, the newborn kidney has limited ability to dilute or concentrate in the presence of excessive or restricted fluid intake. In adults, when fluid restriction occurs, the kidney can concentrate up to 1400 mOsm/L, while in newborn, the maximum concentration the kidney can achieve is approximately 800 mOsm/L. Similar limitation is present for diluting mechanism when faced with excessive fluid intake (5). Therefore, the neonates, particularly the low birth weight infants are more at risk for dehydration and fluid overload when inappropriate fluid therapy is instituted. Another important consideration is that in the previous studies where the adaptive renal mechanism of the low birth weight infants was studied, the infants examined were relatively large prematures(average birth weight of 1700 grams). This data may not be applicable for the current survivors who are often very low birth weight (weighing less than 1000 grams),who may have an even more limited renal adaptive mechanism,who may have difficulty in concentrating or diluting when inadequate or excessive fluids are administered.

Table 2. Inulin Space (ml/kg) in Infants Receiving High or Low Fluid Intake Between Day 2 and 8 of Age.

	AGE OF STUDY (DAY)	
FLUID INTAKE GROUP	2	8
LOW n=8	343±30*	272±24*
HIGH n=9	310±10	309±58

M±SEM

*Significantly different, $p < .05$

From Stonestreet, B.S., et al.: Am. J. Dis. Child., In press (3).

GUIDELINES FOR FLUID THERAPY IN LOW BIRTH WEIGHT INFANTS

The principle of fluid therapy is to provide maintenance, replace the fluid loss, and replace the current loss while fluid therapy is being instituted. In newborns, particularly low birth weight infants, the majority of fluid therapy is for maintenance purposes. The maintenance requirement generally consists of fluid required for insensible water loss, water for urine formation, replacement of water loss through the stools and water for growth. In the first week of life, the amount of stool losses is very small and growth is not a consideration. Therefore, the two major parameters that need to be fulfilled in providing maintenance fluid therapy in the first week of life are required for insensible water loss and for urine formation. The amount of water required for urine formation is dependent on the renal solute load. In the first few days of life, the renal solute load is derived primarily from an endogenous source which approximates 5 mOsm/kg/day. As the solute intake increases, the renal solute load also increases which will require the additional amount of water for the formation of urine. The amount of water required for renal solute excretion will range from 30 ml/kg/d during the first day to approximately 60-70 ml/kg/d by the end of the first week to ten days of life (6,7).

In regard to the insensible water loss, the requirement can be quite variable depending on the therapeutic, environmental and physiological factors involved. Table 3 lists the factors that might increase or decrease the insensible water loss in infants. It is apparent that each infant may have different insensible water loss requirements depending on the infant's level of maturity, ambient temperature, and relative humidity, and whether the infant is being treated with phototherapy or not. While a certain amount of fluid can be calculated and given during the first day of life, the subsequent course of fluid management should be calculated on a day-to-day basis using a system of monitoring to estimate the daily requirement.

Table 3. Factors Affecting Insensible Water Loss (IWL).

IWL Increases	IWL Decreases
1. Decreasing birth weight or gestation	1. High ambient relative humidity
2. Ambient temperature exceeding neutral thermal zone	2. Use of ventilator
3. Fever	3. Use of heat shield or double wall incubator
4. Phototherapy	
5. Radiant Warmer	
6. Low ambient relative humidity	

The fluid requirement for the first day is generally dependent on the gestational age and birth weight of the infant and whether radiant warmer or phototherapy is used. Thus, for a full term infant who is being treated with phototherapy and is cared for in an incubator, the fluid requirement would consist of 20 ml/kg/d for insensible water loss, 40 ml/kg/d for renal solute excretion, amounting to a total of 60 ml/kg/d for the first day of life. An infant weighing 1000 grams at birth generally requires the use of a radiant warmer for appropriate temperature control and for better access to the infant for intensive care; this would increase the insensible water loss by approximately 50% of his requirement under incubator care. Therefore, the requirement for this infant during the first day would be 30 ml/kg/d for urine formation and 60 ml/kg/d for insensible water loss. Since we anticipate a weight loss of 10 g/kg/d for removal of body fluid during the first day, we would then have to give only 80 ml/kg/d to allow for a negative water balance. As indicated previously the requirement for the next few days would be dependent on the performance of the infant under various circumstances.

The fluid balance can be monitored with a system that is fairly simple but requires meticulous collection of pertinent data, appropriate organization of this data into a tabulated form, and daily physiologic interpretations of these data. The pertinent data includes intake, output, urine specific gravity, acute changes in body weight, and serial serum electrolytes. These data are generally easy to collect, except for the urine volume which is often difficult to obtain because of the size of the infant and the problem of urine spillage, particularly in small female babies. Fortunately, various ingeniously designed urine collectors are available which make urine collection feasible in small infants. In male infants, urine collection can be done by placing the penis in a test tube with a catheter in place to asperate and measure the urine whenever the infant voids. In the female infants, the urine collection can be extremely difficult. In these instances, pre-weighed diaper can be used and urine volume estimated by the difference in diaper weight before and after voiding. The data should be tabulated preferably following the schedule of the nursing staff (7 a.m. to 3 p.m., 3 p.m. to 11 p.m., and 11 p.m. to 7 a.m.) since nurses are the key persons in the collection and documentation of this information. This information can then be interpreted on a regular basis to assess the fluid balance of these infants. It should be emphasized that the goal of fluid balance in the first week of life is to achieve a negative balance with an anticipated weight loss of approximately 10% during the first week of life. This reduction in body weight reflects the normal contraction of the body fluid along with some tissue breakdown because of relatively inadequate caloric intake during this period of time. Allowance for 1 to 2% per day of weight loss during the first week of life is essential to avoid fluid overload or dehydration.

ADVERSE OUTCOME OF FLUID THERAPY IN LOW BIRTH WEIGHT INFANTS

Because of a marked variability in the fluid requirement of the low birth weight infants, adverse problems may occur particularly in the daily monitoring and adjustment if fluid intake is not done. Dehydration with hypernatremia and fluid overload with subsequent cardiopulmonary complications may occur. Dehydration may occur if intake is far short of the requirements and the situation is undetected for several days.

The diagnosis of dehydration is generally not difficult; weight loss in excess of the physiologic limits along with significant elevation in serum sodium as well as blood urea nitrogen are the usual manifestations. The problems can be reversed readily by appropirate documentation of the degree of dehydration and prompt replacement of losses.

Fluid overload on the other hand can precipitate the onset of symptomatic patent ductus arteriosus (PDA) particularly in low birth weight infants with respiratory distress syndrome. This observation was initially documented by Stevenson (8) and subsequently confirmed by a prospective randomized study by Bell and his co-workers (9). In the latter, a group of infants weighing less than 2000 grams were prospectively randomized into a high (exceeding 160 ml/kg/d) and low (no more than 130 ml/kg/d) fluid intake to assess its effect on the incidence of symptomatic PDA. Since the sodium concentrations in the infusate were not varied, the high fluid intake group also received a higher sodium intake (4.5 vs. 2.5 mEq/kg/d). The studies showed conclusively that high fluid intake increases the incidence of symptomatic PDA. Fortuitously, the same authors also found that the incidence of necrotizing enterocolitis is also higher in those infants who received high fluid intake (10). In addition, a parallel physiologic study also showed that infants who received high fluid intake had an expanded extracellular fluid compartment in contrast to those who received low fluid intake who had the normal contraction of the extracellular fluid during the first week of life (3). This expanded extracellular fluid compartment does not entirely account for the increased incidence of symptomatic PDA and NEC, but it does point out the importance of allowing for the physiologic transition of the infant from fetal to neonatal state with reference to the redistribution of the body fluid.

In summary, the management of fluid therapy in low birth weight infants is a delicate process which requires understanding of the physiologic characteristic of this group of infants, recognizing that the renal function has some limitations with regard to dilution and concentration mechanisms, that the fluid requirements could be very variable from day to day depending on the physiologic and therapeutic modalities applied to these infants and that lack of a monitoring system to assess the fluid therapy status could result in adverse outcomes in the form of dehydration and overhydration, the latter with serious cardiopulmonary consequences.

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RENAL SALT EXCRETION IN THE LOW-BIRTH-WEIGHT INFANT

A. APERIA, M.D.

Renal function is not fully developed at birth. The glomerular filtration rate (GFR) is low and many tubular transport systems are immature (1,2). The coordination of function in different tubular segments is sometimes poorer than in the adult nephron. The low renal functional capacity in the perinatal period is largely attributed to renal structural immaturity (3). One expression of renal immaturity at birth is a limited capacity to regulate sodium balance.

It is the rule in biology that the functions which are necessary for normal differentiation and growth develop early. The retention of salt is necessary for normal growth. Newborn full-term infants are able to retain sodium, but are unable to excrete sodium when in positive sodium balance (4,5). Pre-term infants born before the 34th gestational week are less well-prepared to meet the demands of extrauterine life than full-term infants. They are unable to retain sodium even when in negative sodium balance and they are also unable to increase sodium excretion when in positive balance. Pre-term infants are therefore highly dependent on a well-controlled salt intake to avoid states of negative as well as states of positive sodium balance.

Sodium-losing states in newborn pre-term infants

When newborn pre-term infants are given a daily sodium intake lower than 1.8 mmol/kg, the sodium excretion generally exceeds the sodium intake and a negative sodium balance will develop (4,6,7,8). When a negative sodium balance develops in the adult, tubular sodium reabsorption increases and the fraction of filtered sodium decreases to less than 0.5 %. The fractional sodium excretion in newborn pre-term infants is about 2% during the first week of life (2,9) and does not change much with the state of sodium balance. One of the mechanisms by which adults retain sodium when they are in a negative salt balance, is to augment the production of aldosterone, which enhances the sodium reabsorbed in the distal parts of the nephron. The aldosterone production is generally

high in pre-term infants (10), but clinical studies suggest that infants born before the 34th gestational week are unable to fully respond to aldosterone (4) in the neonatal period. The limited availability of pump-sites for active sodium transport of Na-K-ATPase (11,12) may be another factor responsible for the inability of the immature kidney to increase tubular sodium reabsorption by physiological needs.

The clinical implications of a negative sodium balance in pre-term infants have not been fully elucidated. Mild hyponatremia is almost the rule in pre-term infants if the daily sodium intake is less than 2 mmol/kg. The increase in the daily sodium intake to 3 mmol/kg generally increases the serum sodium value in pre-term infants to that observed in full-term infants, older children and adults (6). The potential dangers of mild to moderate hyponatremia, however, are not so well known. In clinical practice, infants appear to withstand serum sodium values between 120 and 130 mmol/l fairly well. It has been reported, however, that a negative sodium balance in pre-term infants retards growth (13) and augments the high production of angiotensin and aldosterone in the neonatal period (10).

Salt retention states in pre-term infants

When pre-term infants are given excessive amounts of sodium they do not immediately increase their sodium excretion as adults and older children do (9). The difficulties of inducing natriuresis in the neonate can be attributed to both a low GFR and immature control of tubular sodium reabsorption.

During the first days of life the GFR when related to body weight and body surface area, is low - about 25% of that observed in the adults, both in pre-term and full-term infants (2,14,15). In full-term infants there is a rapid almost two-fold increase in the GFR during the fist week of life. This accelerated increase is not so apparent in pre-term infants. In pre-term infants with a gestational age of 32-34 weeks the GFR increases linearly from 15.9 $\pm$ 1.9 ml·1.73 m^{2-1} ·min^{-1} ($mean_1$ $\pm$ 1 SE) at 1-2 days of age to 37 $\pm$ 3.7 ml·1.73 m^{2-1} ·min^{-1} at 3-5 weeks of age.

The low sodium excretory capacity following a saline load in the neonate is probably not only ascribable to the low GFR. When adults are given a saline load, fractional sodium excretion generally increases to between 5% and 10% of the filtered load. In the pre-term neonate the fractional sodium excretion rarely increases above 5% (9). The same relative differences in fractional sodium excretion following a saline load are also observed between the adult and infant rat (16) and lamb (17). The reasons why the immature kidney cannot adequately inhibit tubular sodium reabsorption when presented with a saline load, have not been fully delineated. Heterogeneous functional development of the nephron with a relative overcapacity of the distal tubule to reabsorb sodium may be

one factor contributing to the difficulty of inducing natriuresis in the infant kidney (16,18).

A low concentrating capacity is also characteristic of the infant kidney (19). When the infant kidney is presented with a saline load, relatively more sodium than water is retained. Infants are therefore predisposed to develop hypernatremia. This condition may occur when acidosis is treated too aggressively with sodium bicarbonate. Hypernatremic and hypertonic conditions are known to predispose to cerebral hemorrhage (20), permanent cerebral damage and damage to other tissues (21).

SUMMARY

Pre-term infants born before the 34th gestational week have a very limited capacity to regulate sodium balance. They are unable to efficiently retain sodium when in a negative sodium balance and to efficiently excrete an excess of sodium when in a positive sodium balance. They are therefore predisposed to hyponatremia and hypernatremia. The serum sodium values should be monitored frequently. Empirically it has been found that a daily sodium intake of 3 mmol/kg/dag results in most cases in a satisfactory salt balance in newborn preterm infants.

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Metabolic Bone Disease in Low Birth Weight Neonates

Craig B. Langman, MD and Eddie S. Moore, MD

Michael Reese Hospital, University of Chicago Pritzker School of Medicine, Chicago, Illinois

Introduction

The marked advances in neonatal care over the last decade have allowed survival of the small premature infant less than 1500 gms. Unfortunately, the advances in survivorship have been accompanied by a multitude of new problems, including the presence of bone disease which may result in short term morbidity and also affect future growth potential.

The manifestations of metabolic bone disease (MBD) are wide; a subclinical disease consisting of osteopenia on skeletal radiographs may be contrasted with overt rickets in the growing premature infant. MBD may also affect more than the skeletal system. Respiratory muscle weakness resulting in prolonged intubation and recurrence of pulmonary dysfunction in the first month of life or unexplained acidosis and poor growth secondary to hyperparathyroidism may be the first clues to the presence of MBD.

To adequately understand the pathogenesis of MBD in the neonate, it will be necessary to briefly review perinatal physiology of calcium, phosphorus and vitamin D.

Calcium

Fetal skeletal growth occurs as a result of a large calcium flux from the maternal circulation, steadily increasing from 118 mg/kg fetal body weight/day at 24 weeks of gestation to between 150-200 mg/kg/day at term (40 weeks), (Kelly 1951; Ziegler 1976). This calcium flux from mother to fetus occurs largely independent of the maternal states of calcium or vitamin D balance, although a recent study does demonstrate an effect of maternal hypoparathyroidism on neonatal parathyroid status (Gradus, 1981). Recently it has been demonstrated that fetal nephrectomy will arrest the maternal to fetal calcium flux, suggesting an important function of the fetal kidney in divalent mineral homeostasis, (Moore 1982).

Normal values in the fetus of total and ionized calcium are 11-13 mg/dl and 5-6 mg/dl respectively, and are clearly elevated over normal maternal values of 8-9 mg/dl and 3.5 mg/dl. Serum immunoreactive parathyroidhormone concentrations are undectable in the fetus while elevated in the mother, (Weiland 1980, Whitehead 1981).

Upon transition to extrauterine environment, the infant must continue to have a marked positive calcium balance to grow adequately. The premature infants's task is to recreate the large in-utero calcium influx to assure normal skeletal mineralization. Because of the lack of maternal input of calcium, neonates must rely on gastrointestinal absorption as the sole means of mineral accretion.

Balance studies to date have demonstrated that low birth weight neonates cannot adequately duplicate the calcium influx provided by the placenta, (Barltrop 1973; Brewer 1981; David 1973; Ghisan 1982; Hillamn 1980; Kulkorni 1980; Levin 1971; Moya 1982; Shaw 1976; Shenai 1981; Steichen 1980; Tsang 1980). Variables influencing calcium retention include the calcium/phosphorus (Ca/P) ratio of the formula ingested, the total amount of formula taken, and the sugar moiety of the formula. Proprietary formulas with higher Ca/P ratios result in a greater accumulation (mg/kg/day) of calcium without reducing positive phosphate balance in the small neonate. Of interest, however, is the observation that the efficiency of absorption (% intake that is retained) of calcium for proprietary formulas is only half that of breast milk (27 vs 54%, respectively), despite the low Ca/P ratio in human milk. This difference in % retention of ingested calcium may be due to the known effect of lactose (the exclusive sugar in human milk) to increase the gastronintestinal absorption of calcium through non-vitamin D mediated mechanisms (presumably, coupled sugar-calcium cotransport). Additionally, the absolute volume the small premature neonate ingests severely limits the supply of calcium, even with very efficient absorptive mechanisms. Recently, in utero rates of accretion have been demonstrated using an experimental formula, (Greer 1982A).

Thus a net deficiency of calcium (when compared to the supply received in-utero) could result from inadequate dietary calcium content intake or inadequate gastrointestinal absorption. The potential role of dysfunction of vitamin D homeostasis in gastrointestinal function will be discussed below.

Phosphorus

Skeletal growth mandates sufficient supply of phosphorus as well as calcium. Little data exist on placental transfer of phosphorus and still less on controlling factors, although active transport of phosphorus is thought to occur from mother to fetus. It is known that the fetus is hyperphosphatemic (8-10 mg/dl) with respect to the mother (2.5-3.5 mg/dl) and to the neonate (5-7 mg/dl). Fetal nephrectomy, but not ureteral ligation with intact kidneys, results in a more severe elevation of serum phosphorus than normal with no change in maternal values, (Moore, 1982).

The relative inability of the neonatal kidney in the first several days of life to respond to exogenous PTH with a phosphaturia may contribute to the presence of hyperphosphatemia, (Connelly 1962). After several weeks however, renal immaturity cannot account for the presence of the hyperphosphatemia, as PTH induces a significant phosphaturic response. The levels of serum calcium and phosphorus (CaxP product) often exceed 70 mg%, a level at which extraosseous

calcification is thought to occur in older individuals. Since there are no reports of deleterious effects in neonates of the elevated CaxP product, protective mechanisms against extraosseous calcification must exist and to date are unknown.

Dietary phosphate restriction significantly lowers the absorption of calcium, presumably by interfering with vitamin D mediated processes at the gut and by altering renal tubular handling of calcium, (Lau 1979). Thus, not only the Ca/P ratio of a formula is influential in determining mineral balance but the absolute amount of phosphate intake may be critical as well.

The composition of hyperalimentation fluids is significantly low in phosphate, due to the limited solubility of many phosphate salts in the fluid itself. Prolonged use of this fluid may lead to hypophosphatemia, and necessitate institution of phosphate supplements, (Klein 1982; Rowe 1979).

Vitamin D

A review of basic vitamin D physiology is beyond the scope of this article, and the reader is referred to recent discussions, (Fraser 1980; Schnoes 1980). Maternal serum 1,25-dihydroxy vitamin D (1,25D) concentrations are elevated over normal values by the beginning of the second trimester of pregnancy, (Whitehead 1981). The elevation presumably results from the need to supply large amounts of calcium to the fetus and thus, the need to increase maternal calcium absorption. Maternal serum 25-hydroxy vitamin D (25D) and 24,25D concentrations reflect the basic vitamin D state of the mother, and are usually in the normal range, (Weiland, 1980).

Recent studies have documented the very close correlation of fetal 25D concentrations to maternal values at term, (Brooke 1981; Greer 1982; Hillman 1977; Sann 1981). Dispute exists over the relationship of 1,25D in fetus and mother. 1,25D in the newborn fetus has been shown to be lower, equal or higher than corresponding maternal values, (Fleischman 1980; Gertner, 1980; Lester 1978; Weisman 1980). More recently it has been demonstrated that fetal 25D is accumulated by placental transport (mother to fetus) but maternal 1,25D does not cross the placenta in the same direction. In fact, fetal 1,25D crosses into the maternal circulation, (DeVaskar 1980). Thus, the presence of fetal 1,25D occurs from fetal produced or placental derived 1,25D. Two studies have suggested that 1,25D in the fetal circulation is the controlling factor for maternal to fetal calcium flux, (Moore 1982, Ross 1979).

After birth neonatal 25D values are influenced by vitamin D intake, (Lester 1981). Data suggest that absorption of vitamin D is diminished in the neonate and that quantitatively more is necessary through the enteral route to achieve adequate 25D concentrations. This may be secondary to a relative cholestasis (Baliestreri 1982), in the premature infant causing vitamin D malabsorption. There does not appear to be a defect in the premature neonate's ability to 25

hydroxylate the parent vitamin D compound in the liver, (Salle 1982). Through ingestion of only 400 IU per day of vitamin D, the premature neonate's 25D levels reliably fall to rachitic values (10 ng/ml) by six weeks postnatally, while normal levels are usually maintained through ingestion of 800-1200 IU daily, (Hillman 1980). Human milk contains virtually no vitamin D or its metabolites (Greer 1981B; Hollis 1981).

1,25D metabolism has not been extensively studied in the low birth weight neonate, but may be substrate dependent as in the older age child and adult. Normal values in the first months of life (80-120 pg/ml) are twice those of other age groups, (Glorieux, 1981; Lund 1980). Decreased function of the enterohepatic circulation present in prematures may cause significant fecal loss of this metabolite (20-30% of daily production), (Kumar 1982). The biologic response to 1,25D, gastrointestinal absorption of calcium, has not been studied in low birth weight infants, although administration of 1,25D is associated with correction of hypocalcemia in several patient groups, (Chan 1978; Petersen 1981).

Dietary calcium restriction has been shown to elevate renal production and hence, serum concentrations of 1,25D in suckling and weanling rats as it does in the older age animal. Thus, the renal 25-hydroxy vitamin D 1-hydroxylase is able to respond in times of calcium stress in the young animal as in the adult, (Langman 1982A).

Metabolic Bone Disease

The presence of metabolic bone disease in the premature neonate is the result of a complex array of actors including calcium and phosphate balance, activity of the vitamin D-parathyroid hormone axis and the state of acid-base balance, (Bosley 1980; Callenback 1981; Chesney 1981; Cifueutes1980; Donovan, 1980; Greer 1981; Klein 1982; Kulkami 1980; Laptsanis 1976; Levin 1971; Pettifor 1979; Rowe 1979; Rudolf 1980; Steichen 1980; Sydow 1945). Although the occurrence of MBD may be initiated by a discrete deficiency of one of the above elements, it is likely that its continued presence involves at least all of the aforementioned processes.

The most obvious case of MBD is that of overt rickets in the premature neonate. Stigmata appreciated on physical examination include areas of hypertophic, unmineralized osteoid and cartilage at the wrist (radial ulnar), the costochondral junctions (the "rachitic rosary") and even in the skull. Biochemically, hypohosphatemia and moderate hypocalcemia are present, usually with serum alkaline phosphatase concentration greater than 700 U, (Kovar 1981). Roentgenographic evaluation demonstrates severe osteopenia, characteristic epiphyseal changes of rickets with or without periosteal abnormalities, (Teitlebaum, 1980).

More common, but less well documented, are cases of subclinical rickets in the premature neonate. By definition, physical examination is unremarkable for bony deformities and routine serum biochemical values (calcium and phosphorus) are generally in the normal ranges. That this form of MBD exists must be

demonstrated through the use of high-magnification skeletal radiographs of areas sensitive to bone dysfunction, through the use of both bone densitometry (BMC) measurements and through measurement of vitamin D metabolites (25D; 1,25D).

High resolution bone radiographs demonstrate osteopenia (when compared to age matched controls) in premature neonates with the subclinical form of MBD. These subtle changes may be more easily shown through measurement of bone desitometry, where age related normal values have been established, (Chan 1981; Greer 1981; Greer 1981A, Greer 1982A; Hillman 1980; Minton 1979; Robert 1981; shaw 1976; Tsang 1980). It is interesting to note that dramatic decreases in bone density may occur in premature neonates and not manifest as overt MBD. It is clear that cases of overt rickets are associated with very low 25D, as is seen in the older infant and child with D-deficiency rickets, (Birkbeck 1980; Cifuentes 1980; Eastwood 1979; Greer 1981A; Hillman 1977; Hoff 1979; Klein 1982; Kulkorni 1980; Papaoulous 1980; Robinson 1981; Sann 1981; Semo 1981), although recent reports documented normal 25D levels in "classical" rickets (Chesney 1981; Greer 1981). However, subclinical form of MBD may also have low circulating 25D. 1,25D concentrations have been reported as low, normal or elevated in neonates with classical rickets, (Chesney 1981; Gradus 1981; Greer 1981; Klein 1982; Salle 1982; Semo 1982; Steichen 1982), but has not been investigated in the subclinical form of the disease. A similar change in 1,25D can be seen in older individuals with rickets or osteomalacia (Eastwood 1979; Papapoulous 1980).

Previous studies have demonstrated an incidence of overt MBD (rickets) in the small premature neonate to be 1-15%. There are no data on incidence of subclinical MBD per se, although significant decreases from normal in bone densitometry measurements and 25D levels may suggest a 25-35% incidence. As our ability to maintain life in the very small and premature neonates increases, it is likely that the occurrence of MBD will also rise.

MBD may adversely affect organ systems other than the bony skeleton. Myopathy associated with either rickets or the subclinical form of MBD may have deleterious effects on pulmonary mechanics, such that intubation and mechanical ventilation are necessary at a time when "pulmonary" disease is not apparent. Also, recurrences of pulmonary failure in the first several months of life have also been attributed to the presence of MBD and its associated myopathy. The effectiveness of respiratory therapy (percussion and postual drainage) may be limited because of the increased likelihood of bony thorax fractures in those infants with MBD (WW Fox, RA Polin: personal communications). In fact, the authors have observed cases of spontaneous fractures of the extremities in the face of routine nursing care in infants with subclinical MBD.

In addition to short-term effects noted, recent data suggest that the presence of MBD early in life, even if corrected, may influence future growth potential at one-year follow-up visits (Greer 1982). Growth processes very early in life are critical for normal growth velocity in later childhood, and as seen in other

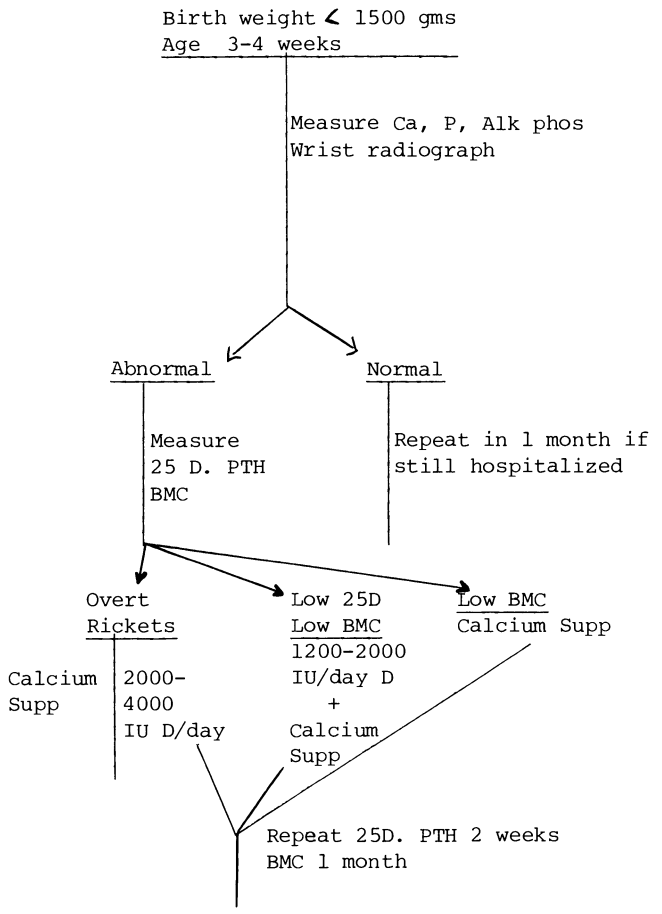

Figure Schema for evaluation of MBD in low birth weight neonates

diseases affecting growth, disruption leads to significant growth retardation and diminished growth velocities (Langman 1982).

MBD may also be a manifestation of systemic disease, including renal insufficiency, renal tubular acidosis,inborn errors of metabolism or liver disease (cystic fibrosis, neonatal hepatitis, biliary atresia). Exclusion of these illnesses should of course be carried out in a premature neonate presenting with overt rickets or even subclinical MBD . Often a mild acidosis may occur with only MBD, and result from the presence of secondary hyperparathyroidism and the known effect of PTH on the renal handling of bicarbonate in states of PTH excess (Hellman 1965).

There are several additional groups of neonates who have a high frequency of MBD. Firstly, neonates on long term parenteral hyperalimentation may develop profound hypophosphatemia and significant rickets. This may be further aggravated by the low amount of vitamin D in most fluid mixtures and the tendency towards an acidosis (a result of the large amounts of chloride salts of the amnioacids in the fluid) and the consequent suppression of 1,25 production by the kidney (Bushinsky 1982). A second group of prematures who may likely develop MBD are those with cholestatic liver disease secondary to prolonged hyperalimentation, even if they are not currently being fed by parenteral alimentation methods. It appears that that liver dysfunction prevents 25-hydroxylation in the liver of the parent vitamin D compound. Also, the bile salt dysfunction leads to calcium malabsorption.

As presented in the Figure, our scheme for investigation of MBD involves surveillance of hospitalized infants with a birth weight less than 1500 gms when they are 3-4 weeks of age. At that time, serum biochemstries are measured and wrist radiographs are taken. If osteopenia is demonstrated alone or in conjunction with hypophosphatemia and/or hypocalcemia, serum 25D, PTH and bone densitometry (BMC) are measured.

Appropriate therapy if overt rickets is documented is 2000-4000 IU/day of vitamin D with calcium supplementation. Subclinical rickets with low 25D and osteopenia is therapied with 1200-2000 IU/day vitamin D and calcium supplementation. The subclinical form of MBD characterized by osteopenia alone and normal 25D levels is therapied with calcium supplementation. When MBD has been demonstrated, follow-up examinationsof 25D and PTH are made in 2 weeks and BMC in one month. Wrist radiographs may be rechecked in 1-2 months.

Hospitalized infants from this population who did not have MBD upon first investigation are reinvestigated if remaining in the hospital one month later. The same diagnostic format is applied.

Prevention of MBD in the small premature neonate is the goal of the clinician. The personal recommendations of the authors include:

a. provision of 160-200 mg/kg body weight/day calcium through special formulas with higher calcium content and through the use of calcium supplements (gluconate, lactate, glucobionate salts)

b. provision of 800-1200 IU/day vitamin D enterally

c. provision of a Ca/P ratio of 2.4-4.1, without decreasing the absolute phosphorus content

To briefly summmarize, neither the true incidence of skeletal dysfunction (metabolic bone disease) in low birth weight neonates nor the specific causative mechanisms are known. However, an understanding of the in-utero physiology of the infant with regard to divalent mineral homeostasis allows us to make a first approximation in diagnosing and treating Metabolic Bone Disease.

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RENAL THROMBOSIS IN THE NEWBORN

L.F. Dominguez, M.D., R. Fojaco, M.D., R. Goldberg, M.D.,
E.S. Setzer, M.D. and J. Strauss, M.D.

Renal thrombosis (RT) in the neonatal period, paradoxically, is infrequently reported even in the very low birth weight (VLBW) infant who requires intensive care. Management of the critically ill newborn has improved greatly and prenatal care has become so widely available that in many situations, predisposing factors for RT tend to disappear. In patients with RT, questions still remain as to the actual incidence of the obvious morbidity in general and of sequelae such as hypertension and chronic renal failure.

MATERIALS AND METHODS

All autopies performed in neonates at the University of Miami-Jackson Memorial Medical Center during the period 1969-1981 were reviewed. The criteria for diagnosis of RT included the presence of renal artery or vein thrombi accompanied by renal parenchymal evidence of reno-vascular circulatory compromise, excluding agonal or post-mortem intravascular changes. In patients with the diagnosis of RT, histological sections of liver, lungs, spleen, intestines, brain and adrenals were also examined for thrombi in small, medium or large blood vessels. IVP and ultrasonography, when available, were used as confirmatory evidence of RT.

The clinical records of the patients with RT were reviewed to ascertain pertinent clinico-histological factors. Included were gestational age, post-natal age at death, sex, race, predisposing factors, and clinical-laboratory course. Factors regarded as predisposing in the mother were diabetes, toxemia, and renal insufficiency; in the neonate, prematurity, pulmonary disorders, sepsis, congenital heart disease, perinatal asphyxia, hyperbilirubinemia, shock, disseminated intravascular coagulation (DIC), congenital renal anomalies, and presence of an umbilical artery catheter (UAC) were included. All determinations were performed in the Clinical Laboratories of Jackson Memorial Hospital, utilizing standard methods.

RESULTS

Of 1,624 autopsies performed in neonates during the period 1969-1981, the Pathology Report of 41 described arterial or venous RT, or both. Application of more uniform criteria by a single pathologist narrowed the study number to 29 patients (2.4/year or 1.7% of all autopsies performed in neonates during the twelve year study period). Renal vein thrombosis (RVT) was present mainly in full-term neonates (62.5%) while

Table 1. Renal Thromboses in 29 Neonates by Gestational Age.

	THROMBOSES				TOTAL	
GESTATIONAL AGE	VEIN		ARTERY			
WEEKS	#	%	#	%	#	%
26-34	1	12.5	11	52.3	12	41.4
35-37	2	25	4	19.2	6	20.7
38-42	5	62.5	6	28.5	11	37.9
TOTAL #, %	8	100	21	100	29	100

Table 2. Renal Thromboses in 29 Neonates by Post-Natal Age at Time of Death.

AGE AT DIAGNOSIS	THROMBOSES				TOTAL	
DAYS	VEIN		ARTERY			
	#	%	#	%	#	%
2	1	16.6	2	9.5	3	10.3
2-4	2	33.3	6	28.5	8	30.8
5	3	50.0	13	62	16	58.9
TOTALS	6	100	21	100	27	100

renal artery thrombosis (RAT) was found mainly in pre-term infants (62.1%) (Table 1). Age at death ranged from few hours to 30 days; age at diagnosis of RT ranged from less than 2 to greater than 5 days with most vein or artery involvement (50% and 62%, respectively) present after 5 days of age (Table 2). There was a slight predominance of white (55%) and female (52%) babies. There was a definite predominance of arterial (72%) over venous (28%) RT (Table 3).

Table 3. Renal Thromboses in 29 Neonates by Anatomic Site of Thromboses

VEIN		ARTERY	
#	%	#	%
8	28	21	72
5R		13B	
3B		5R	
		3L	

All live born babies with RT had had an UAC inserted. The catheter had been left in place less than 3 days, 4-10 days, or longer than 10 days. There were similar numbers of babies with arterial thrombosis regardless of duration of catheterization, but larger numbers with venous thrombosis as duration of catheterization increased (Table 4). Other predisposing factors present most frequently for RAT (each in 15% of patients) were prematurity, pulmonary disorders, and sepsis; for RVT, included were prematurity (18.8%), sepsis (13.5%), and congenital heart disease (13.5%) (Table 5). All live born infants with RT were anemic; a majority had thrombocytopenia (84%), hyperkalemia (71%), and azotemia (59%) (Table 6).

There was a preponderance of bilateral (18/29) and branch vessel (16/29) localizations of thrombi (Table 7). Of the 21 babies with RAT, 57% also had other arterial thrombi (Table 8).

Table 4. Renal Thromboses in 27 Neonates* by Duration of Umbilical Arterial Catherization

THROMBOSES	DAYS			TOTAL
	<3	4-10	>10	
VEIN	2	---	4	6
ARTERY	8	8	5	21
TOTAL #	10	8	9	27
TOTAL %	37	30	33	100

*2/29 were stillborn with renal vein thromboses.

Table 5. Predisposing Factors in 29 Neonates with Renal Thromboses

PREDISPOSING FACTORS	THROMBOSIS		
	VEIN (8 CASES)	ARTERY (21 CASES)	TOTAL (29 CASES)
MATERNAL			
DIABETES MELLITUS	-	1	1
TOXEMIA	-	1	1
RENAL FAILURE	1	-	1
NEONATAL			
PREMATURITY	3	15	18
PULMONARY DISORDERS	1	16	17
SEPSIS	2	13	15
CONGENITAL HEART DISEASE	2	9	11
PERINATAL ASPHYXIA	1	7	8
HYPERBILIRUBINEMIA	3	5	8
SHOCK	1	4	5
DIC	1	3	4
CONGENITAL RENAL ANOMALIES	1	2	3
TOTAL	16	76	92*

*This total reflects the fact that each of the 29 neonates had more than one predisposing factor.

DISCUSSION

RT has been reported to occur in less than 1% of all patients in the pediatric age group admitted to hospitals (22); of these, 60% occur in the neonatal period (23). When autopsied neonates were reviewed, 0.8% of the offspring of non-diabetic mothers had RT (24); this value is close to the 0.5% incidence obtained in our study of all babies autopsied in the last 12 years at our Medical Center which included those of diabetic mothers. The similarity of the above percentages may be due to improved prenatal management of diabetes plus prompt and aggressive management of these babies in neonatal intensive care units.

Table 6. Renal Thromboses in 27 Neonates* by Abnormal Laboratory Results

THROMBOSES	URINE	BLOOD					
	≥5 RBC/HPF	PLATELETS ≤100,000/mm^3	Hb ≤10g	Na+ ≤130 mEq/L	K- ≥5.3 mEq/L	BUN ≥20 mg/dl	S Cr. ≥ 1.0 mg/dl
VEIN	2/4	2/4	3/4	2/5	4/5	3/5	2/3
ARTERY	11/21	9/9	21/22	8/18	11/16	10/17	3/8
TOTAL	13/25	11/13	24/26	10/23	15/21	13/22	5/11
%	52	84	92	43	71	59	45

*2/29 were stillborn with renal vein thromboses

TABLE 7. Renal Thromboses in 29 Neonates by Localization of Thrombus

ANATOMIC DIAGNOSIS	#	UNILATERAL	BILATERAL	MAIN VESSEL	BRANCHES	TOTAL
VEIN	8	3	5	8	--	8
ARTERY	21	8	13	5	16	21
TOTAL	29	11	18	13	16	29

The role that UAC plays in the development of umbilical artery thromboses has been debated extensively and remains unsettled. This complication was reported in 3.5-9.5% of neonates in a clinical and radiographic study (25) and in 15% of autopsied infants studied (7). Both studies included only neonates with UAC. This evidence of a high rate of serious complication prompted an editorial statement in which UAC was associated with vasospasm, thrombi, emboli and infection and declared to be dangerous probably regardless of "high" or "low" position or manufacturing characteristics (56).

The incidence of renal artery thrombosis may be higher with low positioned catheters (57). In one study, unilateral or bilateral renal artery thrombi were found in almost 3% of all neonates with an UAC; all of them were hypertensive (57). In another study, 4 of 10 hypertensive neonates were found to have indications of renal artery or aortic thromboses (9). In another, of 112 patients with UAC, 48 were autopsied and 2 (4.2%) had evidence of arterial thromboses in such a location that the kidneys would likely be affected (7). In our series, the thromboses occurred in 1.3% of the autopsies, mainly in premature babies older than 5 days of age; RAT was 2.6 times more frequent than RVT and was not influenced by duration of catheterization. Of interest is the fact that even in studies questioning the cause and effect relationship between catheter and thrombosis, no artery or vein occlusion was found unless there had been a catheter in the umbilical artery or vein. In our study the only exceptions were 2 stillborn babies with RVT.

RVT among infants and children seems to be most frequent in the first year of life (74%). Sixty percent occurs within the first month of life (23). RVT has been found in association with maternal diabetes or toxemia, difficult delivery, birth asphyxia, prematurity, sepsis, congenital renal anomalies and congenital cyanotic heart disease (58,59).

This retrospective study was undertaken in order to evaluate factors which might be relevant to the genesis of RT in the neonate. It is hoped that a prospective study will result once the questions become more sharply focused and new technology is utilized in a consistent assessment of measurable variables.

TABLE 8. Renal Artery Thromboses in 21 Neonates by Involvement of Other Arteries.

THROMBOSES	SUB TOTAL	TOTAL CASES	(%)
I. RENAL WITH OTHER ARTERIES			
A. LARGE			
1. ABDOMINAL AORTA.....11			
2. ILIAC AND MESENTERIC..... 1	12		
B. MEDIUM SIZE			
1. PULMONARY..... 1			
2. SPLENIC, UMBILICAL AND ADRENAL..... 3	4	12	(57)
C. SMALL (MICROCIRCULATION)			
1. NEC..... 1			
2. DIC..... 1	2		
II. RENAL WITHOUT OTHER ARTERIES..... 9	9	9	(43)
TOTAL THROMBOSES		21	(100)

NEC = Necrotizing Enterocolitis

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DISCUSSION

José Strauss, M.D., Moderator

QUESTION: In your collection of data on the umbilical vessels' catheters and the incidence of thromboses, have you looked at the placement of the arterial catheter? Were they high in the thoracic aorta or were they at the bifurcation? How does the location relate to the thrombosis?

RESPONSE: We have asked that same question but could not have the answer in time for this Seminar. Again, it is the limitation of retrospective evaluations; but we feel that from the neonatology notes, we will have some idea. What we have concluded is that the only way to look at this material is prospectively, hoping that we are going to be around for the next ten-fifteen years and be able to acquire enough material. But, yes, it is very easy to put the catheter too far up into the main vessels. We will have to look at that question, undoubtedly.

COMMENT: You might check X-ray reports if you can't tell from the neonatologist's notes. We write lousy notes.

QUESTION: One speaker explained her reasons for expressing the sodium requirements in body surface area. The other was speaking about body surface area as playing a role in water evaporation. What is your technique for measuring body surface area? Is it easy? Could we use it for each child?

RESPONSE: I guess that it does not give us a very accurate measurement. We obtain it by the usual index for surface area but it's not quite accurate in pre-terms. We are well aware of that but it's one way of expressing the results. We could also express them in kilogram of body weight. What I wanted to show in this was just the differences between pre-term and full-term and they hold whatever you express them in. But I guess that is more crucial for you to have the absolute values.

COMMENT: It's a very good point, as a matter of fact. I don't know whether you remember, but about ten years ago there was a big debate as to how you should express the various metabolic parameters in infants. Should it be body weight, surface area, extracellular fluid compartment, lean body mass? You name them. There was a lot of discussion. A very elegant paper was written - I think it was in the Pediatric Clinics of North America - making the point that the best way of expressing the data is extracellular fluid--at least in humans. You can't get lean body mass, you can't get carcass weight. But the problem is, from a practical point of view, it's not that easy to get even the extracellular fluid value. So, for the easiest, from a convenience point of view, body

weight is the best. It's true that surface area is difficult to calculate in low birth weight infants, particularly if you get down to the 1000 grams, 600 grams range because there really is no normative data in that particular group. This is why most people use the body weight for expressing the fluid or electrolyte requirements. I think that's more of a logistic problem. From a science point of view, one really shouldn't use either one. The best is lean body mass or extracellular fluid but you can't do that in clinical settings. So, the best available data you can have as the baby gets to the unit is the body weight. It's the single easiest parameter to obtain. To try to extrapolate that to surface area by using a nomogram which does not apply to that baby, I think probably would give you more trouble than benefit.

COMMENT: As a non-neonatologist trying to be a little more accurate, we used electronic scales and found exactly the same data as you have shown--variation of the electronic device with temperature.

RESPONSE: That is a good point. There are a couple of commercial companies who are trying to design an electronic scale which would be built into the incubator or a radiant warmer which would continuously record the weight of the infant. That kind of information is important because in order to rely on those numbers you must make sure that the scale's temperature is always equilibrated. Otherwise, you get all kinds of crazy numbers.

QUESTION: In regards to the study on thromboses, I would like to know if you had heparin in your infusate. Also I would like for some of the discussants to comment on the pros and cons of heparin in infusates given to premature infants.

RESPONSE: Again, these are data we don't have at this time. I would ask anyone in the Panel: what do you recommend in the management of venous and arterial umbilical catheters?

RESPONSE: To answer your question directly, I personally don't like to use heparin for two reasons. One is you could easily get into trouble with overdose no matter how good your nursing and medical crews are, accidents occur and that's one potential complication. The other reason, actually more important, is that if you gave the dose you are supposed to give - 100 units/100 ml over a 24 hour period - it is enough to generate quite a bit of metabolic changes, including a fairly significant elevation of free fatty acids. That, as you know, is a very important anion that will compete for albumin binding sites. Lots of problems are involved in terms of potential complications of increased fatty acid content in the plasma. I don't think there is a good deal of evidence to support the contention that putting heparin into the line would necessarily reduce the incidence of thrombosis - not just renal vein but umbilical artery and even aortic thrombosis - per se. I think it's more dependent on a number of other things such as the size of the catheter in relation to the size of the baby, the number of invasions you do to the catheter, the number of infusate changes you make, and duration of catheter placement. So, there are a number of factors which could influence your incidence of thrombosis. I don't think heparin necessarily would reduce that incidence. That's my bias, I guess. I suspect if you

ask for an opinion from this audience of neonatologists, whether they use heparin, a minority would say "yes"; a majority would say "no".

COMMENT: You are talking about the size of the vessel, not the size of the catheter.

RESPONSE: Yes, excuse me, the size of the vessel. I'm taking about if you put a No. 5 French catheter in a 700 gramer, you probably will get more trouble. You couldn't get it in, in the first place, but I am trying to dramatize the point. It has some bearing in terms of the incidence of thrombosis. The question that was raised earlier about the location of the catheter probably is not an important factor. Even if you put a low catheter - not because I'm biased for high even though we do use high catheters - if the thrombosis begins, the thrombus will spread upward anyway. It doesn't make much difference up above the major vessels or below. Once it occurs, as shown by some radiologists, a couple of years ago, it will spread up; it doesn't matter where your catheter is.

MODERATOR: That is interesting. The time that I spent with Dr. Stanley James - as far as I know, he is the one that started umbilical catheterization - made me an "expert" in that area. So, in 1961, I was invited to go to Uruguay to demonstrate the placement of the umbilical catheters. I was very nervous. I had a large group of people around me while I attempted to catheterize the baby's umbilical vessels. I was so happy that I was able to get the arterial catheter in easily, that I kept going and going and going. So, they took an X-ray and the catheter was all the way up in the heart, all curled up. The moral is that it really is something you can easily accomplish if you do not follow the various guides as to the catheter location.

QUESTION: In Costa Rica we are seeing an increase in rickets in premature and low birth weight infants who are in the nursery for a prolonged period of time. We usually think - maybe in an old-fashioned way - that the lack of sun exposure is an important factor during these one or two months that they are admitted. My question is: do you think sun exposure is important as part of the treatment? The other question is: why the number of units of vitamin D you recommend instead of another figure--maybe 2,000 or less?

RESPONSE: The only relationship that I am aware of is the study showing that the concentration of 25 hydroxy vitamin D in the newborn varies with the concentration of that metabolite of vitamin D in the mother. The percent of 25-D_3 in the baby has a linear correlation with the mother's concentration of 25-D_3. However, there was not a clear-cut demonstration of significant changes in maternal 25-D_3 in the summer versus the winter. If Dr. Freundlich is here maybe he could comment further on that because I may not have the maternal studies correct. But I don't think that the lack of exposure of the mother before delivery would play a role and I don't think sunlight should be considered in the therapeutics of the problem in the infant.

COMMENT: In that same study there was a difference in the season of sampling. In spring-winter there was a lower 25-D_3 level than in the summer. There was a straight correlation between mother and infant 25-D_3 levels, implying that no matter what happens, the baby is born with an armentarium coming from the mother.

COMMENT: Which could be used further to interpret that, if the mother's vitamin D status is in great disarray at delivery because of poor nutrition, then the infant's starting out level would therefore reflect the mother's level. In terms of your question, why 400 units, it has been suggested that maybe 800 units would be a better figure. I really can't disagree with that. We had to choose a number. I indicated yesterday that despite some of my wild statements, I think it came through today in my recommendations as to how to proceed in the evaluation of infants, that we became conservative. I think that the field of hypercalcemia is real so far as we are concerned and we would rather see a conservative approach in the infants who are not very small or are not very sick. But as the number of variables began to enter into play, such as the use of anticonvulsants in a very small infant, then clearly the dose of vitamin D that we would give would probably increase as well as the dose of calcium. The smaller the baby the more problems are present that could play a role in vitamin D physiology. For example, with use of anticonvulsants, which we did not talk about, the dose would have to change in an upward manner.

COMMENT: Let me say a few words on calcium, the rickets business. I don't think that the issue is the dosage. As pointed out, 400 is probably the number that you need to give. I don't think that the dose is important. It's the ability of the infant's kidney to convert the vitamin D to the 24 or 1,25 metabolites. The most important factor, at least my bias, is that they don't receive or retain enough calcium. I do have some data to support that in terms of balance studies we have done using breast milk. One of my previous fellows has done some work looking at premature mother's breast milk, feeding low birth weight infants to see whether calcium balance would improve or not. As you know, the premature mother's breast milk has a much higher content of calcium in the first fourteen post-partum days, lactating days. It turned out that there was no difference in terms of the net calcium balance. The problems in seeing a large number of rickets - as was pointed out it is about 12%, a figure that is pretty close to the real incidence - I think they are twofold. I don't think it necessarily is due to vitamin D deficiency. It may be a factor but it may not be the most important factor. The real reason is that many of these babies do not get the calcium supplementation in the first two or three weeks of life when they are only on parenteral nutrition. We tried to generate a study but finally had to give up, trying to supplement these babies in the first three weeks with calcium IV and phosphate. In order to achieve that 90 mg/kg/day net balance which is the conservative figure - others use 120 mg/kg/day - you almost have to give calcium to produce hypercalcemia. The other real problem is in trying to mix calcium and phosphate in the same container; you are going to end up with a lot of crystals in the IV fluid. So what we did was to do alternating twelve hour programs with twelve hours calcium gluconate and twelve hours phosphate without calcium. But we still run into trouble with the real problem of acute hypercalcemia. We were trying to give the amount

of calcium to achieve the 90 mg/kg/day retention. That is a real dilemma in our hands - trying to give enough calcium in the first three weeks. As was pointed out very nicely a bit earlier here, those three weeks are the most active calcium deposition phase. Yet we cannot simulate the placenta without getting into logistic problems. So, the best alternative is to try to give the most we can without producing hypercalcemia. That is to supplement with the calcium that was mentioned. I hope you are talking about total calcium salt, not ion. That will translate into 2.5 g/day. At least 250-500 mg/kg/day would give you a balance of about 60-70 mg/kg/day. At least not complete deficiency. Then, as the baby gets into the feeding phase - which is between three to eight weeks of age in the 1500 gramer - we can use the so-called special care nursery formula. This formula has some merits in terms of improving calcium retention as shown by some authors. Although their data are from a small number of patients and there is some problem with the statistics, at least they showed that their patients could have 80 mg/kg/day calcium retention during the feeding phase using this formula. The only precaution that one should have when using that formula is to be sure to shake the bottle well; otherwise all the calcium will be precipitated at the bottom of the bottle and you will be feeding non-calcium-containing formula. There's a lot of nitty-gritty things you don't realize that can make you end up with complications. That's one of them. The Ross people tell you that you have to be sure to shake the bottle. So, there is a way of trying to prevent rickets without getting into the extreme of producing rickets because of inability to give the calcium that you want to give or the other extreme of producing the iatrogenic problem of hypercalcemia. We had serum calciums in the range of 12 to 13 mg/dl when we gave IV calcium the way I told you. It was scary. So, we stopped the study.

COMMENT: I would like to thank you for supporting what my bias is, which I stated before and needs to be restated. It is that I think the calcium supplementation is more important than the provision of vitamin D. What you have stated better than I and I'd like to re-emphasize is that, in the first three weeks of extrauterine life in a low birth weight infant, a reasonable approximation of what the placenta was doing can be done by giving a larger amount of calcium than has traditionally been done. I don't think that the amount of vitamin D is important. In fact, if one does not give too much vitamin D, then the probability of hypercalcemia is less real with the addition of increased calcium than it is from giving increased calcium and more vitamin D. I would like to believe that the mechanics of calcium absorption are such that there tends to be less absorbed when one gets into either a normocalcemia or something to do with balance. The specific mechanism which decreases the rate of calcium absorption is not clear but I think that the protective mechanisms are greater if one concentrates, in the first three weeks, on getting in more calcium.

MODERATOR: I think that that is a very important practical question. In the last few weeks we were faced with such a question. I was asked what should be done with a low birth weight baby who had problems with rickets and they had kept going on with higher and higher doses of vitamin D. What both of you are saying is very important because it is

not as simple as giving vitamin D. As we were saying earlier, there are side effects from the vitamin D and one can get into serious problems.

RESPONSE: If you say that the infant has rickets, clearly demonstrable, then we are not talking about the first three weeks of life where they don't have rickets. Those are two different areas, further confusing the whole issue: whether there is active rickets versus a low birth weight infant who is potentially likely to get rickets.

QUESTION: Referring to the treatment of rickets in your scheme, after you diagnose it and everything is abnormal, then you give 1,200 units of vitamin D?

RESPONSE: That was for the treatment of what, to the best of our diagnostic abilities,is called rickets. In that circumstance what we really believe is not on that slide. We think that the combination of 1,25 and 25-D_3 is the most effective in treating rickets. There is a paper showing that bone healing occurs best with 25 and 1,25-D_3 in combination; better than with 1,25-D_3 alone, better than with 25-D_3 alone. So, actually the written statement for this presentation will state that we believe the combination of the 25 hydroxy metabolite and the 1,25 dihydroxymetabolite provide the most effective way of rapidly correcting what we call rickets. I'm glad you brought that up because it gave me the opportunity to state that.

COMMENT: Related to the information presented showing a rather dramatic gradient between the maternal serum calcium and the fetal serum calcium, if you consider that the fetal total protein at those times must be extremely low, then those differences would become spectacular. What I'm asking is, why are we still seeing these data presented in mg/dl, especially with the tremendous fluctuation in protein levels? Why are we not seeing free calcium data or is that not of any importance?

RESPONSE: You are not seeing it because the studies are going on in the lab now. The data I showed you were from previous studies by other investigators. It is not our own data. I agree with you and we are focusing on transport, looking at free-calcium as you imply. When we get more data we will present them.

COMMENT: The milliequivalents of calcium that are available physiologicall are not as different in these groups as we think.

RESPONSE: I don't believe that. That's why I lean toward early supplementation with calcium.

COMMENT: About our intention of trying to give babies after birth as much calcium as they are obtaining before birth, this may not be a valid requirement simply because rates of growth after birth often are slower than before birth. Therefore, the calcium requirement might be significantly less. It would not be surprising, if we are foisting all this calcium on the patients, that they will develop hypercalcemia! That may not be the problem but their ability to utilize the calcium when administered is at fault and that is why the thrust must be for more vitamin D rather than just for more calcium and/or phosphorus.

RESPONSE: The question as to whether the provision of calcium may not be appropriate because extrauterine growth rates are lower is the proverbial "which came first, the chicken or the egg?" The traditional provision of calcium is less than the accumulation rate in utero and therefore I would assume that bone assimilation of calcium would have to decrease and therefore growth rate would have to decrease too. So, I personally would be at a loss to determine which came first. The question is also whether or not the utilization of calcium is different in extrauterine life than during intrauterine life. As you saw in the slides, there is little 1,25-D_3 yet there is bone growth and the slide on vitamin D physiology said that 1,25-D_3 was necessary for bone growth; if there is no PTH in extrauterine life where the synthesis of 1,25-D_3 is not different, then I don't see why there should be any differences in utilization of calcium in extrauterine life than there would have been during intrauterine life. This is another reason why there is no need to give large doses of vitamin D and I lean to giving more calcium.

COMMENT: I agree with both of you, actually. I think I am inclined to be a "nice guy". To some extent the problem we see with the so-called low birth weight infant's rickets, it's really not the rickets that we see in older kids with true vitamin D deficiency. It's a calcium deficiency rickets. From the standpoint of clinical problems, with the exception of some very extreme cases where you see fractured ribs and fractured bones, it is generally a mild disease. Let me just make sure that we have a common ground in terms of looking at the magnitude of the severity and morbidity in the low birth weight infant. Considering that - there is a program on a Boston radio station called "All Things Considered" - the rickets that we see in the six-eight weeks old baby with low birth weight is probably not the kind of rickets that would be considered the most or the highest morbidity from the standpoint of its severity. To get very agressive about trying to prevent that, the cure probably will give you more trouble - that's why I say that we ought to be very careful about being too agressive. We know that we need to give them a little bit more calcium but maybe not to the 120 mg/kilo/day. I agree with you wholeheartedly that there is a problem in the data we have available as reference standards; those data are based primarily on the ash content and the calcium content of dead fetuses. There's no way to compare that with what we see in a live low birth weight infant for one thing. Also, there are a lots of complicating mechanisms involved in the placenta in transporting calcium. It's not a simple business of plasma calcium gradient between the mother and the baby. It's a very active placental mechanism involving various enzyme systems that accounts for the calcium transport from the mother to the baby. There's no way you can simulate that in the low birth weight baby. You try to do the best you can and you wind up with trouble. Not only in terms of hypocalcemia - which is the acute problem - but we might overdo things and produce all types of real, serious complications as when we give calcium and phosphorus in the same line. I think we ought to balance that in terms of the kind of problem you are talking about and the potential iatrogenic problem it could induce. If you try to get too aggressive...nature has a way... we didn't save 700 gramers twenty years ago. We're getting all these problems and we've got to find a new way to solve them. Trying to be too agressive is not the way to go. I think you get into trouble. We started a study and ended up doing only

three babies and we quit. We couldn't go on, with a calcium like 13-14 mg/d It's a good thing we were measuring it. Your point is well taken. These babies are not intrauterine babies. They are extrauterine and their calcium assimilation is different; their growth rate is different. Because of a lot of factors you cannot use the intrauterine data to try to treat a baby in th extrauterine environment.

QUESTION: I have one more calcium question. Are there any long term follow up data on the neurodevelopmental outcome or growth or any other parameters in these infants with metabolic bone disease which indicates that in the vas majority of infants there are no subsequent problems like fractures, etc.?

RESPONSE: I don't know whether this is in print yet but some say that the low birth weight infants who had metabolic bone disease which was corrected, at the end of one year of life their growth rate is still less than what would have been expected for low birth weight infants who did not have rickets. This further gets us into the issue of growth and vitamin D physiology. I hope that I am not revealing information that shouldn't be - that the long term follow-up of the infants at one year of age indicated a retarded growth rate which is the reason why in our own studies which are going on now, we have a recall evaluation of the infants for the first two years of life to see how long this growth rate retardation will continue. That's the only data I know of.

COMMENT: One series of 8 infants that was reported in Archives of Diseases of Childhood about 6-8 months ago did have a follow-up. They all recovered pretty nicely. That's one point. Now, there's a catch - 22 phenomenon abou the growth rate problem. You've got to be very careful about the data you quoted because the nutritionally more deprived infant is the one who will have more problems with rickets. Therefore, the growth rate may not be as good as in the other group. You've got to be careful about making that interpretation.

QUESTION: I'd like to ask a sodium question. Data were presented here by somebody else yesterday which concluded that low birth weight infants were in negative sodium balance initially, thus concluding that the kidneys couldn't conserve sodium normally. Today you more or less stated that these infants had high extracellular fluid volumes which you felt they should lose naturally. I would conclude that that would necessitate a negative sodium balance for the first few days of life which would be a more or less normal phenomenon.

RESPONSE: I agree with you. Your reasoning is exactly like mine. But I don't think that what was presented yesterday is necessarily contradicting what I said. The two are consistent in the sense that there are two physiologic phenomena occurring in the same subject. Meaning that with an expanded extracellular fluid compartment and a contraction in the first week of life, the mobilization of approximately 150 ml of extracellular fluid which is equivalent to 150 ml saline will necessitate excretion of that amount of sodium which is about 15 mEq/kg over a 5-7-10 days period. I think that the point made yesterday is that there is also a concomitant morphological immaturity. I hate to use the word "immaturity". My teacher, Jack Metcoff, always said "those babies are not immature; they are appropriately mature for their gestational age". It is a very nice way of putting it. The morphological and biochemical difference in

maturity will account for that sodium-losing phenomenon in response to the changing body composition in that first week of life. So, I think the two jive together. It makes good physiological sense as far as I am concerned. This is why I am not surprised about the data shown yesterday. One of our fellows studied that and found that in the first five to seven days there is a negative sodium balance in infants under 32 weeks of gestational age. That negative sodium balance is a reflection of the removal of sodium from the body fluids. I don't think there's any contradiction.

COMMENT: I would like to comment on that. First of all, I don't think that you should hesitate that much to use the term "immaturity" because there is really a difference in the degree of differentiation if you look at the tubular cells. I don't see "immaturity" as a "bad word". The second comment is that sodium balance is negative in relation to water balance. That's a sign that the sodium concentration in the extracellular fluid is lower than it should be, I think. When I talk about negative sodium balance, it's in relation to water balance. That is an effect of the - may I use the word "immaturity"? - immature homeostatic property of the kidney. It loses more sodium than water and cannot compensate for sodium losses as well as water losses and therefore sodium balance becomes negative in relation to water balance. In addition, I think there is an actual negative sodium balance because otherwise why should we have an augmented renin and aldosterone production? And why should we reduce renin and aldosterone production when we give supplemental sodium and get a normal serum sodium concentration?

QUESTION: My colleague here nicely showed that first, the premature babies are salt-losers. Then, that they are unable to respond to a sodium load by excreting that sodium load. Then, neat studies suggested that they could be resistant to aldosterone. On the other hand, we know that they have difficulties in concentrating the urine because they have short loops of Henle in superficial, underdeveloped nephrons. So, my question is, where do they reabsorb sodium?

RESPONSE: They reabsorb sodium along the nephron and I think in the distal convoluted tubule. Aldosterone works in the very distal parts of the tubules. Nephron studies have not allowed us the study of the collecting tubule and the cortical collecting duct. Those parts of the nephron might be immature with regard to the aldosterone responsiveness. The distal convoluted tubule is fairly efficient in reabsorbing sodium and has a relative overcapacity to reabsorb sodium. One could say that sodium cannot be reabsorbed - it's also very relative because sodium can be reabsorbed to say 95% of the filtered load but not to that last 5%. If we compare sodium reabsorption in the different segments, it is highest in the distal convoluted tubule. It's relatively high in the proximal convoluted tubule and it might be low in the very distal parts of the tubule, the collecting tubule and the cortical collecting duct in the very immature infants due to aldosterone unresponsiveness.

QUESTION: Don't you find it difficult to understand that when there is a state of sodium depletion the distal convoluted tubule is not able to reabsorb sodium, behaving as a salt-loser, and when there is a sodium load, it reabsorbs too much?

RESPONSE: In the distal convoluted tubule, there are no aldosterone receptors. The distal convoluted tubule might reabsorb sodium but that just stands for a fairly low proportion of the filtered sodium. What I mean is that when the infants are salt-loaded, sodium reabsorption in the proximal tubule is inhibited. Thus, the distal convoluted tubule is getting a larger load of sodium, but the distal convoluted tubule is the only part of the nephron which can increase its sodium reabsorption. So, it can increase the sodium reabsorption to a certain extent. Also, that's not the only explanation for the low sodium excretion in the pre-term infants. It's primarily due to the low glomerular filtration rate.

COMMENT: That's what I was going to remind my colleague. The delivery of sodium to the kidney is probably the most important. The tubule does the fine tuning.

MODERATOR: Is that settled? Are we clear?

QUESTION: It was stated that it is possible to induce sodium-potassium ATPase with physiologic doses of aldosterone and yet how do you jive that with the data showing that these low birth weight infants have very high levels of aldosterone? Why doesn't that induce the enzymes by itself? Or were you using higher doses?

RESPONSE: We were using higher doses. This was just an example. I think we were using a dose of 40 microgram/100 g. So that would give a serum level of aldosterone that is somewhat higher than they produce themselves. It is not a pharmacological dose.

COMMENT: In San Antonio at the Pediatric Research meeting, we presented data obtained in piglets with high dose sodium intake. We were unable to produce a change in sodium-potassium ATPase.

QUESTION: In most of the low birth weight infants who are exposed to phototherapy, we use an increment of 20% of maintenance. Do you think that 20% should be uniform for all the infants of all gestational ages? Most of the time we seem to use the same amount of fluid in term and pre-term infants when we put them under phototherapy.

RESPONSE: As far as I know, the magnitude of change with relation to gestational age is the same. The same kind of magnitude could be used. We actually demonstrated that you need 50%. Twenty percent represents approximately 5-10 ml difference in a full term baby and 10-15 in a larger baby. The kidney probably could handle that so probably it doesn't matter. You use 20%, I use 50%; it doesn't make too much difference. To answer your question specifically, I think the magnitude is the same. It's the same kind of phenomenon that's present.

QUESTION: Concerning calcium and phosphorus metabolism, it's my understanding that in premature infants the normal values of serum phosphorus may be a little higher for a normal full term infant and maybe when you see it fall with an elevated alkaline phosphatase it may be time to get concerned about clinical rickets. What is your opinion on that?

RESPONSE: One has to try to determine what are normal values. The neonatologists and nephrologists will never agree as to what is the lower limit of normal for serum phosphorus. The endocrinologists would get into the fray also. I think a value of 4 mg/dl is low in a low birth weight infant and it's approaching low in a term infant.

COMMENT: I have no problem with 4 mg/dl being low. What's wrong with that?

COMMENT: When a distinguished researcher came as a visiting professor he mentioned that in most of the premature infants that he had studied the normal lows for a premature infant between 28 and 32 weeks of gestation was between 5 and 7 mg/dl. That's the reason I brought it up.

MODERATOR: I think that's an important point. We have had to deal with those curves that show that neonates may have a normal level of 6 mg/dl. Do you think that those curves are outdated? They are reproduced in manuals and so on. What would your recommendation be for people to use as normal levels?

RESPONSE: What did you say, 5-7 mg/dl? That's about what most people use.

MODERATOR: Therefore you would agree that 4 mg/dl is low?

RESPONSE: Yes.

COMMENT: About six years ago, a fellow with me did some studies in low birth weight infants, renal function studies in our own unit in a hundred and some babies under 2,000 grams who appeared to be relatively healthy. The mean value of serum phosphorus was 5.6 mg/dl or something of that order. I've forgotten what the standard deviation was. So, clearly, 5 mg/dl would be a good lower limit of normal.

QUESTION: I would like to go back to something that we touched on earlier, umbilical catheters. At present we are not putting in too many lines. Most of the time we monitor our babies with hyaline membrane disease with $TcPO_2$ monitors and we seem to do fine. The only problem we do have is with these babies with persistent fetal circulation. What we saw as first signs of thrombosis may be diminution in the peripheral blood flow. Dopler ultrasound techniques showed the reduction in blood flow. Also, changes in the temperature and the color of the limb were very early indications of something going on. Maybe if intervention is done at that stage one would prevent further thrombosis.

MODERATOR: Yes, that is true. One of my ex-associates, Tony Beran in California, showed that implanting tissue O_2 or O_2a electrodes (as we call them) that we had designed could identify problems in terms of catheterization though as I recall, just the catheter itself, not necessarily the presence of a thrombus, decreased the perfusion to the limb.

We have in the audience a neonatal pulmonary physiologist. Would you like to comment on the way you manage those babies and whether you use catheters or not?

COMMENT: In terms of the management of our babies with PFC,we are doing what has been tried and recommended in most of the recent publications. We try first to correct the acidosis which most of those babies have. If that does not bring about an improvement in the oxygenation, we have tried to support the blood pressure with dopamine because in some of those babies it is not so much a spasm of the pulmonary arterioles as a decreased cardiac output that leads to the shunts. And under those conditions it seems to be of advantage to use dopamine to bring up the blood pressure. An approach to the problem is to measure simultaneously arterial and venous blood pressure because if you have an elevated venous pressure it can tell you something about the degree of heart failure. So, the initial approach is just alkalinization and hyperventilation; if this does not succeed, it will be an advantage to have a central venous line and measure central venous pressure.

MODERATOR: What about the use of catheters versus the transcutaneous monitoring?

RESPONSE: I try to emphasize that in a rational management of those patients,you have to have an idea about the blood pressure. The transcutaneous electrode just can give you an idea about the PO_2 in the upper and lower extremities. This is not sufficient in most of the cases.

QUESTION: I would like to return to a question about calcium metabolism. In view of the problems with calcium retention in the baby on exclusive breast feedings, I know that some people are recommending calcium and phosphorus supplementation for those very low birth weight infants. Would you comment on this?

RESPONSE: This is a very important question. I'm afraid there is no good answer. I am not trying to give you a cop-out answer. I can give you an answer but it is very anecdotal and I don't like to give an anecdotal answer. There are no real data to show that supplementing calcium and phosphorus in the breast milk fed baby would necessarily eliminate the problem of rickets. There is a potential reason for doing so but I don't know that there are any data to prove that that is so. The premature baby' mother's breast milk has a calcium content about twice higher than the normal term pool breast milk. Also,the viability of the calcium through the gastrointestinal tract seems to be better in those milks. So, you could conceivably increase the retention rate. I think one approach is to try to encourage the use of the mother's own milk to feed the premature baby and try to sequentially feed the milk to those infants because if you start feeding the two weeks old milk to the baby,that's not going to do any good. The two weeks post-lactation calcium content is exactly the same as the pool breast milk. You are not doing any good to the baby. But to try and feed the earlier part of the milk would do some good, I think. That's one approach. Whether

one should go around supplementing those babies with calcium phosphate, I really don't know that I could give you the answer, to be very honest with you.

COMMENT: I agree with what was said; I cannot add anything further.

COMMENT: I have a comment about what we heard as an explanation for the high aldosterone and renin levels in the newborn. You mentioned that inordinate sodium loss in the tubules leads to increased serum aldosterone and renin. I have an alternate explanation which is really not mine. That is that morphologically the tubules are more immature than the glomeruli in the newborn and that high renin-aldosterone serum levels are needed to confine or contain the GFR so that the tubular leak will be decreased. As we know,renin and angiotensin act at the afferent and efferent arteriolar level. They decrease the GFR just so less filtrate will be formed and less leakage will occur. Do you have any comments on that?

RESPONSE: No. I completely agree with you that those salt and water regulating hormones, most of them have other target cells and other functions in the developing kidney than later on. We know rather little about this right now but lots of studies are under way. This is probably one of the main functions of the renin-angiotensin production. With regard to your first comment that the change in renin-angiotensin was not secondary to changes in sodium balance, I think that some studies have shown that after giving furosemide acutely to pre-term infants there was an immediate increase in both renin-angiotensin and in aldosterone.

COMMENT: I didn't mean that would be the sole explanation because the levels of aldosterone and renin are high even in the cord blood.

QUESTION: In your retrospective study of patients who had renal thromboses: were there thrombi within the glomeruli or within the venules of the kidney? Where does the thrombosis start? In the major vessels or in the smaller vessels in the kidney?

RESPONSE: A good question. That is something we have asked but Dr. Fojaco has not been able to review all those biopsies prior to this presentation. She has been in Miami for the period of time of the retrospective study but she did not do all those autopsies herself; she will review every single case in order to be consistent with the criteria used but we do not have that data now. The reports in the clinical records are difficult to classify and sketchy at times. What we would like to do is have her - one observer - read all the microscopic sections so that we may be able to answer those questions. But not right now; it will be done for the paper in the book.

QUESTION: Concerning that calcium business of low-weight premature babies, I thought that there are some data showing that very low premies, despite receiving 400 international units/day of vitamin D, develop rickets. Also, that when patients are given supplemental calcium

not only do they prevent rickets,they also cure it. So, I wonder really if supplemental calcium does not play in a particular group of babies--I am very cautious about that--a prominent role in prevention and cure of established rickets.

RESPONSE: The answer is yes. That was based, as a matter of fact, on a very elegant study looking at bone density. It has to be both. I'm not saying that you shouldn't give vitamin D. Please don't misunderstand me. I think they both play an equal role in terms of the pathogenesis and also in terms of the treatment. Not only should you give them vitamin D in proper amounts but also calcium supplementation I agree that you shouldn't give 2,000-4,000-6,000 units of vitamin D because I don't think you need to give that much and you are just asking for trouble in terms of inducing hypercalcemia which could be a very serious complication. But I fully agree that calcium supplementation is another important treatment modality that you should apply.

QUESTION: My point is, will you defend calcium more than vitamin D? I advocate more calcium rather than vitamin D.

RESPONSE: I'm not saying that you shouldn't give more calcium. The question is: how much more <u>should</u> you give and how much more <u>can</u> you really give without getting into trouble. That's really my point.

MODERATOR: We have obtained a great deal of information from the panelists. Thanks to all of you for your participation.

III

FUNCTIONAL AND ORGANIC EVALUATION

OF THE NEWBORN

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ADAPTATION OF THE KIDNEY TO EXTRAUTERINE LIFE

J.-P. GUIGNARD, Service de Pédiatrie, CHUV, Lausanne, Switzerland.

Fetal Maturation

The fetal kidney does not carry excretory responsibilities. Urine formation is however present from the 9-12th week of gestation, and increases progressively throughout gestation to reach 28 ml/h shortly before birth (Fig.1). Fetal urine is the major constituent of amniotic fluid.

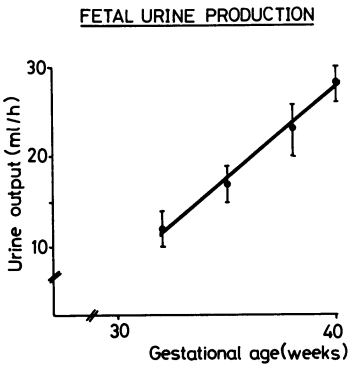

FIGURE 1. Fetal urine output during the last 12 weeks of gestation (Modified from Campbell et al.,1973).

During the last 20 weeks of gestation, renal growth is progressive, kidney weight bearing a linear relationship to gestational age, body weight and the body surface area (Fig. 2). Nephrogenesis proceeds in a centrifugal pattern, achieving the full complement of 1.2 millions nephrons by the 35th week of gestation.

The development of GFR and effective renal plasma flow during the last 3 months of gestation has been assessed in premature and term neonates. These infants were studied on the first 2 days of life, at a time when postnatal maturation was not yet playing a major role (3,4,5). GFR, as measured by the standard inulin clearance, increases linearly from the 28th to the 35th week of gestation (Fig. 3). This probably reflects functional changes in existing nephrons. From the 35th week of gestation, GFR, when expressed in relation to the body surface area, levels off up to the time of birth; this reflects a parallel increase in renal mass and function (3,5).

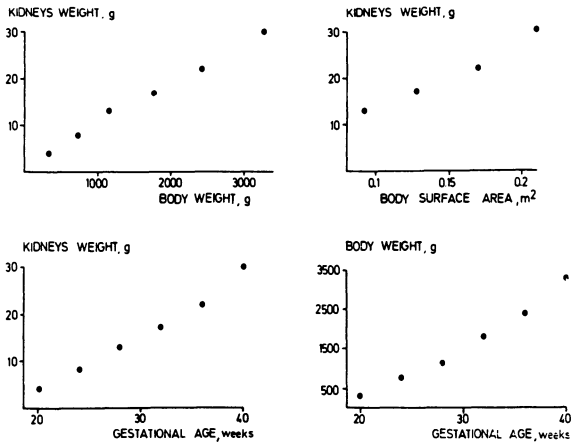

FIGURE 2. Relationship between kidneys weight and body weight, gestational age and body surface area, or between body weight and gestational age. (Modified from Schulz et al., 1962).

Effective renal plasma flow, as assessed by the standard clearance of PAH, follows the same pattern (4). However, because of the low extraction of PAH in the newborn infant, PAH clearance does not reflect true renal blood flow and must consequently be interpreted with caution at this age. The progressive increase in systemic blood pressure observed in the last 3 months of gestation is probably partially responsible for the development of renal blood flow and glomerular filtration.

Tubular functions also mature rapidly during fetal life, and the transport of several solutes is effective long before birth. Animal studies have clearly demonstrated that the fetal kidney is able to dilute, slightly concentrate and acidify the urine.

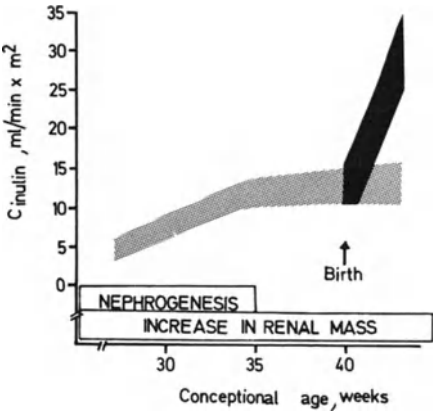

FIGURE 3. Maturation of glomerular filtration rate (C_{inulin}) during gestation and postnatal life (conceptional age). (Modified from Fawer et al., 1979).

POSTNATAL MATURATION

Glomerular filtration rate and renal plasma flow

During gestation the placenta acts as an endocrine gland and an hemodialyser perfectly adapted to the fetal needs. Clamping of the cord is the signal for striking changes in renal function (3,5,6), full homeostatic responsibility being now thrusted on the previously dormant kidney. An initial increase in urine output, GFR and effective renal plasma flow is followed by a decrease to low values by 3 hours of life (5). The large scatter of values observed at birth is significantly reduced by 4 hours of age. The narrowing of the range of renal function in the first hours of life probably reflects the achievement of stability of renal circulation, following adaptation to a variety of neonatal stresses.

The early postnatal period is characterized by a rapid increase in GFR which, from a low value of 10 ml/min per m^2 at birth increases to 20 ml/min per m^2 during the second week of life (Fig.4) (3,5). GFR is lower in very premature infants but appears to mature at comparable rates (3,5,7).

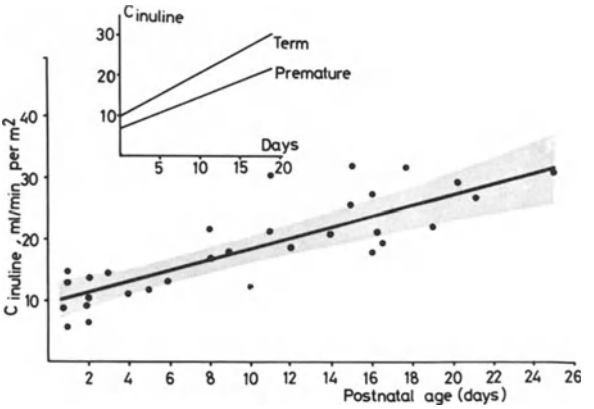

FIGURE 4. Maturation of glomerular filtration rate in relation to postnatal age. The inset compares the maturation in term and premature neonates.(Modified from Guignard et al., 1975).

Clinically, the rapid increase in GFR during the first weeks of life is evidenced by a striking decrease in plasma creatinine which stabilizes around 35 µmol/l after the 5th day of life (8). (Figure 5).

Hemodynamic and morphological changes occurring in the newborn kidney account for the rapid maturation of renal

functions : an increase in systemic arterial pressure (3), a decrease in renal vascular resistance (9), a large increase in glomerular filtering area and glomerular permeability (10). The hemodynamic changes are also partly mediated by vaso-active substances.

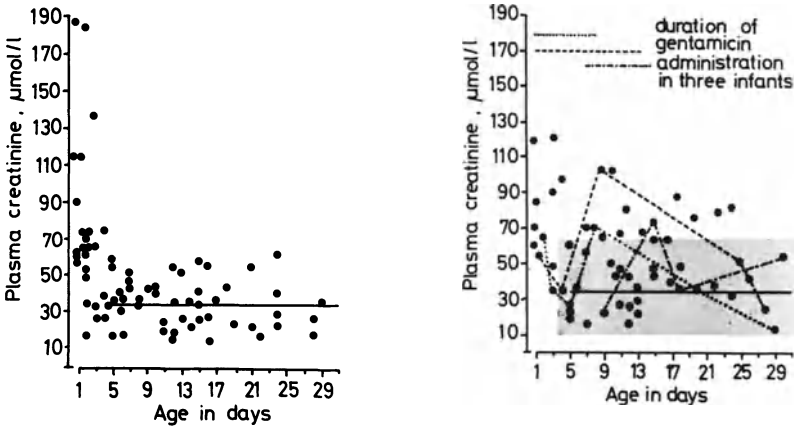

FIGURE 5 . Plasma creatinine concentrations during the first month of life of control neonates (left) and neonates receiving gentamicin (right). (From Feldman and Guignard, 1982, with permission).

Tubular functions

Urine concentration

In response to severe dehydration, the neonatal kidney is unable to increase urine osmolality above 700 mOsm/kg H_2O, as compared to the adult value of 1200 mOsm/kg H_2O (11). This represents a definite risk in the face of severe gastro-enteritis, vomiting or profuse sweating. The concentrating defect is explained a) by the scarcity of osmotically active urea available for deposition in the renal medulla of the newborn in high anabolic state, b) the immaturity of the adenylate-cyclase-ADH system, c) the shortness of the loops of Henle, and d) the interference of the prostaglandins with the action of vasopressin (12). The concentrating ability is consequently limited more by the renal immaturity than by lack of endogenous vasopressin. Maximal concentration of urine improves rapidly when the newborn is fed a diet supplemented with proteins (11). Because of decreased maximal concentrating ability, the renal requirements for excreting a definite solute load will be greater in the young infant as compared to older children. Dehydration and renal impairment are thus a serious threat in infants receiving large amounts of hyperosmotic substances, such as radiographic contrast media (13,14).

Urine dilution

The newborn infant is able to decrease urine osmolality to values as low as 40 mOsm/kg H_2O (15). Because of his low GFR, the premature infant may however have difficulties to excrete large amounts of free water (16). The ability to excrete dilute urine may be impaired during severe respiratory distress syndrome (Figure 6) (4,15).

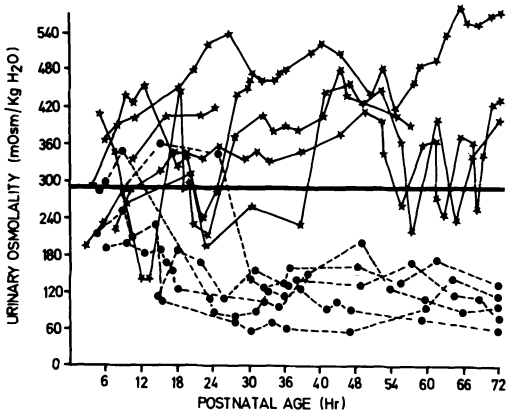

Figure 6. Urine osmolality in the first 72 hours of life of control neonates (●) and neonates with severe respiratory distress syndrome (✱) (Modified from Torrado et al., 1974).

Urine acidification

The newborn kidney is able to lower urine pH in response to a decrease in plasma bicarbonate (Figure 7) (15).

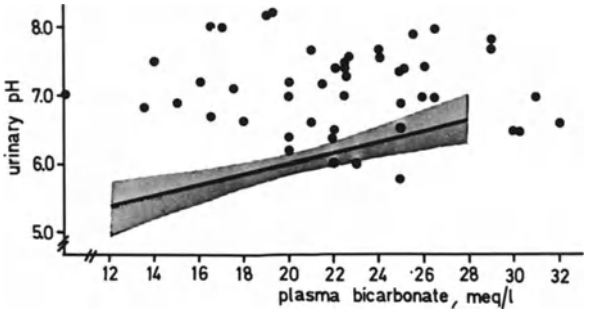

Figure 7. Urine pH in relation to plasma bicarbonate in control neonates (regression line) and in neonates with severe respiratory distress syndrome (●). (From Torrado et al., 1974, with permission).

The renal threshold of bicarbonate is fixed at 20-22 mmol/l (15), some 4-6 mmol/l below that present in the adult. The threshold may even be lower in the low-birth-weight neonate, resulting in "late metabolic acidosis" during the second and third weeks of life. This condition does not need treatment, as self correction ensues in the following weeks (17). The response to ammonium chloride loading is somewhat deficient in premature neonates, as compared to term neonates whose urine pH decreases to lower values and net acid excretion increases to higher values. The difference abates with age, and the renal handling of the acid load is comparable in both preterm and term infants by 4-6 weeks of age (18). A state of renal tubular acidosis has been described in premature neonates with severe hyaline membrane disease (Figure 7)(15).

Sodium excretion

Several factors participate in the regulation of sodium excretion : 1) the glomerular filtration rate, 2) the concentration of circulating aldosterone and 3) a third factor, the exact nature of which is still debated. The newborn kidney is characterized by marked glomerular preponderance. Glomerulotubular balance for sodium is maintained however, so that a relatively constant percentage of filtered sodium is reabsorbed. In the term newborn infant, sodium fractional excretion is elevated at birth, but stabilizes to 1 per cent or less by the third day of life. The response to sodium loading is blunted (19) probably because of the high aldosterone concentration present in the neonate (20). Very low-birth-weight infants excrete 3-5 per cent of filtered sodium, and behave as salt losers (16,21). A defect of sodium transport related to tubular immaturity and/or partial resistance to aldosterone (21,22) is probably responsible for the sodium wasting. A state of "late hyponatremia" may occur in these neonates (23), which can be prevented by sodium chloride supplementation (21).

Hormonal regulation

Plasma concentrations of renin, angiotensin and aldosterone are high in the newborn infant (24). They decrease throughout the first weeks of life. Prostaglandins synthesis also decreases following birth, but prostaglandins production may be stimulated by various neonatal stresses. The exact role of the renin-angiotensin system and the prostaglandins in regulating renal perfusion, water and electrolytes excretion is not yet established. The occurrence of total anuria in a neonate whose angiotensin II formation had been blocked in utero by an inhibitor of the converting enzyme given to the mother emphazises the role of vasoactive hormones in the adaptation of the kidney to extrauterine life (25).

Pathophysiology of the renal adaptation to extrauterine life

Endogenous and exogenous stresses may profoundly affect the function of the neonatal kidney.

a) Respiratory disturbances : Perinatal anoxia and postnatal hypoxemia, as seen during severe respiratory distress syndrome can induce renal failure in the newborn infant (4,26). Renal blood flow and glomerular filtration rate are depressed, water excretion is decreased and urine dilution is impaired. The impairment of renal function seen during severe RDS is reversible upon restoring normoxemia, extracellular fluid volume and cardiac output. The pathogenesis of the hypoxemic/asphyxic renal failure is not yet clear. Hypoxemia, hypovolemia and hypotension, which can all occur during RDS, could induce renal vasoconstriction. Clinical and experimental studies indicate that this effect could be mediated by the renin-angiotensin system (27,28,29,30).

b) Iatrogenic factors : The function of the neonatal kidney can be affected by iatrogenic manipulations such as artificial ventilation and drug administration :

1) artificial ventilation : In experimental animals, both intermittent positive pressure and constant positive airway pressure ventilation can impair cardiac output and decrease renal perfusion and glomerular filtration rate (31, 32, 33). Whether the same effect applies to human neonates remains to be determined.

2) diazepam : Intravenous diazepam, frequently used to control seizures in the newborn, can depress both glomerular filtration rate and effective renal plasma flow (34).

3) indomethacin : Indomethacin, sometimes used to achieve closure of the patent ductus arteriosus in premature neonates, can induce a transient decrease in glomerular filtration rate and free water excretion (35,36). The long term effect of indomethacin on renal maturation is unknown.

4) tolazoline : Tolazoline, an alpha-adrenergic blocking agent can be used as a pulmonary vasodilator in newborns with persistent pulmonary hypertension and severe hypoxemia (37). Acute renal failure has been observed in human neonates receiving tolazoline. Animal studies have shown that this drug can induce intense renal vasoconstriction, probably because it retains a partial alpha-agonist action (38).

5) aminoglycosides : The nephrotoxicity of aminoglycoside is well established in adults but has not been demonstrated in newborns. The relative safety of gentamicin in neonates has however been questioned recently in studies demonstrating an elevation of urinary tubular enzymes (39) or an

increase in plasma creatinine in newborn infants given gentamicin (Figure 5) (8). Creatinine clearance studies suggest that the impairment of glomerular filtration rate is more pronounced in term than in premature infants (41).

Conclusions

Advances in the care of premature infants and high-risk newborn infants have increased their exposure to a number of drugs or medical manipulations. Their beneficial effects on target organs can be counterbalanced by their action on other systems. The developing kidney, which receives a large part of the cardiac output, is particularly at risk of being harmed by the side effects of therapeutic manoeuvres, which can impair its perfusion and its excretory capacities.

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HYDROGEN ION BALANCE IN THE NEONATE

G. Zilleruelo, M.D., S. Sultan, M.D., E. Bancalari, M.D., B. Steele, M.D. and J. Strauss, M.D.

It is well known that neonates, particularly low birth weight (LBW) infants, tend to develop acidosis (1-3). The relation between maturity and degree of metabolic acidosis in the perinatal period and in early infancy is still controversial. Direct correlation between LBW and metabolic acidosis has been found by some investigators (4,5) but not by others (6). Using adult standards, renal "immaturity" has been described for many functions of the neonatal kidney including the renal acidification mechanisms (7). However, results obtained from acid-base studies in the neonatal period are particularly difficult to evaluate due to the multiplicity of factors involved (Table 1). Among these factors are: different birth weights; gestational and postnatal ages; different clinical situations such as acidotic (acute vs chronic, spontaneous vs induced) vs non-acidotic; different dietary conditions (breast milk vs cow's milk, fasting, etc). In addition, methodological and technical problems in obtaining urine and blood samples make even more difficult the evaluation of results obtained in this age group. Other factors such as perinatal events, environmental temperature and growth rate, may also influence acid-base equilibrium. In this paper, we will review some concepts about normal acid-base physiology and the response obtained in the neonate with metabolic acidosis at different gestational ages.

Table 1. Multiple variables involved in renal acidification mechanisms.

ACID-BASE STUDIES IN NEONATES ARE PARTICULARLY DIFFICULT TO PERFORM AND COMPARE BECAUSE OF:

1. Different populations (race, body weight, gestational and postnatal ages).
2. Different clinical situations {acidotic (acute-chronic), non-acidotic}.
3. Different dietary conditions (breast milk vs. cow's milk vs. fasting).
4. Technical difficulties in sample obtention.
5. Laboratory methodology
6. Other factors (perinatal events, environmental temperature and humidity, growth rate, etc).

NORMAL ACID-BASE PHYSIOLOGY IN THE MATURE KIDNEY

The body maintains its normal acid-base equilibrium by respiratory and renal control of buffers (modifiers of acid-base derangements). Normal arterial blood pH (the inverse of H^+ concentration or activity) is maintained at 7.4 and within the narrow range of 7.35-7.45. Although pH is maintained in all age groups within these limits, plasma PCO_2 and total CO_2 are lower in early infancy than in older children or in adults (Table 2) (8). To explain these differences there are several possible mechanisms: a) the more rapid respiratory rate in infants and young children; b) increased hydrogen ion production from the rapidly growing skeleton in infancy and childhood,and c) an "immature" renal tubule with lower HCO_3^- reabsorption (HCO_3^- TR).

Several buffer systems are required to compensate for the endogenous acid production and for unusual losses from, or gains to the body of either acid or base. The circulating blood buffers are of the bicarbonate or non-bicarbonate type. Although the most important buffer in the body is bicarbonate, other important systems (non-bicarbonate buffers) include hemoglobin, organic and inorganic phosphorus, and plasma proteins (Table 3).

The largest portion of acid produced daily is derived from intermedia: metabolism as CO_2 , which in its volatile form (H_2CO_3) is eliminated by the lung. There is also production of non-volatile hydrogen ion from the catabolism of proteins, mineralization of bone and synthesis of soft tissue solids (9). This non-volatile acid load must be excreted by the kidneys. Endogenous acid production varies in different age groups. Net acid production, and therefore excretion, is significantly higher in children than in adults, especially in the fast growing period. In the age group of eight to twelve years, it is significantly higher than in the group of five to seven years (Figure 1). Interestingly, there is no significant difference in net acid production between premature and full-term infants (10).

Table 2. Normal (Mean ± S.D.) Blood Acid-Base Data in Various Age Groups

	Premature Infants 2nd to 3rd Week of Life	Neonates	Children	Adults
Blood pH	7.40±0.08	7.40±0.06	7.40±0.04	7.40±0.03
Plasma PCO_2 (mm Hg)	34.0±9.0	33.5±3.6	33.9±3.5	39.0±2.6
Plasma total CO_2 (mEq/L)	21.0±2.0	21.0±1.8	21.2±1.4	25.2±2.8

From Chan, J.C.M.: Renal acidosis. In Duarte, C.G. (ed.): Renal Function Tests. Clinical Laboratory Procedures and Diagnosis. Boston: Little, Brown and Co., 1980, p.239.

Table 3. Distribution of Blood Buffers

NON HCO_3^- BUFFERS	% BUFFERING
Hemoglobin + Oxyhemoglobin	35
Organic Phosphorus	3
Inorganic Phosphorus	2
Plasma Protein	7
Total	47
BICARBONATE BUFFERS	
Plasma HCO_3^-	35
Erythrocyte HCO_3^-	18
Total	53

The lungs have an important role in the maintenance of hydrogen balance with the excretion of large volumes of generated CO_2. The kidney is another major site of hydrogen excretion (the only one for non-volatile acids). It accounts for the excretion of 4,500 mEq of acid/1.73 m^2 in exchange for the reabsorption of all filtered bicarbonate and it is responsible for the excretion of 1-3 mEq/kg/day of acid in the form of titratable acid and ammonium (11). The three main mechanisms for renal acidification are represented in Figure 2. Almost all (approximately 85%) of the filtered bicarbonate is reabsorbed and hydrogen ion secreted in the proximal tubule lumen; however, no net hydrogen excretion occurs. Mechanisms for this bicarbonate absorption include hydrogen ion secretion or so-called bicarbonate reclamation that is dependent on the enzyme carbonic-anhydrase (C-A) in the tubular cell (luminal surface) (12,13). A C-A independent system has been shown after experiments with blockade of C-A (14). Direct bicarbonate absorption possibly accounts for a minimum of the total bicarbonate absorption (15). Juxtamedullary nephrons may account for the largest bicarbonate absorption.

In the distal tubule cell (luminal surface), the proximally excreted hydrogen ion combines with filtered phosphate to form titratable acid and is eliminated in the urine. In addition, the deamination of glutamine in the distal tubular cell provides ammonia which may combine to form ammonium ion in the tubular lumen.

Functional evaluation of renal acidification usually includes exploration of proximal and distal tubular function. The proximal tubule has a high capacity system with 90% of the hydrogen ion transported there. Since this is a low gradient system, there is little change in urinary pH. Fractional excretion (% excreted from what is filtered) of bicarbonate

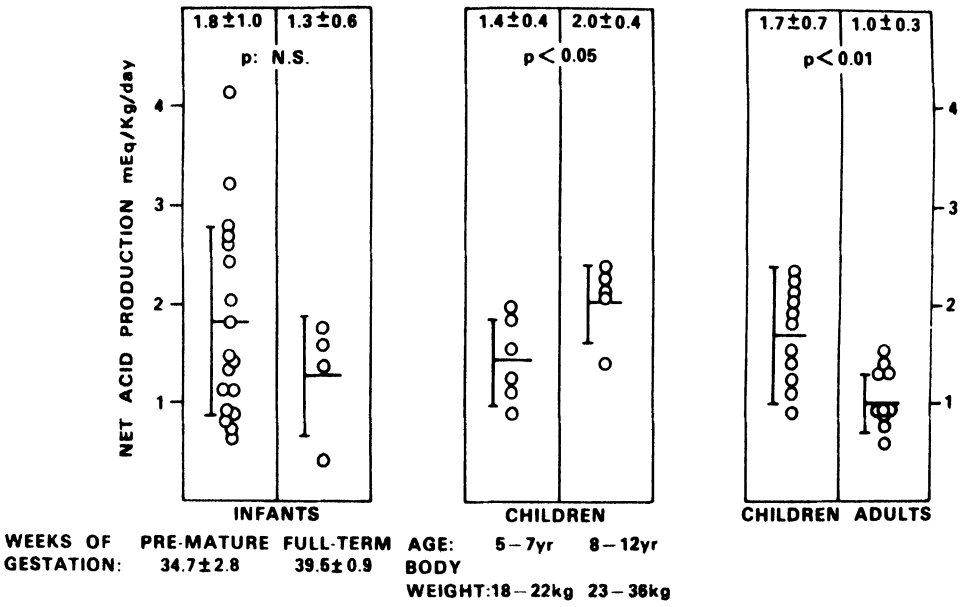

FIG. 1. Endogenous acid production in various age groups. (Reproduced from Chan, J.C.M.: Renal acidosis. In Duarte, C.G. (ed.): Renal Function Tests. Clinical laboratory procedures and diagnosis. Boston: Little, Brown and Co., 1980, p. 239, with permission).

with normal plasma bicarbonate should be always under 10 or 15%. The distal tubule has a low capacity system responsible for about only 10% of hydrogen transport; it is a high gradient system with a large change in urinary pH. During spontaneous or ammonium chloride induced acidosis, urine pH is < 5.5, ammonia excretion is > 35 μEq/min/1.73 m^2 and titratable acidity is 25 μEq/min/1.73 m^2 (16).

In summary, the kidney regulates extracellular fluid hydrogen ion concentration or activity by promoting both bicarbonate absorption and hydrogen ion excretion. Disturbances of the hydrogen ion balance will occur when there are unusual losses or addition of either acid or base which are not adequately compensated by renal and respiratory control of buffers. Net acid excretion is less efficient in early infancy, especially in premature infants, and consequently these infants may normally be more susceptible to metabolic insults that induce acidemia.

METABOLIC ACIDOSIS IN THE NEONATE

Two main types of acidosis are described in this age group. Early acidosis is usually a mixed type with respiratory and metabolic components in which insufficient amounts of oxygen and excessive amounts of lactic acid play important roles (17). This type of acidosis needs rapid correction of the underlying cause by improvement of ventilation or through administration of alkali. Otherwise, circulatory, vascular,

enzymatic and other metabolic derangements may occur secondary to the acidosis. Late metabolic acidosis is mainly observed in premature infants between 1 and 3 weeks of age (18). The term has been widely used in the past and usually describes the presence of blood base deficit > 8 mEq/L with a total CO_2 < 18 mEq/L in 3 consecutive days, impaired weight gain and usually associated with a high protein intake (19).

Reclamation and Regeneration

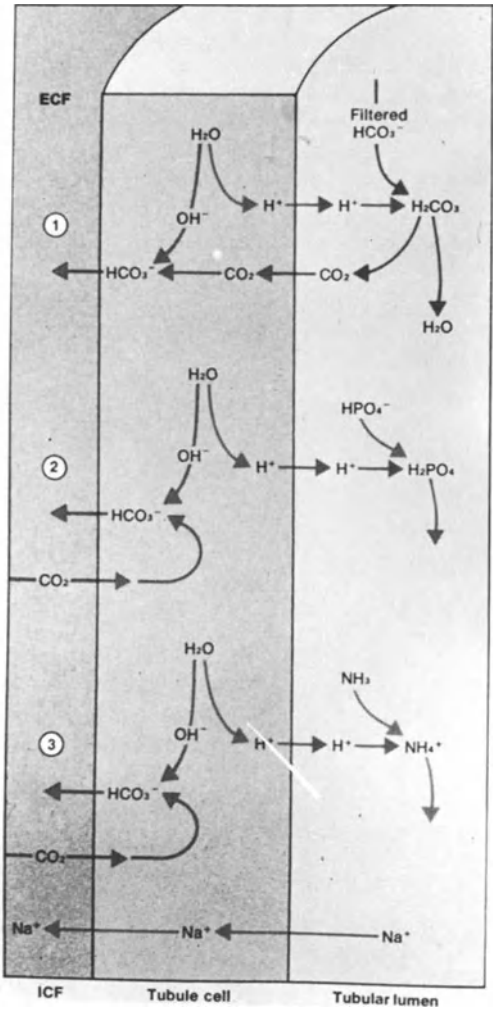

FIG. 2. Schematic representation of the mechanisms for renal acidification: Bicarbonate reclamation with reabsorption of filtered bicarbonate ①, and Bicarbonate regeneration with the acidification of phosphates ② , and the formation of ammonium ③ .

A recent study (20) of 114 low birth weight infants identified a total CO_2 increase from a mean of 18.6 at birth to a mean of 20.3 mEq/L at 3 weeks of life (Figure 3). The frequency of distribution of total CO_2 values did not show any significant deviation from normal (Figure 4). There was no difference in the rate of growth between the hypobasemic untreated infants with decreased total CO_2's and those treated with oral bicarbonate. The interpretation of this transient hypobasemia is not clear but it may be linked to other findings such as those reported by Svenningsen and Lindquist (21). These investigators studied postnatal development of renal hydrogen ion excretion capacity in relation to age and protein intake. After a short term ammonium chloride loading test, maximum hydrogen ion excretion capacity was studied in preterm and term infants between 1 and 6 weeks of postnatal age. Results showed that maximum net acid excretion capacity (NAE) is lower in preterm than in term infants at 1 to 3 weeks of age (Figure 5). However, when approaching full gestation there is a considerable increase in NAE. In the group of preterm infants with repeated studies later on in life there was not only increase of maximal NAE induced after acidosis but also an enhanced cumulative hydrogen ion excretion rate. Cumulative excretion rates of hydrogen ion as ammonia were also linear and not related to protein intake. In addition, titratable acid normalized completely in preterm infants and was related to protein and phosphorus intake (Figure 6

These results indicate that there is a rapid maturation of renal acidification capacity around the first 3 weeks of postnatal life. Nevertheless,NAE, in particular ammonium secretion, appears more closely related to gestational age than to postnatal age.

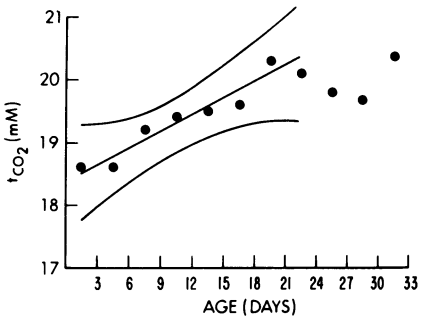

FIG. 3. Regression and confidence limits of plasma total CO_2 in low birth weight infants as a function of age. The points represent the mean value for each age interval. (Reproduced from Schwartz, G.J., Haycock, G.B., Chir, B., et al.: Late metabolic acidosis: A reassessment of the definition. J. Pediatr. 95:102, 1979, with permission).

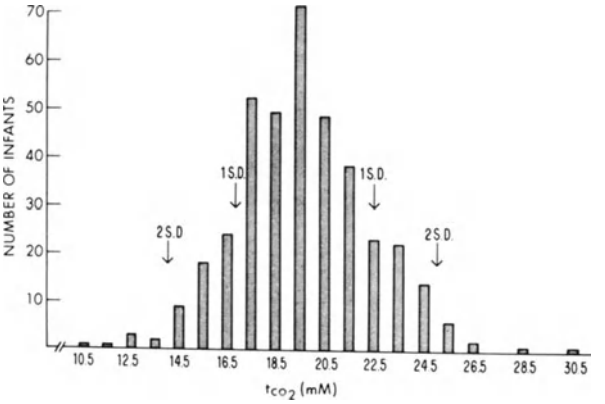

FIG. 4. Frequency distribution of total CO_2 in 114 LBW infants. Note that 2 SD include values as low as 14.5 mM. (Reproduced from Schwartz, G.J., Haycock, G.B., Chir, B., et al.: Late metabolic acidosis: A reassessment of the definition. J. Pediatr. 95:102, 1979, with permission).

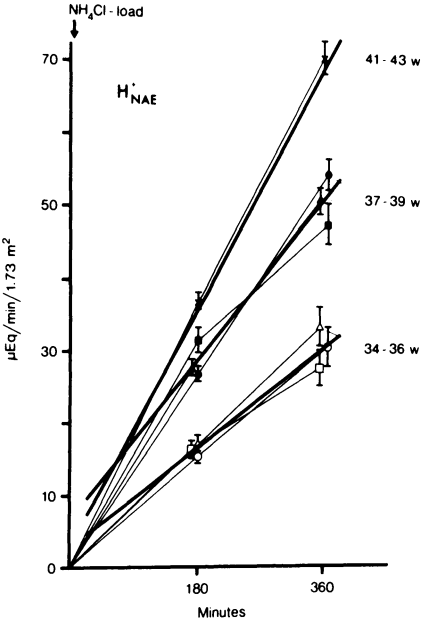

FIG. 5. **Cumulative** excretion of net **urinary** hydrogen ions after NH_4Cl loading in preterm infants studied at 34-36 and again at 37-39 weeks of gestation compared to term infants studied at 41-43 weeks of gestational age. Different symbols represent different protein intakes. (Reproduced from Svenningsen, N.W. and Lindquist, B.: Postnatal development of renal hydrogen ion excretion capacity in relation to age and protein intake. Acta Paediatr. Scand. 63:721, 1974, with permission).

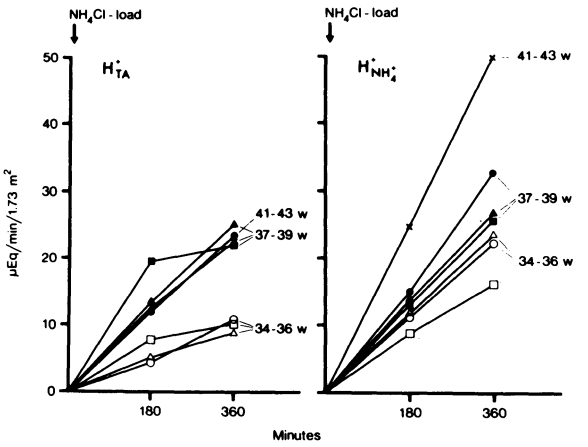

FIG. 6. Increments of excretion of urinary titratable acid and ammonium over preloading control levels during induced acidosis. Symbols as in FIG. 5. (Reproduced from Svenningsen, N.W. and Lindquist, B.: Postnatal development of renal hydrogen ion excretion capacity in relation to age and protein intake. Acta Paediatr. Scand. 63:721, 1974, with permission).

Suljok also found a significant correlation of NAE capacity with birth weight (22). In this study the ratio of sodium to hydrogen ion excretion gradually increased in urine, suggesting a progressive renal increase in sodium-hydrogen ion exchange in the distal tubule as the baby grew older and heavier. Sodium/hydrogen exchange and sodium/potassium ratio in urine seem to be related to mature aldosterone secretion or tubular responsiveness to aldosterone in those infants (22).

NAE in premature infants was determined weekly from 1-6 weeks of postnatal age (23). When maximally stimulated by systemic acidosis, NAE was less than half that found in older infants at 1 week, 2/3 at 2 weeks, and reached maximal level at 4 weeks of age. Therefore, any disease or factor increasing the acid load imposed to the kidney in a premature infant under 3 weeks of age would result in a rapidly developing metabolic acidosis. The increase and considerable rise in NAE with postnata age may reveal both increased endogenous production of hydrogen ion and increased capacity to excrete this ion.

However, several factors that normally regulate distal secretion of hydrogen ion should be considered in the interpretation of these findings (Table 4). NAE increases when there is an increased hydrogen ion production without adequate excretion (10), an increase in aldosterone secretion, or increased tubular response to aldosterone, a decrease in total body potassium usually reflected as a lowered serum potassium (potassium depletion produces a state of intracellular acidosis), or an increase in the distal delivery of sodium with an increased exchange with hydrogen in the distal or collecting tubule (23).

Another aspect of renal acidification still controversial in neonates is the so-called bicarbonate threshold. This bicarbonate threshold is usually defined as the plasma bicarbonate level at which excretion of bicarbonate is > 20 μEq/100 ml of GFR (24). A practical approach to estimate threshold is to use the total CO_2 value of blood at which urine pH=6.1. Svenningsen (25) has shown that after 8 days of age in term infants and preterm non-acidotic infants, bicarbonate threshold is ± 23 mEq/L. However, in preterm acidotic infants it is only 18 mEq/L.

There are many factors which may influence bicarbonate tubular reabsorption (HCO_3^-TR) and thus, renal bicarbonate threshold (Table 5). Factors that directly correlate with HCO_3^-TR include carbonic anhydrase activity, $PaCO_2$, filtered bicarbonate, aldosterone, calcium and phosphorus. The role of vitamin D, thyroid hormone and gestational age in HCO_3^-TR is not clear yet. There are other factors which inversely correlate with HCO_3^-TR; these factors include: plasma pH, serum potassium and chloride, effective arterial blood volume, and parathyroid hormone. An increase in these factors will result in a decrease in HCO_3^-TR; a decrease will result in increased HCO_3^-TR.

In order to obtain further insight on this aspect of neonatal function, we recently studied fractional excretion of bicarbonate in low birth weight infants with metabolic acidosis (25). The objective was to evaluate tubular bicarbonate handling during the first week of life in LBW infants with metabolic acidosis and at different gestational ages. Simultaneous arterial blood and anaerobic urine samples were collected before and during intravenous bicarbonate infusion. Sodium bicarbonate was given diluted at normal maintenance rate. These samples were analyzed for pH, PCO_2, bicarbonate, sodium, potassium, chloride and creatinine. Special precautions were taken to avoid any sudden volume expansion. Urine bicarbonate and urine pH had a significant direct correlation with blood bicarbonate. Blood hydrogen ion concentration had an inverse correlation with fractional excretion of bicarbonate. None of these infants had significant bicarbonate excretion when the blood hydrogen ion concentration was over 60 nmol/L which is equivalent to a pH of <7.22. All patients with pH< 7.22, PCO_2 > 48 mm Hg or base deficit >5 mEq/L had minimal or absent fractional excretion of bicarbonate.

Table 4. Factors Increasing Distal H^+ Secretion

↑ H^+ availability (acidosis)
↑ Aldosterone production
↓ Total body potassium (intracellular acidosis)
↑ Distal delivery of sodium

Table 5. Factors Regulating HCO_3^- Tubular Reabsorption

A) HCO_3^-TR directly correlates with:

Carbonic anhydrase activity
$PaCO_2$
Filtered HCO_3^- (GFR + $PHCO_3^-$)
Aldosterone
Calcium-Phosphorus
Vitamin D?
Thyroid Hormone?
Gestational Age?

B) HCO_3^-TR inversely correlates with:

Plasma pH
Potassium
Chloride
Effective arterial blood volume
Parathyroid hormone

We have concluded that LBW infants have an adequate HCO_3-TR during metabolic acidosis. Blood hydrogen ion concentration and arterial pressure of CO_2 seem to play significant roles as stimuli for bicarbonate reabsorption. Distal tubular secretion of hydrogen ion appears to be the limiting factor for maintenance of a normal acid base balance in LBW infants, but NAE tends to normalize around four weeks of life in these infants. Still, there is a small group of infants that will present with persistent metabolic acidosis. In this particular group, a thorough work-up for this abnormality should be done. This work-up is summarized in Table 6. It is worthwhile to emphasize that with only a few simple tools, the physician dealing with an acidotic neonate can obtain a great amount of information if appropriate interpretation of the results is done.

In summary, we have reviewed some aspects influencing the H^+ion balance in the mature and neonatal kidney. Mechanisms for renal acidification and functional exploration of proximal and distal tubular function have been described. Finally, results obtained in neonates at various postnatal and gestational ages in response to acidosis have been analyzed.

Table 6. Work-up of a Neonate with Acidosis.

TEST	RESULT	INTERPRETATION
Serum HCO_3^-	Low	Low	Acidosis
Serum Cl^-	Normal + ↓ HCO_3^- ↑ AG	Acidosis due to {excess fluid / renal failure
	Elevated + ↓ HCO_3^- N AG	Acidosis due to {HCO_3^- losses / RTA
Blood pH	Low (venous or arterial)	Acidemia
Blood PCO_2	Low (venous or arterial)	Pulmonary compensation
Blood PO_2	Low (arterial only)	Hypoxia and Secondary Lactic Acidosis
Urinalysis (fresh urine)	High pH (+low blood pH) Low pH Ketones	RTA Normal renal response Acid overproduction or calorie deficit
BUN and Creatinine	Increased	Renal failure
Blood glucose	Low	Hypoglycemia
Organic acid screen (urine)	Increased	Inborn errors of metabolism
Aminoacid screen (urine, blood)	Increased	Inborn errors of metabolism
Lactic acid (blood)	Increased	Inborn errors of metabolism

AG = Anion Gap $\{Na-(HCO_3^- + Cl)\}$
RTA = Renal Tubular Acidosis

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CALCIUM, VITAMIN D AND PARATHYROID HORMONE. RELATED ASPECTS IN THE NEONATAL PERIOD

Michael Freundlich, M.D. and José Strauss, M.D.

During the neonatal period, a host of biochemical and hormonal factors play an important role in calcium homeostasis. Among these factors, the metabolism and action of vitamin D and parathyroid hormone (PTH) are of prominent significance.

In recent years, a body of knowledge has accumulated regarding the understanding of the different steps involved in the synthesis and metabolism of vitamin D. A complete in-depth description of those aspects is beyond the scope of this chapter; those interested are referred to several excellent reviews (1-3). Provitamin D_3 (7-dehydrocholesterol) existent in the skin, is converted to previtamin D_3 upon ultraviolet radiation. Previtamin D_3 thermally isomerizes to vitamin D_3 (Figure 1). This process is slow, and upon ultraviolet radiation (sun exposure), the inactive metabolites tachysterol and lumisterol are generated. This may represent the first defense mechanism against vitamin D toxicity. Vitamin D_3 produced in the skin or ingested from animal sources, and vitamin D_2 (ergosterol) ingested from plant sources, are both bound to a specific blood vitamin-D-binding protein, an alpha-globulin, and transported to the liver. This binding protein has a much higher affinity for vitamin D_3 than for previtamin D_3; so that the previtamin D_3 is essentially limited to skin. In the liver, vitamin D_3 is converted to 25-hydroxyvitamin D_3 ($25\text{-}OHD_3$). This hydroxylation at the 25-position takes place in the liver microsomes and this reaction requires NADPH, molecular oxygen and magnesium ions.

From the liver, $25\text{-}OHD_3$ bound to the transporting globulin reaches the kidney where it is further metabolized to 1,25-dihydroxyvitamin D_3, $\{1,25(OH)_2D_3\}$, the most potent vitamin D metabolite. The 1- α-hydroxylation takes place in the proximal convoluted tubules and the reaction is dependent upon a cytochrome P-450 enzyme. The renal 1- α-hydroxylase is stimulated by hypophosphatemia, hypocalcemia and PTH. Conversely, hyperphosphatemia, hypercalcemia, calcitonin and absence of PTH inhibit the 1- α-hydroxylase enzyme but promote 24-hydroxylation. This results in the generation of another metabolite, namely 24,25-dihydroxyvitamin D_3. The exact biological role of this and other metabolites remains under investigation (2,4). $25\text{-}OHD_3$ and $1,25(OH)_2D_3$ are the best known and most extensively studied metabolites. $25\text{-}OHD_3$ is the most prevalent metabolite in human serum with a concentration 1000 times that of $1,25(OH)_2D_3$. However, $1,25(OH)_2D_3$ exerts a 1000-fold more potent action than $25\text{-}OHD_3$ in stimulating intestinal calcium absorption or bone resorptive action when judged in absolute terms. Thus, at their physiological concentrations in circulation the two metabolites probably exert equivalent biological actions (5). $1,25(OH)_2D_3$ mediates three major effects: increases

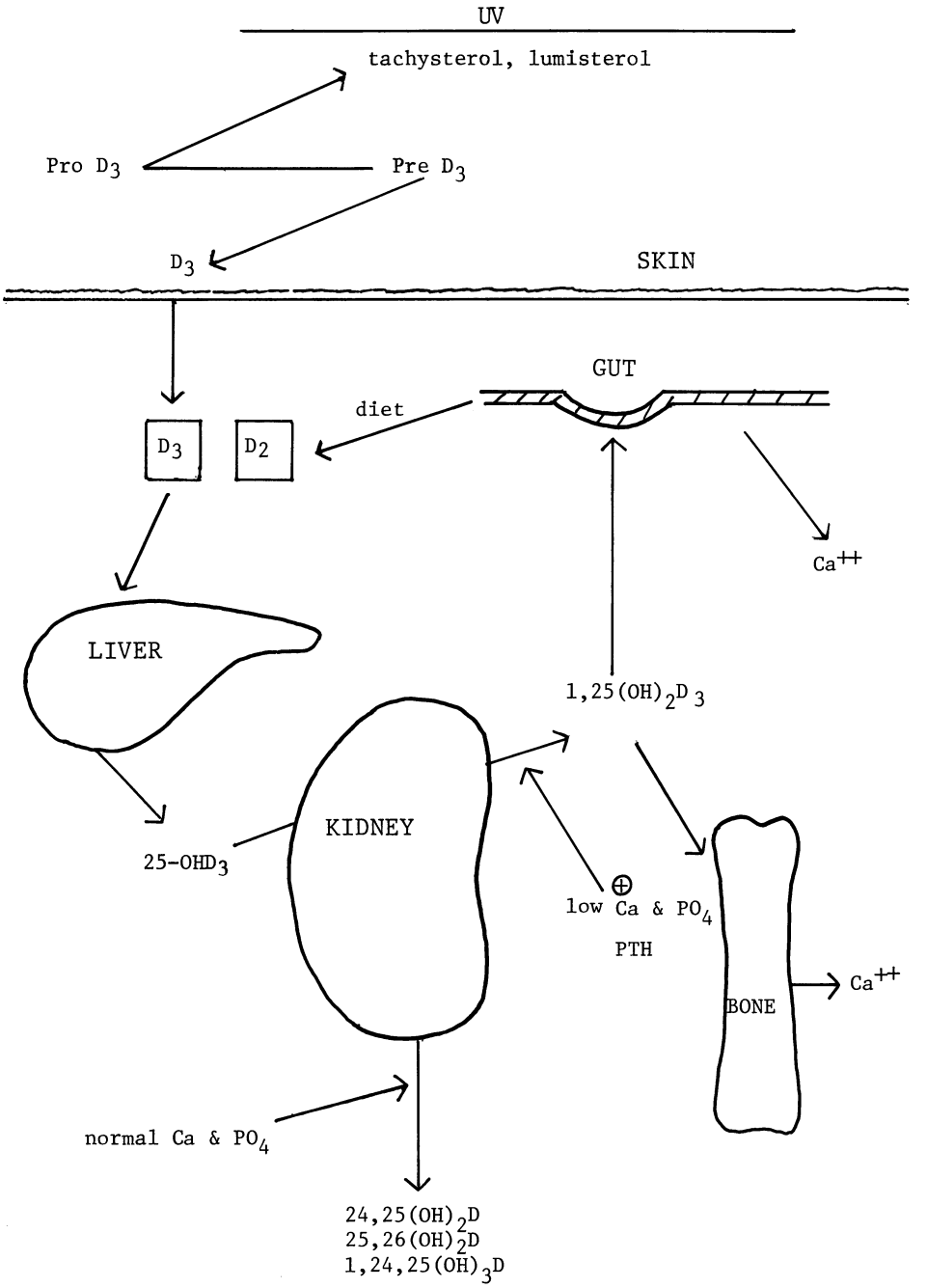


Figure 1. Biosynthesis and action of vitamin D metabolites.

intestinal calcium and phosphate absorption, mobilizes calcium and phosphate from bone and promotes renal calcium and phosphate reabsorption. The latter effect, however, remains a matter of controversy (6).

The main functions of vitamin D include prevention of the following: rickets and osteomalacia (promotes mineralization of bone and epiphyseal plate), hypocalcemic tetany, osteoporosis (particularly in aged individuals) and muscle weakness. Most of these functions are achieved by a series of interactions between vitamin D and PTH.

PTH is secreted by the parathyroid gland into the circulation as a mixture of the intact hormone (9,500 molecular weight) and lower molecular weight fragments. These hormonal fragments (Figure 2) are comprised of the biologically active amino-terminal fraction (N-terminal) and the carboxy-terminal fraction (C-terminal) (7,8). Several radioimmunoassays have been developed and vary in their ability to recognize either the intact hormone or the different hormonal fragments. In most clinical

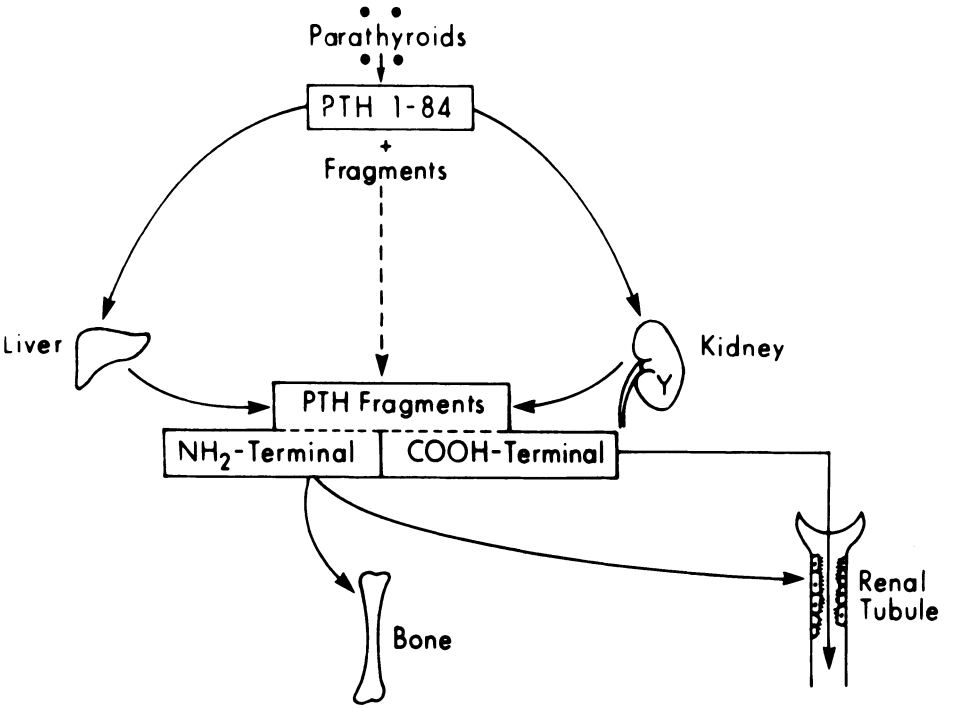


Figure 2. Possible scheme for the peripheral metabolism of parathyroid hormone. Reproduced with permission from Martin, K.J., Freitag, J.J., Courades, M.B. et al.: Selective uptake of the synthetic amino terminal fragment of bovine parathyroid hormone by isolated perfused bone. J. Clin. Invest. 62:256-261, 1978.

circumstances, radioimmunoassays recognizing the C-terminal portion are utilized; since their reliability and specificity vary, it is important to become acquainted with the advantages and shortcomings of the available assays (9). Secretion of PTH is mainly regulated by the concentration of serum ionized calcium: it is stimulated by acute or chronic hypocalcemia (10).

The net effect of PTH action on kidney, gut and bone is to increase calcium and to decrease phosphate concentration in the extracellular fluid. However, under certain circumstances, blunted calcemic response to the action of PTH (11) or an inappropriate parathyroid response to hypocalcemia may exist (12). The actions of PTH on different organs are closely linked to and dependent upon other factors like vitamin D and magnesium concentration. PTH also plays a prominent role in bone remodeling.

The physician taking care of newborns is frequently confronted with two circumstances: neonatal hypocalcemia and osteopenia of prematurity. Let us briefly touch upon some data pertinent to the perinatal metabolism of vitamin D and calcium in order to gain insight into the understanding of the possible events leading to the above mentioned pathological states.

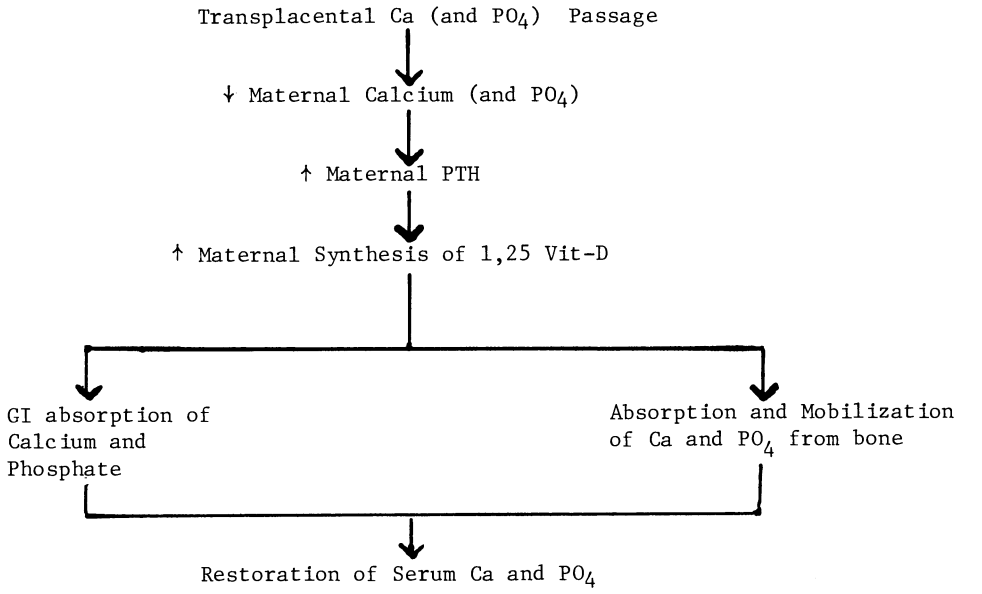
In the pregnant human, serum 25-OHD_3 levels have been found to be either decreased or normal. It is speculated that increased conversion of 25-OHD_3 to 1,25$(OH)_2D_3$ may be the cause of the low 25-OHD_3 levels (13). Indeed, serum 1,25$(OH)_2D_3$ concentration is elevated during pregnancy (14). However, assays detecting 1,25$(OH)_2D_3$ measure the metabolite bound to protein, and D-binding globulin concentration is elevated in pregnancy.

Experimental data as well as studies in humans have clearly demonstrate an extra-renal source for 1-α-hydroxylation and recent evidence points towards the placenta as the site for this hydroxylation (15). This possible explanation for the increased serum concentration of 1,25$(OH)_2D_3$ during pregnancy would be consistent with a special protective mechanism for the maintenance of a positive mineral balance in the fetus.

During pregnancy, a series of adjustments are required in order to comply with maternal and fetal demands (Figure 3).

Calcium is transfered form mother to fetus through an active placental transport mechanism. During the last trimester of pregnancy, maternal-fetal calcium transfer amounts to 100-150 mg/kg fetal weight/day (16). Fetal blood and cord blood of infants have serum concentrations of calcium significantly higher than those of maternal blood. After birth, the ongoing transplacental transfer of calcium is suddenly interrupted and this requires the implementation of several adaptive mechanisms. Not unexpectedly, serum calcium falls in the neonatal period and occasionally this fall precipitates an array of symptomatology: twitching, jitteriness, convulsions, cyanosis and vomiting. Most neonatologists define hypocalcemia as a serum calcium below 7 to 7.5 mg/dl (16). Neonatal hypocalcemia has two peaks of highest incidence: during the first two days of life ("early" hypocalcemia) and towards the end of the first week of life (classical neonatal tetany, "late" hypocalcemia) (17). These two types of hypocalcemia will be discussed below, and followed by a brief comment on Metabolic Bone Disease of Prematurity.

Figure 3. Vitamin D Adjustments in Pregnancy



EARLY NEONATAL HYPOCALCEMIA

Several contributing factors have been incriminated in the genesis of early hypocalcemia (Table 1).

As early as 12 weeks of gestational age, there is evidence of parathyroid gland secretory capability in the human fetus (18). However, the degree of activity varies with gestational age and degree of stimulation or suppression, mainly through the level of fetal plasma calcium. Because of the active transplacental transfer of calcium and the consequent elevated fetal ionized calcium concentration, PTH is relatively suppressed in utero. Most studies have shown a low or undetectable level of PTH in cord blood (19,21); however, when PTH is measured at 48 hours of age, the data are controversial: some studies have reported gestational age- and postnatal age-dependent PTH response capability which suggests that younger prematures elicit a blunted response to hypocalcemia when compared with more mature prematures or term infants (20). Others have demonstrated a clear elevation of PTH at 48 hours of age in both prematures and full-term infants, with even slightly higher concentrations in prematures (19). These differences may be methodological since different assays for PTH were utilized. N-terminal (active component) assays best represent acute secretory changes but underdetect PTH in chronic conditions; C-terminal assays are widely utilized under chronic conditions but may overestimate serum PTH because of their basic recognition of inactive fragments.

Table 1. Neonatal "Early" Hypocalcemia

Transient Hypoparathyroidism
Hypercalcitoninemia
Vitamin D Deficiency
Defective Vitamin D Metabolism
End-organ Resistance to PTH

Furthermore, if renal degradation of PTH fragments is impaired in premature infants, this could cause overestimation of PTH secretion when C-terminal assays are utilized.

Calcitonin (molecular weight 3200), secreted mainly in the thyroid gland, plays an important role in neonatal calcium homeostasis. Its main actions include: decreased bone mobilization and increased renal excretion of calcium and phosphorus and decreased phosphorus absorption. These actions result in decreased serum calcium and phosphorus concentratio Several studies have demonstrated elevated levels of calcitonin in the neonatal period (19,21), particularly in premature infants and independent of serum calcium levels; there is no clear explanation for this finding. The early hypercalcitoninemia, by contributing to the genesis of hypocalcemia, may induce the early increase in serum PTH levels. Since calcitonin also inhibits the 1-α-hydroxylation of vitamin D, it leads to a decreased intestinal calcium absorption. Calcitonin may play a role in promoting pre- and post-natal bone mineralization, and in placental transport of calcium.

In the human, cord blood 25-OHD_3 levels correlate well with maternal levels regardless of whether the infant was born at term or prematurely (22). Vitamin D deficient mothers give birth to neonates with low 25-OHD_3 levels irrespective of gestational age; this is consistent with a passive transfer of 25-OHD_3 across the placenta. Maternal serum 25-OHD_3 levels seem to be related to food intake and time of year (23). Postnatal changes in serum 25-OHD_3 levels were similar in full-term and premature infants, at birth and at seven days, although the premature infants had significantly lower serum calcium concentrations at 48 hours (19). These studies suggest that vitamin D deficiency plays no role in early neonatal hypocalcemia.

After 32-36 weeks of gestation (22,24), the liver can hydroxylate vitamin D and maintain or restore normal concentration of 25-OHD_3. Also, after 32 weeks of gestation, the gut can absorb and the kidney can hydroxylate vitamin D (24); this again supports the concept that early neonatal hypocalcemia cannot be explained on the basis of defective vitamin D activation.

End-organ resistance to PTH has been postulated as another explanation for early hypocalcemia; this conclusion is based on several studies. Infants born at term show an increase in urinary cyclic AMP and urinary phosphate excretion parallels PTH increase throughout the first thr days of extrauterine life (25); exogenous PTH induced similar changes. Conversely, hypocalcemic premature infants failed to increase urinary cyclic AMP in response to exogenous PTH (26).

Based on the above, the management of early neonatal hypocalcemia has included active vitamin D metabolites which have yielded successful results for some (7) but not for others (8). Accordingly, the utilization of active vitamin D metabolites in the newborn period remains controversial and should be viewed still as experimental.

LATE HYPOCALCEMIA

This occurs around five to seven days of age, and is mainly due to a high phosphate load contained in milk formulas (Table 2). There also seems to be a higher incidence and a more severe form of late hypocalcemia in premature infants with low 25-OHD_3 levels due to maternal vitamin D deficiency (29,30). Supplementation of vitamin D to pregnant women resulted in elevated cord blood levels of 25-OHD_3 and a lower incidence of late neonatal hypocalcemia (31).

Table 2. Neonatal "Late" Hypocalcemia

High phosphorus and low Ca/PO_4 in formula
Maternal Vitamin D Deficiency
Infant Vitamin D Deficiency

METABOLIC BONE DISEASE OF PREMATURITY

Osteopenia or rickets of prematurity is a disease that has achieved statistical relevance since current technology and sophisticated skills have resulted in increased survival rates of prematurely born infants. The clinical spectrum of undermineralized bone structures in the premature includes: gross radiologic demineralization (osteopenia), overt rickets, fractures, and late respiratory distress syndrome associated with myopathy due to vitamin D deficiency (32).

With the recent acquisition of bone densitometry, it is possible to evaluate prospectively changes in bone mineral status in children (12) as well as in infants (33). Several studies have shown the beneficial effects of therapeutic intervention (with added calcium and/or vitamin D metabolites) on extrauterine bone mineralization rates. Still, it must be emphasized that these treatments should be undertaken with caution, frequent re-evaluations, and by people experienced in the avoidance and treatment of complications.

A group of prematures fed an experimental formula containing 1,260 mg Ca, 630 mg P and 1,000 IU of vitamin D/Liter led to a bone mineralization rate parallel to that of intrauterine life (33). Supplementation with vitamin D (1200 IU/Liter) in addition to increased calcium (1,400 mg/Liter) and phosphorus (750 mg/Liter)intake has been found to be beneficial in a group of very low birth weight infants (34). The type and composition of milk formulas utilized in the alimentation of prematures is also an important consideration; for example, soy isolate formula does not provide sufficient minerals to maintain their intrauterine accretion rates (35).

Summarizing the available information, it seems that prematurely born infants benefit from larger daily intakes of calcium, phosphorus and vitamin D. The amounts provided by standard commercially available formulas appear to be insufficient for the premature's needs (33-35).

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HIGHLIGHTS: RENAL CONCENTRATING CAPACITY IN THE NEWBORN. DEVELOPMENT, CLINICAL DISORDERS, EVALUATION, AND MANAGEMENT.

Eddie S. Moore, M.D., Pricha Tanphaichitr, M.D., Craig B. Langman, M.D. and Mahmoud Loghman-Adham, M.D.

Polyuria, the excretion of an excessive volume of dilute urine, is a potentially lethal disorder in the neonate. Since body water accounts for roughly 60-70 percent of lean body mass in the newborn, loss of body water without adequate replacement may lead to circulatory collapse and death of the infant. The capacity of the kidneys to elaborate urine hypertonic to plasma or the concentrating capacity, involves many physiologic processes. These include countercurrent multiplication, recycling of filtered urea, antidiuretic hormone (ADH), solute delivery to the distal nephron, and the adenylate cylase (cyclic AMP) system. Although urine elaborated by the kidney in utero is normally hypotonic to plasma, development of the capacity to excrete a concentrated urine begins early in fetal life.

The countercurrent multiplication process in urinary concentrating ability involves increasing the osmolarity of glomerular filtrate from its initial isotonicity to plasma to a significantly hyperosmotic state. This requires the development of a steep osmotic gradient in the renal interstitium from cortex to medulla and a tubule of appropriate length. We investigated the intrarenal solute gradient in fetal lambs and found a steep interstitial osmotic gradient present by the beginning of the third trimester. We concluded that limitation in the capacity to concentrate the urine in prematurely born as well as full-term infants is not due to developmental inability to establish an intrarenal solute gradient.

Recycling of filtered urea from the renal tubule to the renal interstitium plays a significant role in the urinary concentrating process. Our studies in fetal lambs demonstrated early development of a large interstitial urea gradient. However, studies by others have shown that intake of dietary protein in the neonatal period can significantly influence the ability of the infant to elaborate a concentrated urine. Infants fed low protein diets can not excrete maximally concentrated urine.

Recent studies have demonstrated adequate circulating levels of ADH in the neonate and appropriate end-organ responsiveness to this hormone. An additional factor involved in the concentrating process that is particularly important in the neonate is solute delivery to the nephron. Urine flow rate may increase obligatorily with a large intake of solute in the ingested formula during the neonatal period.

The definitive demonstration of impaired renal concentrating capacity requires induced hydropenia. However, deprivation of fluid to the neonate with a suspected concentrating defect to produce hydropenia is unjustified.

The diagnosis of impaired renal concentrating capacity in the neonatal period should rely on careful record keeping including fluid intake and losses, weight, blood pressure, general physical assessment, and the simultaneous biochemical assessment of blood and urine.

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RADIO-SCINTIGRAPHIC EVALUATION OF THE KIDNEYS IN THE NEONATE

G. N. Sfakianakis, M.D.

INTRODUCTION: RADIOPHARMACEUTICALS

The last decade witnessed a tremendous expansion of clinical Nuclear Medicine in general and of Pediatric Nuclear Medicine in particular. The introduction of the gamma camera improved resolution, shortened the time required for studies and enabled sequential imaging in the form of dynamic flow and function studies.

The development of short lived gamma emitters like Tc-99m and I-123 allowed the clinical use of higher doses of radioisotopes thus permitting better quality images, increased resolution and greater statistical reliability of function studies. New carriers amplified the spectrum of the organs and diseases studied as these molecules efficiently labeled with the short lived radioisotopes provided high quality scintigrams in shorter time and with less radiation exposure to the patient. Old radiopharmaceuticals (for example Hg-197-chlormerodrin) were replaced by new Tc-99m complexes, such as Tc-99m-DTPA, Tc-99m-Glucoheptonate and Tc-99m-DMSA for renal imaging and function.

Computer assisted acquisition, storage and analysis of imaging or counting data further expanded the efficiency of nuclear medicine studies and prompted quantitation of functions with significant clinical applications. Finally, animal and clinical research helped clarify clinical problems, solve dilemmas and develop new methods and techniques.

Twelve years ago Mercury labeled diuretics such as Hg-197-Chlormerodrin were the only renal scanning radiopharmaceuticals, and I-131-ortho-iodo-hippurate probe renography the only in vivo renal function test. With the introduction of the camera in the early seventies, renography became more specific as kidneys could be better outlined and cortices could be separated from collecting systems and split renal function quantitation materialized. Dr. C. Raynaud in Paris amplified the use of Hg-197-Chlormerodrin for renal function quantitation.

Today several Technetium-99m labeled complexes are in clinical use, helpful in studying pediatric renal anatomy and function (Tc-99m-$T_{\frac{1}{2}}$= 6hr, gamma rays = 140 KeV). Tc-99m-diethylene-triamine-penta-acetic acid (Tc-DTPA) has been widely used for renal clearance (glomerular filtration rate, GFR) measurement and for scintigraphic semiquantitative studies of renal blood flow and function including drainage. Anatomical information also can be obtained during the first several minutes after injection.

Tc-99m-dimercaptosuccinic acid (Tc-DMSA) is an excellent imaging agent because it accumulates in the tubular cells (about 40% of the dose at 6 hr) and enables excellent scintigraphy of the cortices after the background act vity clears (8-24 hrs post injection). Tc-99m-Iron-Ascorbate complex (Tc-Fe has analogous properties. Part of DMSA and Tc-FeA are cleared by glomerular filtration.

A very useful radiopharmaceutical in clinical practice is Tc-99m-Gluco heptonate (Tc-GH). It is a blend of DTPA and DMSA. Most of Tc-GH is handled by glomerular filtration thus enabling the study of renal blood flow, glome ular function and drainage semiquantitatively as Tc-DTPA. A small but suffi cient proportion of Tc-GH (about 10% of the injected dose in 6 hr) accumula within the tubular cells like DMSA thus enabling delayed scintigraphy of th cortices (3-6 hrs). Compared with Tc-DMSA, Tc-GH has the advantage of lower renal radiation thus allowing the use of higher doses which permit better f function drainage studies; however it is excreted in the bowel and perplexi images may result from scanning at 6-24 hrs post-injection, particularly wh renal insufficiency exists.

Finally, I-123-ortho-iodo-hippurate, an optimally labeled (I-123, $T_{\frac{1}{2}}$=1 gamma rays 159 KeV) radiopharmaceutical is a very efficient renal imaging function agent since it is almost totally cleared from the blood of the ren artery by glomerular filtration (1/8) and tubular excretion (7/8). This ess ial renal plasma flow agent (ERPF) combines the excellent renographic prope ies of hippuric acid derivatives with the proper scintigraphic characterist of I-123, thus providing quick functional information and simultaneous anat images.

I-123-Hippurate has been used more effectively in Europe than in the United States. Our experience is limited because this radiopharmaceutical i not available commercially and the radioisotope currently available has hig energy impurities which result in images inferior to those obtained with Tc complexes.

For renographic studies we still use small dosages of I-131-Hippurate although its long half-life (8 days) and its beta emission and hard gamma rays (364 KeV) make it less desirable than I-123. I-131-Hippurate however i much less expensive and can be used simultaneous (dual imaging) with Tc-stu ies, following, or preceding them.

The radiation exposure for a "standard man" in mrads/mCi is indicated in the following table. With properly adjusted doses for children, a somewh higher exposure is expected. As for I-131-Hippurate a total dose of 200 μCi would deliver in a "standard man" 20,700 and 8,000 mrads to the total body, kidneys and bladder wall (under the worst voiding conditions and normal ren function). When renal insufficiency exists the above numbers increase.

	Total Body	Kidneys	Bladder Mucosa
Tc-DTPA	16	40	600
Tc-GH	7	200	800
Tc-DMSA	16	600	300
I-123-Hippurate	8	20	700

TOTAL RENAL FUNCTION (CLEARANCES)

For measurement of clearances without urine collection, radioisotope studies were developed based either on the classic method of multiple blood sample collection (Sapirstein) or on the observation that the distribution volume and concentration of an ERPF or GFR agent at a specific time after injection reflects the agent's overall renal clearance which can be calculated by quadratic formulae experimentally defined. In children the classic approach with several modifications works with acceptable accuracy. However, distribution method does not provide consistent results.

SPLIT RENAL FUNCTION

To calculate the function of one kidney as compared to the other without collecting urine from each ureter is a rather easy task within certain limits in any Nuclear Medicine Laboratory with a camera and a mini-computer. There are two techniques: a) quantitation of radioactivity from the kidneys the first 2-3 minutes after injection before entering the ureters; b) quantitation of cortical activity after the collecting systems are emptied (usually at 24 hours).

The first approach can be applied using practically any radiopharmaceutical which is excreted by the kidneys. Background correction and, at least theoretically, blood pool activity correction, are required, thus agents with greater renal clearance are better suited. Hippurate (I-123 or I-131) is the best; Tc-DTPA and Tc-GH are less effective but clinically acceptable unless renal failure exists. This approach is quick and not affected by obstructive uropathies.

The second approach requires the use of tubular accumulating radiopharmaceuticals, such as Hg-197-Chlormerodrin, Hg-197-Cl_2 or Tc-DMSA. At 24 hours usually there is no need for background correction but severe obstruction may affect the results. The greatest disadvantage is the need for a return visit by the patient on the following day.

The "split renal function" computed with any of the above methods or radiopharmaceuticals merely represents function at the time of the study and not renal function reserves. Claude Raynaud has proposed Hg-197-Cl2 uptake as an index of absolute individual (split) renal function, whereas all the other approaches provide only relative function of one kidney as compared to the other.

The "split renal function" obtained with any radiopharmaceutical reflects that part of the kidney function which is responsible for accumulation of the specific agent. Renal blood flow is a determinant of any agent's availability and thus affects the "split renal function" results. When GFR agents (DTPA, Glucoheptonate) are utilized, "split renal function" reflects both renal blood flow and glomerular function. When DMSA is used, "split renal function" probably reflects blood flow and tubular function. When ERPF agents (Hippurate derivatives) are utilized, "Split renal function" reflects renal blood flow, glomerular and tubular functions. Thus hippurate studies are more representative since they combine all the components. Due to intrinsic interactions, when one component of the renal function is reduced the others are also affected and, in most cases the combined results are identical to those of the individual components.

SIMULTANEOUS TOTAL AND SPLIT RENAL FUNCTION

Tauxe and his colleagues have developed a "comprehensive" renal protocol to study total and split renal function and drainage using O-I-131-Hippurate during one visit. Piepz has developed a program which gives total and split GFR using Tc-DTPA. The approaches are somewhat different but both methods utilize one blood sample and camera imaging with computer analysis.

IMAGING AND RENOGRAPHY

General

In practice, sequential imaging as 1 min flow (1-2 sec images) or 30 min function (usually 30 sec images in computer and two min images on radiographic film or polaroid)is a series of scintigrams commonly supplemented by computer generated time-activity graphs (renograms).The information can be of the total kidney or its parts such as upper and lower poles. Graphs are extremely important in follow-up studies. They can be analyzed semiquantitatively (slopes, peak-times, half-times, etc.), and commonly amplify the ability of the image observer to detect subtle changes. Delayed scintigrams at 3-6 hr (Tc-GH) or 6-24 hr (Tc-DMSA) are especially useful.

It is desirable for the patient to be supine, well hydrated, calm and comfortable in a warm environment with the parent present. An experienced person should insert an indwelling needle in a peripheral vein just before injection and verify that extravasation does not take place. Tc-DTPA and Tc-GH can be injected IV at 200 μCi/kg, Tc-DMSA at 100 μCi/kg (Tc-99m minimal dose 500-1000 μCi). I-131-Hippurate can be injected IV at 20 μCi/kg, minimum 50 μCi and I-123-Hippurate is recommended in a dose of 2 mCi in the adult and appropriately reduced for children.

The Normal Scintigram

Flow studies. Tc-DTPA, Tc-GH and Tc-DMSA show equal activity in both kidneys with at least the intensity of the aorta, appearing simultaneously with the distal aorta, iliac arteries or the spleen. A good bolus results in a positive deflection on the 1 sec sequential flow graph followed by a decline before functional accumulation is superimposed. This is not evident in hippurate studies.

Parenchymal accumulation and excretion - ureteral and bladder appearance After the first pass (Tc-complexes) or from the beginning (Hippurate) activity increases in the cortex for 2-5 min. Peak activity of the cortex occurs between 2 and 5 min. The familiar bean-shaped normal kidneys appear on the scintigrams in the normal position, under the spleen (L) and liver (R) and with the normal size for age. The collecting system appears at 2-5 min. The ureters may become visible at 3-30 min but in the normal and well hydrated patient ureteral visualization is not continuous. If it is continuous there may be obstruction, compression, megaureter or dehydration. Bladder activity is usually visible at 3-8 min. Peak renal (including collecting system) activity occurs after 3-5 min. Cortical activity declines after 5 min and totally disappears at 20-30 min with DTPA; it is stabilized and slowly increases with DMSA and GH. At 20-min the collecting system normally empties and only traces are visible.

Postural pooling can be ruled out by obtaining a post voiding or post upright raised image. Renal insufficiency and dehydration delay the above time sequence even without anatomical pathology.

Delayed images. The 24 hr images show the kidney cortical activity only. Depending upon size of the kidneys and resolution of the camera, the image can be that of a bean (small kidneys, low resolution) or the pelvic and calyceal areas impression as negative (activity void) may appear through the cortical outline. The margins are smooth and lobulation can be appreciated by combining the calyceal early images. Indentation of the periphery with thin underlying parenchyma and proximity of a group calyceal activity signifies pathology (pyelonephritis, scar, trauma, space occupying lesions). The collecting system must be empty. Visualization of the collecting system signifies obstruction (anatomical) or functional (reflux). Renal insufficiency and dehydration may result in delayed collecting system visualization even without anatomical abnormalities. Indentation by the spleen is a common finding and should not be confused with space occupying lesions.

The normal abdominal background. The spleen and liver are visible but with much less activity in the parenchymal image (3-5 min) than the normal kidneys. The full bladder may appear as a photon deficient region before excreted activity reaches that level. The full stomach also produces a photon deficient region superiorly and laterally to the left kidney. The rest of the abdomen usually shows smooth and equal background activity in the normal state. Background defects (photon deficient areas) signify some kind of pathology usually related to the kidneys except if explained anatomically as above or if the result of severe intestinal dilatation, a large cyst or an ischemic lesion.

Hepatic and intestinal activity may be visible on delayed views because Tc-GH normally is excreted there, particularly if renal insufficiency exists. This activity should be differentiated from ureteral activity.

Renogram. The renograms from the two kidneys should be nearly identical in shape and slopes. Slight differences due to kidney size, normal variation, or position and technical reasons are expected. Following the first pass (not visible, however, in 30 sec sequential histograms) the activity peaks 3-5 min and then declines because of both blood activity drop (renal accumulation and extravascular distribution) and excretion into the ureter. From then on activity falls, precipitously for hippurate, less steeply for DTPA and GH. At 30 min hippurate renal activity usually is less than 20% of the original whereas DTPA and GH usually are less than 50%. The cortical graphs are more steep (upslope and downslope and earlier peaking).

Renal insufficiency. An advantage of scintigraphy over excretory urography is its ability to visualize kidneys even in renal failure. Time delay, lower intensity of the urinary tract activity, and increased background activity are pertinent characteristics of renal insufficiency. Associated parenchymal abnormalities, such as dysplasia, obstruction, ectopia, etc. complicate the appearance but in most instances interpretation is possible. In those cases renography is characterized by flat graphs.

CONGENITAL RENAL ANOMALIES

Agenesis. No kidney is visible and there is smooth background activity Imaging should be continued including delayed views in which hepatic and intestinal activity is present. Agenesis may be bilateral or unilateral. It should be differentiated from ectopia, dysplasia, obstruction or renovascular accidents.

Ectopia. Normal or abnormal ectopic kidney exhibits the characteristics of the organ in a lower, pelvic or contralateral position. The time sequence of the vascular, cortical and excretory components of imaging must be as with the normally located kidney, otherwise ectopia is associated with obstruction, dysplasia, etc. The most difficult to diagnose is ectopia with dysplasia.

Dysplasias. Dysplastic hypoplastic kidneys usually occur from renovascular accidents (artery or vein thrombosis) or infection. The multicystic kidney with or without foci of functioning renal tissue has a characteristic scintigraphic image associated with a palpable abdominal mass. It appears as a photon deficient region (hole in normal background) without peripheral rim of hyperactivity; if islets of functioning tissue exist, they show up as foci of increasing activity usually in the central-medial aspect of the photopenic area. On delayed views, activity may fill all or part of the photopenic region. Multicystic kidney is practically unilateral. Medullary sponge kidneys may show as large bizarre kidneys without any specific image of hypofunctioning large units with recognizable anatomical pattern. Of all the above dysplasias, the multicystic kidney is by far the most common in the newborn and infant; the baby usually is referred to us because of an abdominal mass.

Horseshoe kidney is readily recognizable because of the proximity of the lower poles of the kidneys and the change in their long axis orientation. An anterior view in delayed images will show the connecting parenchym

Duplication can be recognized particularly if associated with obstruction of both or usually one component.

Hydronephrosis is characterized by an initial image of central photopenia and a peripheral rim of hyperactivity, an image which is opposite to that of multicystic kidney. Depending on the degree of obstruction, the size of the kidney is increased, the collecting system is larger and the function is compromised . During the study time (3-20 min) the collecting system will slowly become visible and remain visible for an extended perio of time amounting to several hours. Continuing the study and allowing enou time (at least 3 hrs), the point of the obstruction will be reached. Activity is not persistent beyond this point unless a secondary abnormality exists (secondary obstruction, reflux, posterior urethral valves, etc.).

It is usually easy to diagnose ureteropelvic junction (UPJ) obstruction because activity stops there, and the ureter never gets enough or persistent activity. Ureterovesical junction (UVJ) obstruction shows persistent ureteral activity but delayed studies must be taken 3-6 hr. Posterior urethral valves produce obstruction which visualizes the collecting system and the bladder persistently. Reflux produced megaureters is not characterized by persistent activity; diuretic renography can be helpful. The presence of refluxing activity during renal scintigraphy or by a retrograde study makes the diagnosis.

Hydronephrosis with infection may be associated with dysplastic small kidneys, irregular parenchyma, scarring (thinning), and usually no persistent activity.

Megaureters of sufficient size and full of non-radioactive urine at the beginning of renal scintigraphy may appear as photon deficient areas below the kidneys and between the kidneys and the bladder. They become radioactive when excreted activity reaches their level; the time depends upon the functional status of the kidney.

Duplication with hydronephrosis of one component will show a hydronephrotic image for half of the kidney and a normal image for the other half.

Filling of a hydronephrotic kidney or part of the kidney from refluxing bladder activity or from the activity of the neighboring collecting system can be recognized by sequential imaging. Recognition of such events helps in a definitive diagnosis. Retrograde urography would be the definitive test.

Ureterocele produces distal ureteric obstruction. Although it is possible to suggest the diagnosis on scintigraphic findings of the bladder, retrograde urography and cystoscopy will establish the diagnosis. Evidence of distal ureteric obstruction by delayed and persistent visualization of the obstructed ureter is the most consistent finding of the scintigraphic studies.

ACQUIRED RENAL DISEASES

Diffuse parenchymatous disorders of the kidneys, such as the nephrotic syndromes,acute glomerulonephritis, and acute tubular necrosis, all produce images of larger than usual kidneys with different degrees of decreased function but diffusely and symmetrically involving both kidneys. Renal insufficiency can be manifested as decrease of the radiopharmaceutical uptake, flattening of the renogram, and prolongation of the different time intervals. Flow studies show symmetric decrease in renal flow.

Infections such as pyelonephritis or abscess produce space-occupying effects on the images of the cortices. Associated Gallium-67 scintigraphy reveals matching foci of hyperactivity. In acute pyelonephritis the lesions are reversible. Chronic pyelonephritic kidneys are characterized by small size, dilated collecting system, and cortical scarring. The latter appears on renal scintigrams as thinned or absent cortical activity.

Renal trauma from accident or surgery produces cortical defects and pictures of extravasation of activity from the collecting system. Renal cortical fractures and contusion are easily recognized in the first 2-3 minutes of Tc-GH or in delayed images of Tc-GH and Tc-DMSA scintigrams. Extravasations are easily found around the bladder, along the ureters and around the kidneys. Intrarenal extravasation requires meticulous attention to the details while attempting interpretation of routine images and commonly would necessitate repeated and multiview scintigrams. Perinephric hematoma is manifested by photon deficient regions, compression, and displacement of the kidney which has decreased function and/or obstruction. Adrenal hemorrhage is expressed by focal photopenic regions over the kidneys.

Renal scintigraphy is very sensitive for diagnosing trauma, more sensitive than intravenous urography or ultrasonography. The sensitivity of computer tomography (CT) is currently under investigation.

Neoplastic lesions produce cortical defects easily recognized most of the time. The small tumor, however, which arises in the vicinity of the collecting system and is manifested by hematuria, may be missed by scintigraphy but is easily recognized by intravenous urography.

Renal artery stenosis is characterized on Tc-complex scintigrams by a small size kidney with delayed arrival and decreased blood flow, impaired and delayed cortical accumulation and collecting system visualization, and delayed excretion. On I-Hippurate scintigrams, characteristically the cortex shows very slow accumulation of activity with a very delayed peak when the normal kidney parenchyma is emptied. Renography shows slow accumulation, lower and delayed peaking and slow emptying, but differentiation from obstru tion has to be performed based on the images which show no collecting system retention. Cortical renography is also helpful.

Renal vein thrombosis in the newborn results in destruction and atroph of the kidney because of lack of collateral veins, at this age. In the acute phase of the neonatal renal vein thrombosis, injection through a foot vein may show inferior vena cava obstruction; the kidney shows decreased flow, is slightly larger, and has decreased cortical function but no obstruction.

After the neonatal period and the development of collateral veins, rena vein thrombosis is not so destructive. The flow is reduced and congestion ma be detected; the kidney is larger with a compressed collecting system and no sign of obstruction.

Acquired obstruction from stone is extremely rare in children. It can be the result of tumor, clot, trauma or surgery, or external compression. Acute total obstruction is characterized by a slightly enlarged kidney without evident hydronephrosis, cortical decreased function and no visualization of the collecting system. There is cortical visualization with relatively decreased activity which however increases slowly and continuously until it reaches a plateau. Chronic total obstruction results in thinned cortices with final atrophy. There is photopenia with a peripheral rim of activity. Partial obstruction has the characteristics of congenital partial obstructio If it persists it will result in atrophic hydronephrotic kidneys; initially there is photopenic and later persistently active collecting system surround ed by a rim of functioning parenchyma.

FOLLOW-UP STUDIES

Renal flow, sequential imaging and late scintigraphy complemented by computer generated renography provide an excellent approach to follow-up renal abnormalities. The natural effect of medical or therapeutic intervention, the superimposition of complications, all can be studied using Tc-complexes supplemented by Hippurate studies. Also, kidney transplants can be studied effectively by radioisotopic approaches since both anatomy and function can be successfully assessed.

CONCLUSION

Results of our experience with renal scintigraphy and of other institutions tend to support the following:

a) Renal scintigraphy in the neonate is nearly always successful, easy to perform and reliable.
b) It provides information about structure and function quickly and efficiently.
c) It readily shows if the kidneys are present and normal without congenital anomalies or acquired disease. Thus, it is particularly useful in patients with extrarenal problems in whom primary renal disease is quickly excluded from the differential diagnosis.

d) In cases of renal abnormalities, scintigraphy provides the correct screening or diagnostic information.
e) It compares favorably with excretory urography and ultrasonography.
f) It is noninvasive except for its radiation exposure, which compares favorably with excretory urography (IVP).

Renal scintigraphy in the neonate is easy, practical and accurate, and recommended for routine use.

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NEONATAL ULTRASOUND OF THE URINARY TRACT

JANE L. FRANK, M.D.

Ultrasound has proven to be a safe and accurate diagnostic tool. In very simplified terms, ultra high frequency sound waves in the range of 3.5 to 7.0 megahertz are focussed into the area to be studied. Sound waves are reflected to varying degrees as the beam passes through structures of different densities. For example, in solid tissue, as the sound beam interacts with different types of tissue of a variety of densities, some of the beam is reflected back to the transducer, which serves both as transmitter and receiver. The structure appears echogenic on the displaying oscilloscope. If, however, a mass were particularly uniform in cell type, the sound beam would pass in a relatively uninterrupted manner from the front of the structure to the back. Few waves (echoes) would be reflected and the structure would appear relatively sonolucent (echo-free). Lymphomatous masses sometimes have this appearance. In the case of fluid-filled structures with no solid particulate matter (for example a cyst), no sound waves are reflected between those coming from the front and back walls of the cystic structure. The cyst is completely echo-free.

In summary, normal organs such as kidney, liver and pancreas have known and characteristic echo patterns based on the nature and homogeneity of the histology of the organ. Echo patterns are routinely classified as echogenic (solid tissue as liver), sonolucent (usually fluid-filled structures such as the gallbladder), and mixed (both fluid and solid tissue such as the kidney). Pathologic organs and masses frequently have characteristic echo patterns as well. Thus, ultrahigh frequency sound waves "map out" the structures under question.

One characteristic of ultrasound of particular importance is its ability to demonstrate anatomic information independent of functional status. This feature has great impact on the diagnostic approach to the neonatal kidney. Because of poor filtration and concentrating ability of even normal kidneys in the first week of life, excretory urography may be inadequate for satisfactory visualization. Ultrasound can document the presence of structurally normal kidneys regardless of the status of renal function. Ultrasound also allows for demonstration of those lesions of the kidney which result in significant impairment of function, such as bilateral hydronephrosis, and poly-

cystic disease. In the extreme, lesions which lead to complete cessation of function such as renal vein thrombosis, renal artery thrombosis, and multicystic dysplastic kidney, can also be identified.

On the other hand, of course, ultrasound can add no functional information regardless of anatomic configuration. Other types of radiographic procedures must be employed. The preferred choice in the first week of life is the nuclear renal scan since it is a test of particular sensitivity. The intravenous pyelogram is generally adequate after the first 7 to 10 days of life.

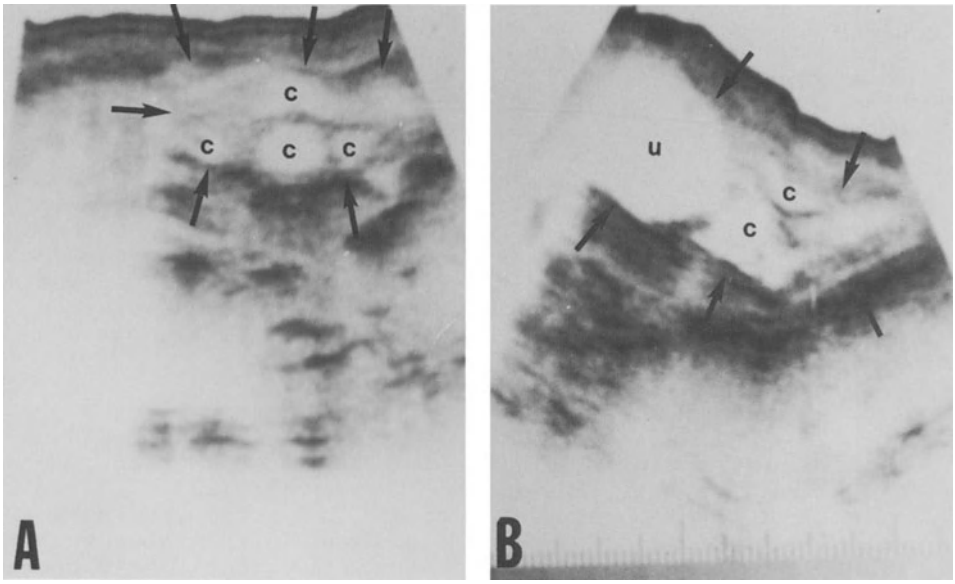

FIGURE 1. Hydronephrosis secondary to ectopic ureterocele. The ureterocele has produced some degree of bladder outlet obstruction. Prone longitudinal scans. A. Opposite (right) kidney (black arrows) with dilated calyces (c). B. Left kidney (black arrows) with obstructed upper pole collecting system (u) and mild dilation of lower pole calyces (c).

The Neonate With An Abdominal Mass

Renal and perirenal abnormalities represent the majority of abdominal and flank masses in the newborn. If ultrasound demonstrates normal kidneys, and the mass is seen to arise outside of the renal and perirenal space (e.g., liver, pelvis), the work-up is tailored to the particular diagnostic problem.

I. Renal:

A. Kidney replaced by cystic structures. Hydronephrosis and multicystic dysplastic kidney (MDK) are by far the two most common causes. Polycystic kidney disease of the infantile variety does not actually have a cystic appearance on ultrasound and will be discussed under Solid Lesions.

On ultrasound, hydronephrosis and MDK can usually be differentiated though both are cystic lesions. In hydronephrosis secondary to any cause, one sees a sac-like echo-free mass representing the pelvis which is larger than and connects to adjacent dilated calyces. If renal parenchyma is present, it can be identified as a peripheral rim of echogenic cortex. If the hydronephrosis is secondary to ureteropelvic junction obstruction, the markedly dilated pelvis has a tendency to cross the midline and extend caudally. Once hydronephrosis is detected, ultrasound guidance for percutaneous nephrostomy can easily be accomplished and permits kidney drainage until such time when optimal conditions exist for surgical correction. In bilateral hydronephrosis, secondary to posterior ureteral valves or prune belly syndrome, and less frequently in vesicoureteral reflux and ureterovesical junction obstruction, one can identify the associated dilated ureters. That finding rules out ureteropelvic junction obstruction. One must then perform voiding cystourethrography for the definitive diagnosis.

Hydronephrosis secondary to ectopic ureterocele produces a different ultrasound (see Figure 1). The obstructed upper pole collecting system has the sac-like appearance described above for hydronephrosis of any cause, but the mid and lower pole architecture of the kidney is usually preserved. The ureterocele can occasionally be identified as an internal cystic sac within the bladder. Again, voiding cystourethrography must be performed to evaluate concomitant reflux and outline the ureterocele.

MDK is generally described as a variable grape-like cluster of large and small cysts haphazardly arranged (see Figure 2). They are not necessarily organized in an orientation of smaller cysts around a central large cyst as in hydronephrosis. There may be many, or just a few. The cysts are not seen to connect.

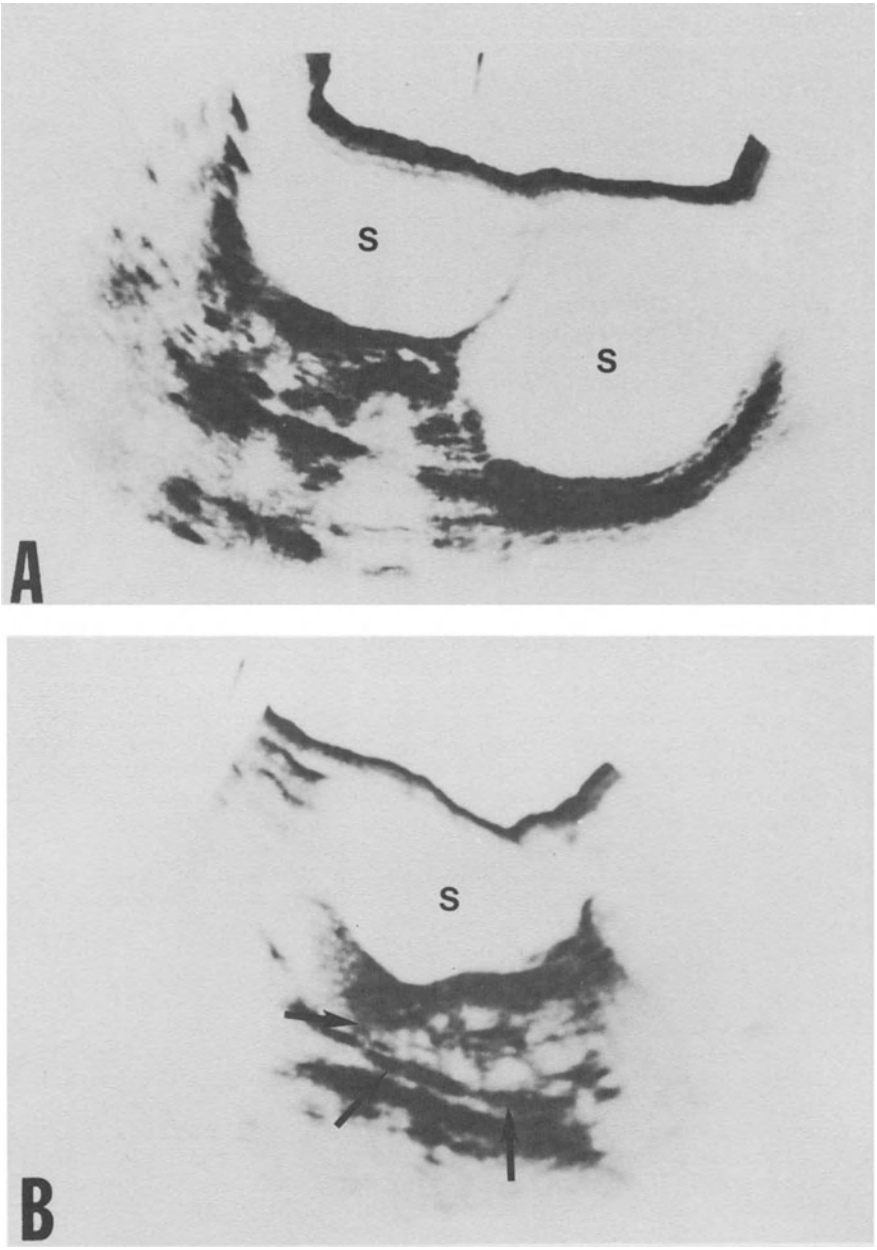

FIGURE 2. Multicystic dysplastic kidney (MDK). A. Supine transverse scan over mid abdomen demonstrates two huge cysts (S) of the left MDK. The mass crosses the midline from left to right. B. Supine longitudinal scan over right upper quadrant shows one of the cysts (S) positioned anterior to the normal right kidney (black arrows).

Once the ultrasound image of cystic, intrarenal mass is obtained and a diagnostic impression made, a functional study is recommended for confirmation of the definitive diagnosis.

B. Kidney replaced by solid structure. Renal vein thrombosis, infantile polycystic disease, and fetal renal hamartoma are the most common causes.

Renal vein thrombosis, most commonly seen in infants following stress or dehydration, produces a diffuse increase in echogenicity of the renal parenchyma with loss of the normal central pelvocalyceal echo pattern. In the appropriate clinical setting, particularly in an infant with hematuria, the diagnosis should be suspected. A nuclear renal scan demonstrates either decreased or absent function.

Fetal renal hamartoma, though rare, is the most common intrarenal tumor of the newborn (see Figure 3). It has the same ultrasound appearance as Wilms' tumor of increased

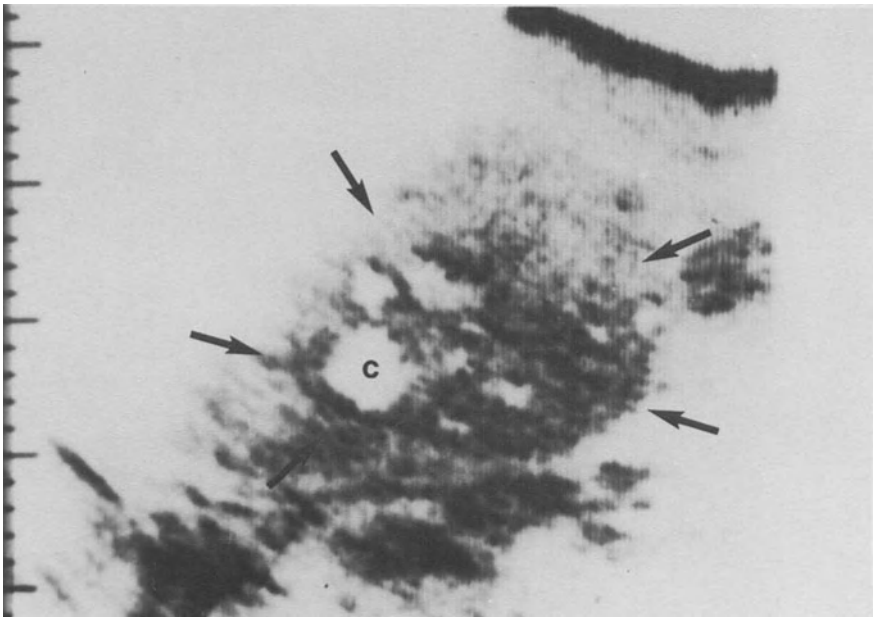

FIGURE 3. Fetal renal hamartoma. Supine longitudinal scan over the left upper quadrant. Mass replacing left kidney outlined by black arrows. Note solid nature of mass (echogenic) mixed with cystic spaces (c) representing areas of necrosis.

echogenicity, at times mixed with cystic spaces representing areas of necrosis. It may actually replace an entire kidney. Functional studies demonstrate absence of function in the affected portion of the kidney.

Infantile polycystic disease appears as bilaterally enlarged kidneys with diffuse increased echoes, presumably representing dilated collecting tubules. It is rare for actual cysts to be identified in the newborn. Scans of the liver may show an increase in echo pattern secondary to hepatic fibrosis.

II. Perirenal:

A. Normal kidney displaced by a solid mass. Solid phase of adrenal hemorrhage and neuroblastoma.

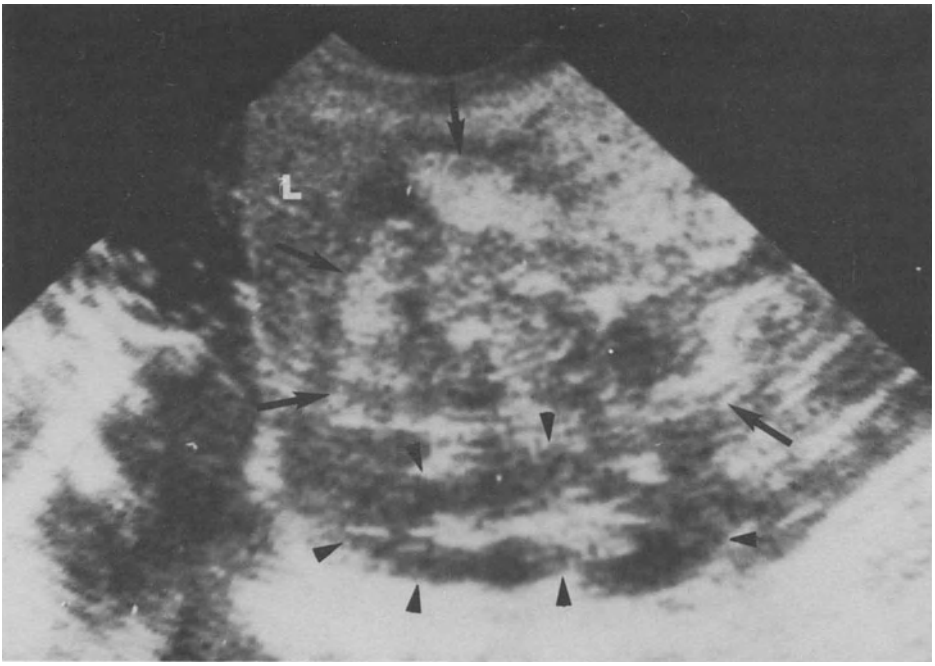

FIGURE 4. Neuroblastoma. Supine longitudinal scan over right upper quadrant of abdomen. Black arrowheads point to normal right kidney. Black arrows outline huge neuroblastoma located between inferior margin of liver (L) and normal right kidney. Note dense echoes scattered within the mass secondary to small deposits of calcium.

Particularly in the newborn who has had a traumatic delivery, and has a palpable flank mass, adrenal hemorrhage should be suspected. The hemorrhage has been variably reported as somewhat echogenic or sonolucent and most examiners agree that both represent different phases of the same process - bleeding with clot formation and gradual resorption. Ultrasound should be used to monitor the progress.

Neuroblastoma has a relatively homogeneous but diffusely echogenic pattern. Tiny flecks of calcium scattered within it may produce areas of relatively dense echogenicity. The calcium may be so fine as to be difficult to detect on plain films of the abdomen and ultrasound may give the only clue (see Figure 4). According to the extent of the neuroblastoma, one may see different ultrasound presentations. If the mass is localized in the adrenal gland only, the structurally

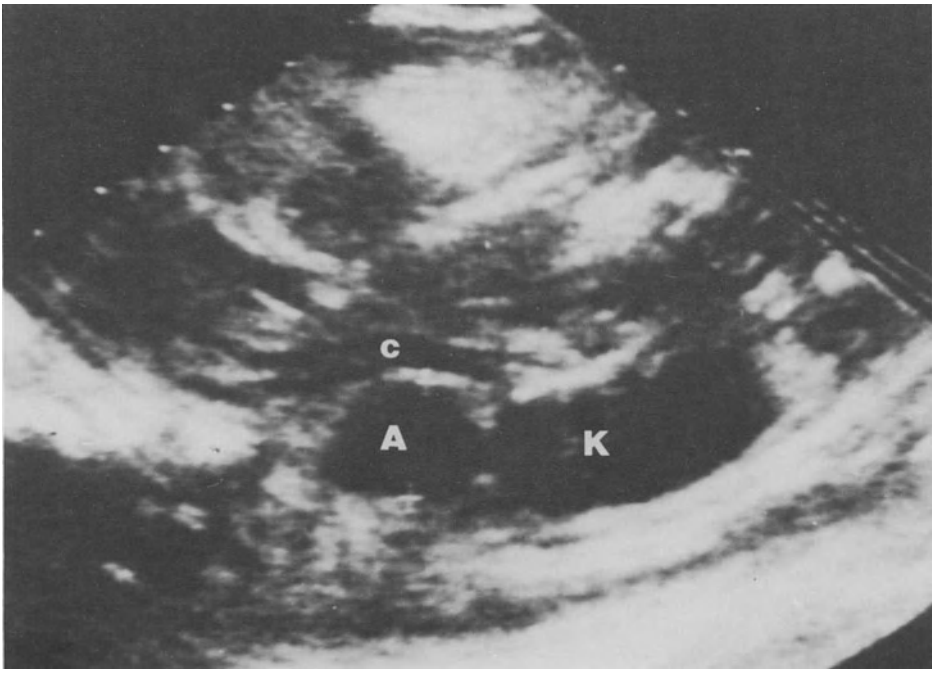

FIGURE 5. Neuroblastoma localized to the right adrenal gland. Supine longitudinal scan over right upper quadrant. A = adrenal mass. K = normal inferiorly displaced kidney. C = inferior vena cava bowed anteriorly by neuroblastoma.

normal kidney is identified being capped by the echogenic mass (see Figure 5). If the tumor is more extensive one can follow the mass across the midline. Neuroblastoma has a propensity to grow around and to encase blood vessels. The aorta may be lifted away from the spine by the mass or the great vessels may be markedly displaced (see Figure 5). The liver may also be involved.

B. Normal kidney displaced by a cystic mass. Cystic phase of adrenal hemorrhage. The entire kidney is identified as normal and intact but positioned inferiorly. Above the upper pole is an area of sonolucency. This is usually seen in the early stage of adrenal hemorrhage though some report it as a late finding. Repeat ultrasoun exams can be utilized ad lib to follow the course of the lesion and to document that it is gradually diminishing in size. It usually takes 2 to 6 weeks for the blood to resorb. Deposits of calcium may be the only sequela.

The Neonate With Impaired Renal Function in the Absence of Abdominal Mass

The causes of renal malfunction in the newborn can be divided into three major categories: prerenal, renal and postrenal. The prerenal causes including hypovolemia, cardiac failure and hypotension present with abnormal lab data, but have anatomically normal kidneys. Ultrasound will confirm the presence of two structurally intact kidneys. Particularly in the premature infant with an umbilical artery catheter who presents with hypertension, renal artery occlusion must be considered. It can also be encountered in babies with dehydration or sepsis. The early, vascular phase of a nuclear renal scan will show no flow to the affected side and no isotope activity over the involved renal fossa. Ultrasound will demonstrate the presence of a structurally intact kidney which, however, is, or becomes, smaller than the normal kidney. Follow-up studies can be used to show progression of disparity in the size of the kidneys.

Renal causes that frequently have the associated finding of flank mass include infantile polycystic kidneys, bilateral cystic dysplasia and renal vein thrombosis. They have characteristic sonographic findings that have already been discussed. Congenital nephritis, nephrotic syndrome, cortical necrosis and acute pyelonephritis are not accurately diagnosed by ultrasound at present. In theory, it should be possible to detect abnormal cortical echogenicity or an abnormally great disparity between the sonolucent medulla and the fine stippled echogenicity of the cortex, but with current standards of technology these findings are extremely difficult to demonstrate in the kidneys of the newborn. The value of ultrasound in these cases is in localization for renal biopsy.

Postrenal causes include obstructive uropathies, and the role of ultrasound is in demonstrating the dilated collecting systems. Functional renal studies and voiding cystourethrography are necessary for the definitive diagnosis of the site of the obstruction.

In summary, ultrasound has proven to be of great value in determining anatomic information. Because it utilizes no ionizing radiation it can be repeated without risk in cases that need close follow-up and review. It can be used not only as a tool in diagnosis, but also for guidance in renal biopsy and percutaneous tube placement for drainage. There is no firm rule as to which imaging modalities one should use in the newborn. It is critical to tailor the type of studies and the order of performance of these to the individual patient. This necessitates a close working relationship between clinician and pediatric radiologist.

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RADIOLOGIC EVALUATION OF THE URINARY TRACT IN THE NEONATE

GEORGE E. ABDENOUR, JR., M.D.

The role of the radiologist or other diagnostician in the evaluation of the neonatal urinary tract is the detection and subsequent work-up of structural or functional abnormalities of the kidneys, collecting systems, bladder and urethra. Diseases of the urinary tract may be manifested by a palpable abdominal mass or masses, infection, oliguria, renal failure, hematuria, proteinuria or hypertension. Because of the wide choice of diagnostic modalities available and their inherent limitations, it is imperative that the radiologist, nuclear physician and ultrasonographer be intimately involved in planning the diagnostic evaluation of these patients. Furthermore, each case must be handled individually, taking into account the history, physical examination and laboratory data. The radiologic evaluation may then be plotted, always considering the sensitivity and specificity of the examination, invasiveness, radiation exposure and cost.

Diagnostic imaging techniques such as intravenous urography, renal ultrasound, radionuclide renal scan and computed tomography contribute varying information regarding the morphology and function of the urinary tract. Generally speaking, ultrasound and computed tomography demonstrate anatomy but offer very little information about renal function. Intravenous urography also demonstrates anatomy and can also provide gross information about renal function. Radionuclide renal scanning, in addition to revealing gross morphology, is an excellent method of demonstrating functional abnormalities of the kidneys, especially when computerized curves of perfusion and excretion are recorded simultaneously with the renal images. Thus, short of the more invasive angiogram, radionuclide scanning is the procedure of choice when renal arterial or venous occlusion is suspected.

The purpose here is to discuss the usefulness and potential limitations of intravenous urography in congenital malformations of the kidney. It is commonly known that in the first several days of life, renal function is less than normal and visualization of even normal kidneys following the intravenous injection of contrast material may be extremely difficult. This is compounded by the invariable multiple air-filled bowel loops which overlie and obscure the kidneys. Tomography should not even be considered in the neonate or

young infant as the exposure time is so long that respiratory motion usually degrades the image even further.

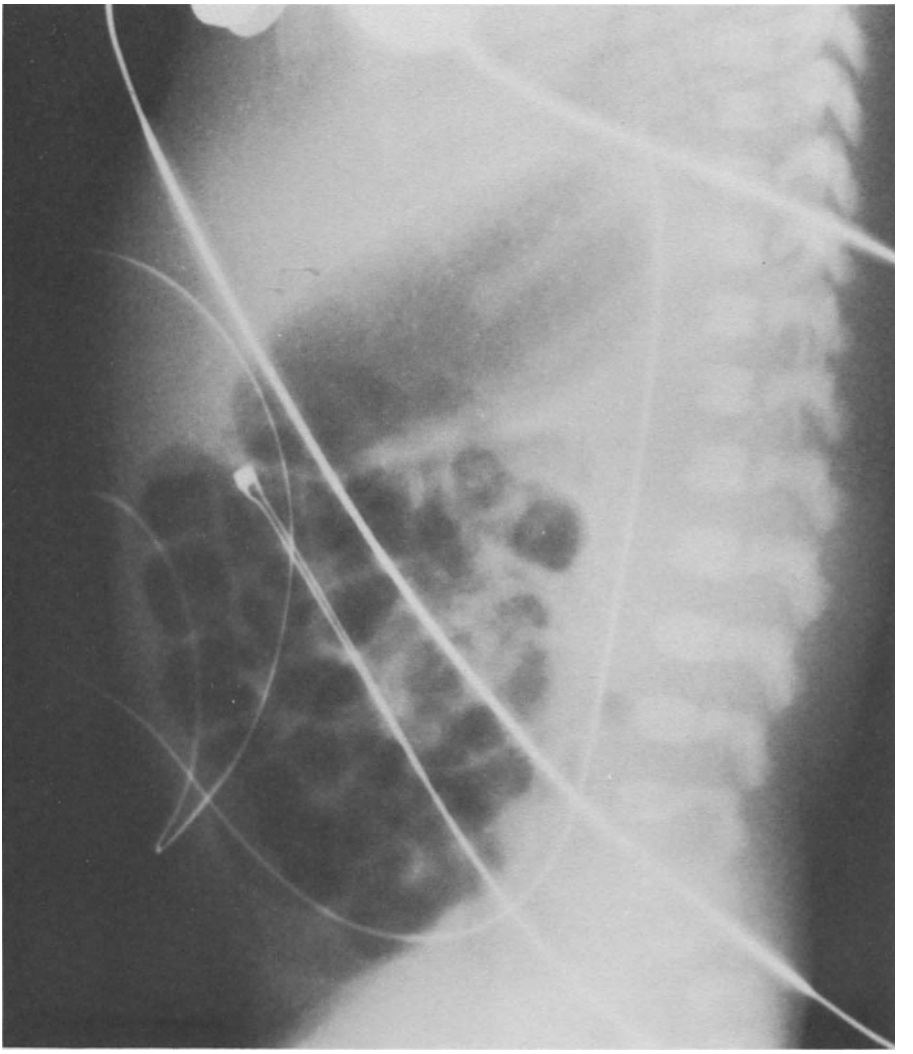

FIGURE 1. Lateral radiograph of a normal neonatal abdomen. The air-filled bowel loops project 2 to 3 centimeters anterior to the spine.

However, if the study is meticulously monitored by an experienced radiologist, a diagnostic intravenous urogram can be obtained even in the first few days of life. Several maneuvers can be employed to improve renal visualization. A dilute carbonated beverage fed to the infant will result in gaseous distention of the stomach. Bowel loops as a result will then be displaced inferiorly and the air-filled stomach will provide a "window" through which to better visualize the kidneys. Rubber compression paddles applied over the area of the kidneys will result in similar displacement of bowel loops. Angulation of the x-ray tube caudally will often project the bowel loops inferiorly and "off of" the kidneys.

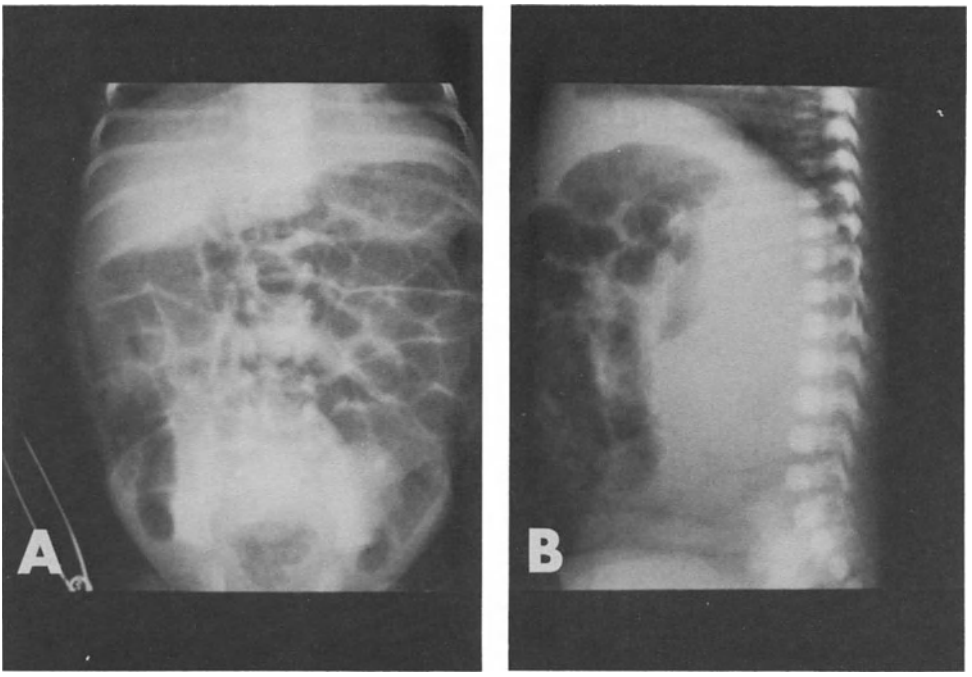

FIGURE 2. A. Anteroposterior and B. Lateral radiograph of a neonate with bilateral hydronephrosis secondary to posterior urethral valves. No obvious mass is identifiable on the frontal view, however, the lateral view demonstrates marked anterior displacement of all bowel loops indicating bilateral retroperitoneal masses. This patient's voiding cystourethrogram is shown in Figure 6.

Before proceeding, the importance of the scout abdominal radiograph must be underscored. When a congenital malformation or tumor is suspected, an anteroposterior (AP) and lateral scout film must be obtained and it is the latter view which is the most crucial. It is not at all uncommon for a retroperitoneal mass to be undetectable on an AP view of the abdomen whereas the lateral view will usually show anterior displacement of air-filled loops of bowel (Figures 1 and 2). The vector of bowel displacement on the lateral view will usually suggest the site of origin of a mass. For example, if an upper quadrant mass displaces the stomach bubble or bowel loops posteriorly, a renal origin would be highly unlikely and therefore an intravenous urogram is not even indicated (Figure 3). The scout film is obviously also important in detecting intraabdominal or retroperitoneal calcifications.

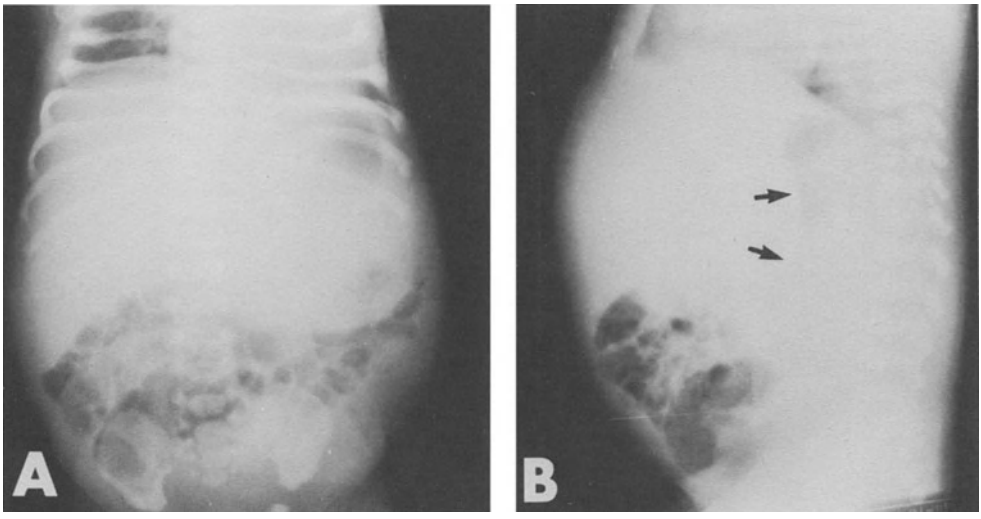

FIGURE 3. A. Anteroposterior and B. Lateral radiographs of a neonate with a left upper quadrant and flank mass. The frontal view shows inferior displacement of the distal transverse colon. The lateral view demonstrates posterior displacement of the gastric air bubble (arrows) and, therefore, excludes retroperitoneal origin of the mass. The mass was proven to be a hemangioendothelioma of the left lobe of the liver.

Approximately 50% of neonatal abdominal masses are renal in origin and another 10-15% arise in other retroperitoneal structures such as the adrenal gland. The vast majority of these lesions are benign and the diagnosis can usually be suggested following intravenous urography.

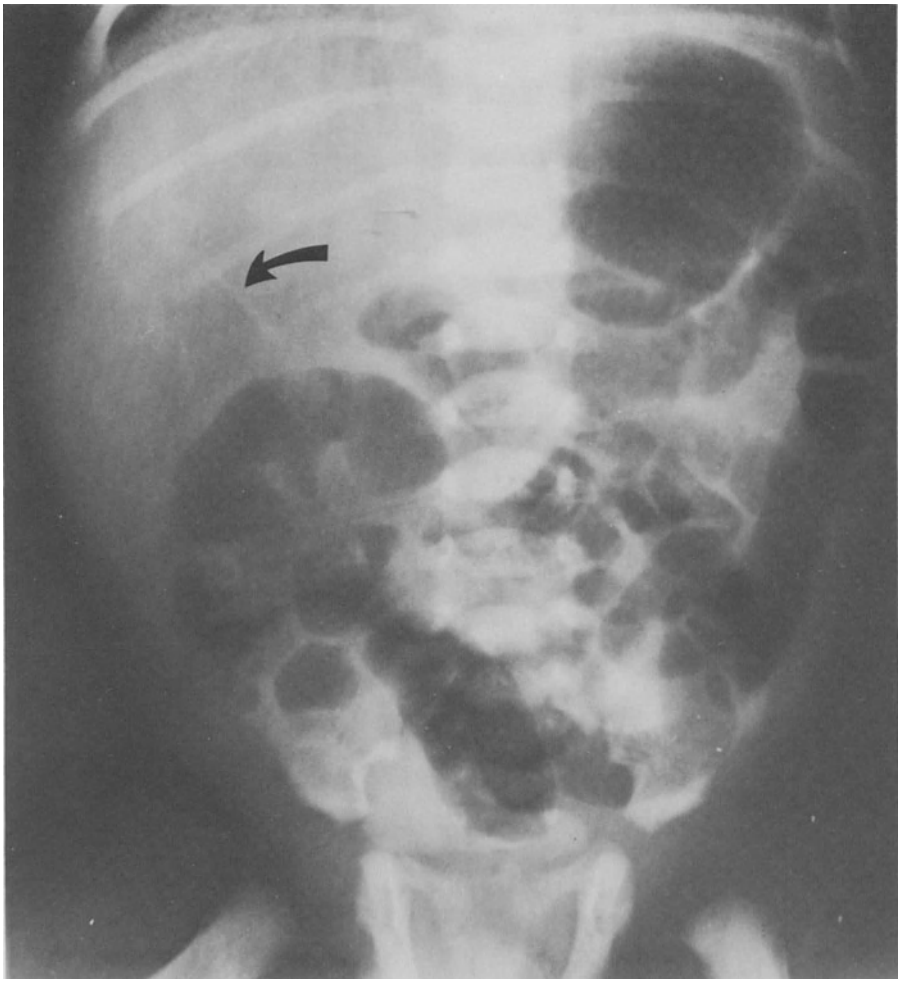

FIGURE 4. Posteroanterior radiograph of an intravenous urogram at 10 minutes in a neonate with a right flank mass. A vague relative lucency is noted in the area of the right renal fossa with a dense line within (arrow) representing a cyst wall in a case of multicystic dysplastic kidney. The left kidney was shown to be normal on subsequent films and there was no function demonstrated on the right side as late as 24 hours postinjection.

Multicystic dysplastic kidney (MDK) and hydronephrosis comprise the majority of neonatal renal masses with such lesions as Wilms' tumor and hamartoma much less common. It can be very difficult to differentiate these two lesions on ultrasound alone and, therefore, most of these infants will require intravenous urography or renal scan for further clarification. There are early radiographic signs on the intravenous urogram which will differentiate MDK from hydronephrosis. In MDK the walls or septae of the cysts may appear as thin linear or curvilinear densities representing contrast in vessels and nephronal elements in the wall of the cysts (Figure 4). A hydronephrotic kidney (Figure 5) may show a relatively thick rim of renal parenchyma surrounding the more lucent nonopacified urine in the dilated pelvocalyceal system--

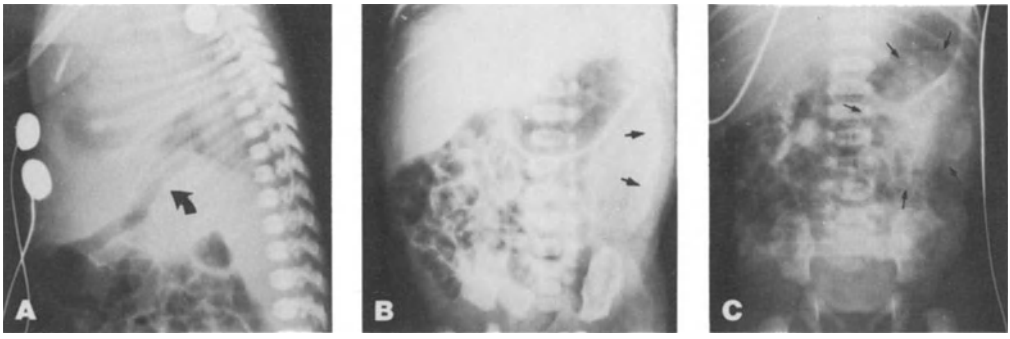

FIGURE 5. A. Lateral chest radiograph on a neonate with mild respiratory distress because of eventration of the left hemidiaphragm. There is a mass effect on the posterior aspect of the stomach (arrow) although a mass was not suspected clinically. B. Anteroposterior radiograph of an intravenous urogram at one minute in the same patient shows contrast in a rim of renal parenchyma (arrows). The kidney is enlarged and the two hour delayed view, C., shows opacification of the markedly dilated pelvocalyceal system (arrows)--hydronephrosis in this case secondary to ureteropelvic junction obstruction.

the so-called "negative pyelogram" effect. On delayed views, it is extremely unusual to see excretion of contrast material in MDK whereas in a hydronephrotic kidney there is usually progressive opacification of the pelvocalyceal system. An intravenous urogram is not complete unless delayed films are obtained as late as 24 hours postinjection in cases of early nonvisualization.

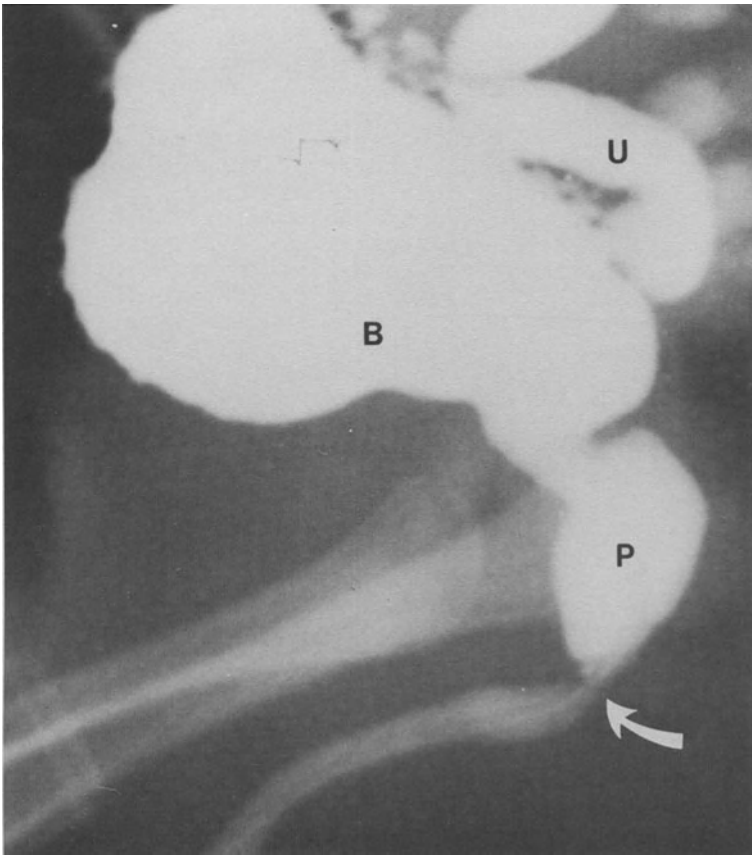

FIGURE 6. Lateral view of a voiding cystourethrogram in a male neonate with bilateral hydronephrosis secondary to posterior urethral valves. The bladder (B) is irregular in outline with pseudodiverticuli on its posterior wall and there is a reflux into one of the ureters (U). The arrow points to the site of the obstruction in the prostatic urethra (P).

The intravenous urogram will usually demonstrate the sit of obstruction in cases of hydronephrosis with ureteropelvic junction (UPJ) obstruction being the most common. If hydronephrosis is the result of an obstructing ureterocele, this is usually visualized as a lucent defect in the posterolateral aspect of the bladder base.

Solid tumors of the kidney are relatively rare in the neonatal period, the most common being mesoblastic nephroma and Wilms' tumor. These kidneys will often function normally but there will usually be obvious distortion, displacement and dilatation of the collecting system. Ultrasonography will usually confirm the solid nature of the mass.

In the neonate with bilateral flank masses, hydronephrosis is the most likely possibility. This is not uncommonly a result of bilateral UPJ obstruction, however, stronger consideration should be given to the possibility of bladder outlet obstruction such as posterior urethral valves in a male or neurogenic bladder. In such instances, voiding cystourethrography is the study of choice (Figure 6). Voiding cystourethrography should also be routinely performed in cases of suspected ureterovesical junction obstruction as reflux alone can give the same urographic picture. Other causes of bilateral flank masses are rare and include such lesions as bilateral multicystic dysplastic kidney, infantile polycystic kidneys, infiltrative diseases such as leukemia, and bilateral Wilms' tumor.

When vascular disorders such as renal artery occlusion or renal vein thrombosis are suspected, the intravenous urogram is usually not helpful. In both disorders there is frequently a delay in excretion or poor visualization on the involved side. In such instances, radionuclide scanning is much more sensitive in demonstrating the vascular basis of the lesion, especially if prior ultrasound has shown a normal-sized, nonobstructed kidney on that side. Renal scanning and ultrasonography are also the procedures of choice in the neonate with renal failure of more than a mild degree.

Computed tomography and angiography play little role in the evaluation of urinary tract disease except in some cases of suspected malignant tumors.

In conclusion, it should be stressed that the various imaging modalities available to the clinician are complementary and demonstrate varying degrees of sensitivity and specificity for each particular problem under discussion. Each case must be analyzed individually and the diagnostic evaluation planned with the radiologist, nuclear physician and ultrasonographer as consultants.

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DISCUSSION

José Strauss, M.D., Moderator

QUESTION: We place a lot of emphasis on the vitamin D related aspects of bone disease in prematurity. I think we know that there is parathyroid function or activity in the neonatal period and at least in a group of patients there is a vitamin D absolute or relative deficient state. Might not those babies have lived in a sort of high risk milieu characterized by metabolic acidosis, a catabolic state, poor intake and so on, and a negative calcium balance? My question is: the bone disease that we see in prematures, is it not really analogous to renal osteodystrophy since it may be that hyperparathyroidism plays a prominent role in the genesis of the bone disease?

RESPONSE: That is a very important question. Some of you who were here for the telephone interview may recall that I posed a similar question but in a different manner. I asked whether or not we should begin to collect data, if possible, on the histomorphology of metabolic bone disease to determine whether we are dealing with osteomalacia or rickets or osteitis fibrosa. I think that that would be important if we truly believe, as it is in the older child and adult, that if this is osteitis fibrosa, 1,25-D_3 would be indicated for treatment; but, if this is osteomalacia, perhaps 25-D_3 alone would be indicated. And, if it is a combination of both, maybe the two drugs would be indicated. So, I think that that postulate is a very good one and only by gathering of information in the future will we be able to sort that out.

QUESTION: First, I want to say that in my country we have the regular IVP but we don't have scintigraphy for the diagnosis of renal masses in children. Sometimes, we have the problem of one excluded kidney in the IVP and the ultrasound cannot tell us, at least in our hands, if this is a hydronephrotic, or a multicystic kidney or what is the height of the obstruction (if one is present). We have tried in a few cases doing a direct puncture with retrograde pyelography. What is your opinion on this method?

RESPONSE: We don't have very much experience. We have done one case a couple of years ago, puncturing the so-called "cystic" space and ran into no difficulty. I can't reiterate strongly enough what was said before, that ultrasound is an art form, it is a "hands on" kind of procedure and the more you do the better you get at it; the more you look at lesions, the more fine details really help you out. Real-time ultrasound, which has become much more popular recently, is particularly helpful in looking at these kidneys in all kinds of orientations without

having to take the transducer off of the baby's abdomen. It is not infrequent that multicystic-dysplastic and hydronephrotic kidneys look very much alike and can be confused with each other. It is for that reason that, unless I feel absolutely convinced on ultrasound, I would demand that we do a functional study, a renal scan. The renal scan will assist and make the definitive diagnosis. Between those two images we can conclude whether we are dealing with a multicystic kidney perhaps with activity in the little bit of functioning tissue, or a very poorly functioning hydronephrotic kidney with activity which eventually collects in the pelvis. If you are dealing with a multicystic-dysplastic kidney and you puncture it, and you inject contrast, it should never go into the bladder, because they always have atretic ureters. You can use that as a helpful sign. Another thing with multicystic kidneys is that, if you inject a cyst, you won't get filling of all the other cystic spaces because they don't all connect.

COMMENT-QUESTION: A couple of times we filled only one cyst; it had the impression of the other cyst over the wall.

RESPONSE: If you can only fill one cyst, you are dealing with a multicystic kidney and never with a hydronephrotic kidney.

COMMENT-QUESTION: Most nephrologists know that when we do a kidney biopsy using ultrasound and we don't get tissue, it is the fault of the ultrasonographer having placed us in the wrong position...I was really struck by the beautiful portrait of a renal vein thrombosis just shown. I find that diagnosing that in the newborn period is difficult and, if ultrasound can really do that, I would rejoice. Can you tell us what is the accuracy of the diagnosis? I would like for the answer (already given to me) to be given in public so that everybody can hear it.

RESPONSE: Clearly, the ultrasound picture of renal vein thrombosis varies according to when you do the study in relation to the insult. If one does the examination at a time when the kidney is markedly edematous, swollen, you will get a picture very much like what was shown earlier. It is not pathognomonic of renal vein thrombosis. Very few things are, on ultrasound, pathognomonic. They have to be used along with the clinical signs, the clinical presentation, so that if you have an infant who has been stressed, who has hematuria, and who has that ultrasound picture, you have a very high clinical suspicion that you are dealing with renal vein thrombosis. I would suggest that, if you have that ultrasound picture in that clinical situation, you do a renal scan to confirm. I want to stress that ultrasound is not the panacea in diagnostic modalities The Nuclear Medicine Radiologist works closely together with the Ultrasoun Radiologist in order to be successful in a good number of cases. The two examinations combined yield very high rates of correct diagnoses.

COMMENT: We work so closely that I don't have much to add. It seems that the information which is in the literature is outdated. There are no combined studies of Nuclear Medicine and Ultrasonography; at least, there are no longitudinal studies to see what is the evolution. In the acute ca the radionucleide study will give us a hint because it will show an enlarg kidney, minimally functioning but not obstructed. We have seen this image in three cases in which there was renal vein thrombosis proven by invasive

methods. We feel confident that in the acute phase we can make the diagnosis with radionucleotides particularly if the ultrasound proves that there is anatomically a kidney in that place. However, as time goes by and the kidney becomes hypotrophic, it becomes smaller, the radionuclear study is not helpful because it doesn't show much out of the kidney. So, after 1-3 weeks it is very difficult to make the diagnosis.

QUESTION: Hypocalcemia is a stimulus for the 1,25 hydroxylation of D_3. I wonder how does it work? Is it entirely because of the PTH stimulation, the direct action? If direct action, is it because of the serum levels or tubular levels of calcium?

RESPONSE: You mentioned one important aspect. It is mediated in part through the action of PTH. There might be other mechanisms that modulate 1,25 hydroxylation as well but probably one of the most important is through PTH, I would think.

COMMENT: Extracellular phosphate concentration is supposed to play a role also.

QUESTION: Have there been any studies in parathyroidectomized animals to see the effect of hypocalcemia on vitamin D_3 metabolism?

RESPONSE: Yes, there is vitamin D hydroxylation proven in the absence of PTH. I cannot recall exactly the data but I know that it is known. Like someone said earlier, hypophosphatemia is also a factor, not necessarily mediated by PTH.

QUESTION: What kind of transducer do you recommend for renal ultrasound? Vector transducer or linear transducer?

RESPONSE: If at all possible use a real-time machine so that you can get the most information as quickly as possible. Linear array is not a good choice because you do not have skin contact over a large enough area. A vector scanner is what you would like and you would like to use a five megaHertz transducer because the kidneys are so close to the skin.

QUESTION: We were shown a slide relating arterial oxygen tension to the percent of fluid intake that was excreted. What were the conditions under which that data were collected? Was it in experimental animals or in babies?

RESPONSE: They were data collected from newborn premature babies; most of them had respiratory distress syndrome secondary to hyaline membrane disease. They were all studied during the first three days of life. Urine was collected by 12 hour periods during these three days of life and then we correlated the urine output in relation to the lowest plasma oxygen tension recorded during the collection period of 12 hours.

QUESTION: Were these observations in infants with cyanotic congenital heart disease?

RESPONSE: Not in newborn babies. But we have made studies reported last year at the International Congress of Pediatric Nephrology on cyanotic congenital heart disease in older children, mainly 1-7 years of age. We also found not a decrease in urine output but a decrease in renal perfusion in relation to the plasma oxygen tension.

QUESTION: You presented some data here showing that in RDS there is an impairment of the ability to get rid of urine after a period of time. There has been a report a few months ago demonstrating that one can determine the long term pulmonary prognosis of patients with RDS depending on how rapidly they develop a diuresis. Those patients who have a diuresis by the second or third day have a far better prognosis than thos who do not have that early diuresis; in the latter the prognosis is worse and they are more likely to develop broncho-pulmonary dysplasia. I wonder if you have any comments on that in relation to your data on the long term follow-up of the patients that you studied.

RESPONSE: I had a slide but I spared it for the sake of time. That slide showed data on the follow-up in these patients with Respiratory Distress where we demonstrated a sharp decrease in renal perfusion and renal glomerular filtration rate. We followed a few patients during the 21 days after onset of RDS later than the first day of life. All the patients recovered complete renal function when the respiratory condition improved. Of course, I am not surprised that the ones having a good diures are the ones doing well. If a patient has a good diuresis and can dilute the urine it means that the renal insult was not very important. When we have a baby with respiratory difficulty who is able to dilute the urine below the isotonic level, we think we have a very good chance that things will go well.

MODERATOR: In some of the studies that I did a number of years ago, I had attempted to induce concentration of the urine by feeding a high protein formula to low birth weight babies of 1-3 days of age. This was the same high protein diet that Edelmann and Barnett gave to premature babies up to the extrauterine age of 2 weeks. I was unable to make a change in their urinary concentrating ability. This may be a point worth discussing as we evaluate the effects of urea and of the administration of various amounts of protein.

In terms of what was mentioned earlier about the osmolal gradient in utero, I wanted to mention that in the two papers published in Pediatrics in 1981 and co-authored by Drs. L. Stanley James and Salha Daniel and myself, we reported some observations with spontaneous osmolalities of up to 600 mOsm/kg in the first minutes (from zero to 120) of extrauterine life. Those osmolalities changed every few minutes; within the first two hours after birth, the babies were able to concentrate and dilute their urines going from one extreme to another very rapidly. They could dilute their urines down to 80 mOsm/kg. Do you have any comments on possible mechanisms or the meaning of those changes?

RESPONSE: Just a very short comment. I remember that the question on the concentrating ability being improved by protein feeding was asked of Chet Edelmann at the International Congress in Philadelphia. He said at the time that they had really to feed them very very large amounts of protein. I'm sure that nobody would do it now. I have just a remark on the concentrating mechanism. In one of the slides it was pointed out

that there could be a defect in concentrating ability when using contrast agents. I want to stress the point that very often what you get is very high urine specific gravity after having done an IVP or angiography so you get a concentrating effect but actually you can be misled just because your specific gravity is very high.

RESPONSE: That's absolutely correct from a clinical standpoint. The osmotic diuresis that prevents adequate urea reabsorption and perhaps diminishes the active chloride and sodium reabsorption occurs but, as he points out, the measured osmolality of the urine would be high because of the osmotic properties of the dye itself. In the studies from Einstein that you referred to, they gave on the order of four to six grams/kg/protein to those little babies and I am sure that no one would do that again. That was in the days before one had to submit protocols to a Clinical Research Committee. That may be the explanation, José, as to why this was not observed in your studies.

RESPONSE: No. We followed exactly the protocol that they did; we fed the same amounts of protein and in the first three days of life, were not able to make any difference, even after giving vasopressin in addition to the increased protein load.

COMMENT: I could only speculate that in the first three days the GFR was so low that the delivery of urea to the nephron was so low that there was the difficulty in establishing the urea gradient. But I don't believe that, based on the studies that we showed today that we did in the fetal lamb. So, I don't understand that.

MODERATOR: Our time for discussion is over. I thank the members of the panel and all the participants for their contributions.

IV

NEONATAL PATHOLOGICAL SITUATIONS

Strauss, J. (ed.) Neonatal kidney and fluid-electrolytes

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MANAGEMENT OF MASSIVELY DILATED URETERS IN CHILDREN

Jorge L. Lockhart, M.D., and Victor A. Politano, M.D.

The presence of a congenital megaureter in infants and children constitutes a therapeutic challenge. This entity predisposes, and many times is associated with profound renal failure. The most important factor in its management is recognition of the precise cause. Medical and/or surgical management are determined by the appropriate etiologic diagnosis. A new classification has been recommended (1), and it should be universally adopted to be able to compare similar groups in future discussions (2,3). Although there are many reports referring to indications and surgical techniques in the management of megaureters, there is little mention of treatment and results of the different groups and subgroups. In the new classification, there are three major categories of megaureters: reflux, obstructed, and nonrefluxing, nonobstructed megaureters. Each is subdivided into primary and secondary types (1-3):

1. Refluxing
   Primary - lateral ectopia, postoperative reflux
   Secondary - bladder neck stenosis, urethral valves, or stenosis; neurogenic bladder

2. Obstructed
   Primary - Intrinsic ureteral obstruction:
     Mechanical - stricture, ectopia, ureterocele
     Functional - Adynamic extravesical ureter
   Secondary - extraureteral obstruction:
     Extrinsic ureteral compression - trauma, tumor, fibrosis, vascular
     Infraureteric obstruction - bladder - neuropathic; urethra - valves

3. Nonrefluxing, nonobstructed
   Primary - Prune belly, megacystitis, megalourethra
   Secondary - Metabolic, toxic, decompensated:
     Polyuria or hypokalemia - Bartter syndrome
     Infection - endotoxin aperistalsis
     Repeated surgical corrective efforts

Some ureters, as in patients with urethral valves, may have reflux associated with obstruction; perhaps a fourth category, refluxing and obstructive megaureter, should be added (3). This occurs most commonly in patients with urethral valves or severe neurogenic dysfunction ; however, a small number of patients with primary refluxing megaureters have asso-

ciated reflux and obstruction (4). The prune belly should be considered separately. Children with this syndrome may have a primary refluxing megaureter; however, the disease constitutes a distinct anatomic entity with its own therapeutic approach and prognosis.

REFLUXING MEGAURETER

Primary refluxing megaureter

This is caused by incompetence of the ureterovesical junction and is associated with a normal bladder and urethra. While correction of the relatively normal refluxing ureter carries a high success rate according to several series, the results with megaureters are less successful. Initial diversion may be a life-saving approach in the newborn or infant with severe renal failure or urosepsis, but in the stable, uninfected child with normal renal function, the controversy between immediate reconstruction and multi-stage procedures, including preliminary diversion, has not been resolved. The parameters to consider should be: degree of decompensation of ureters, status of renal function, associated renal dysplasia (5), pelviureteral obstruction (6), and, of course, the adequacy of surgical reconstruction (2).

When surgery is indicated, reimplantation with or without ureteral tailoring is the ideal modality of treatment. Retik et al. (7) reported excellent results with this modality in 9 children; one secondary ureteropelvic junction obstruction resolved after reimplantation and tailoring, and eventually none of the patients required upper tract surgery. The authors insist that long-term radiologic follow-up should be done since definitive improvement with stabilization does not occur until two years later (7). For that reason, further reconstructive procedures should be delayed since some of the kinks and ureteral tortuosity disappear with growth (8). Good results with immediate remodelling and reimplantation have been reported by Hendren (9). He emphasizes that the procedure should be undertaken by an experienced surgeon, with expert anesthesia and supporting pediatric intensive care services (9). The same author admits that some of the massive upper and lower tract reconstructions performed in the past could have been avoided with an adequate lower tract repair (10). Other authors advocate upper tract reconstruction first (11). However, if this is the case, a second operation would be necessary to stop the vesicoureteral reflux. The fact that the upper tract dilatation improves after reimplantation would rule out initial upper tract repair as the preferred modality in the management of this problem. However, some discouraging results also have been reported. Derrick (12) presents 10 patients with disastrous results after reimplantation and tailoring. Most ended in upper tract diversion (12). After retrospective analysis, he recommends supravesical diversion before reconstruction (12). Discouraging results have been reported by others (6,13,14); Filmer, King, and Belman (13) presented 40 per cent successes, with obstruction as the most common complication. Johnston and Farkas (6), as a consequence of their poor results with tailoring and reimplantation, advocate a more conservative approach using surgery only when infection or obstruction are superimposed. They believe that reflux causes ureteral kinking and angulation, producing secondary obstruction. Based on this they improved their results in 3 megaureters of 2 patients after pyeloureteroplasty (6). Lockhart, Singer,

and Glenn (2) reported 60 per cent success in bilateral megaureters. In their cases previous diversion in the form of nephrostomy and ureterostomy did not improve results (2); since this was a retrospective analysis, it is possible that the cases previously diverted had maximal decompensation of their ureters and nonrecoverable renal function.

Rabinowitz et al. (15) reported 94 per cent success in the management of 80 megaureters, of which 55 were of the refluxing type. Twenty-five per cent of their patients had preliminary nephrostomy, but an important conclusion of their article is that only 3 per cent of megaureters required upper tract reconstruction after lower repair. Also, approximately one third of the patients with initial nephrostomy did not require ureteral tailoring at the time of reimplantation. In another publication, the same authors reported somewhat worse results using primary ureterostomy and reconstruction (16). However, this was the group of patients with uncontrolled infections, sepsis, azotemia, significant ureteral redundancy, and questionable over-all renal function (16).

In the massively dilated, refluxing ureter, without an obstructive component at the ureterovesical junction, Politano (8) recommends vesical diversion in the form of indwelling Foley or cystostomy drainage for several months. A good alternative currently used by some authors to decompress upper tracts in patients with urethral valves is a cutaneous vesicostomy (17). Reimplantation may then be performed without the need of tailoring. At the same time, in infants, diversion decompresses the system until the child reaches a more suitable age for reimplantation.

Due to the multiple modalities of treatment and results, it is difficult to compare the different series. However, a general plan can be suggested:

1. Initial reconstruction should be avoided by the inexperienced urologist.
2. The infant with the disease, or the child with superimposed azotemia, urosepsis, recurrent infections, and renal dysfunction should first be diverted as a potentially life-saving alternative. If catheter drainage does not solve the problem, supravesical diversion in the form of cutaneous pyelostomy, nephrostomy, or cutaneous ureterostomy may be applied. In this circumstance, the necessity of several further reconstructive procedures makes it less advisable.
3. In the clinically stable child with massively redundant and tortuous ureters, a vesical decompression for several months will avoid the need for ureteroplasty, unless there is an obstructive component at the ureterovesical or pyeloureteral junction.
4. Initial reimplantation with tailoring should be performed by surgeons familiar with this entity, and with expert anesthesia and supportive intensive care unit.

Secondary refluxing megaureter

This type of megaureter appears secondary to infravesical obstruction or a neuropathic bladder, and as a consequence, high intravesical pressure overcomes the competent ureterovesical mechanism and reflux appears. The bladder and/or urethra are abnormal as differentiated from the primary refluxing type. The most common source of infravesical obstruction in children is urethral valves. The initial management of these patients

includes bladder drainage (feeding tube or suprapubic intracath), and correction of urosepsis, hydroelectrolytic imbalance, and acidosis, if present. The transurethral resection of the valves should be undertaken, and a watchful waiting period should start (18,19). Initial ureteral tailoring and reimplantation together with destruction of the valves (20) is not indicated in view of the satisfactory results obtained with the more conservative approach (19). Initial upper tract diversion is indicated in severely ill infants, where the treatment is lifesaving (21). If the child remains free of infections with satisfactory renal function and thrives, the ureters are likely to straighten (8,18). Duckett (17,18) believes that if the ureters remain wide and atonic after removal of the valves, the situation may be improved with a cutaneous vesicostomy. When bilateral reflux persists, it can be corrected at a later date; however, different series have found reflux not to be a serious complication in the management of the patient with valves (18,22,23). When unilateral reflux is present, a massively dilated ureter is associated with a nonfunctional unit in high percentages of cases (19,21). Other authors deny suprapubic cystostomy as a satisfactory modality of drainage since many patients treated that way required supravesical diversion (24). Singer and Glenn (25) believe that the persistent hydroureteronephrosis is due to fibrotic transmural ureteral compression, as a secondary change to the profound hypertrophy of the bladder wall that follows severe infravesical obstruction. This is emphasized by the largest series of 207 patients reported in which the decreased mortality in a group of boys under one year of age was attributed to better medical management and a more aggressive use of temporary upper tract diversion (26). They advocate temporary lower cutaneous ureterostomies, followed by reimplantation of a decompressed ureter (26). Therefore, the plan to treat patients with valves would require careful observation after initial medical support and resection of valves. If deterioration persists, diverting cutaneous vesicostomy or lower cutaneous ureterostomies have been reported as satisfactory for upper tract decompression, before a major reconstructive procedure is undertaken. In experienced hands, good results may be obtained with initial reconstruction without prior diversion (20,21,27).

Bladder neck stenosis is rare. If present, it should be corrected by transurethral resection, incision, or Y-V-plasty. Careful follow-up is necessary and will indicate if further procedures are necessary. There are not many reports of urethral stenosis and secondary refluxing megaureters. It happens more often in females, and dilatation with or without reimplantation is accompanied by a high success rate (2). Treatment in this situation should be oriented first to the management of the stricture and after a period of careful observation, re-evaluation for persistence of reflux.

OBSTRUCTED MEGAURETER

Primary obstructed megaureter

Primary obstruction occurs when the blockage is directly related to the ureteral wall. Among the mechanical causes of primary obstruction, intrinsic factors, such as ureteral valves or primary congenital stenosis, are extremely rare in children.

Ureteroceles are more common in females, and the disease should always be suspected in a female child with infection and bilateral megaureters (28,29). The management of ureteroceles in patients with urosepsis consists of surgical decompression. Although the value of unroofing of ureteroceles has been denied by some authors (30), others in the past (28,29), and the present authors, believe that it still has a place in these selected patients. An alternative in this situation would be preliminary cutaneous flank drainage. The above, particularly unroofing, which leads to vesicoureteral reflux, are not permanent modalities in the management of ureteroceles, and for that reason Hendren (30) recommends that in the small infant with serious infection, an upper pole partial nephrectomy be used as surgical decompression. All the aforementioned situations, of course, later require lower ureteral reconstruction.

In the clinically stable child, the alternatives are nephroureterectomy, partial nephrectomy (leaving a distal stump to drain, or collapse), pyelopyelostomy (removing a ureteral stump) (31), and transvesical excision and reimplantation (32-35). In a high percentage of cases, the obstructed upper segment is not worth saving. In this case, removal of the diseased kidney with reimplantation of the lower segment is indicated. In Hendren's (32) series, upper poles recovered function only in small ureteroceles with little ureteral dilatation. If the upper segment is salvageable, a double reimplantation or pyelopyelostomy should be performed.

In the situation of an ectopic ureterocele the approach is similar, but special care is needed to reconstruct the bladder and urethral wall to prevent stress incontinence and diverticulum formation due to the weakness of the muscular layer. Development of a mucosal flap to act as an obstructing valve-like mechanism should be avoided (35).

Kroovand and Perlmutter (31), who advocate an extravesical dissection of the ectopic ureter and resection at the level of the detrusor muscle, state that the ureterocele will collapse against the muscular backing; no herniation occurred in 9 patients (31).

The most common type of primary obstructed megaureter is seen in conjunction with a functionally obstructive segment (36-48). With the new techniques of ureteral reimplantation and tapering, the results have improved when the surgical indication is correct. An entirely conservative approach as suggested many years ago by Nesbitt and Withycombe (44), is not applicable nowadays. Although a group of patients presenting with only lower ureterectasis may be followed conservatively, the presence of progressive dilatation, parenchymal damage, or recurrent urinary infections are indications for surgical reconstruction (46,47). If severe infection or massive dilatation is present, initial decompression with cutaneous pyelostomies or nephrostomies should be considered. The results with the different techniques performing excision of the obstructed segment and reimplantation with and without tailoring are satisfactory (2,9,10, 49-52).

Secondary obstructed megaureter

Secondary obstruction due to external ureteral compression is possible, although very rare in children. This type of megaureter is associated with severe infravesical obstruction and hypertrophy of the bladder wall, the latter compressing the transmural ureter (2). If this compression is established on a chronic basis, it may predispose to fibrosis and perpetuate obstruction (25). Obviously, in these circumstances, vesical diversion is not sufficient. This type of megaureter is occasionally observed after

resection of urethral valves. As previously discussed, while analyzing secondary refluxing megaureters, lower cutaneous ureterostomy followed by reimplantation of the decompressed ureter, appears to be a satisfactory modality (26). However, since the contracted bladder causing ureterovesical obstruction is thick-walled with fibrotic changes, the success of reimplantation may be less than in an organ having only reflux. At the same time, in a report comparing the different groups of the classification, the patients with secondarily obstructed megaureters had maximal renal dysfunction and upper tract anatomic decompensation on initial presentation (2

The neuropathic bladder associated with megaureters presents a very difficult management problem. Obviously, these are patients who have failed with more conservative measures, such as neuropharmacologic agents and self-catheterization. It is clear that reimplanting dilated ureters into an abnormal bladder may not be successful (7,53), but if temporary diversion improves ureterectasis, the results with reimplantation are better (54). Alternatively, an external sphincterotomy can decrease the intravesical pressure while reducing the bladder contractility against a spastic external sphincter; in this situation ureterectasis improves and reimplantation is feasible (55). This is a satisfactory alternative in male patients. The next step, of course, would be supravesical diversion.

NONREFLUXING, NONOBSTRUCTED MEGAURETER

Although the prune belly syndrome is usually associated with vesicoureteral reflux, its management is different from that of patients with primary reflux. It constitutes a therapeutic challenge and should be placed in a special category in every classification. In this entity, the degree of renal dysplasia with consequent prediction of renal function recoverability will rule the modality of treatment (56-59).

The conservative management advocated by many experienced authors is based on the fact that the final evolution of the disease cannot be changed with extensive reconstructive procedures (60,61). Of course, there are many patients with mild features of the syndrome and most of them can be followed conservatively (62). The patients in whom complications develop, such as urinary retention, urinary infections, urosepsis, or azotemia, will require surgery. Williams and Burkholder (61) performed high loop cutaneous ureterostomies with the purpose of decompressing the collecting system. Renal biopsy was used to evaluate the degree of renal dysplasia. This approach permits careful follow-up, and later it may be decided whether or not other reconstructive procedures might be indicated (61). Woodard (62) advises the avoidance of the use of the upper ureter for diversion, since it is essential in further reconstruction; cutaneous pyelostomy or vesicostomy are the alternatives.

Massive surgical reconstruction has been advocated by Woodard (62), who reported excellent results with primary or staged operations. Demos, Lockhart, and Politano (63) presented 2 patients treated with ileal sleeves, but one of them has gone to renal failure ten years after the procedure. The controversy between conservative and aggressive management will not end until the follow-up of the patients recently operated gives us an idea of the long-term results. The secondary type of nonrefluxing, nonobstructed megaureters may be observed as a result of toxic or metabolic phenomena, as with the decompensation observed in Bartter syndrome (64), peristaltic failure with severe infection (65), or the irrecoverably decompensated ureter that may result from repeated surgical corrective efforts (2).

There are situations in which, in the absence of reflux, a persistently dilated ureter could be secondary to obstruction or simply aperistaltic and decompensated. In this situation, probably the most reliable method to distinguish between obstruction and decompensated dilatation, is the performance of antegrade pressure-flow studies, such as the Whitaker test (66). Diuretic radionuclide urography may be used, but the results sometimes are difficult to quantitate (67). Of course, the more classic techniques, such as catheterization of the ureteral orifices, with retrograde studies and intravenous pyelography with serial and delayed films, are extremely useful in classifying this problem (3).

If the ureters are chronically dilated, nonrefluxing and nonobstructed, and when complications develop, such as deterioration of renal function or uncontrollable infections appear, there are not many alternatives to supravesical diversion. Replacement by small intestine (68,69) or placement of an ileal sleeve around the ureters (63) seems to be the most successful modality.

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FLUID BALANCE IN SICK NEWBORNS

EDUARDO BANCALARI, M.D.

Water and electrolyte balance is frequently altered in diseases affecting the newborn. This is because the neonate has limited capability for controlling his fluid intake, has a large surface area in relation to body weight and his endocrine and renal systems have not developed the full capacity for compensation. Secondary alterations in water and electrolyte balance frequently have an adverse influence in the course of primary diseases making the management of these patients more difficult.

1) Alterations of Fluid Balance in the Fetus.

The fluid balance in the fetus is maintained by swallowing amniotic fluid, by elimination of urine and lung fluid into the amniotic cavity and by transfer of water and electrolytes across the placenta and fetal skin. Under certain conditions this balance can be disrupted and total fetal water can increase producing a "hydrops fetalis." Among the most common conditions that can result in fetal hydrops are anemia due to Rh incompatibility, renal anomalies with obstruction, heart failure due to congenital malformations or arrhythmias and chronic intrauterine infections. Although hydropic infants have a marked increase in total body water, the fluid is predominantly in the extravascular space while the blood volume may be normal or even decreased.(1) In these infants it is sometimes difficult to expand the blood volume because a large portion of the fluids infused leak out of the vascular space due to increased capillary permeability.

Another situation in which infants may be born with increased total body water occurs when large amounts of parenteral fluids are administered to the mother during labor. If these fluids do not contain electrolytes, the infant develops hyponatremia that in some cases may produce CNS symptoms such as irritability and convulsions.(2)(3)

2) Fluid Administration During Resuscitation.

The asphyxiated infant frequently presents with signs of cardiovascular failure. This can be secondary to

peripheral vasoconstriction and myocardial failure due to hypoxia and acidosis. Blood volume can be decreased if abnormal blood losses occur, but most infants who suffer perinatal asphyxia have a normal or even increased blood volume.(4) Because of this and the possibility of myocardial damage, volume expansion should be used with extreme caution in the asphyxiated newborn. This is even more important in the preterm infant in which rapid volume expansion in the absence of hypovolemia may increase the incidence of intracranial hemorrhage.(5) When hypovolemia is suspected because of a history of blood loss, low arterial blood pressure, poor peripheral perfusion, low hematocrit and a low central venous pressure, volume expansion is indicated. This can be accomplished by infusing 5-10 ml/kg body weight of plasma or blood obtained from the placenta using aseptic technique.

Severe perinatal asphyxia is always accompanied by metabolic acidemia due to accumulation of organic acids. This acidosis resolves spontaneously in most cases after normal oxygenation and circulation are reestablished. If the acidosis is severe it may result in myocardial depression and pulmonary hypertension and in this situation requires rapid correction. This can be achieved by the infusion of sodium bicarbonate through the umbilical vein or artery. The dose varies depending on the severity of the acidosis but in most cases 2-4 mEq of sodium bicarbonate per kg of body weight are sufficient to partially correct the base deficit and bring the pH to a normal range. The infusion of hypertonic bicarbonate carries several risks, such as CNS hemorrhage, vascular damage, tissue necrosis, respiratory depression and hypercapnia and decrease in ionized calcium. The risk of these complications can be reduced by administering a diluted bicarbonate solution (1 mEq in 2 ml water) at a slow rate. It is also important to establish adequate ventilation before its administration to avoid CO2 retention.

3) Fluid Balance After Perinatal Asphyxia.

The management of fluids in the infant who suffered severe perinatal asphyxia is complicated because of the simultaneous alteration of many organ systems. As mentioned earlier, the asphyxiated infant frequently has myocardial damage and depression with signs of heart failure. The occurrence of hypoglycemia or hypocalcemia may aggravate this myocardial dysfunction. Fluids may also be retained if renal failure occurs as a consequence of the hypoxia and renal ischemia.(6) These infants may also develop excessive secretion of ADH and severe oliguria with fluid retention.(7) The resultant increase in total body fluids may have disastrous consequences because it may aggravate the heart failure, increase the possibility for brain edema

and also increase lung fluid producing a deterioration in pulmonary function. Increased capillary permeability due to hypoxic endothelial damage will also favor leak of fluids and proteins into the extravascular space.(8) It is essential therefore to avoid overhydration of infants who suffered perinatal asphyxia. Close monitoring of cardiovascular function, urinary output, serum and urine osmolarity and body weight are essential to maintain a normal fluid balance. Daily fluid intake must be initially restricted to 40-60 ml per kg body weight until adequate diuresis is established. In cases of heart failure inotropic agents such as Dopamine or Dobutamine may be indicated. Fluid intake should be increased to 120-150 ml per kg per day only after adequate diuresis is established (2-3 ml per kg per hour) and body weight starts to decrease.

4) Fluids in Acute Respiratory Failure.

Many conditions that produce acute respiratory failure in the newborn are characterized by an increase in lung fluid content. The increased interstitial lung water may be secondary to increased capillary permeability, decreased lymphatic drainage, increased pulmonary hydrostatic pressure or decreased oncotic pressure. Increased capillary permeability may be due to prematurity or to inflammation. This can be caused by infection or chemical injury due to high inspired oxygen concentration or aspiration of meconium or feedings. Lymphatic drainage can be reduced by decreased tidal volumes or by an increase in central venous pressure. Hydrostatic pressure is increased in cases of left heart failure,a frequent finding in preterm infants with a patent ductus arteriosus (PDA). Low colloid osmotic pressure occurs as a consequence of a low serum protein concentration, also a common finding in preterm infants.(9) All this can be aggravated by variable degrees of renal failure and water retention that may occur in infants with severe respiratory failure.(10) The consequences of an increase in interstitial lung fluid are a decreased pulmonary compliance, increased airway resistance and probably also a reduced diffusion capacity. These alterations lead to further impairment of lung function with hypoxemia and hypercapnia.

It has been suggested recently that the improvement in lung function observed in infants with RDS during the 3rd and 4th day of life may be secondary to the increased diuresis observed in some of these patients before arterial blood gases improve.(11) Attempts to accelerate this improvement by administration of diuretics has resulted in contradictory results,(12) except in infants in which RDS is complicated by a persistent ductus arteriosus and heart failure. There is some evidence suggesting that excessive fluid administration to infants with RDS may increase the

risk for developing chronic lung disease.(13) This is most likely related to worsening of left heart failure in the presence of a patent ductus arteriosus.(14) This makes necessary the use of ventilator assistance for longer periods of time and with higher peak inspiratory pressures and inspired oxygen concentrations.

It is apparent then that excessive fluid administration must be avoided in infants with acute respiratory failure, especially if they are preterm, have evidence of a PDA or depressed myocardial function.

5) Fluids in Chronic Respiratory Failure.

Infants with chronic lung disease, especially those with bronchopulmonary dysplasia have a poor tolerance to fluid overload. In fact, many of them do not even tolerate the normal amount of fluids required to provide an adequate caloric intake. As soon as fluid intake is increased many of these infants show a deterioration in pulmonary function with increasing distress and deterioration of arterial blood gases. The chest radiograph shows increased densities compatible with pulmonary edema. In most cases these changes are reversed by fluid restriction or diuretic therapy. The exact mechanism for this tendency to develop pulmonary edema has not been established. It is possible that lymphatic drainage may be reduced due to increase in central venous pressure secondary to the right heart failure that is present in some of these infants. Another mechanism is left ventricular failure, a frequent finding in patients with chronic respiratory failure.(15) Many of these infants have poor nutritional status with low total proteins and this may also favor fluid accumulation in the interstitial space of the lungs. Capillary permeability in the lungs may also be altered by chronic exposure to high oxygen concentrations and by pulmonary hypertension. It is likely then, that the tendency of these infants to accumulate fluid in their lungs is the result of several contributing factors and efforts should be made to try to correct each of these alterations. This includes fluid restriction, providing concentrated formulas, and if necessary protein supplementation. Maintenance of a PaO2 over 50 mmHg is crucial to avoid pulmonary hypertension and probably also left ventricular failure. When respiratory function deteriorates sometimes it becomes necessary to use mechanical ventilation to maintain adequate arterial blood gases. Use of chronic diuretic therapy seems beneficial in some of these infants but no data are available in the literature to prove this.

6) Fluid Administration and Patent Ductus Arteriosus.

Premature infants and especially those with respiratory failure have a high incidence of patent ductus arteriosus (PDA). The decrease in pulmonary vascular resistance that occurs after birth leads to left to right shunting through the ductus arteriosus and increased pulmonary blood flow. This produces overload of the left ventricle and frequently left heart failure with increase in left atrial and pulmonary venous pressures. The increased hydrostatic pressure in the pulmonary capillaries results in an increase in interstitial fluid in the lungs and a deterioration in gas exchange. This process is exaggerated when larger volumes of fluids are administered and for this reason fluids should be restricted in any premature infant with evidence of a PDA.(14) If signs of left heart failure are present, diuretics are indicated in order to avoid pulmonary edema and hemorrhage until the ductus closes. When the prostaglandin inhibitor indomethacin is used to induce pharmacologic closure of the ductus,one of the side effects is decreased glomerular filtration and oliguria. This may result in more fluid retention and aggravation of the left heart failure. This can be avoided by close monitoring of fluid balance after indomethacin administration and further reduction in fluid intake if necessary.

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RENAL FUNCTION IN INFANTS WITH ASPHYXIA AND RESPIRATORY DISTRESS SYNDROME

A. APERIA, M.D. and U. BROBERGER, M.D.

Several reports suggest that both glomerular and tubular function are impaired in asphyxiated infants with the respiratory distress syndrome (RDS). Some of them show conflicting results, especially with regard to the effect of RDS on the glomerular filtration rate (GFR). The potential disturbances of glomerular and tubular function that may occur in asphyxiated infants are therefore described separately. The factors that may be responsible for renal function impairment in asphyxia and RDS will then be discussed.

Glomerular function in RDS and asphyxiated infants

In 1962 , Cort (1) first drew attention to the occurrence of renal failure in RDS. She reported a low urinary excretory capacity and a high serum urea in infants with the RDS syndrome. In 1974-76, Guignard et al. (2,3) systematically studied renal function in 20 infants with RDS. These infants had severe RDS and six of them died. The daily fluid intake was low, 70 ml/kg. They found a marked decrease in inulin as well in PAH clearance in neonates with RDS, as compared to control infants of similar postnatal and gestational ages. Moreover, they observed that when the plasma volume was expanded with hypertonic mannitol the GFR increased in the three infants treated in this way. These studies stimulated interest in this problem (4,5,6) and different methods were proposed for preventing and treating renal failure in the respiratory distress syndrome.

Three independent groups, Siegel, Fisher and Oh (7), in 1973 and more recently Broberger & Aperia in 1978 (8) and Müller et al. in 1980 (9), however, have found a normal GFR in infants with RDS.

It seems that the RDS cases studied by Guignard and collaborators were more severely affected and received a lower fluid intake than the other infants reported.

During the past two years, renal failure has been exceptional in RDS infants and it is generally agreed today that infants with RDS who are treated according to current concepts, are not particularly predisposed to a decrease in the GFR that is severe enough to cause renal failure.

Tubular function in RDS and asphyxiated infants

Several types of tubular disturbance have been described in RDS infants. A high sodium excretion due to a reduced tubular reabsorption was observed by Cort (1), Broberger et al. (8) and by Müller et al. (9). On the other hand, Siegel et al. (7) found no difference in the sodium excretion between their asphyxiated and control infants. The study by Broberger et al., showed that the increase in fractional sodium excretion could occur even in infants who were not treated with any drugs that could interfere with tubular sodium transport.

A low tubular bicarbonate reabsorption and a high urinary bicarbonate excretion in RDS infants were found by Torra et al. (2) and by Müller et al. (9). Urinary bicarbonate loss contribute to metabolic acidosis.

Disturbances in other tubular transport systems have also been observed in asphyxiated infants. Svenningsen & Aronsson found that the urinary concentrating capacity was lower in RDS infants than in control infants, matched with regard to gestational and postnatal age (10). Broberger & Aperia found that the excretion of β_2-microglobulin (11), a small peptide that is almost freely filtered and reabsorbed only in the proximal tubule, was higher in RDS infants than in controls also matched with regard to gestational and postanatal age.

Possible mechanisms responsible for renal dysfunction in asphyxiated and RDS infants

Several factors besides asphyxia may be theoretically responsible for the renal failure occasionally observed in newborn infants with RDS asphyxia. The state of hydration appears to be important for the maintenance of a normal GFR. The infants studied by Guignard et al. received a very small daily fluid intake and the GFR increased when the plasma volume was expanded. Hypotension appears to be the rule early in the course of RDS (12). The impact of hypotension on renal function in infants has not been systematically studied. Moreover, we know little about the influence of drugs on renal function in infants. Our findings (8) suggest that treatment with digitalis and ampicillin does not influence the GFR in RDS infants. The use of ventilators in RDS infants whose renal function has been studied has remained approximately the same throughout the seventies.

Some clues concerning the mechanisms responsible for renal dysfunction in asphyxiated infants may be derived from experimental studies. These studies have been performed in neonatal mammals, since it is very likely that the effects of hypoxia on mature and immature cells differ. Although most or all nephrons have been formed about the time of birth, maturation of the glomerular and the tubular cells continues for some time in the postnatal period (13,14). Two groups have studied the effects of hypoxia on renal function in the fetal

lamb (15) and the newborn pig (16). The results of these studies agree well. In both studies hypoxia resulted in an acutely increased renin production and increased renal vascular resistance, but in no change in the GFR.

In fetal lambs it was also observed that hypoxia increased the release of epinephrine and arginine vasopressin. Since the effects of persistent hypoxia on renal function in the neonate have not been studied extensively, it is not possible to predict whether the increased release of vasoactive hormones may subsequently reduce the GFR. Hypoxia also caused a significant decrease in the tubular reabsorption of sodium in both the fetal lamb and the newborn pig. Both the increases in renal vascular resistance and in sodium excretion caused by hypoxia were reversible.

SUMMARY

Asphyxiated infants with RDS who are treated according to current concepts usually have a normal GFR. Dehydration may precipitate renal failure in severely asphyxiated infants. Urinary sodium excretion and urinary bicarbonate excretion are generally increased and predispose to hyponatremia and metabolic acidosis. Experimental studies imply that the increased sodium excretion is a direct effect produced by hypoxia on the neonatal kidney. The concentrating capacity may be somewhat reduced in asphyxiated infants. Fluid and electrolyte metabolism should be carefully monitored in asphyxiated infants with the RDS syndrome.

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The Oliquric Neonate

Eddie S. Moore, Martina S. Evans, Craig B. Langman

Department of Pediatrics and Nursing, Michael Reese Hospital, University of Chicago Pritzker School of Medicine, Chicago, Illinois

Introduction

Recent improvements in medical and nursing care of the newborn infant have resulted in a significant decrease in infant morbidity as well as mortality. In the main, these improvements have been technological with development of sophisticated monitoring devices and expansion of nursing care to that of clinician/practitioner with independent but supervised diagnostic and treatment skills. The latter has greatly enhanced successful implementation of improved monitoring technology. Despite technological advances, high-level care of the newborn infant requires continued use of traditional data gathering skills by history taking and physical assessment. Evaluation of the neonate with apparent oliguria is a classic example of the need to merge traditional techniques with current technology.

Factors Influencing Urine Flow in the Neonate

During the past decade, infant feeding practices have changed considerably with emphasis on early hydration. Nonetheless, variability in renal functional development related to gestational age of the infant, obstetrical practices during delivery of the infant, and time of first feeding, make it difficult to establish precise values for urine flow rate during the first one to two days of life. After this period, definition of expected urine flow rates becomes more precise. Normal urine flow during the first one to two weeks after birth varies widely and is reported to be from 0.5 to 5.0 ml/kg/hr.[1] Others define oliguria as less than 15 to 20 ml/kg/24 hours after the first few days of life.[2] Because many variables contribute to urine production and urine flow in the neonatal period, we suggest that urine flow rates of less than 0.5 ml/kg/hr in infants of any size be considered as abnormal and the diagnosis of oliguria established. Important factors influencing urine production and subsequent urine flow rate in newborn infants are listed in Table 1.

Table 1. Factors influencing urine production and urine flow rate in newborn infants.

A. Perinatal Factors	B. Factors After Birth
Gestational age	Time of initial fluids
Renal functional development	Volume of initial fluids
Birth weight	Body temperature
Time of cord clamping	Phototherapy
Apgar score	Infant warmers
	Diuretics

We previously reported that the most common explanation for apparent failure of the infant to void within the first forty eight hours of life ("pseudoanuria") is unobserved spontaneous voiding during or shortly after delivery.[3] The tremendous stimuli to the autonomic nervous system during birth that triggers micturiction is analogous to uncontrolled spontaneous voiding in children with seizure activity. Thus, it is not surprising that in one series, ninety-two percent of newborns voided close to or shortly after delivery.[4] The term "pseudo-oliguria" in the neonate can be used to refer to a decrease in urine flow secondary to medical care rather than to a primary disturance in body fluid physiology or renal function in the infant. This term is not intended to be confusing nor indicate that urine flow rate is normal. We advocate this terminology to emphasize the importance of early recognition of decreased urine flow rate in neonates resulting from failure to provide adequate fluids. Prompt recognition and correction of this problem should, in most cases, prevent subsequent severe renal ischemic damage. Usher et al. demonstrated that time of clamping of the umbilical cord after delivery of the infant significantly influences total volume of blood transfused to the infant.[5] Placing the newly delivered infant on the mother's abdomen and delay in clamping the cord results in transfer of an additional 60-125 ml of blood to the infant. Clearly, this volume of blood will greatly increase renal perfusion pressure and subsequent urine formation. This observation was subsequently confirmed by the studies of Oh and Lind.[6]. Considerable discretion is advised, however, and the delay in cord clamping should not be excessive to avoid producing polycythemia in the infant.

Most neonatologists now recommend provision of oral fluid to the infant within the first four to six hours after birth. This practice is to be encouraged and should not be influenced by the status of the infant. The sick and/or distressed infant most likely requires an adjustment in the compostion and volume of fluid to be administered rather than omission or delay in administering fluid. In these sick infants, intravenous fluids are usually begun immediately upon arrival in the special care nursery. Recommendations for volume of fluid to be provided during the first two days of life vary while there is uniform agreement to provide judicious amounts of glucose. It has been reported that the minimal metabolic rate during the first fews hours after birth is 32 cal/kg/day in full-term infants with slightly higher rates in low birth weight infants.[7] This rises rapidly to a value of 43 cal/kg/day by the fourth day of life. Based on this metabolic rate, a typical maintenance water requirement during the first day of life is approximately 80 ml/kg. This value is increased daily to a rate of at least 150/ml/kg/24 hours by 5-7 days of age. This minimal value provides no fluid allocation for growth nor does it meet additional needs imposed by cold stress. Brück showed that when challenged by hypothermia, both full-term as well as premature infants attempt to maintain body temperature by increasing rate of heat production.[7] This results in as much as a 2-3 fold increase in water requirements for these infants. Despite the low glomerular filtration rate at birth (see below), approximately 50 to 100 ml/100 calories expended will be excreted as urine.

Recently, Bell et al. and Baumgart et al. reevaluated the effect of routine use of radiant warmers on insensible water loss.[8,9] These studies demonstrated that insensible water loss may increase as much as 30 percent by use of radiant warmers compared to traditional incubators. Therefore, the minimal fluid volume for administration recommended above, should be adjusted upward as necessary

depending upon the extent of use of these warmers. Unfortunately, additional routine but unvoidable medical practices further influence the rate of urine formation and urine flow in the neonate. Phototherapy and diuretic therapy may each result in significant water losses and production of classic pre-renal failure and oliguria. Recognition of and prompt replacement of on-going losses from these procedures should avoid significant depletion in body water and oliguria in infants receiving this type of therapy.

The above discussion emphasizes the important role of early fluid administration or early recognition of significant fluid losses secondary to standard treatment practices. Failure to do so could result in a net decrease in the infant's total body water and intravascular volume with a significant decrease in renal perfusion pressure. This could in turn result in ischemic tubular or cortical necrosis. The practical difficulty with this recommendation for early and judicious fluid administration to the neonate is the theoretical if not real possibility of maintenance of a patent ductus arteriosus. This medical dilemma is not easily resolved. The obvious but difficult objective for the clinician is to achieve an intravascular volume that assures optimal renal perfusion pressure but avoids contributing to a hemodynamic state that maintains ductus patency. This condition probably obtains if sufficient fluid is given to produce lower but normal urine flow rates.

Renal Functional Development in the Neonate

Several excellent reviews of developmental renal function have recently appeared.[10,11] Ethical considerations justifiably limit knowledge of renal functonal development in human fetuses. Nonetheless, from studies of human abortuses and from data drawn from experimental models in other mammals, certain valid speculations can be made regarding intrauterine renal function in human fetuses. The fetal kidney is capable of producing urine by the third month of gestation. The percentage of cardiac output received by fetal kidneys is approximately four percent compared to twenty percent in the adult. Renal vascular resistance is greatly elevated throughout gestation and total renal blood flow is quite low. Fetal renal vascular resistance increases further with gestational age but fetal renal blood flow remains unchanged. Immediately after birth, renal vascular resistance begins to fall and renal blood flow rises. Studies in piglets showed a significant indirect correlation between the fall in renal vascular resistance and a rise in renal blood flow during the first thirty days of postnatal life.[12] Studies of glomerular filtration rate in utero showed values that range from 0.75 to 1.4 ml/min/kg fetal weight in sheep.[13] At birth, glomerular filtration rate in human infants is approximately 30 ml/min/1.73m^2. Immediately thereafter, glomerular filtration rate begins to rise and there is a 20 to 25-fold increase between birth and adult life.[14] The major factor mediating this change is an increase in glomerular capillary surface area.

Robillard *et al.* demonstrated that fractional renal tubular reabsorpton of Na^+ and Cl^- in fetal sheep was 0.90 and 0.98 respectively.[15] Fractional Na^+ and Cl^- reabsorption increased with gestational age and the increase was more rapid than the increase in glomerular filtration rate. Additonal studies of fetal renal tubule function have shown low rates of reabsorption of K^+ and phosphate.[16] With increasing gestational age, K^+ reabsorption increased and was directly

related to fetal plasma aldosterone concentration. Low urinary phosphate excretion during fetal life and in the neonatal period occurs despite relative hyperphosphatemia. Aperia et al. as well as several other groups showed that fractional Na+ reabsorption in the proximal tubule is less in the neonatal period than at an older age.[17] Spitzer proposed that immediately after birth, glomerular filtration remains low and glomerulotubular balance is present.[18] With increasing glomerular filtration rate, tubular reabsorption of Na+ also increases to maintain glomerulotubular balance. In studies of human infants, Edelmann et al. showed that limitation in urinary concentrating capacity resulted from a low rate of urea excretion.[19] Finally, studies of Arant et al. and Brodehl et al. demonstrated that maximal capacity to reabsorb glucose and amino acids in infants is not different from that for older children.[20,21]

In summary, the kidney in the neonate is characterized by low but rapidly increasing rates of blood flow and glomerular filtration. Appropriate changes in fractional tubular reabsorption of filtered sodium and water occur in response to known extrarenal stimuli as is true for later or adult life. Limitations in the ability of the kidney in the neonate to respond to extrarenal stimuli is principally a result of the low glomerular filtration rate.

Pathophysiology and Causes of Oliguria in the Neonate

Table 2. Major causes of true oliguria in the newborn period.

A. Extrarenal Causes	B. Primary Renal/Urinary Tract
Heart failure	Acute tubular necrosis
Sepsis	Acute cortical necrosis
Respiratory distress	Renal vein thrombosis
Hypothermia	Congenital glomerulonephritis
Perinatal asphyxia	Hydronephrosis
Intraventricular hemorrhage	Neurogenic bladder
Inappropriate ADH	Posterior urethral valves
Excess fluid losses	Urethral meatal stenosis

Disturbances in any aspect of urine formaton and egress of urine from the urinary tract can obviously result in either diminished urine production or urine flow rate. Disturbances in function or structure that may result in oliguria are, 1) myocardial functon, 2) body fluid volume and distribution, 3) glomerular capillary integrity, 4) renal tubular integrity, and 5) patency of the excretory urinary tract. Normal myocardial contractility and cardiac ejection volume are essential for maintenance of renal perfusion pressure. Thus, congestive heart failure is a common cause of oliguria in all ages including the neonate. A priori, the etiology of oliguria in congestive heart failure is diminished renal ultrafiltration secondary to decreased perfusion pressure. However, a common additional explanation is acute tubular necrosis secondary to renal ischemia. In additon to myocardial function, renal perfusion pressure and plasma flow rate are directly related to intravascular volume. Conditions that result in a net decrease in intravascular volume in the newborn infant with or without a decrease in total body water, can result in oliguria. An example of oliguria in neonates secondary to intravascular volume depletion without a decrease in total body water is oliguria associated with necrotizing enterocolitis.

Assuming that the kidney in the neonate has optimal perfusion pressure and renal plasma flow, glomerular ultrafiltration characteristics (hydraulic coefficient or k_f) must be normal to maintain adequate urine flow. Although extremely uncommon, congenital glomerulonephritis has been reported as a cause of oliguria in the neonate. The oliguria in this case results principally from decreased glomerular hydraulic conductance. Glomerular filtrate entering the first part of the proximal tubule (S_1 segment) is an ultrafiltrate of plasma whereas the final urine voided by the infant contains little, if any, of the original solute and approximatey one percent of the filtered water. Healthy intact renal tubules selectively alter the composition of glomerular filtrate based on the needs of the infant. The vast majority of work performed by the tubule to alter glomerular filtrate is accomplished by changing the rate of reabsorption of filtered sodium. Perinatal asphyxia or other conditions that result in renal ischemia is an obvious cause of oliguria secondary to disturbed tubule function. Paradoxically, the high degree of maturation of tubule function present in the neonate is responsible for oliguria secondary to the syndrome of inappropriate antidiuretic hormone. (SIADH)

In addition to the causes of oliguria previously discussed, respiratory distress and ventilatory therapy can produce oliguria in the neonate. The mechanism of the oliguria is probably pooling of large amounts of fluid in the lungs which decreases effective intravascular volume. The association of oliguria with respiratory distress is not without controversy. Guignard showed a direct correlation between urine output and arterial oxygen saturation.[22] However, recent studies by Langman et al. showed that urine output increased several hours before improvement in arterial O_2 saturation in newborn infants with respiratory distress and oliguria.[23] This study suggests that the improvement in respiratory symptoms is secondary to renal excretion of fluid previously pooled in the lungs. We reported that chronic intermittent respiratory therapy in infant monkeys resulted in redistribution of intrarenal blood flow.[24] Oliguria in this instance results from shunting of blood away from more mature functioning nephrons.

Intraventricular hemorrhage can produce oliguria as a result of loss of large amounts of blood into the site of bleeding. In addition to blood loss at the site of hemorrhage, studies in adults have shown that severe intracranial events can produce acute tubular necrosis probably as a result of renal nerve stimulation.[25] Oliguria in the newborn infant secondary to renal causes such as renal vein thrombosis, acute tubular or cortical necrosis, and congenital glomerulonephritis, results from "leakage" of filtrate through damaged tubules, or by blockage of urine flow from tubule obstruction. Finally, congenital obstructive uropathy produces oliguria either through a significant decrease in ureteral peristalsis or partial obstruction of the excretory system.

Evaluation and Diagnosis

Establishing a diagnosis of true oliguria in the neonate requires differentiation between failure of or decrease in urine formation versus failure to void urine. As mentioned previously, we believe that urine flow rates of less than 0.5 ml/kg/hr in neonates of any size be considered abnormal and the diagnosis of oliguria established. A careful review of the history beginning, prior to and at delivery is esstential. If the infant voids during delivery, this

should be promptly noted in the record. The appropriateness of fluid administration versus fluid losses via all routes should be carefully calculated. Because of difficulty in detecting mild to moderate volume depletion by physical assessment in the neonate, these examinations should be performed on a serial basis and related to changes in the infant's systemic blood pressure, pulse rate and additional parameters reflecting fluid status as available. The presence of a palpable bladder indicates urine formation but on the other hand, suggests outlet obstruction. An attempt should be made to assess kidney size, patency of urethral meatus, and to determine if physical stigmata suggestive of multiple organ abnormalities are present. These include low set ears, widely spaced nipples, and only two umbilical vessels instead of the normal three, among others.

Laboratory studies for true oliguria should be based on contemporary understanding of renal function and body fluid homeostasis in the neonate. (Table 3)

Table 3. Recommended laboratory tests for evaluation of neonates with oliguria.

Blood

- Electrolytes
- BUN, creatinine
- Osmolarity

Urine

- Routine analysis
- Na, K, Cl
- Osmolarity
- Urea, creatinine

Others

- Ultrasound
- Dynamic renogram

The fractional excretion of sodium (FE_{Na}) or the renal failure index (RFI) is used to determine integrity of the renal tubule in altering compostion and volume of glomerular filtrate. These are applicable to the newborn infant and are calculated as follows:

Fractional excretion of sodium (FE_{Na})
$FE_{Na} = (U/P_{Na})/(U/P \text{ creatinine})$
Renal failure index (RFI)
$RFI = (U_{Na})/(U/P \text{ creatinine})$

Normal values for both are the same and are as follows:

low birth weight infants - $\lessdot 2.5 - 3$
full-term, AGA infant - $\lessdot 1.5 - 2$
older infants/adults - $\lessdot 1.0$

FE_{Na} (or "RFI") greater than normal is highly suggestive of impaired tubule function (ATN) or conditions where urinary sodium excretion is regularly increased such as with volume expansion (with normal kidneys) or with inappropriate antidiuretic hormone. In the latter instance, oliguria is present, whereas with the former there is an increase in urine flow rate. Urine/plasma osmolar ratio is also helpful in differentiating the elevated FE_{Na} of acute tubular necrosis from that produced by inappropriate ADH. During acute tubular necrosis, urine/plasma osmolar ratio is less than one whereas with inappropriate ADH, it is greater than one. However, because of low protein intake and the effect of low urea excretion (see above) on urine osmlality, this ratio is of questionable value in the newborn period. If serial physical assessment and the above laboratory studies are not revealing, ultrasound of the kidneys and, perhaps, the entire urinary tract, may be useful and has the additional advantage of being noninvasive. Because of low blood flow and low concentrating capacity in the neonate, the dynamic renogram is preferred to the intravenous pyelogram to evaluate renal gross structure and renal function.

Management

The most common cause of oliguria in the newborn period is inadequate fluid administration compared to fluid losses. The obviously difficult problem for the clinician is to provide necessary drugs and treatment modalities for the infant which in some may be life saving. Most clinicians initially take great care to adjust volumes of administered fluid to compensate for treatment modalities such as infant warmers. However, oliguria in the neonate usually appears after several days (in our experience, after 5-8 days of age) when the additive effect on water loss of multiple treatment regimens is obscured by the multiplicity of therapeutic maneuvers. In this instance, a plethora of data generated from use of multiple sophisticated monitoring devices tends to create a situation where the etiology of the oliguria is nebulous and one "cannot see the trees for the forest". A conscious and, more importantly, continuous on-going awareness of potential fluid losses and prompt replacement of these losses is the most effective means of achieving as well as maintaining a steady-state in fluid homeostasis in these infants.

Oliguria resulting from other discernible causes of decreased renal perfusion such as heart failure is obviously most effectively managed by specific treatment. In those instances where oliguria results from intrinsic renal damage, conservative medical treatment with fluid restriction to evaporative losses plus urine output is indicated until healing occurs. Finally, for infants with oliguria secondary to congential obstructive uropathy, prompt consultation by a pediatric urologist should be obtained.

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DRUGS AND THE NEWBORN INFANT

S. Singh, M.D., D.C.H.

Drugs and the newborn infant

The physiologic changes in organ function which accompany maturation have a significant influence on drug utilization. The disposition and effects of drugs in the newborn infant are substantially different from that in the older child or adult and intensified or toxic effects observed in this age group are related to the developmental pecularities of drug disposition or receptor reactivity. Thus, the rate of drug metabolism and elimination is impaired in the neonate due to hepatic and renal immaturity respectively and is reflected in prolonged biologic half-lives of drugs. As these organs mature during the later half of the first month of life the rate of disposition of drugs is increased and is accompanied by a concomitant decrease in drug half-lives. Safe and rational drug therapy of the sick newborn infant, therefore, requires an appreciation of the developmental factors which affect drug efficacy and disposition.

The purpose of this review is to discuss some of the factors which influence drug effects and disposition in the newborn infant and to point out the special therapeutic situations which may result from these maturational phenomena.

Drug absorption

No systematic studies of absorption of drugs in the newborn infant have been conducted, however, several lines of investigation suggest that the bioavailability of drugs administered orally differs significantly from that in the adult apparently due to the marked changes in gastrointestinal function which occur after birth. These alterations of gastrointestinal function include decreased gastric acidity, prolonged transit time and increased permeability.[1]

The gastric pH is alkaline at birth but falls quickly and values of 2.5 to 3.5 are reached within a few hours.[2,3] Reduction in gastric acid secretion and relative achlorhydria is characteristically present in the first 8-10 days of life. A gradual increase in acidity begins in the 3rd or 4th week and normal values are reached by 3 to 4 years of age.[4]

The relative achlorhydria of the first few days of life is responsible for the higher bioavailability of Penicillin G., ampicillin and nafcillin observed in the neonate.[5,6] In contrast, the absorption of phenobarbital,[7] diphenylhydantoin[8] and

acetaminophen[9] is reduced in the neonate. Digoxin administered orally in elixir form is efficiently absorbed and the bioavailability is comparable to that observed in the adult.[10]

There is wide variation in gastric emptying in premature and term infants and emptying times ranging from 1.5 to 24 hours may be observed. Good peristaltic function is achieved by the time the infant is 3 months old.[11] Gastric peristalsis is modulated by diet and feeding schedule and may have significant influence on the rate of absorption of drugs. For example, the absorption of riboflavin is lower in the neonate than in the older infant and proceeds for a longer time, at least in part, because of delayed gastric emptying.[12] The altered transit time and mucosal function associated with gastroenteritis may also affect drug absorption.[13]

Other factors which may play a role in drug absorption include the colonization of the gastrointestinal tract by microbial flora, high levels of β-glucuronidase in the newborn intestine and maturation of biliary function.[1,13] The high β-glucuronidase activity of the bowel mucosa of the newborn infant may influence the absorption and disposition of compounds such as bilirubin which undergo enterohepatic circulati after glucuronic acid conjugation.[1] The variable maturity of the biliary function and steatorrhea of the preterm and term newborn may influence the absorption of lipophilic compounds although, the clinical significance of this association remains to be determined.

Absorption of some drugs after intramuscular administration is erratic in the newborn infant. For example, the absorption of gentamicin, kanamycin[14] and digoxin[13] is reduced i the newborn infant. The absorption of diazepam from the intramuscular site appears delayed whereas phenobarbital is readily absorbed.[13] Since the absorption of intramuscularly administered drugs is mainly dependent upon regional blood flow it may be significantly affected in certain pathophysiologic states e.g. exposure to a cold environment, congestive heart failure, respiratory distress syndrome and hypoxia.

Several reports of percutaneous drug absorption and resultant toxicity suggest that cutaneous absorption of drugs and chemicals occurs more rapidly and to a greater extent in the newborn infant. The bathing of newborn infants with soap containing hexachlorophene has been associated with significant absorption of the drug.[15] Cutaneous absorption is encouraged when the topical preparation is applied to abraded, denuded or burnt areas of the skin or when repeated applications are made to the diaper region of infants wearing disposable plastic diapers or water-proof plastic pants. Cutaneous permeability to drugs or chemicals is age related and decreases with increasing gestational or chronologic age.[16]

Systemic availability of most drugs is complete after intravenous injection and is lower after oral administration, however, chloramphenicol appears to be an exception. Recent data suggest that oral chloramphenicol palmitate may provide more bioavailable chloramphenicol than intravenous chloramphenicol succinate.[17,18] Chloramphenicol succinate administered I.V. has bioavailability ranging from 55 - 92% since the hydrolysis of the ester is highly variable and the inactive

ester persists in the plasma for several hours after administration.[19,20] In contrast, chloramphenicol palmitate is hydrolyzed by the pancreatic lipases to free chloramphenicol which is then readily absorbed.[20] Comparative studies in pediatric patients have demonstrated that chloramphenicol palmitate leads to higher areas under the serum concentration time curve,[17] higher peak CSF chloramphenicol concentration[18] and higher mean peak chloramphenicol serum concentrations[17,18] than chloramphenicol succinate.

Drug distribution and protein binding

Once absorbed, the drug distributes to the extracellular fluid, plasma and tissue binding sites, target organs and organs of elimination. The rate of distribution is dependent upon the physicochemical properties of the drug, relative size of the body compartments, plasma protein binding and circulatory factors. The various body compartments in the newborn period are different in their absolute and relative size than in the adult. Body water content of the newborn is higher than that in the adult and varies from 85% of the bodyweight in the premature infant to 70% in the term infant.[1,13] The ratio of the extracellular to intracellular water is higher and the quantity of muscle mass and fatty tissue is reduced with a more marked decrease occurring in the premature infant.[1,13]

Several reports suggest that plasma protein binding in the neonate differs significantly from that seen in the adult.[21,24] Plasma protein binding of drugs such as ampicillin,[21] benzylpenicillin,[21] salicylate,[22] dexamethasone[23] and quinidine[24] is reduced in the newborn infant whereas, diazepam and sulfisoxazole may be more extensively bound to protein in cord serum[23] and the protein binding of phenytoin and bilirubin is similar in cord blood and maternal serum.[23]

The differences in protein binding between newborn infants, children and adults are related to a variety of factors. The concentration of plasma proteins, particularly albumin, is lower in the newborn and there may be qualitative differences in the binding capacity of proteins.[1,22] The qualitative differences consist of the persistence of fetal albumin with lower affinity for drugs and a lower level of α-globulins and lipoproteins.[13] In addition, it is possible that high concentrations of free fatty acids and unconjugated bilirubin and other endogenous substances, especially hormones transferred via the placenta may occupy binding sites and thus reduce plasma protein binding capacity.[21,22] Blood acid-base fluctuations which are associated with hypoxemia and respiratory distress syndrome may significantly influence the plasma and tissue binding of compounds such as phenobarbital which have a pKa close to physiologic pH.[13]

The alterations of body compartments and plasma protein binding may significantly influence drug distribution in the newborn infant. The reduced protein binding of drugs in the neonate may result in increased apparent volume of distribution of certain drugs and a given plasma concentration in the newborn infant may reflect a larger amount of drug in the body than in the adult. Additionally, drugs may alter binding of

endogenous compounds in newborns. Acidic drugs such as salicylates and most sulfonamides, which are highly bound to plasma albumin, may compete with and displace bilirubin from plasma albumin binding sites and result in toxic bilirubin concentrations in brains of susceptible neonates.

Drug biotransformation

The biologic action of most drugs is terminated by biotransformation or excretion or a combination of the two processes. Polar compounds with substantial solubility in water at physiologic pH are generally excreted unchanged whereas, hydrophobic drugs require biotransformation to facilitate elimination. Amongst the various biotransformation reactions, oxidation reactions catalysed by the cytochrome P450 monooxygenase system are most common and include aryl or alkyl hydroxylation, epoxidation, N and O dealkylation and S-oxidation. Common conjugation reactions result in the formation of glucuronides, sulfates, acetates, mercapturates and glycinates.

Most of the activity of the cytochrome P450 monooxygenase system is located in the hepatic endoplasmic reticulum although some may also occur in the mitochondria and extrahepatic tissue such as kidney, lungs, adrenals, etc. Hepatic monooxygenase activity appears as early as the 6th week of gestation and increases to a plateau by the 13th-25th week.[25] There are few data relating to the activity of the hepatic monooxygenase activity between the 25th week of gestation and delivery, however, it appears that the plateau is maintained until birth.[26] Although, activity of most microsomal oxidation enzymes is present in the livers of premature and fullterm infants at birth, the cytochrome P450 content and activity of NADPH cytochrome C reductase, NADPH oxidase, aminopyrine N-demethylase and aniline-p-hydroxylase enzymes are lower than the corresponding values obtained in liver tissue of adults when the data are normalized for the protein content.[27] As a generalization, catalytic activities of the monooxygenase system of the neonate against most substrates approximates one fourth to one half of the adult value per gram of liver tissue.[26] Conjugatio pathways are impaired to varying degree in the newborn infant.[2] Sulfate[9,29,30] and glycine conjugation[9,30] appear to be relatively intact whereas, glucuronidation is substantially reduced.[9,28-30]

Pharmacokinetic data in the neonate, although sparse, suggest that drugs which require metabolic oxidation prior to elimination are disposed of slowly in the immediate postnatal period.[26] Impaired rates of elimination of phenobarbital,[7,31] phenytoin,[26,31,32] tolbutamide,[33] diazepam,[34] amobarbital,[35] mepivacaine,[36] indomethacin,[37] theophylline[38] and caffeine[39] have been documented in the newborn infant. Hepatic function and drug metabolizing capacity mature quickly and rapid changes in rates of elimination are seen after birth. This is best illustrated by the changes in the elimination of phenobarbital and phenytoin in the neonatal period. Thus, fullterm newborns have approximately 30% of the adult capacity to eliminate phenytoin at birth but adult rates of elimination are achieved by 1 to 2 weeks of life.[26,31] Neims et al.[31] derived mean

phenytoin half-life of 80 hours for newborns 0-2 days of age, 15 hours for infants 3-14 days old and 6 hours in infants varying in age from 14-150 days. The maturation of phenobarbital elimination as a function of postnatal age follows a similar pattern.[7,31]

Elimination of drugs which undergo synthetic conjugation is also impaired in the early neonatal period. For example, elimination half-life of salicylates[30] and chloramphenicol[40,41] is prolonged in the newborn infant due to the deficient glucuronide conjugation. In the case of acetaminophen, however, deficient glucuronidation is compensated by the relatively well developed sulfate conjugation and elimination half-lives are similar in neonates, older children and adults.[29] Glucuronide conjugation can be enhanced by pretreatment with enzyme inducing agents such as phenobarbital.[42] Phenobarbital given to the mother before delivery or to the newborn infant directly results in significantly lower concentrations of serum bilirubin when compared with untreated control groups.[42,43] Besides its effect on glucuronidation, phenobarbital also causes increased hepatic uptake of bilirubin, increase in biliary flow and increase in hepatic cytoplasmic anion binding fraction, called Y protein.[1]

Drug elimination

Urinary excretion is the major route for the elimination of drugs, unchanged or metabolized, from the body. Traditional parameters of renal function, glomerular filtration rate (GFR) and renal plasma flow (RPF) are low in the newborn infant at birth and approximate 20-40% of values obtained in the adult.[44,45] However, dramatic changes in GFR and RPF occur in the immediate postnatal period and by the fifth postnatal day GFR and RPF increase by 40-50%.[44] These changes are related to a decrease in renal arteriolar vascular resistance and increase in the fraction of the cardiac output distributed to the kidneys.[13,44] The low GFR and RPF characteristic of the early neonatal period have significant influence on the renal clearance and plasma half-life of drugs which are eliminated by glomerular filtration. The low clearance and prolonged plasma half-lives of aminoglycoside antibiotics, indomethacin and digoxin illustrate this point and are responsible for the increased risk of toxic effects in the newborn infant.[13] Thus, the renal clearance of digoxin which is low in the first month of life (50 ml/min/1.73 cm^2) increases progressively and adult values of 130-150 ml/min/1.73 cm^2 are reached by about five months of age.[46] Howard and McCracken[47] reported that kanamycin plasma half-life in term infants was 5.7 hours at 0-3 days of age and decreased to 3.8 hours by the second week of age. Kanamycin half-life was related to gestational age and was 8.6 hours in premature infants with gestational age of 30-33 weeks. Other investigators have suggested that the decline in plasma half-life of drugs is a function of postnatal age and that the rate of change is identical in all infants despite marked changes in birth weight and maturity.[48]

Tubular function is more depressed compared to glomerular function in the newborn infant and this differential has been

called 'glomerular-tubular imbalance'. Depressed glomerular function of the neonate is characterized by a low tubular transport capacity for endogenous compounds such as glucose, phosphate, bicarbonate and aminoacids.[13,44] Likewise, the elimination and biologic half-life of compounds such as penicillin and furosemide which are dependent upon glomerular filtration and tubular excretion are prolonged in the immediate postnatal period. McCracken et al.[49] reported that the average half-life of penicillin G was 3.2 hours in neonates 0-6 days of age and 1.4 hours in infants 14 days of age or older. The prolonged diuretic effect of furosemide in newborn infants is related to the slow elimination of the compound and consequent prolonged half-life ($T_{\frac{1}{2}}$ 7.7 $\pm$ 1.0 hours).[50]

Other variables which may be important in the renal handling of drugs by the newborn infant include a lack of diurnal rhythm, low urinary pH and 'physiologic' proteinuria of the neonatal period.[13]

Concluding remarks

The newborn infant presents a therapeutic challenge, in so far as safe and effective therapy is concerned, due to dramatic changes in organ function. There is increased risk of overdosing and toxicity in the presence of slow drug metabolism and elimination in the first postnatal week. Subsequently, underdosing becomes a possibility when drug disposition rates increase to high levels during early infancy. Individualization of dosage regimens, therefore, becomes a difficult problem. Disasters can be prevented when good clinical judgement is combined with judicious therapeutic drug monitoring.

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Strauss, J. (ed.) Neonatal kidney and fluid-electrolytes

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MANAGEMENT OF ACUTE RENAL FAILURE

J.-P. GUIGNARD , Service de Pédiatrie, CHUV, Lausanne, Switzerland

Acute renal failure (ARF) is defined as a sudden impairment of glomerular filtration rate resulting in oliguria or anuria, water and electrolyte imbalance, acid-base disturbances, and accumulation in the body of nitrogen waste products. The causative factors of ARF may be prerenal, renal and postrenal.

Prerenal causes : impairment of glomerular filtration rate is the consequence of a decrease in cardiac output or a reduction in effective plasma volume resulting in poor renal perfusion. Perinatal hypoxemia, asphyxia, sepsis and cardiac surgery can all interfere with renal hemodynamics.

Renal causes : congenital or acquired lesions of the renal parenchyma may lead to ARF. Renal dysplasia, cystic kidney diseases, renal vein thrombosis, disseminated intravascular coaqulation and acute pyelonephritis are the major causes of intrinsic ARF.

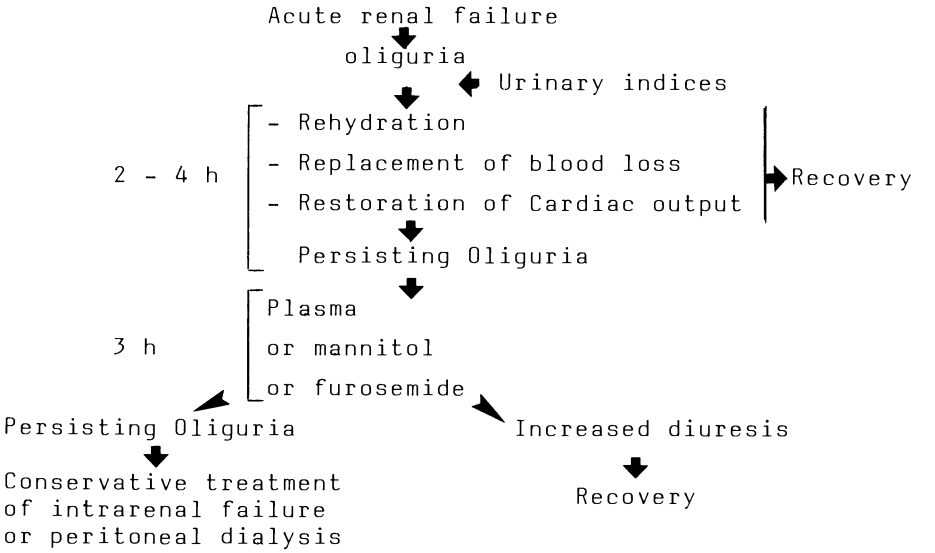
Postrenal causes : obstruction to urine flow may result from congenital malformations or acquired injury to the urinary tract. Imperforate prepuce, urethral strictures, urethral diverticulum, posterior urethral valves and pelvic ureteral obstruction are the major postrenal causes of ARF.

MANAGEMENT OF ARF (Fig.1)

The underlying cause of ARF should be first established together with secure baseline laboratory data. Prerenal factors such as hypovolemia, hypotension, and hypoxemia should be rapidly corrected. Adequate ventilation along with adequate hydration are mandatory.

Dehydration : the first measure taken consists of the correction of the fluid deficit over 2 hours with a solution, the composition of which depends on the nature of the dehydration. Using an isotonic saline solution or an isotonic sodium solution containing 20-25 mmol/l of bicarbonate is the safest method. If the state of renal failure is prerenal diuresis should begin in the next few hours.

Figure 1 : Management and Treatment of Acute Renal Failure



CONFIRMATION OF THE TYPE OF RENAL FAILURE

If diuresis does not occur within a few hours after correcting the fluid deficit, and if some doubt persists as to the nature of the ARF, the following manoeuvres can be tried :

a) administration of a circulating volume expanding agent such as plasma or 20 per cent albumin at a rate of 20 ml/kg over 2 hours, when some doubt persists concerning the state of hydration.

b) when the state of hydration is satisfactory, 20 per cent intravenous mannitol in a dosage of 2.5 ml/kg, or intravenous furosemide, 1-3 mg/kg, is given.

In potentially reversible prerenal failure, a diuretic response is evident during the next 3 hours. Urine output reaches a rate of at least 2-3 ml/kg per hour. Persistence of oligo-anuria indicates the presence of potentially irreversible renal damage.

CONSERVATIVE TREATMENT OF INTRINSIC RENAL FAILURE

A. Fluid administration

Water requirement is limited to insensible loss and replacement of urinary output. Body weight is the only effective means of monitoring fluid balance. The newborn must be weighed twice daily. Caloric needs cannot be attained in an oligo-anuric neonate, so that a daily loss of 0.2 - 1.0 per cent of body weight is expected. Insensible water losses

are estimated as follows :

- Term neonate : 0.7 - 1.0 ml/kg per hour
- Preterm neonate : 2.0 - 2.5 ml/kg per hour
- Infants subjected to phototherapy : 0.6 - 0.8 ml/kg per hour must be added to the normal insensible losses.

Insensible water losses are replaced as 10 per cent glucose (555 mmol/l) given intravenously.

B. Sodium

The hyponatremia accompanying ARF is often due to the inability of the patient to excrete free water. Thus this dilutional hyponatremia must not be corrected by sodium administration, but rather by decreasing the administration of free water. However, if a state of salt wasting has been documented, sodium losses must be replaced by the use of isotonic sodium chloride or isotonic sodium bicarbonate, the latter also correcting the acidosis. Peritoneal dialysis is indicated whenever hyponatremia is associated with fluid overload and congestive heart failure.

C. Potassium

Hyperkalemia can profoundly affect cardiac depolarization and may be a threat to life. The serum potassium level should be determined immediately and a baseline electrocardiogram should be obtained. ECG must be monitored continously if there is any sign of cardiac toxicity. Ventricular arrhythmia or cardiac arrest may occur whenever the classic sine wave of hyperkalemia is present.

The fastest means of reversing the effects of hyperkalemia is to antagonize the peripheral neuromuscular effects of potassium. This can be achieved by raising the extracellular calcium concentration. Ten per cent calcium gluconate is administered intravenously at a rate of 0.5 - 1. 0 ml/kg for 2-4 minutes. Calcium therapy has an onset of action within minutes but the action is of short duration.

Redistribution of potassium from the extracellular space into the intracellular space is also an effective treatment of hyperkalemia. This can be accomplished by administering 2 ml/kg of 8.4 per cent sodium bicarbonate. Intravenous administration of 20 per cent glucose, 4 ml/kg, may also drive potassium into the cells. Alkalinization and glucose therapy have an onset of action within 30 minutes and last for several hours.

Permanent loss of potassium can be accomplished with exchange resins (Kayexalate) administered orally or rectally in a dose of 1g/kg q 6h. The resin is diluted in 10 ml of 20 per cent sorbitol. One gram of kayexalate removes approximately 1 mmol of potassium from the body.

D. Acidosis

Symptomatic metabolic acidosis must be treated by the administration of sodium bicarbonate, but only if serum calcium is normal. If serum calcium level is low or unknown, calcium gluconate should be administered before correcting the acidosis.

E. Anemia

Severe symptomatic anemia should be corrected by the administration of 10 ml/kg of fresh packed red cells, infused slowly over two hours. The risk of hyperkalemia and congestive heart failure must be borne in mind.

F. Arterial hypertension

The most frequent cause of arterial hypertension is iatrogenic fluid overload. The condition usually responds to fluid restriction. Hypotensive drugs should be used with caution in persistent hypertension. Exact doses are not well established in the neonate and the response to hypotensive drugs may be variable among newborn infants. Reasonable guidelines for dosage are given in Table 1.

Table 1. Antihypertensive drugs

Agent	route of administration	dosage (mg/kg per day)
hydrochlorothiazide	O	1 - 3
furosemide	O, iv	1 - 3
diazoxide	iv	2 - 5
hydralazine	O, iv	1 - 4
α - methyldopa	O, iv	5 - 40
Na-nitroprusside	iv	2 - 5
propranolol	O, iv	0.5 - 2

Persistent hypertension requires investigation. Refractory renin-dependent hypertension may respond to inhibitors of the renin-angiotensin system.

G. Convulsions :

They are generally secondary to an electrolyte imbalance (e.g. hyponatremia, hypocalcemia, hypomagnesemia) or secondary to arterial hypertension. The symptomatic anti-convulsions therapy consists of the administration of intravenous phenobarbital, 6 mg/kg, or diazepam, iv or rectally, 0.3 mg/kg.

H. Infections

Infections are frequent in infants presenting with ARF and sepsis is a frequent cause of death. Infections must be treated with appropriate antibiotic agents, the dosage of which is adapted to the degree of renal failure.

PERITONEAL DIALYSIS

An uremic infant whose cardiac failure, hypertension, acidosis or electrolyte imbalance are uncontrollable by conservative treatment is in urgent need of dialysis. In the neonate, peritoneal dialysis is preferred due to its simplicity, relative safety and rapid institution. A specially designed infant's catheter is inserted into the abdominal cavity, under local or general anesthesia. A previously warmed dialysate solution (30-50 ml/kg) is introduced by gravitational flow into the peritoneal cavity, and the dialysis cycles are started. Cycles are usually of 1 hour duration at the onset of treatment : 10 min are allowed for infusion of the fluid, 40 min for exchanges and 10 min for drainage. The rate of cycles can be decreased to 4-6 a day when the clinical condition of the neonate is stabilized. Dialysate outflow must be cultured every day or whenever the outflow is cloudy. The incidence of peritonitis has been dramatically decreased by the use of new "luer-lock" connections (Fresenius, Hamburg, Germany) between the dialysate plastic bag and the peritoneal catheter.

The solutions commonly used for peritoneal dialysis are described in Table 2 :

Table 2. Dialysis solutions

		isotonic	hypertonic
Na	mmol/l	134	134
Ca	mmol/l	1.75	1.75
Mg	mmol/l	0.5	0.5
Cl	mmol/l	104	104
lactate	mmol/l	35	35
glucose	g per cent	1.5	4.25
osmolality	mosm/kg H_2O	358	512

Complications

Major complications of peritoneal dialysis include peritonitis, sepsis, hypovolemic shock, congestive heart failure, seizures, hemorrhage in the peritoneal cavity, intestinal or bladder perforation, hypoproteinemia and drainage difficulties. Peritonitis is treated by administering

antibiotics directly in the peritoneal cavity (Table 3). Antibiotics rapidly diffuse into the blood, reaching equilibration within 8-12 hours. A priming dose can be given orally, parenterally or intraperitoneally.

Table 3. Recommended doses of intraperitoneal antibiotics for the treatment of peritonitis

Agent	Dose (mg/l) loading	maintenance
amikacin	250	50
amphotericin B	2	1 - 2
ampicillin	500	50
cephalotin	500	250
clindamycin	300	50
cloxacillin	1000	100
cotrimoxazole	80 TMP	5 TMP
5- fluorocytosin		100
gentamicin	2 mg/kg BW iv	10
penicillin	10^6 U/l	0.5 x 10^6 U/l
ticarcillin	1000	100
tobramycin	1.5 mg/kg BW iv	10
vancomycin		30

PROGNOSIS OF ARF

Prerenal failure has a good prognosis when the predisposing factors are quickly and efficiently corrected. However, intrinsic renal failure may have a poor outcome, the degree of recovery of renal function being dependent on the nature of the parenchymal lesion. Postrenal failure has a favorable prognosis whenever the obstruction is corrected early and before parenchymal injury occurs.

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DISCUSSION

José Strauss, M.D., Moderator

MODERATOR: I understand that there are some disagreements as to the serum creatinine levels and some of the indices that were presented earlier. I would like also to assess the best approach to protect the baby as a whole and then, various organs. What should we protect preferentially: the kidneys, the lungs, the brain, the heart? Maybe we can come out with an agreement that the baby as a whole is indeed what we need to protect and then, there may not be the need to protect any organ in particular.

COMMENT: I would like to say something regarding a slide that was shown on Captopril. In 1976 we published data on inhibition of angiotensin II in fetal lambs. In an acute experiment using angiotensin II inhibitors with a fall in angiotensin levels and renin levels, urine flow fell markedly. This was associated with an increase in filtration fraction. We postulated that, during **intrauterine** life at least, the high renin levels are necessary to maintain vasodilation of the efferent arteriole which may be opposed by prostaglandin and, as a result of the lack of angiotensin II, there was an increase in intraglomerular pressure, increased filtration fraction, and reduced urine output. I think that that is consistent with the data that **were shown where Captopril on a sustained basis, at least in an infant, resulted** in total anuria. The question of the serum creatinine values has come up. I was told by several people that the values that I had given appeared to be at variance with what had been said earlier. The serum creatinine values given by others here, for the newborn in the first 2-3 days of life, are not higher than the mother's values and thereafter they are around 0.5 mg/dl. This is in contradiction to other people's values. **They** are certainly in variance with the data from our unit which **were published in 1974; but I did make one** cop out statement. I said that with all other factors being ignored, the serum creatinine itself may not be reflective of renal failure. What I was trying to say was that the single observation of a creatinine of 1.2, 1.5 mg/dl in a 1,200 gram infant by itself may not indicate renal failure.

COMMENT: One of the problems may be that I am using SI units and I'm saying that about 50 micromoles/liter is what we should expect as the highest level which is approximately **0.5 mg/dl.** I think that the group at Albert Einstein more recently found that they should range around 0.5 mg/dl (the equivalent of our 50 micromoles/liter) and that is about the normal level we find in newborns who are in the third day of life. Before that there is a big scatter and they reflect the mother's but unless there is renal failure, it is not higher than in the mother. If it's higher than in the mother, it reflects severe renal failure.

COMMENT: I want to repeat what I said earlier, that when we measured serum creatinine in newborns with the kinetic method which is a little more specific, we didn't get any value above 62 micromoles/liter. That means 0.65 mg/dl after day five. All values above that could be related either to gentamicin or to a state of pre-renal failure. The mean of plasma creatinine after day five was 35 micromoles/liter which is about 0.4 mg/dl. I think that that goes well with what my colleague here reported, a bit lower than what my colleague there reported.

COMMENT: We have always measured so-called "true creatinine" removing the chromogens that may interfere and give artificially high levels. Against these two people who are ganging up against me, I think the data from Denver for low birth weight infants tend to approach the values that we have given. The only way I can suggest that any agreement can be made (not that I would agree with either one of them) is that we need to look at other parameters along with the serum creatinine and I only urge a little bit of conservatism in looking at the serum creatinine by itself and saying "ah, the reason, the problem with this child's renal system is renal failure".

COMMENT: I don't know whether I should get in the middle of this. I cannot give you figures for our unit but I can tell you that very frequently we have disagreements with our colleagues in nephrology because they tell us that the creatinine should be under 0.6 mg/dl in our newborns. Dr. Strauss will have to help me in defining the methods used in our central laboratory because I am not familiar with that--but I can say that a significant number of our babies, sick or not sick, have creatinines way over 1 mg/dl during the first two or three weeks of life. We just had the experience a few weeks ago with one of the nephrologists who said "this creatinine of 1.2 mg/dl is abnormal and you should do something about this baby". I asked our fellow to go through the unit and get all the creatinines, routine creatinines. These were not babies who were in renal failure. From ten there were at least five who were over 1 mg/dl. So, something is different between this side of the ocean and the other side. Maybe the technique used in the serum creatinine determination.

MODERATOR: We had a meeting with the pathologist in charge of the clinical laboratory and we reviewed that subject. He agreed that those results over 0.4 mg/dl are abnormal, as far as the "normal" figures for the method he was using. That is an automated method first by Technicon and now by Beckman. The method has been compared successfully with other centers through the International Study of Kidney Disease in Children. In our preliminary report on renal thromboses for which Dr. Dominguez obtained the data, we used a value of 1.0 mg/dl. He had started using a 0.2 mg/dl value which is really what most people report; but, because of that problem, we compromised and settled with 1.0 mg/dl. We will have to resolve this problem. It may be methodological.

COMMENT: I think that a serum creatinine of 0.8 mg/dl certainly reflects GFR that is below 50 ml/min/1.73 m^2. Maybe it reflects a GFR of around 30. It doesn't mean that the infant is in renal failure but that it has a lower GFR than it should actually have for the age. We don't have to do anything about it but still it's something that we should notice.

MODERATOR: I hope that that was the point the pediatric nephrologist was trying to convey. Don't start dialyzing the infant but be aware and keep an eye on what is going on like we do with urine output and so on.

COMMENT: I would like to make sure that there is no misunderstanding with the neonatologists. For the first five days of life, creatinine levels are high. They reflect the mother's creatinine and the rate of decrease depends on the patient. We don't interpret creatinine levels during the first five days. But after five days we get levels of about 0.4 mg/dl.

COMMENT: Those levels I was talking about are way above five days of age.

MODERATOR: What about the renal failure indices? Do we have anybody courageous enough? What about the use of Schrier's ARF index for the neonate?

RESPONSE: I'm not quite sure that you could always use it because, for instance as shown in the asphyxiated infants, there might be a discrepancy between glomerular and tubular damage. In moderately asphyxiated infants, the kind of respiratory distressed infants that we today find in the wards, there is a normal GFR for age but still an **increased** sodium excretion and a reduced tubular reabsorption. So, in those infants the fractional sodium excretion is increased but it's no sign of decreased GFR.

COMMENT: The creatinine values, trying to determine what is within an acceptable range for fractional excretion of sodium in a low birth weight infant or a neonate, points out clearly that if we are not fully awake when we go to the bedside to determine what's going on, we will have difficulty and probably will end up examining each other and treating each other while the poor infant will still remain there undiagnosed because we can't get the data to agree with each other.

MODERATOR: Yes, but it has been said that the indices would not be applicable to children and even less to neonates. Have you looked at this critically? Do you feel that the renal failure index is solid in terms of its applicability to the neonate, infants and children?

RESPONSE: One modification and reservation that I think makes everyone in agreement is that if we talk about the first five to seven days of life or the first week of life, then I believe that fractional excretion of sodium along with all of the other values put together will give you the best opportunity to make a clinical diagnosis as to what's going on. But to use any of the parameters by itself will be **frought with a lot of** pitfalls, possible misinterpretation and erroneous diagnosis. So, I think that in the very first week of life one has to gather all of this data together. If it all falls into a pattern then one may be able to make a diagnosis. After the first week of life then there will be such an array of different interpretations it may become even more difficult.

COMMENT: We can all agree that an increased fractional sodium excretion is an index that something is going on with the kidney. It is not functioning as it should be. It might be that an increased fractional sodium excretion precedes a fall in the GFR. That is another reason for us to observe the infant from a renal point of view.

MODERATOR: My question is about the actual figures that we take. The concept, we all agree.

COMMENT: There have been some data published on this particular question in the Series of Nephrology of which Brenner is the editor. In the issue on acute renal failure there are data to show that in the neonate there is tremendous overlap, as far as the renal function is concerned, between the patients with pre-renal and those with intrinsic renal failure The suggestion from that is that the renal function index would not be a very good parameter. If one looks at the data published there on fractional excretion of sodium,there's far greater separation although there is still some overlap. That might be far more important. In the renal function data there is tremendous overlap one with the other and that wouldn't be applicable.

Could I go back to some of the previous discussions? The cord blood or early neonatal plasma creatinine may be a reflection of maternal creatinine. If the mother has a serum creatinine of 1.0,she has significa renal insufficiency. During pregnancy the glomerular filtration rate rises and usually the GFR should be able to bring down the maternal serum creatinine below .6. I think most perinatologists look at serum creatinin levels greater than that as being indicative of renal insufficiency in the mother. I am not quite sure what the exact relationship should be between maternal blood creatinine and cord blood creatinine but certainly if one gets high levels in the cord blood that would probably indicate maternal disease.

COMMENT: The infants that we have been talking of are not generally the products of normal pregnancies. I don't think that the serum creatinine levels in those mothers--some of them have received diuretics, etc., is the same as in normal pregnancies. I don't know that they have been established but I would expect that the average would be higher.

COMMENT-QUESTION: Before going to the next question I would like to come back to the urinary indices. When you are with a patient what you want to do is do something. I wonder if one of the best urine indices is not the response of the kidney to mannitol. We usually give hypertonic mannitol as a tryout and see if urinary output increases. It is very ofte the best index because you get the response within a few hours, you don't have to wait for the lab, and it's the best answer. How does the kidney respond to an osmotic load? I don't know what is the feeling about it by my co-panelists.

COMMENT-RESPONSE: In terms of relationship between maternal and cord creatinines, I really don't have any information so I couldn't comment. In terms of the use of mannitol as a diuretic, again I would make an exception probably of the use of mannitol in the pre-term infant. In full term infants we don't have the risk of intracranial hemorrhage and mannitol has been used in asphyxiated babies trying to control brain swelling. So, I think that it's common practice. In the pre-term infant I would again emphasize the risk of sudden increase in blood volume and in this way predispose these babies to intracranial hemorrhage. Again, I am talking about the baby under 1,500 grams where the incidence of bleeding is very high.

COMMENT: One of the problems of this type of panel discussion and this type of symposium is that I believe that we, like doctors always do, can be talking about different things and that is the source of disagreement. I believe that the fractional excretion of sodium in a prematurely born infant is not the same as it is in an infant born after 36 weeks of gestation. If it is, then all the studies in intrauterine life are wrong. So, the values we obtained were highly related to the weight of the infant; this I interpret to be probably prematurity but I will redefine it to say that an infant under 34 weeks gestation will be having a high fractional excretion of sodium which may not mean renal failure. Again, in an attempt to find out what's going on, if the fractional sodium excretion is high in a 2,500-3,000 gram infant I would have trouble believing that is what that infant should be doing. I would assume that there was something wrong with the tubules. But if it's a 32 week gestation infant, I would say that that may be normal and I would have to get something else to look at. Regarding mannitol, you should know that I often ask the question: "Should mannitol or furosemide (Lasix) be given?" I have really strong feelings against using mannitol and Lasix, not because of intracranial hemorrhage but because it may cause an artificial increase in urine flow when there is pre-renal volume depletion. Any mannitol that gets to the kidney could induce an osmotic diuresis. Certainly furosemide could cause excretion of whatever sodium is being reabsorbed and cause an increase in urine flow. I think one may be misled and look at the increase in urine flow and not be aware that there should be fluid given. So, I have real fears about the use of mannitol and Lasix in trying to determine why there is decreased urine flow--unless it is given along with fluids.

COMMENT: I hope you looked at my second slide because on it I showed that mannitol should only be given after adequate hydration of the patient.

RESPONSE: I will have to apologize. One does not return to my frozen land in a tropical suit. I had to leave and change clothes when you started talking so I did not see that.

MODERATOR: That is very gentlemanly in terms of apologizing. A margarita will do next time.

COMMENT-QUESTION: I was struck by what was said earlier since I thought that neonatologists used to avoid administering hypertonic solutions to the neonate because of the high correlation with intracranial bleeding. Would you be precipitating intracranial bleeding by giving a very high osmolar solution like mannitol? Is that a problem or has that never been looked at?

RESPONSE: I thought I just made that point. I don't know of any data specifically on use of mannitol in pre-term infants and incidence of hyaline membrane disease but there are data on use of bicarbonate and intracranial hemorrhage and as I showed, there are data also on rapid volume expansion with colloid and increasing risk of intracranial hemorrhage. So, I think it is reasonable to expect that if you use any other substance that will suddenly change blood volume in the pre-term infant, the risk will be there. Again, I don't know how aware

nephrologists are about the problem but without any doubt, intracranial hemorrhage is the major problem in a nursery and it really is a big problem. As you know, it has been reported now in more than 50% of babies under 1,200 grams. Not only is it causing mortality but it probably is the biggest cause of long term sequellae in survivors of premature infancy. We have to be extremely careful with anything we do.

COMMENT: I don't think you have to worry about the long term sequellae. They grow up to be nephrologists!

MODERATOR: I should say that, for other than diagnostic purposes, the danger of increasing a dehydrated state or a hemo-concentrated state, is real at all ages. In a study on nephrotic children that we are reporting (Gaston Zilleruelo is the senior author) we have found that mannitol and Lasix hemo-concentrated further these patients while albumin and Lasix did not. Again, the situation is different because as was being pointed out, in the low birth weight or premature infant, we have to be concerned about the problem of intracranial hemorrhage and that albumin has been found to increase the incidence of that complication.

COMMENT: I don't want to stretch too much the discussion on mannitol but I don't like to compare the osmotic load given by sodium bicarbonate with that given by mannitol. If you read the summary which I gave for this meeting, we recommend a dose of 2.5 ml/kilo of 20% mannitol. That means for a low birth weight infant something between two and three ml of 20% mannitol. We don't repeat it so I don't think that this osmotic load will be harmful for the brain. I may be wrong but I think it is a very low osmotic load.

COMMENT: I don't think there are data for mannitol. I guess I would like to ask a question. I know that at least in the indication of mannitol for infants with asphyxia, one of the problems that was raised was that because of the increased capillary permeability in the prematures or the full term who was asphyxiated, there was the distinct possibility that mannitol would leak very rapidly into the interstitial fluid. I wonder how that should be considered in this situation. The only other point that I would try to make is that probably the most common cause of renal failure in a pre-term infant is a preceding intracranial hemorrhage, at least in our experience. So, I think that we are dealing with a patient who is already bleeding and I think that's one of the reasons we have to be so extremely careful not to increase the chances for making it worse.

MODERATOR: That even applies to situations where we increase the GFR. In a study that we conducted (Dr. Bancalari's and our group) we were correcting the hypoalbuminemia by giving albumin infusions, we increased the arterial blood pressure and increased the GFR. But in a concomitant study pursued by the neonatology group, the complication of intracranial hemorrhage finally led to the discontinuation of the albumin infusion labeled "routine".

COMMENT: I would like to pick a quarrel with the nephrologists because it seems to me that we are talking of pre-renal azotemia or pre-renal oliguria. What you really want to do is increase renal blood flow. Giving mannitol or giving furosemide, that's not what you are really trying to do. Also, the pharmacological response that you would get would depend on how much of these compounds is actually secreted. They are not secreted if your renal blood flow is low. Then, you are really chasing the tail rather than treating the cause. What you ought to be doing is increasing renal blood flow by whatever mechanism; whether you use volume expansion or use a vasodilator of some form, you ought to improve renal blood flow before you use those modalities.

RESPONSE: I assume that mannitol has two effects. It does expand the extracellular volume and that is why it is being used. The infant kidney undoubtedly is much more sensitive to changes in extracellular volume; with an expansion you could get a twofold increase in GFR due to an increase in renal plasma flow.

COMMENT: I think that the studies on cell swelling and CNS show that on an acute basis, the ability of the intracellular osmolality to respond to extracellular changes is better, if one wants to look at it that way, with a sodium load than it is with mannitol. So, I would disagree. I thought the implication of what was said was that maybe mannitol is not as bad in terms of intraventricular hemorrhage as the Hypernatremic Syndrome.

COMMENT: If one goes to the original data from 1949, one sees it is not necessary to raise the serum osmolality in order to induce a diuresis in animals which were made shocky, that increasing the serum osmolality was not a prerequisite to induce a diuresis. It could be that with very small doses of mannitol, it might be safe. Although it may participate in increasing intravascular volume, it is not an essential requirement.

MODERATOR: Let me ask one of the panelists a related question. Is it true that all substances need to be filtered and be present in the tubular lumen for them to exert their effect? Furosemide was mentioned, that it has to be in the tubule and there are reports on the lack of action when the filtration is reduced. What about substances like mannitol? Does mannitol have to be in the tubular lumen also?

RESPONSE: I'm not a nephrologist; I'm a cardiologist. So, as far as I'm concerned, you have to deliver a substance to the kidney in order for it to work. If the heart does not work, nothing works; but let me answer your question.

MODERATOR: But some people say that the reason why the heart pumps is to send blood to the kidneys, right?

COMMENT: Let me try to answer your question. I think it is very clear that most of the diuretics work on the luminal side of the tubule so that you need to excrete the diuretic inside the lumen of the tubule in order for it to be effective. That is certainly true of furosemide. For example, if you have patients who have large proteinuria, where furosemide would be then bound to the protein inside the tubule, you would find that

the response that you get with furosemide would be much less. This has been clearly shown at the University of Minnesota. I think that is true of mannitol too. For you to have an effective diuresis you would have to get mannitol in the lumen so that it can hold on to the fluid inside the lumen which could then be excreted.

COMMENT: I will apologize for not having read the studies on protein and Lasix but that has never stopped me from responding before. One of the points among the billion that I advocate on clinical rounds is that we must remember in using Lasix or any of the loop diuretics, that if the pre-renal volume is diminished as it would be if there is significant hypoproteinemia, then there is very little filtrate reaching the site of action and consequently, the clinical effect would be minimal. The small pharmacological effect could probably be observed if one wanted to be that detailed in the evaluation. But in a nephrotic or in someone who has a protein that's low enough to cause decreased perfusion, then Lasix bound or unbound will not exert a significant clinical diuresis that would achieve anything.

COMMENT: I don't have any disagreement with you on that. What I am trying to point out is that another factor that you would have to consider in the pharmacological responses of diuretics like furosemide is that these compounds are very highly bound to protein. So, whatever little amount gets filtered into the tubule, a large fraction of it could be bound to the protein and whatever response you are going to get in the absence of protein, would be even less when protein is present.

COMMENT: I have a question about the Syndrome of Inappropriate ADH Secret of Antidiuretic Hormone (SIADH). First of all, how frequent is the proble really, in newborn nurseries and, in particular, in premies? We know it exists but how frequently does it exist? Many of those premies receive Lasix because of many reasons and it is sometimes tough to make the diagnosis of SIADH when Lasix is on board. In adults Lasix takes about 12 hours for its maximum effect--18 maybe if you want to stretch it a lot. Is it different in premies? If a premie got a dose of Lasix three days ago, can we still say that the natriuresis is on the basis of the Lasix effect?

RESPONSE: I am glad that the subject was brought up because this is the question that I have been trying to introduce for a long time. I don't believe in the Syndrome of Inappropriate ADH Secretion during the first week of life. I think it's a physiological condition for the following reasons. In this hypothetical case you saw a urine osmolality of about 700 but I don't think we ever observed that during the first week of life in very low birth weight infants. If we give antidiuretic hormone to test the urinary concentrating capacity (that is, we give an excess of antidiuretic hormone) we get a maximum urine osmolality of about 300 mOsm/kg and 60 mOsm/kg in pre-term infants. It's even lower in asphyxiated infants. The scatter of osmolality is not that high. In addition, there is no stimulus as potent as birth for the release of antidiuretic hormone. That has been shown by many English groups and rather recently published by a Finnish group in the Journal of Pediatrics-that birth, preceeded by labor, increases the serum concentration of antidiuretic hormone to about 1000 fold. We do not see urine osmolalities of 700 mOsm/kg in the first urines of infants. So, I think that antidiuret

hormone cannot do very much, has not a very harmful effect on fluid balance because it cannot cause water retention. The tubular system is too immature to respond to antidiuretic hormone. Antidiuretic hormone is there as a vasopressive rather than as an antidiuretic agent. It's there to control blood pressure, jejunal blood flow, etc. I think we should rather look at what does it do for blood flow, for cerebral perfusion, and other similar aspects of the small neonate's physiology.

MODERATOR: I wonder whether or not the panelist next to you has a comment on this subject. She has measured ADH in the fetal lamb. Do you have any comments in terms of what functions it has in the perinatal period, under normal or abnormal conditions?

RESPONSE: I agree entirely with what was said. I don't have that much to add. ADH by itself does not raise urine osmolality, at least in the newborn lamb, beyond 300 mOsm/kg no matter how much you give. So, by definition, it's not hyperosmotic urine and even in those animals that had very high levels of serum ADH measured after birth, the urine osmolalities were not that high.

MODERATOR: What about the vasoactive component? Do you feel that without ADH there will be hypotension or hypoperfusion?

RESPONSE: The high levels of vasopressin that are equivalent to what you see at birth or in asphyxia do raise blood pressure in the lamb. Whether or not this is what ADH is doing in the asphyxiated neonate or at birth I don't know. There is no direct evidence as to whether it is catecholamines or vasopressin or angiotensin; it's really not very easy to distinguish among them since they are all high at birth. Presumably that is what their function is, namely, to maintain blood pressure.

COMMENT: Maybe we could consider that all the vasoactive compounds which are found are really due to the body trying to preserve function. The kidney is not important there; it's the heart that is important. That's what the heart is trying to do to preserve perfusion to more important vascular beds. That's why we have those vasoactive compounds around.

COMMENT: As shocking as it may be, parts of the statements made regarding the stimulus for vasopressin release at birth and shortly thereafter, are correct. The measurements and levels are there but in the real world of the nursery there is a syndrome that is observed in which there is a falling serum sodium and osmolality and a urine osmolality that is higher than that and it is not by one or two milliosmols--it may be by as much as or more than 300--that is "easily corrected" by inducing a diuresis and giving salt. Now, that is the classic way to treat inappropriate ADH secretion in 400 year old people. Now what this syndrome is in the newborn special care nursery, I don't know; but, since I don't know any other term to call it, I call it SIADH.

MODERATOR: In some places water restriction also is used to manage those patients. What about that approach? Do you use that?

RESPONSE: I think that the treatment should be inducing a diuresis to get rid of the surfeit of water, to give salt, and that is best accomplished by the simultaneous restriction of water-intake also.

QUESTION: Just repeating the question, how often do you see that?

COMMENT: If we can't give it a name I don't know how we can come up with a frequency.

RESPONSE: Again, sure, we cannot give any figures or incidence if we are not sure of what we are talking about. In pre-term infants, we do not see very often what we call inappropriate ADH secretion. In babies who are born after severe perinatal asphyxia and in a good number of neonates with bacterial meningitis, we see a syndrome that we call inappropriate ADH and that follows exactly the same description that was just given.

COMMENT: One of the problems that we are all sharing today is the definition of acute renal failure in the neonate. Should it be based on oligo-anuria? If so, what is oligo-anuria? Do we accept the presented figures universally? Or do we go by serum creatinine as an indicator? Our observation is that the majority of babies, particularly tiny premies, tend to have serum creatinines above one. I don't know whether that represents failure or it's just not clinically significant which may be th important factor. But my observation has been that babies who have had anuria for three or four days and who would generally clearly be considered to have intrinsic renal failure, alias acute tubular necrosis, recover in far less than the classic 21 days or three weeks that one would find in the adult or older child. I wonder if the panel members cou discuss their experience in terms of duration of the anuria. And, if it is different from adults, what is the pathophysiology? What is actually going on in the kidneys of these patients?

RESPONSE: We are all saying the same thing, that the prematurely born or the very low birth weight infant is certainly a difficult problem of assessing the hemodynamics of the kidney, function of the kidney, cardiovascular hemodynamic status and one will get frustrated as to whether urine flows, as was suggested, are in fact low. Are they appropriate for the given age of the baby or size of the baby? It's just a very difficult picture or story to put together in totality. I don't think there is an answer that can be given that will explain or clarify anything. I think that the best answer is that we need to continue to observe these babies and gather data.

QUESTION: I cannot pass the opportunity of asking a question that has been bothering me for many years. There is a large amount of literature on renal function in babies with hyaline membrane disease. My understandi is that the changes are, at least in part, related to the fact that those babies are hypoxic. The truth is that today there are very few babies with hyaline membrane disease who are hypoxic in the nurseries. So, what happens with renal function in babies with hyaline membrane disease treate in an intensive care unit today where the PO_2 usually remains normal?

RESPONSE: I don't think that the well taken care of babies today have much problem with the GFR. There still will be a certain degree of salt-wasting, a certain reduction of the concentrating capacity which makes fluid and electrolyte balance a bit more difficult to monitor but I doubt that the severely reduced GFR is any longer a problem, the way we take care of infants today.

COMMENT: I agree. When we made our study which was published in Journal of Pediatrics in 1976--we made the study between 1972 and 1974--we observed a definite decrease in GFR in severe respiratory distress syndrome. At the time we were giving 65 ml/kg/day. The conclusion of this work was that we did not give enough water. Since then we have increased the water intake or water infusion to these babies to 100 ml/kg/day (80 in the first day and then going to 100) and we have the impression that renal function is much better. We have not seen any important defect in GFR in the last two-three years. I agree that nowadays if you look well after your patients and you care not to have them dehydrated, renal function will stay stable. I'm sure that the hypoxemia itself has an effect. After these studies in newborn babies we started to have an animal model and we took the rabbit and made the rabbit hypoxemic. I don't want to extrapolate our studies because they were made on adult rabbits and the rabbit is a very special animal with physiological responses different from humans. Still, when we made rabbits hypoxemic at a level of 50 mmHg or 45 mmHg or 40 mmHg we could see renal vascular resistance increasir steadily and GFR going down, renal perfusion going down. Then, when in these rabbits, we measured the renin-angiotensin system activity, we found a high stimulation of the activity. Then, the last studies we did, in the last two years, we have prevented the effect of hypoxemia in these animals by giving them several drugs. The most effective drug was Verapamil, which interferes with the action of angiotensin at the cellular level by blocking the movement of calcium through the smooth muscle cell. So, we really have the feeling that, at least in the animal model, adult animal rabbit, that hypoxemia itself decreased renal perfusion by increasing renal vascular resistance and it appears that this effect is mediated by the renin-angiotensin system.

MODERATOR: Obviously, the effect of hypoxia is variable and influenced by age, species, method of inducing hypoxia, etc. In piglets we observed polyuria which we assumed reflected at least an unchanged and maybe an increased renal perfusion. Regarding the effect of hormones on the neonate, I would like to share with you an experience which we never reported. While at Babies Hospital in New York, I studied the response of low birth weight babies to exogenous vasopressin injection during the first three days of extrauterine life. I had calculated the dose to be administered I.M. and left instructions for 1:20 dilution; the instructions were misinterpreted and one baby received x20 our pharmacological dose. We followed the baby carefully and there was no hypertension or clinical evidence of ill effect resulting from that high dose of vasopressin. The urine total osmolality (only isotonic with plasma in other babies) remained unchanged. Could we now take the last few minutes to hear from the panelists their position on fluid administration? Should we give more fluids so as to increase the GFR or are we doing more harm to the lungs, to the brain, to the heart, to the baby as a whole? What would be the consensus of the group? Did you have any negative, deleterious effects from the increase in the fluid administration?

RESPONSE: I don't think we did but we are still on the low side. We give 80 ml/kg/day on the first day and 100 on the second day. I don't think that's very much as compared with people who have been giving 120 or 150. I don't know if my colleague would agree that 100 is not very much or too much.

COMMENT. I think that in neonatology, like in most other new fields where we know very little, the pendulum tends to go from one extreme to the other. About five or six years ago after all of the studies of insensible losses and effect of radiant warmers, phototherapy and this and the other, babies were given huge amounts of fluids. It was not unusual to see a small **pre-term infant getting 180 or 200 ml/kg/day. The result of that** was a huge number of babies with significant patent ductus arteriosus (PDA heart failure, pulmonary edema, babies who were staying in the ventilator for weeks and ultimately developed broncho-pulmonary dysplasia (BPD). The pendulum probably has gone to the other side now, with these publications of increases in PDA and BPD. We have become extremely conservative with fluid but certainly 100 **ml/kg/day is a relatively small** amount of fluid intake in a small premature infant, especially if he is cared for under a radiant warmer. In our unit the gross guideline is t start with 60-80/kg/day the first day and then increase up to 120-140 aft the third day of life. The most important thing is that you cannot apply rules to a small premature infant. The variables are so many that these numbers may change completely. It all depends upon whether the baby is under a radiant warmer or not, whether he goes immediately in the incubator or not, and many other factors which were emphasized here and I won't repeat now.

COMMENT: I just want to stress a point which has been made on several occasions during this meeting. In healthy neonates the best guide to how much fluid should we give is the urine specific gravity. If you have a urine specific gravity above 1.008 or 1.010, you can be sure you are stressing the kidneys so you should remain at a low hypotonic level, between 1.004 or 1.006, as was **emphasized earlier.**

MODERATOR: I want to thank everyone, the panelists and all the faithful participants who have stayed with us through every session. Thank you for coming. We look forward to hearing from you with suggestions or criticisms, and to seeing all of you next year.

V

WORKSHOPS

Strauss, J. (ed.) Neonatal kidney and fluid-electrolytes

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WORKSHOP: GENERAL DISCUSSION ON MINERAL METABOLISM

José Strauss, M.D., Moderator

QUESTION: We have had several questions and stimulating discussions on metabolic bone disease in low birth infants. One question in particular relating to bone formation or abnormality of bone formation was whether or not a low phosphate in the newborn infant along with calcium disturbances, perhaps with vitamin D disturbances, could play a contributing role if not a primary role in the development of bone disease. So, the specific question is, do you believe that a significant amount of attention should be devoted to the infant's serum phosphorus and phosphorus balance in an attempt to prevent bone disease?

RESPONSE: Yes indeed. As a matter of fact, hypophosphatemia is **most** likely to produce severe osteomalacia. As you can imagine, in a newborn baby or a young person in whom remarkably high amounts of phosphates are necessary in conjunction with calcium and magnesium to calcify the osteoid tissue, any disturbance in phosphate balance obviously will either precipitate or at least will be an important factor in the development of bone disease. There is an experimental model in young rats. The researcher in charge has clearly shown the importance of severe bone resorption and the production of osteomalacia in these growing animals. I believe that in general you do not have any problems with hypophosphatemia unless you have the situation in which there is **a tubular** defect in the newborn baby. In those situations, obviously, you could have severe hypophosphatemia.

COMMENT: You also said that in terms of calcification of osteoid tissue, you would add magnesium as being in the equation. In this Seminar, we haven't talked at all, until now, about magnesium. I don't remember reading in the literature in papers being published on metabolic bone disease that magnesium is being discussed. Would you postulate that perhaps at least in the animal model or in our thinking process, **magnesium ought to be entered into the equation?**

RESPONSE: Let's talk about the animal model. First of all, 60% of the amount of magnesium in the body is present in the skeleton. The bone is the main source of magnesium. Second, in magnesium deficiency there is a remarkable resistance to the action of parathyroid hormone at the level of the bone. Many studies in humans, and studies done also in babies which are now being published, have shown profound hypocalcemia and tetany and even death in situations of hypomagnesemia. In hypomagnesemia there are two main defects. One, the parathyroid gland fails to secrete PTH and even in the presence of profound hypocalcemia, when the gland is loaded with parathyroid hormone, there is an abnormality

in adenylcyclase and PTH will remain inside the parathyroid gland. However, some patients with PTH in serum at normal or even high levels, develop hypocalcemia due to the fact that the bone became resistant to the mobilizing effect of parathyroid hormone. Magnesium plays an important role not only in calcifying the osteoid tissue, helping to build up new bone, helping the osteoblasts and making the bone receptors ready to respond to the action of parathyroid hormone, but also in controlling and regulating the secretion of parathyroid hormone.

QUESTION: Which of the vitamin D metabolites, if any, do you know of or speculate are involved specifically in the homeostasis of magnesium in the body?

RESPONSE: As far as I know, and I may be wrong, vitamin D does not increase magnesium absorption in the gut or magnesium mobilization from bone. Although there is a paper in the American Journal of Physiology showing that 1,25 dihydroxycholecalciferol increases magnesium absorption in uremic patients, we cannot reproduce those results. As a matter of fact in our patients who received 1,25-D_3 and became hypercalcemic and hype phosphatemic, there was no change whatsoever in the levels of serum magnesium. Moreover, I have injected intravenously 1,25-D_3 to dogs with normal or with abnormal renal function. They produced hypercalcemia and hyperphosphatemia and the levels of magnesium in serum did not change. Besides, I don't have any good evidence to support the concept that 1,25-D_3 affects very much the absorption or the mobilization of magnesium in bone.

QUESTION: I don't know how much you have talked about this, but here I suggested that perhaps the combination of the 25-hydroxy metabolite and the 1,25-dihydroxy metabolite together could be more effective in causing healing of the metabolic bone disease in the newborn infant. Do you have any thoughts on that?

RESPONSE: Yes, I do agree with you. As you know, many years ago a doctor in Paris treated patients for nutritional rickets (these are not children but adults). He divided the population in two groups. To one group he gave 1,25-D_3 and to the second group he gave 25-hydroxycholecalciferol. Both groups increased calcium absorption. However, the patients who received 1,25-D_3 did not decrease the amount of osteoid tissue and did not increase the mineralization or calcification of bone. On the other hand, the patients who received 25-hydroxy, they corrected part of the osteoid problem and they mineralized very well. Moreover, patients who receive phenobarbital and dilantin, they may develop osteomalacia. These patients have normal levels of 1,25-D_3 and low levels of 25-hydroxy-cholecalciferol. Recently, in a paper published in Lancet, it was shown that several patients with nutritional rickets had normal levels of 1,25-D and very low levels of 25-hydroxy-D_3. What we don't know is which is the metabolite that is responsible for the mineralization of the osteoid. I believe that most endocrinologists and nutritionists will accept the fact that 1,25-D_3 is the most active metabolite of vitamin D at the level of the gut. It's about a hundred times more effective in increasing calcium absorption at the level of the gut. Maybe because of that (it is not known for sure) we cannot use large doses because

the patients do become hypercalcemic. On the other hand, 25-hydroxy is not very effective at the level of the gut and we can use fairly large doses. We can, by using large doses, calcify the osteoid tissue. In studies that we have done in dogs with renal failure, we treated them from day one with 25-hydroxycholecalciferol; after two years we performed bone biopsies. In sequential biopsies, the dogs had normal bone histology. In the adult, if the main problem is hypocalcemia, I prefer to use $1,25\text{-}D_3$ because it is more effective and the half-life is very short. If I get in trouble with hypercalcemia I stop the drug and the hypercalcemia subsides in a short period of time. If I am going to treat metabolic bone disease, mainly osteomalacia, I use in general 25-hydroxycholecalciferol.

COMMENT: I can't comment on that. I don't think the state of the art in regards to metabolic bone disease in the newborn has progressed to the point where there are data to separate the lesions into osteomalacia, osteitis or just what. So, a decision to use $1,25\text{-}D_3$ alone or $25\text{-}D_3$ alone or in combination would have to come from, I guess, some speculation based on data in the adult.

COMMENT: Right. And if a patient is hypocalcemic at the same time, $1,25\text{-}D_3$ is extremely effective and with the combination of drugs one should be able to correct the hypocalcemia in a very short period of time.

COMMENT: I believe that the data do show that in cases of metabolic bone disease in the newborn, hypocalcemia is the rule.

QUESTION: We had set up a fetal lamb model to investigate a lot of problems related to the developmental aspects of vitamin D and divalent mineral physiology and since the 24,25-dihydroxy metabolite is very high during intrauterine life and since the synthesis rate of $1,25\text{-}D_3$ doesn't occur until after the 14th-21st day of age even though the one-alphahydroxylase is present, would you speculate that perhaps $24,25\text{-}D_3$ may play a role in bone development in the first few days in the life of a human infant? -particularly in view of the data on the possible effect of $24,25\text{-}D_3$ on chondrocytes in bone.

RESPONSE: I personally don't have any experience in that particular field that you mentioned but studies by others - you know when they deprive chickens of $24,25\text{-}D_3$ the hatching process is decreased and the newborn chickens have a very high mortality. It would seem that to start them very early in their life on $24,25\text{-}D_3$ may play an important role. Unfortunately, I don't work with that system. I work with a totally different system which is a group of adult dogs with renal insufficiency. Perhaps we cannot equate one situation with the other. In our animals with renal insufficiency we have not been able to improve the osteomalacic component with $24,25\text{-}D_3$. I mentioned a few minutes ago that we were able to prevent bone disease with 25 hydroxy-D_3 but when we treated the second group with $24,25\text{-}D_3$ we observed no improvement whatsoever. I am not answering your question because I don't have any experimental results from our own laboratory. The studies we are doing are in a totally different model.

QUESTION: Do you know of any conditions, abnormal or normal where the synthesis of 24,25-D_3 in the adult animal is increased?

RESPONSE: As you know, 24,25-D_3 is rather low in serum - about two nanograms. It's determination has been very controversial for the past three or four years because there was a contaminant. Recently, by using double high performance liquid chromatography, finally most biochemists are really able to measure this metabolite. The many results in the past are difficult to interpret because of the contamination with some lactone groups. But there are many projects going on in this subject. There are whole sessions of meetings on the controversial aspects of 24,25-D_3. Again, some patients in renal failure and severe osteomalacia who were given the combination of 1,25-D_3 and 24,25-D_3 had remarkable improvement.

QUESTION: I would like to ask you about the excretion of phosphate in **pre-term infants.** The fractional excretion of most electrolytes in **pre-term infants is higher than in term infants and with regard to** phosphate it is about four times higher.

QUESTION: In which situation?

RESPONSE: During basal conditions. With comparable intakes the phosphate excretion in very low birth weight infants is much higher than in term infants - about four times higher. Total phosphate excretion related to body weight is about two times higher in low birth weight infants than in full term infants. Now, those rather moderate urinary phosphate losses that take place during the first two weeks of life, do you think they have any importance for the overall phosphate metabolism?

COMMENT: It is not clear to me. When you mention the overall metabolism, over what period of time are you thinking? If this happens over a short period of time, I can imagine that eventually it will be corrected. I don't think it would produce damage on a permanent basis. You mentioned a negative phosphate balance for just ten days to two weeks; is that the period you are asking about?

RESPONSE: Yes. There are larger phosphate losses during the first two weeks of life in the very low birth weight infants.

QUESTION: In the premature infants?

RESPONSE: Yes.

QUESTION: And after two weeks they will go back to normal phosphate balance?

RESPONSE: After two weeks they can retain as much phosphate as the full term infant.

QUESTION: Do they become hypophosphatemic?

RESPONSE: No. Serum phosphate does not change.

COMMENT: It's a very hard question. Again, I do not deal with this kind of problem. I do not think that two weeks of negative phosphate balance will produce permanent damage. Obviously hypophosphatemia, if it were to develop and persist will affect many many organs, not only the skeleton but the clotting mechanism, the life of the red cells, the 2 - 3 DPG's. There are hundreds of abnormalities in electrolytes, in titratable acidity, gluconeogenesis, in ammoniagenesis, in acidification of the urine, in hypercalciuria, hypermagnesemia. There are many many effects but I cannot conceive that two weeks of negative phosphate balance probably will produce permanent damage. Perhaps temporary changes in electrolytes but very likely the body will repair those two weeks of imbalance and hopefully will not produce any change on a long term basis.

QUESTION: What happens if this high fractional excretion is combined with an inadequate intake, therefore compounding the negative balance?

RESPONSE: As you know, it has been reported that patients with profound hypophosphatemia can develop muscle disease (rhabdomyolysis). It can produce changes in CPK and aldolases; also, intracellular alkalosis. There are a series of metabolic disturbances that don't require a profound degree of phosphate depletion. What I don't know is whether or not these babies, who have an increased fractional excretion of phosphate and now in addition they have a poor intake, have a tremendous hypophosphatemia. When I am talking about severe hypophosphatemia I am referring to the one we see in patients who ingest alcohol, increase their fractional excretion of phosphate; they are not ingesting proteins with their food, they are taking phosphate binders because they have gastric ulcers and they run a phosphorus between 0.5 and 1 mg/dl. These patients can develop some of these abnormalities. What I don't know is the degree of hypophosphatemia about which you are talking. Is it profound or just the serum phosphorus dropped from seven to five mg/dl?

RESPONSE: We do not generally see marked hypophosphatemia in low birth weight infants but I would like to ask you, how soon do you expect negative phosphate balance to be reflected in hypophosphatemia?

RESPONSE: In the adult it doesn't take very long. Probably with ten days to two weeks you will start seeing it. You don't see it immediately - after day one or two - but after roughly ten days of phosphate depletion - and we do this study all the time in dogs. In adult dogs it takes roughly three weeks to four weeks before we see hypophosphatemia. It's very difficult to see hypophosphatemia in adult dogs before two to three weeks of phosphate depletion. However, there are changes which do not need the presence of hypophosphatemia. As you know, hypophosphatemia or phosphate depletion increases the activity of the 1-hydroxylase. After 3 days of phosphate depletion in which the serum phosphorus did not change already there is an increase in almost 100% in the concentration of 1,25-D_3 in the serum. Obviously, the increase in 1,25-D_3 will also mobilize calcium and phosphate from bone and in part that's why we don't see hypophosphatemia right away. We are paying a price and the price is calcium and phosphate coming out of the bone. That's why patients who have low phosphate develop hypercalciuria because of increased calcium mobilization from bone.

COMMENT: This is an important clinical question for us because if negative phosphate balance is reflected so easily in the serum phosphate level, we might just follow the serum phosphate and wait until the serum phosphorus goes down to supplement the infants with phosphate.

COMMENT: I think it is very difficult to look at levels of serum; this applies also to potassium and magnesium whose main localization is intracellular. In other words, when we talk about cations or anions which are present mainly inside the cell, it is very difficult to judge the degree of negative balance by looking at the serum. This is so because the serum represents maybe a half of one percent **or one percent** of the total pool and before the serum shows a change you must have a significant degree of depletion. If you have a baby on whom you know what the GFR is, you know what the serum phosphorus is and the fractional excretion of phosphate is 50 to 100% greater than you expect to find under normal conditions, and you know how much he is ingesting, you can calculate the balance. My gut reaction would be to supplement then; not to allow him to become phosphate depleted - I mean to develop hypophosphatemia. If I were managing that baby and if I saw a fractional excretion of 70% and I could see that he is losing 100-150 mg phosphorus/day, perhaps I would start to supplement the diet with that amount. Very likely it would not produce hyperphosphatemia. You have to avoid producing hyperphosphatemia because that is another problem since there is the possibility of producing at the same time hypocalcemia and, at least in the adult, we have seen patients who have developed tetany. It's a difficult question because any time we talk about a solute which is **present inside the cell in much higher concentration than outside the cell, it is very difficult to predict the balance of that solute by looking only at the serum concentration.**

COMMENT: Your comment about the fact that serum concentration will be protected by mobilization of phosphate from bone goes back to my question to you earlier. What would you speculate about the effect of phosphate in the development of metabolic bone disease in low birth weight infants? The point that these infants are excreting large amounts of phosphates, if our neonatal practices are such that we don't provide enough phosphate, then a combination of the two will lead to an earlier development of some type of bone disease. Is that your thought?

RESPONSE: I agree with you.

QUESTION: I have trouble understanding the vitamin D levels in the blood. For example, in metabolic bone disease of newborn, 25-hydroxy-D_3 levels have been found to be low and 1,25-dihydroxy-D_3 levels have been found to be high. How do you explain higher levels of 1,25-D_3 if the 25-D_3 has to undergo 1-hydroxylation in the kidney?

RESPONSE: Remember that the concentration of 25-hydroxy-D_3 is in nanogram per ml and normal concentration is roughly 30-40-50 nanograms. The concentration of 1,25-D_3 is in picograms 20-30-40-50 (it depends on the **method) per ml - a** thousand fold difference between nanograms and picograms. Then, you can have low levels of 25-D_3 but if you have hypocalcemi

and if you have secondary hyperparathyroidism, PTH can increase the activity of the 1 -hydroxylase and you could still provide enough substrate because it is present in astronomically large amounts. There is a thousand-fold difference between 25-D_3 and the 1,25-D_3; then, you may have high levels of 1,25-D_3. I'm not sure who has published the results that you mentioned. The ones I am aware of in adults have low levels of 25-D_3 and normal levels of 1,25-D_3.

RESPONSE: I will let another speaker comment on that because apparently what he presented was somebody else's data, too.

COMMENT: There was one infant reported in 1980 and then there were seven infants who had metabolic bone disease, five of whom had elevated 1,25-D_3 reported in 1981.

COMMENT: Again, this indicates to me that 25-D_3 may play an important role in the calcification of bone. We come back to the original question: which one is the metabolite of vitamin D which is more effective at the level of the bone? It is possible that when the whole story is known that we have four or five metabolites and they all interrelate to each other and each has different functions. For example, maybe the function of 1,25-D_3 is the regulation of minerals at the level of the gut. Perhaps 25-D_3 is responsible for the calcification of the osteoid tissue. For example, 24,25-D_3 increases calcium balance but 24,25-D_3 does not produce hypercalcemia, does not increase bone resorption, and perhaps the role of 24,25-D_3 is just to increase the deposition of calcium and phosphate inside bone but does not increase the resorption of bone. We have to leave the door open. We cannot be dogmatic at the present time because not all the information is in and we are learning. Potentially, each metabolite may contribute to each other but each may have a totally different function in life.

QUESTION: In patients with renal failure, we are routinely now using 1,25 vitamin D_3. This may keep the serum calcium level normal but we are wondering if it is affecting the bone adversely because, as you just mentioned, 24,25-D_3 may be as important and we probably are suppressing the formation of 24,25-D_3 by keeping the serum calcium level normal.

RESPONSE: If a patient has renal failure the levels of 24,25-D_3 also will be low. Most of the results coming out now indicate that the patients with advanced renal insufficiency also have low levels of 1,25-D_3 and low levels of 24,25-D_3. Isn't it so?

QUESTION: Yes. Are we harming these patients at the level of the bone?

RESPONSE: I don't think we are harming them. First of all, in metabolic bone disease there are several components. One is the osteitis fibrosa which is the manifestation of secondary hyperparathyroidism; 1,25-D_3 is a very, very effective drug - perhaps the best because obviously it will increase very rapidly ionized calcium, will suppress secondary hyperparathyroidism which is perhaps the most serious problem we have in the adult population with chronic renal failure. The degree of bone resorption decreases, bone formation changes and the degree of marrow fibrosis

decreases. In some patients the anemia gets better. Again, when we talk about metabolic bone disease, unless we have a bone biopsy it is difficult to know which component is the most important one. Are we talking about osteitis fibrosa? Are we talking about osteomalacia? Osteomalacia is an increase in the osteoid tissue and a defect in its mineralization. As I mentioned to you before, if I know in advance- because I do have a bone biopsy- that the main lesion is osteomalacia, I would prefer to use 25-hydroxy-D_3. However, this still is a very controversial issue because if you talk to people in Los Angeles, they treat most of their osteomalacic patients with 1,25-D_3. And about 50% of those patients get better. That is not our approach; for that situation we prefer to use 25-hydroxy-D_3.

QUESTION: Since we moved into the field of renal failure, which takes us away from the neonate a little bit, what are your thoughts as to whether or not 1,25-D_3 given to treat bone disease in chronic renal failure causes the serum creatinine to go up? Before you answer, I'll tell you that within the last 8 months I gave 1,25-D_3 to two adolescents and their serum creatinines went up in the order of 2-3 mg/dl. I lost 3 years of my life in worrying about that. I would like to know what your thoughts are on that.

RESPONSE: You put it in very good terms. This is very controversial. Nobody, as far as I know, has a long follow-up,a large number of patients, with mild renal insufficiency, with moderate renal insufficiency, etc. receiving 1,25-D_3. But some authors have shown in a group of patients that received 1,25-D_3 that there was a decrease in the GFR and they were very concerned about that. However, an editorial in Kidney International reviewed and criticized those papers; it argued that the most likely explanation was the development of hypercalcemia. In a long term study of patients with moderate renal insufficiency, no decrease in GFR has been observed when 1,25-D_3 was administered. I think that if we are going to use this medication we will have to be extremely careful because what we don't want to do is to cure the bones and destroy the kidneys. If we have a patient with a GFR of 30 or 40 ml/min, then I think that 1,25-D_3 **is an outstanding drug which has specific indications. If a patient** with a GFR of 20-30 ml/min is going to receive 1,25-D_3, I want to be sure that the patient is not first hyperphosphatemic and now he becomes hypercalcemic, exceeds the calcification product, develops metastatic calcifications and decreases his GFR. If we can watch this very closely and we avoid the development of hypercalcemia, I don't think that at the present time, we have enough information to state that the patients' GFR will deteriorate. But again, there are very few studies and I think that if anybody is going to use 1,25-D_3, that one has to be very careful. As a matter of fact, the drug was not approved for that use. It was approved for patients on dialysis, not for patients who have a moderate degree of renal insufficiency. Only you can use it under a special protocol, special permission of the FDA for special studies. And that is because the FDA is very concerned about the decrease in GFR.

MODERATOR: We are participating in a multicenter prospective study and hopefully in the next few years we will **have an answer to that question. Or at least a better idea of what 1,25-D_3 does to the glomerular function.**

Going to another subject which came up earlier in this Seminar, there were questions regarding the treatment of rickets or hypocalcemia in the neonate. Would you have any preference as to the administration of vitamin D or one of its metabolites versus correcting the hypocalcemia by the administration of calcium? Do you have any suggestions?

COMMENT-RESPONSE: Vitamin D per se doesn't work. It has to be metabolized and it takes time because it has to overcome the amount of 25-hydroxy-D_3 present in the blood, it has to overcome the liver to have very high levels of 25-D_3 and then 25-D_3, at very high levels in the serum, will work without requiring further metabolism. But, if the main problem is hypocalcemia, why go to all this trouble? We have a very effective drug which is 1,25-D_3. In a short period of time, 1,25-D_3 will correct the hypocalcemia and if, by any chance, the patient becomes hypercalcemic, the half-life is only 19 hours. When you stop the medication in two or three days the calcium will return back to normal. If you get in trouble with 25 hydroxy-D_3, it has a half-life of 19 days. First of all you may have to use large amounts because it is not very effective at the level of the gut.

If the main problem is hypocalcemia and tetany, I don't have any question in my mind that I would use 1,25-D_3 and I would increase the amount of calcium in the diet. By doing those two procedures over a short period of time you would be able to correct the hypocalcemia. I would not use 25 hydroxy-D3 for treatment of hypocalcemia.

COMMENT: You are at a slight disadvantage not to have heard all the discussions preceeding this Panel and the recommendations that different ones of us were making. A point was made about the possibility that, in infant animals, the receptors in the GI tract for 1,25-D_3 did not appear until what would be equivalent to two to three weeks of age in the human infant. So, although calcium absorption occurs, it appears to be not mediated through 1,25-D_3. I think that hypocalcemia is present but whether or not the major problem is hypocalcemia rather than a massive deficit in calcium, I don't know. One of the points I have tried to make is that a prematurely born infant can start out with a negative balance of 68 grams of calcium and a serum calcium of 8.1-8.2 mg/dl. Since it has been shown that increased calcium supply to these low birth weight infants in the order of 140 mg/kg/day will cause calcium accretion at the rate that it would have occurred if the infant had continued in intrauterine life receiving calcium from the mother, I recommended increasing calcium supply to these infants and to give only a rather small amount of the current recommendation of 400 units vitamin D/day. That was my recommendation based on my perception of what the data are at the moment.

QUESTION: In other words you would increase the amount of calcium in the diet and nothing else?

RESPONSE: Not nothing else. I would provide a minimal amount of vitamin D, not necessarily 1,25-D_3. In fact, my own bias is to stay away from 1,25-D_3 unless there is overt rickets.

COMMENT: Well, I'm not talking about rickets; I am talking about hypocalcemia. Maybe that's the difference. If you can correct it with just increasing the amount of calcium in the diet and by increasing the transfer of calcium from different points which are not dependent on

the transport induced by the action of 1,25-D_3, that's fine. Nothing wrong with that. As a matter of fact, that is the very safest thing to do because if you start to develop hypercalcemia you decrease the amount of calcium and you correct the whole problem. I do agree with you. If you can correct hypocalcemia by increasing the amount of calcium, that's very reasonable to me.

RESPONSE: I think some of the confusion even among ourselves is that we are not clearly differentiating our efforts to prevent the development of metabolic bone disease in the low birth weight infant (which does not occur until after 21 days of age) from our active treatment of the infant who unfortunately develops overt rickets. So, my position is that, in the first three weeks of life after birth, if we were to increase the calcium intake above what is traditionally done, perhaps we could more rapidly correct the negative calcium balance. In addition, by giving a minimum amount of vitamin D, perhaps we can prevent the development of overt rickets. If overt rickets occurs, you should be aware that I did not recommend giving 1,25-D_3; I recommended giving plain old vitamin D.

RESPONSE: We are talking about two different things. One is the hypocalcemia in the first few days and then the subsequent manifestations, prolonged negative balance of calcium. If we can correct it very easily at the beginning by just giving calcium, why not? It's the cheapest way and the safest one.

MODERATOR: I think we had an exciting exchange during which many clinical and experimental questions were raised. We must thank all the participants for their contributions.

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WORKSHOP: CLINICOPATHOLOGIC CORRELATIONS

José Strauss, M.D., Moderator

MODERATOR: We will start the workshop with two cases. **Dr. Rita Fojaco** will present the histopathology; then we shall ask everyone to participate and in particular, the faculty, for the various implications of the cases. **The first case is a white female newborn who was admitted to Jackson Memorial Hospital on 3/8 and died on 4/12. Clinical diagnosis: 1. Wilm's tumor, left kidney. 2. Communicating hydrocephalus. 3. Liver metastasis.**

Operations: 3/13 Ventriculoatrial shunt; 3/26 Left nephrectomy and adrenalectomy, liver biopsy.

This baby was transferred from another hospital with diagnosis of left renal mass one day after birth. Delivered using forceps; weighed 8 lb. 10 oz. at birth, with head circumference of 15 inches. Mother had no problems during pregnancy.

Baby was noted to have enlargement of left lower quadrant. An IVP was done and showed left renal mass. Pulse 140 b/min and respiratory rate 40/min. Neurologically appeared intact with Moro, grasp and suck reflexes present. Abdominal X-ray showed persistence of left renal mass. Skull X-ray was non-diagnostic; sutures were wide apart. Probable communicating hydrocephalus was diagnosed. High pitched cry. Head circumference 39 cm., boxy head, full fontanelles. Negative transillumination of cranium; flat optic discs.

Impression was megalencephaly, secondary to bilateral subdural hematomas versus progressive hydrocephalus, congenital cerebellar tumor with ventricular obstruction. The baby had ventriculogram on 3/12 which revealed communicating hydrocephalus. A ventriculoatrial shunt was placed on 3/13. Hemoglobin on that day was 15.6 g%, PT 12.4/30 sec., PTT 36 sec., hematocrit 40.5%, serum chloride 100 mEq/L, CO_2 22 mM/L, potassium 4.2 mEq/L, sodium 145 mEq/L, BUN 17 mg/dl, Glucose 50 mg/dl. The baby had an operation for Wilm's tumor on 3/26, left nephrectomy, left adrenalectomy and liver biopsy.

On 3/27 the baby had generalized seizure with eyes deviated to the right (lasted 20 seconds) and then resumed normal respiratory pattern. There was no cyanosis, but later on she developed focal seizures of upper and lower extremities. On 3/30 she was afebrile, no seizures. Estimated weight 3240 grams. On 4/1 the baby had a seizure and received phenobar-

bital intramuscularly. She had radiation therapy to the metastatic lesions in the liver. On 4/6 the baby was having more difficulty in feeding, did not suck, the buttocks were escoriated. Temperature was 99 to 100°F. She did not void and gram-negative sepsis was established (Klebsiella, E.Coli, Pseudomonas).

Baby was treated with antibiotics -- Actinomycin, Oxacillin and Gentamycin; phenobarbital was given for seizures. On 4/12 platelet count was 106,000/mm^3, hemoglobin 8.2%, hematocrit 24%, WBC 19,000/mm^3.

The baby's condition deteriorated and she died on 4/12.

MODERATOR: Dr. Rita Fojaco who is an Associate Professor of Pathology at the University of Miami School of Medicine will present the histopathology and discuss the implications of this case.

DR. FOJACO: We chose to present this case because it has some of the not very frequent findings associated with Wilm's tumors, namely, being congenital with metastases, having hemihypertrophy and, in addition, having a second primary tumor in the CNS. Histologically it is an example of a variant of Wilm's tumors recently recognized as having an "unfavorable" histology and poor prognosis. This variant of Wilm's frequently is associated with a second primary tumor of the CNS. In children, hemihypertrophy may be present in cases of Wilm's and other tumors as well.

We shall discuss the case from the Wilm's tumor point of view only in order to review some conclusions of the recent report of the National Wilm's Tumor Study Group. The immediate cause of death in the first case was Pseudomonas sepsis following chemotherapy.

This autopsy was done in 1974 when many facts about Wilm's tumor were not accepted or not known, such as the existence of congenital Wilm's. The case was published and there was an extensive exchange of letters with the reviewers because of these matters.

The second report of the National Wilm's Tumor Study has demonstrated that there are two groups of Wilm's tumors: one with "favorable" histology in which 89% of the patients survive, and a second group with "unfavorable" histology in which the survival rate is only 39%. Only 12% of the Wilm's tumors have "unfavorable" histology.

The group with "unfavorable" histology is subclassified into four subgroups: focal anaplasia; diffuse anaplasia; rhabdomyosarcoma type -because it resembles the rhabdomyosarcoma; and clear cell sarcoma type. These last two have characteristics not seen in the classical Wilm's tumor.

The rhabdomyosarcoma type may be associated with central nervous system disease which may be metastatic or a second primary tumor. The clear cell sarcoma type is associated with bone metastases.

In summary, this infant had a congenital Wilm's tumor with visceral metastases and hemihypertrophy. Histologically the tumor had "unfavorable" histology, rhabdomyosarcoma type with a second primary tumor in the CNS. The immediate cause of death was Pseudomonas sepsis following chemotherapy.

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MODERATOR: We shall go now to the next case. The patient was a six day old product of a 32 week gestation, premature black male born on 6/3 by a breech presentation to a 24 year old Haitian, G3 para 2-0-0-2. At delivery he required ventilation and Apgar Scores were 3 at 1 and 5 minutes. The baby weighed **1,550 g with flat fontanelles and slight bruises** of the lower extremities. He was transferred to the Newborn Intensive Care Unit and required intubation. The baby had a pH of 6.99 and bicarbonate was given. Impression was prematurity with respiratory distress syndrome secondary to hyaline membrane disease or a Beta streptococcal **infection.** On 6/4 the baby had problems with hypotension necessitating pressor agents. There was also oliguria, and questionable bilateral flank masses not initially felt at birth. The baby continued to be ventilated but his arterial blood gases worsened. On 6/5 he had seizures and on 6/6 there was bulging of the anterior fontanelle; an intracranial drain was attempted but a good flow could not be established due to blood clots. Intraventricular hemorrhage was documented by ultrasound. The baby then continued on a downhill hospital course with increasing bradycardia. He expired on 6/9.

QUESTION: What were the hematocrits?

DR. FOJACO: The clinical history you got was taken from our autopsy report. It represents only a summary. I am sorry it does not contain all the answers to your questions.

QUESTION: What about platelets? Also, what were the electrolytes in this patient, sodium, potassium?

MODERATOR: Unfortunately we don't have any of the clinical data. We have the histopathology only.

COMMENT: I am anticipating that this patient has a renal hemorrhage.

DR. FOJACO: I chose the case from the pathological viewpoint. The information that is pertinent for the autopsy findings is in the clinical summary.

MODERATOR: That's fine. You are stimulating us. So there is a proposal that the baby had **renal hemorrhage.** Dr. Fojaco says that we have the information in the summary. Any other possible **diagnoses?**

COMMENT: Two other possibilities, bilateral renal vein thrombosis or the baby might have had a urinary tract obstruction with hydronephrotic kidneys. That also may have been why he was oliguric.

MODERATOR: Good point. The oliguria was recorded. There was hypotension which might have been related to or be one of the causes of the oliguria.

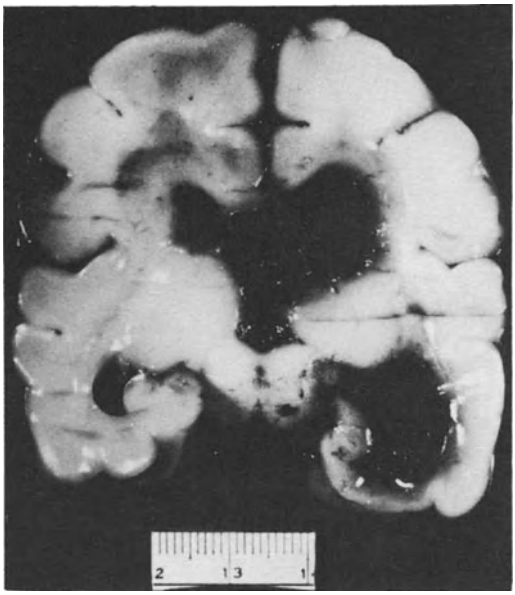
QUESTION: With a vascular accident you might have in the adrenals and/or the kidneys, you might have bleeding into the brain (intraventricular hemorrhage). **What about that possibility?**

MODERATOR: Certainly there was an hemorrhage in the brain since blood was obtained on the attempted intracranial drain.

DR. FOJACO: The diagnosis at Jackson Memorial Hospital was intracranial hemorrhage. This was the immediate cause of death in addition to pulmonary insufficiency **(Figs. 1 and 2).** The possibility of renal vein thrombosis is a very good one because there were renal masses and hemorrhage. Renal hemorrhage also has to be considered in the differential diagnosis.

This case represents an unusual subtype of infantile polycystic renal disease (IPCD). This variant does not cause death in the newborn period. This child certainly didn't die because of his renal lesion. The kidneys were enlarged but were not as big as the classical IPCD. The combined weight was 47 grams; normal for the age of the infant is 20 grams. In the classical IPCD the weight may be 300 grams or more. Figure 3 shows the characteristic renal histology with dilatation of the tubular system; however, the changes do not involve all or most of the tubules. The glomeruli are normal, except that there is glomerulogenesis still present because **of the age of the infant, 32 weeks of gestation. What may be significant for the diagnosis of IPCD in this infant is the presence in the liver of hamartomatous changes of the bile ducts with prominent fibrosis (Fig. 4). I would like to review with you now, for** comparison, the classical IPCD, which all of you have seen many times.

FIGURE 1



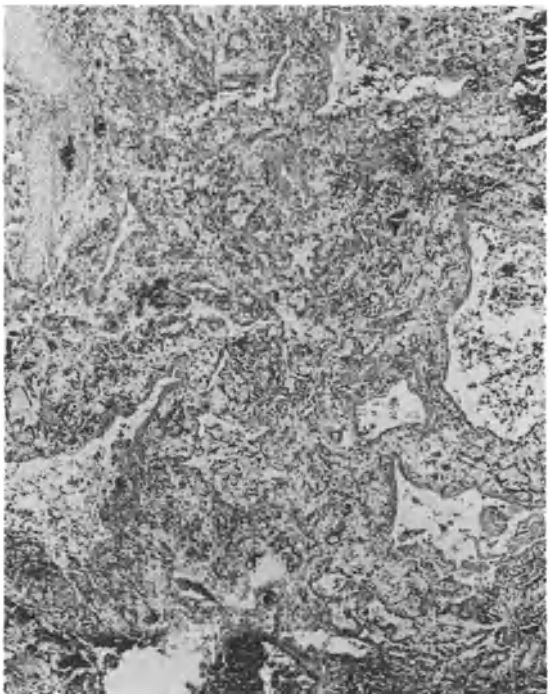


FIGURE 2

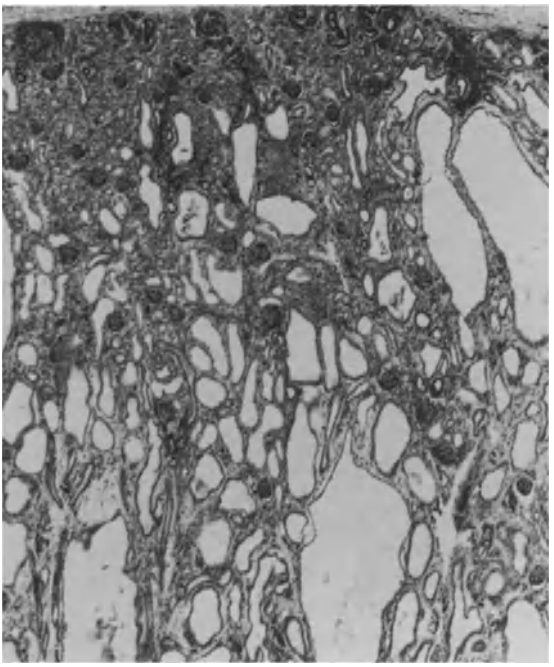


FIGURE 3

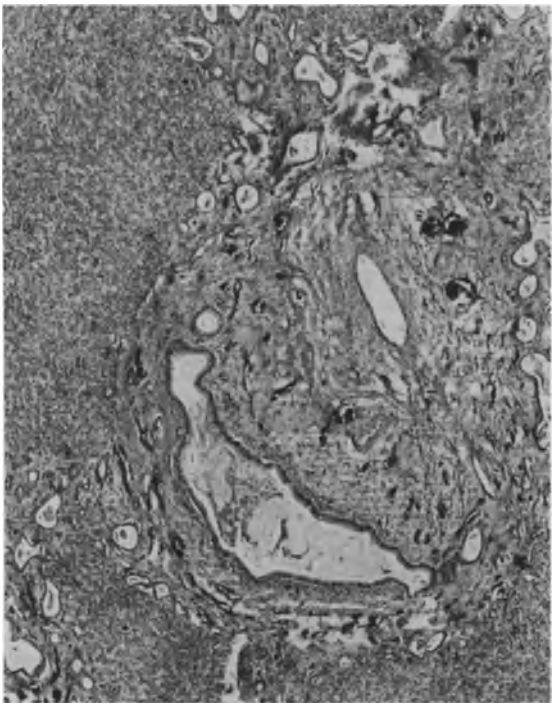


FIGURE 4

The face of these infants can be overlooked, but it may be very helpful in the diagnosis, the Potter's face. The examination of the placenta also demonstrates the lesion associated with oligohydramnios, amnion nodosum.

Accumulation of cases and family histories in cases of IPCD have demonstrated that there are variants of the disease. They have been subclassified according to the degree of renal and liver involvement, in addition to the age of presentation. There are four subtypes: *perinatal* in which about 90% of the tubules are involved; *neonatal* with about 60% tubular involvement; *infantile* with 25-50% tubular involvement and *juvenile* with less than 25% of tubular involvement. As the tubular involvement decreases, the amount of fibrosis in the portal areas of the liver increases. The juvenile type may be the same disease as congenital hepatic fibrosis. This concept is not accepted by some authors. Patients in this last subgroup are teenagers or young adults, with clinical presentation of portal hypertension and no liver failure. When they are explored because of the portal hypertension they have the fibrosis and hamartomatous bile ducts in the liver. If the kidneys are inspected at the time of the operation, they show the cystic lesions.

IPCD is inherited as a recessive autosomal disease. The liver is involved in 100% of cases. Our patient belongs to the neonatal or infantile type; because of incomplete glomerulogenesis, we are not sure. This child probably would have survived at least a few years without knowledge of his renal disease.

QUESTION: Could you comment on the status of this baby's lungs? Much of the clinical data that you presented looked like this baby had a pseudo-Potter Syndrome. The difficulty with ventilation with this baby throughout its course suggests hypoplastic lungs in addition to the renal and hepatic involvement.

ANSWER: This baby's birthweight was 1,780 grams. There was hyaline membrane disease, the yellow type. There was also evidence of O_2 toxicity (Fig. 2). The size of the lungs was not very small. They were not hypoplastic. The combined weight was 55 grams; normal for the age is 40 grams. The increase in weight was, at least in part, due to the fibrosis, hyaline membrane and some hemorrhage.

QUESTION: Did you find any evidence of vascular malformation in the brain?

ANSWER: The brain was soft with extensive hemorrhage. The hemorrhage started in the subependymal area with rupture into the lateral ventricle, and extending to the aqueduct, fourth ventricle and subarachnoid space. If you are thinking of an aneurysm of the vessels in the base of the brain, no, there was no aneurysm. The aneurysms are associated with the adult type of polycystic renal disease. As far as I know they have never been described in the infantile type. Aneurysms of vessels in the base of the brain are present in 10-15% of patients with adult polycystic renal disease. This is a different disease inherited as an autosomal dominant.

COMMENT: I could think of two reasons for the cerebral hemorrhage. One is an overdose of sodium bicarbonate resulting in a hypernatremia which is one of the more common causes of cerebral hemorrhage. The second reason is hypertension because in our experience, neonatal polycystic disease of the kidney is the most common cause of severe renal hypertension in neonates.

RESPONSE: That is a very interesting comment because certainly this hemorrhage with intraventricular extension is extremely rare, practically unknown in babies of this size. Usually you see that in very small babies. In our experience with infantile polycystic kidney--we have quite a few--usually they die very early post-nataly. The problem is that they have hypoplastic lungs; people try to resuscitate these babies and they develop pneumothorax. They die really because of renal and respiratory insufficien and not only renal failure. We had two siblings. One was born in the hospital and just in trying to resuscitate the baby, apparently the baby developed pneumothorax and died. The sibling was born in another hospital where apparently they were not so aggressive and the baby lived for four months. In that baby the cause of death was mainly infection. Apparently those glomeruli were functioning and it was really infection of the kidney (pyelonephritis) that was the main cause of death but the kidneys were very similar.

MODERATOR: It's interesting. Last night we were talking about a study that was done here with the group of Dr. Eduardo Bancalari (Neonatology) and my group (Pediatric Nephrology) in which we evaluated the glomerular filtration rate after the administration of albumin which at the time was routine in the nursery. Since then that procedure, the administration of albumin, has been discontinued because of the occurrence of intraventricula hemorrhage. Apparently it is caused by expansion of the intravascular volume which increases the intracerebral pressure, if I understand it correctly. Do you think that the sodium bicarbonate acts on that basis or on the basis of hypernatremia?

RESPONSE: I think that it's an osmotic effect. In experimental studies the hyperosmosis as such has been considered to be the primary cause of hemorrhage. So, this large hemorrhage might be in fact hyperosmosis but both factors can kill you. I would also like to comment on the very severe acidosis. I wonder if it is only respiratory. It's a real acidosis, too, and I think that acidosis is the most prominent symptom of renal insufficie in infants. The capacity to reabsorb bicarbonate and excrete hydrogen ion is markedly reduced always in renal insufficiency.

COMMENT: To respond to the statement by the pathologist that this infant didn't die a renal death which then leads to one of the previous statements, I would find it difficult to imagine that the infant would have died a renal death so early on and I was thinking that this acidosis was not at all related to the kidney. There is an absence of data on renal function studies which may have been deliberate. Do we have that information as to whether BUN, creatinine were elevated in this infant?

RESPONSE: No. I am sorry, I don't have that information.

QUESTION: How old was the infant when he died?

RESPONSE: Six days. Apparently, from the information that I have, they noticed some enlargement of the kidneys, some renal masses, but they didn't suspect the disease.

COMMENT: If the infant had been fed or even if he hadn't been fed maybe there was renal acidosis but I couldn't believe that complete cessation of renal function would have caused the infant to die at six days of age, even with this lesion.

RESPONSE: This baby in my opinion was a combination of respiratory insufficiency because of the hyaline membrane **(hypoxia) and the massive** brain hemorrhage. I am sorry I don't have the data about renal function.

COMMENT: I think **those** are two very good reasons why this baby would have had severe acidosis terminally. The first one is that size intraventricular hemorrhage. We find in the clinical situation that babies who have intraventricular hemorrhages crash out. They drop their pH's and they are extremely difficult to oxygenate. Those two in combination will produce a severe acidosis.

COMMENT: I would like to mention something first reported in the American Journal of Medicine in 1965 on the association of acute tubular necrosis with intraventricular hemorrhage. I wonder whether there was pathological evidence of basement membrane disruption or anything suggestive of acute tubular necrosis in the infant.

RESPONSE: There was no evidence of acute tubular necrosis. There is something with some of these cases; for example, even if these babies are in shock usually you need a few days-at least **two days or so-to see** the lesion of acute tubular necrosis. That doesn't mean that this baby was not in shock. The histology of it, we don't see.

COMMENT: I'll caution about the diagnosis of autosomal recessive polycystic kidney disease unless we go into detail with the family history. Patients with tuberous sclerosis may present with cystic kidney disease and these kidneys **may** look exactly like autosomal recessive polycystic kidney disease. There have been newborns described with Potter Syndrome with bilateral polycystic kidney disease and the mother had adenoma sebaceum and other manifestations of tuberous sclerosis. So, if we find this sort of clinical picture, before labeling it autosomal recessive polycystic kidney disease one has to go through the family history to make sure there is no tuberous sclerosis.

RESPONSE: In this case with the renal lesions and the liver lesions-that combination-I don't think it is anything else. Again, there are different variants; it is not total. In this particular case the glomeruli are totally normal. I will not be surprised if next year I can give you a follow-up that we have another sibling with the same disease. **But just with what we have I don't have any doubt that the diagnosis is infantile polycystic kidney.**

COMMENT: Although the case history is quite brief, it clearly suggests to me that cerebral hemorrhage was a rather sudden event, that the infant was moderately uremic, and it was the cerebral hemorrhage that resulted in hypotension. This decreased the renal function further and the infant became suddenly oliguric. I believe that the hemorrhage was precipitated by something; for instance, a hypertensive crisis.

RESPONSE: As a matter of fact you can see from the gross pathology picture that there are a few milliliters of blood in that brain. There were about 10 to 15 in the lateral ventricle--massive hemorrhage.

COMMENT: I think that the observation that the kidneys were not palpable on the first day of life is an important one because it is clearly telling us that something that suddenly made those kidneys grow rapidly-in 24 hours-was going on there. That is the reason why, without any more information available in this history, we cannot even guess the diagnosis of polycystic kidney disease.

COMMENT: The fact that the kidneys weren't palpable on the first day of life probably reflects the fact that they weren't examined. This infant was admitted in shock, with a pH of 7.0. Probably no one examined him.

QUESTION: I'd like **to ask you to put for us the mesoblastic nephroma which is another congenital renal tumor in the spectrum of Wilm's tumors.**

RESPONSE: I didn't want to complicate things but mesoblastic nephroma is a tumor that usually is seen in newborns-usually it is a big mass of 6-7 centimeters. It is a benign tumor. At first it was **included in the** Wilm's type category. This is totally different. For example, Wilm's tumor is a tumor well encapsulated or pseudoencapsulated and you have an epithelial component. In the fibrous hamartoma the tissue that you see is connective tissue, mainly smooth muscle or fibrous tissue. It's a type of lesion that infiltrates. Sometimes you can see a tremendous amount of mitotic activity. But what that represents is the **growth of the baby: if you have this tumor in a premature baby you will** see a lot of mitosis but it is a benign tumor. There have been a few reports that some of these tumors may be malignant but if they are, they are extremely rare. These are supposed to be hamartomatous lesions. The Wilm's tumor is a neoplastic process. Hamartomatous, by definition, is an increase of a type of tissue that is present in the organ but the growth is more than expected. For example, a hemangioma would be a hamartomatous lesion. They are neoplastic entities. There is another entity that is becoming clear now. That is what is known as multilocular cysts of the kidney. Again, this is not totally accepted but for some people, and I am in that group, the multilocular cysts of the kidney is a mature Wilm's tumor. You have to demonstrate that with examples but that is something that is under discussion.

QUESTION: A question on the relationship of hypernatremia and intraventricular hemorrhage : **usually the flux of fluid, at least acutely,** is from the vascular space into the cells of the central nervous system.

That condition causes brain swelling. Recently, the theory has been put forth that says that it's a failure of autoregulation that causes maximal dilatation of the cerebral blood vessels and that superimposed on that situation,an increase in pressure or an increase in volume may rupture the cells. If the flux of fluid is out of the vascular space, how can you explain an increased intravascular volume of the magnitude to give you intraventricular hemorrhage just with hypernatremia alone?

RESPONSE: Hypernatremia is a much more common cause of cerebral hemorrhage in premature infants than in full term infants. We know very little about the control of cell volume in the cell that is under development. We cannot apply our regular thinking. I don't think that it is a flux of fluid as such. Maybe the hypernatremia causes a greater resistance and a higher perfusion rate in the small vessels that are not used to it. That might be why the vessels burst.

QUESTION: Could it also be related to the fact that giving sodium bicarbonate, as in this case, is going to cause hypernatremia? It will also cause, since bicarbonate is basically an extracellular ion, an expansion of the extracellular fluid space. If you have vessels that are not autoregulating well, could this cause rupture of the vessels? Could it also be that both of them-hypernatremia and expansion of the extracellular space-are related in that they have the same cause rather than a hypertonic state causing intraventricular hemorrhage?

RESPONSE: There are certain experimental evidences suggesting that the hyperosmotic effect as such is of importance for the cerebral hemorrhage. It's probably because of the local osmotic effect on the blood flow. Whether it causes a local expansion in the capillary bed or not, I don't know,but fluid expansion as such is less dangerous than hypertonic fluid expansion.

QUESTION: In the presence of such severe acidosis you don't know whether it is metabolic or respiratory. Do you think that peripheral perfusion would be so poor that whatever fluid you infuse is not going to go to the systemic circulation?

RESPONSE: You should compensate with fluids, too, not only with sodium bicarbonate. You should give it somewhat diluted.

COMMENT: I would like to go back to the previous discussion on intraventricular hemorrhage. One of the possible reasons for the effect of sodium on intraventricular hemorrhage is actually a spin-off where the sodium diffuses into the brain cells causing cerebral edema. The cerebral edema then has an effect on venous drainage with a back pressure into the subependymum. That causes rupture of the vessels.

MODERATOR: I want to thank everyone for participating, particularly Dr. Fojaco for sharing those cases with us.

APPENDIX

PARTICIPANTS

Program Chairman

José Strauss, M.D., Professor of Pediatrics; Director, Division of Pediatric Nephrology, University of Miami School of Medicine, Miami, Florida, USA.

Guest Faculty

Anita Aperia, M.D., Associate Professor of Pediatrics, Karolinska Institute, St. Göran's Childrens Hospital, Stockholm, Sweden.

Salha Daniel, Ph.D., Research Associate in Anesthesiology. College of Physicians and Surgeons, Columbia University, New York, New York, USA.

Robert Good, M.D., Member and Attending Physician, Sloan Kettering Institute, New York, New York, USA.

Jean-Pierre Guignard, M.D., Associate Professor of Pediatrics; Director, Division of Pediatric Nephrology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.

Eddie Moore, M.D., Associate Professor of Pediatrics, University of Chicago School of Medicine; Director, Division of Pediatric Nephrology, Michael Reese Medical Center; Chairman, University of Chicago-Michael Reese Joint Program in Pediatric Nephrology, Chicago, Illinois, USA.

George McCracken, M.D., Professor of Pediatrics, Southwestern University Medical School, Dallas, Texas, USA.

William Oh, M.D., Professor of Pediatrics and Obstetrics, Brown University; Pediatrician in Chief, Women and Infants Hospital of Rhode Island, Providence, Rhode Island, USA.

Eduardo Slatopolski, M.D., Professor of Medicine, Renal Division, Washington University School of medicine, St. Louis, Missouri, USA.

Local Faculty

George E. Abdenour, M.D., Assistant Professor of Radiology and Pediatrics, Division of Diagnostic Radiology, University of Miami School of Medicine, Miami, Florida, USA.

Eduardo Bancalari, M.D., Professor of Pediatrics; Director, Division of Neonatology, University of Miami School of Medicine, Miami, Florida, USA.

Charles R. Bauer, M.D., Associate Professor of Pediatrics, Division of Neonatology, University of Miami School of Medicine, Miami, Florida, USA.

Jerome Beloff, M.D., Associate Professor of Pediatrics; Professor of Family Medicine; Medical Director, Community Health of South Dade, Inc., University of Miami School of Medicine, Miami, Florida, USA.

Alexander A. Bezjian, M.D., Associate Professor; Director, Diagnostic Ultrasound, Department of Obstetrics and Gynecology, University of Miami School of Medicine, Miami, Florida, USA.

Hernan M. Carrion, M.D., Associate Professor of Urology, University of Miami School of Medicine, Miami, Florida, USA.

Jane L. Frank, M.D., Assistant Professor of Radiology and Pediatrics, Division of Diagnostic Radiology, University of Miami School of Medicine, Miami, Florida, USA.

Michael Freundlich, M.D., Clinical Assistant Professor of Pediatrics, Divi: of Pediatric Nephrology, University of Miami School of Medicine, Miami, Florida, USA.

Ronald Goldberg, M.D., Assistant Professor of Pediatrics, Division of Neonatology, University of Miami School of Medicine, Miami, Florida, USA.

Steven Goldman, M.D., Assistant Professor of Pediatrics, Division of Neonatology, University of Miami School of Medicine, Miami, Florida, USA.

Helen M. Gorman, M.D., Clinical Assistant Professor of Pediatrics, Divisio of Pediatric Nephrology, University of Miami School of Medicine, Miami, Florida, USA.

George K. Kyriakides, M.D., Associate Professor of Surgery, Division of Transplantation, University of Miami School of Medicine, Miami, Florida, USA.

Jorge L. Lockhart, M.D., Assistant Professor of Urology, Department of Urology, University of Miami School of Medicine, Miami, Florida, USA.

Herbert Lubs, M.D., Professor of Pediatrics; Director, Division of Metabolic Diseases and Genetics, University of Miami School of Medicine, Miami, Florida, USA.

Charles M. Lynne, M.D., Associate Professor of Urology, Department of Urology, University of Miami School of Medicine, Miami, Florida, USA.

Edward A. Moses, M.D., Clinical Assistant Professor; Chairman, Medical Education, Department of Family Medicine, University of Miami School of Medicine, Miami, Florida, USA.

Victoriano Pardo, M.D., Professor of Pathology; Director, Electron Microscopy Laboratory, Veterans Administration Medical Center, Miami, Florida, USA.

Gwendolyn Scott, M.D., Assistant Professor of Pediatrics, Division of Infectious Diseases, University of Miami School of Medicine, Miami, Florida, USA.

Emmalee S. Setzer, M.D., Assistant Professor of Pediatrics, Division of Neonatology, University of Miami School of Medicine, Miami, Florida, USA.

Sharanjeet Singh, M.D., Clinical Pharmacologist, Division of Pediatric Cardiology, University of Miami School of Medicine, Miami, Florida, USA.

José Strauss, M.D., Professor of Pediatrics; Director, Division of Pediatric Nephrology, University of Miami School of Medicine, Miami, Florida, USA.

Gaston Zilleruelo, M.D., Associate Professor of Pediatrics, Division of Pediatric Nephrology, University of Miami School of Medicine, Miami, Florida, USA.

Other Contributors

*U. Broberger, M.D., Department of Pediatrics, Karolinska Institute, St. Göran's Childrens Hospital, Stockholm, Sweden.

*Martina S. Evans, R.N., B.S., Neonatal Nurse Clinician, Department of Pediatrics and Nursing, Michael Reese Hospital, University of Chicago Pritzker School of Medicine, Chicago, Illinois, USA.

*L. Stanley James, M.D., Professor of Pediatrics, Obstetrics and Anesthesiology, Division of Perinatal Medicine, College of Physicians and Surgeons, Columbia University School of Medicine, New York, New York, USA.

*Craig B. Langman, M.D. Assistant Professor of Pediatrics, Michael Reese Hospital, University of Chicago Pritzker School of Medicine, Chicago, Illinois, USA.

*Mahmoud Loghman-Adham, M.D., Fellow, Department of Pediatrics, Michael Reese Hospital, University of Chicago Pritzker School of Medicine, Chicago, Illinois, USA.

*Margarita Ocampo, B.S., Division of Pediatric Nephrology, Michael Reese Hospital, University of Chicago Pritzker School of Medicine, Chicago, Illinois, USA.

*Victor A. Politano, M.D., Professor of Urology; Chairman, Department of Urology, University of Miami School of Medicine, Miami, Florida, USA.

*Bernard W. Steele, M.D., Assistant Professor, Department of Pathology, University of Miami School of Medicine, Miami, Florida, USA.

*Sahid Sultan, M.D., Division of Neonatology, University of Miami School of Medicine, Miami, Florida, USA.

*Pricha Tanphaichitr, M.D., Department of Pediatrics, Michael Reese Hospital, University of Chicago Pritzker School of Medicine, Chicago, Illinois, USA.

*Co-authors

AUTHOR INDEX

SUBJECT INDEX