



3502937-4-00-01

vartis Pharmaceuticals
Over, New Jersey 07936-1080
MANDATORY REPORT

Mfr report # USA/00/00632/SAS
UF/Dist report #
FDA Use Only

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Page 1 of 2

A. Patient information			
1. Patient Identifier [redacted]	2. Age at time of event: 24 days or Date of birth: [redacted]	3. Sex <input type="checkbox"/> female <input checked="" type="checkbox"/> male	4. Weight 10.78 lbs or [redacted] kgs
B. Adverse event or product problem			
1. <input checked="" type="checkbox"/> Adverse event and/or <input type="checkbox"/> Product problem (e.g., defects/malfunctions)			
2. Outcomes attributed to adverse event (check all that apply)			
<input checked="" type="checkbox"/> death [redacted] (mo/day/yr)		<input type="checkbox"/> disability	
<input type="checkbox"/> life-threatening		<input type="checkbox"/> congenital anomaly	
<input type="checkbox"/> hospitalization - initial or prolonged		<input type="checkbox"/> required intervention to prevent permanent impairment/damage	
<input type="checkbox"/> other: _____			
3. Date of Event (mo/day/yr) 02/17/2000	4. Date of this report (mo/day/yr) 05/15/2000		
5. Describe event or problem			
INTESTINAL NECROSIS, DEATH			
A pharmacist reported that a neonate, being treated unsuccessfully with glucagon and intravenous Sandostatin for uncontrolled hyperinsulinemia, was transferred to [redacted]. Sandostatin was discontinued, and another unspecified agent was started. The neonate became hyperglycemic, and underwent surgery, which uncovered necrosis of the entire bowel. It was also noted that the neonate exhibited variant vascular anatomy. Following surgery, the neonate died. The neonate was [redacted] days old at the time of death. The reported suspected Sandostatin as the cause.			
Follow-up received 12 May 2000: The patient was [redacted] days old at the **MORE**			
6. Relevant tests/laboratory data, including dates			
GLUCOSE, SERUM OR PLASMA - 67 to 100 mg/dl - [redacted]			
GLUCOSE, SERUM OR PLASMA - 70 to 100 mg/dl - [redacted]			
GLUCOSE, SERUM OR PLASMA - 60 to 70 mg/dl - [redacted]			
GLUCOSE, SERUM OR PLASMA - 317 to 467 mg/dl - [redacted]			
7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)			
1) Fluid overload secondary to diazoxide - prior to 09 Feb 2000			

DSS

MAY 18 2000

C. Suspect medication(s)			
1. Name (give labeled strength & mfr/labeler, if known)			
#1 SANDOSTATIN (octreotide acetate)			
#2 _____			
2. Dose, frequency & route used		3. Therapy dates (if unknown, give duration from/to (or best estimate))	
#1 25 MCG, FOUR TIMES		#1 Unspecified	
#2 _____		#2 _____	
4. Diagnosis for use (indication)		5. Event abated after use stopped or dose reduced	
#1 HYPERINSULINEMIA		#1 <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> doesn't apply	
#2 _____		#2 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply	
6. Lot # (if known)		7. Exp. date (if known)	
#1 UNK		#1 UNK	
#2 _____		#2 _____	
8. Event reappeared after reintroduction			
#1 <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> doesn't apply			
#2 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply			
9. NDC # - for product problems only (if known)			
#1 _____			
#2 _____			
10. Concomitant medical products and therapy dates (exclude treatment of event)			
1) Diazoxide (UNKNOWN TO 02/09/2000)			
2) Furosemide (02/09/2000 TO 02/25/2000)			
3) Glucagon (02/11/2000 TO 02/15/2000)			
4) Dextrose 20% (glucose) (02/11/2000 TO UNKNOWN)			
MORE			
G. All manufacturers			
1. Contact office - name/address (& mfring site for devices)		2. Phone number	
Novartis Pharmaceuticals Corp. 59 Route 10 East Hanover, NJ 07936-1080 USA		800-378-8567	
4. Date received by manufacturer (mo/day/yr) 05/12/2000		5. NDA# 19-667 (A) IND# _____ PLA # _____	
6. If IND, protocol #		pre-1938 <input type="checkbox"/> yes OTC product <input type="checkbox"/> yes	
7. Type of report (check all that apply)		8. Adverse event term(s)	
<input type="checkbox"/> 5-day <input checked="" type="checkbox"/> 15-day		INTESTINAL NECROSIS, DEATH	
<input type="checkbox"/> 10-day <input type="checkbox"/> periodic		MAY 17 2000	
<input type="checkbox"/> Initial <input checked="" type="checkbox"/> follow-up # 1		[Circular stamp: EVALUATION AND RESEARCH, MAY 17 2000, CDR]	
9. Mfr. report number USA/00/00632/SAS			
E. Initial reporter			
1. Name, address & phone #			
[redacted]			
2. Health professional? <input checked="" type="checkbox"/> yes <input type="checkbox"/> no		3. Occupation RPH	
4. Initial reporter also sent report to FDA <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> no			

FDA

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.



3502937-4-00-02

Novartis Pharmaceuticals
Emeryville, New Jersey 07936-1080
INDIVIDUAL SAFETY REPORT

Mfr report #	USA/00/00632/SAS
UF/Diet report #	
FDA Use Only	

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Page 2 of 2

Continued information

B5 Describe event or problem:

time of admission (not time of death as previously reported), and was admitted to [redacted] on [redacted] while receiving octreotide 12.3 mcg subcutaneous every six hours (starting date not specified). The patient was also receiving furosemide intravenously for fluid overload believed to be caused by diazoxide. The diazoxide was discontinued upon admission. On [redacted], the octreotide was discontinued. Glucagon 8.5 mcg/kg/h continuous infusion, 20% dextrose, and oral feeding were started, and were well tolerated. Serum glucose levels ranged between 67 and 120 mg/dl. On [redacted], the glucagon infusion was discontinued, and the 20% glucose continued. Serum glucose levels were 70 to 100 mg/dl. On [redacted], octreotide continuous infusion was started at a rate of 0.2 mcg/kg/h. On [redacted], oral intake was down. On [redacted], the octreotide infusion continued at 0.2 mcg/kg/h, and 20% dextrose was at 3 mL/h. Oral feeding was at 20 to 80 mL every three hours, and nursing reported good sucking, but the patient was arching, crying, and grimacing after 2 or 3 swallows. On [redacted] glucose levels decreased. The 20% dextrose was increased to 5 mL/h, and octreotide was increased to 0.4 mcg/kg/h. Oral feeding became increasingly difficult, and the patient was receiving about one-half via a nasogastric tube. Ranitidine was started for clinical reflux. On [redacted], the administration of octreotide was changed to 18 mcg subcutaneous every six hours. The patient was also receiving oral metoclopramide 0.4 mg four times a day and simethicone 20 mg four times a day. Glucose levels were 60-70 mg/dl. On [redacted], octreotide was increased to 20 mcg subcutaneous every 6 hours, and as per endocrinology recommendation, a nicardipine 1.5 mcg/kg/min continuous infusion was started. Glucose was at 60 to 70 mg/dl. On [redacted] oral intake continued to be poor with the patient in obvious distress, and octreotide was increased to 25 mcg subcutaneous every 6 hours at 2400 hours. The octreotide and nicardipine were discontinued, glucose levels were 317 to 467 mg/dl, and the patient was with increased irritability and abdominal girth. On [redacted] between 0300 and 0700 hours the glucose continued to fluctuate. Abdominal changes were seen on the film, and the girth was up to 38. The patient was taken to the operating room at 0715 hours where necrotizing enterocolitis was found extending from the gastroesophageal junction to the rectum. A decision was made to close and return the patient to the unit where he expired at 0957 hours. Autopsy results are pending, but Sandostatin was considered a SUSPECTED cause of the necrotizing enterocolitis. The reason for the rise in glucose was not clear.

Novartis Comments: "Serious spontaneous report, DEATH, assessed as unlisted according to the Basic Prescribing Information. The information provided in this individual case does not warrant a change in the Basic Prescribing Information text. The topic will be monitored closely & will be reevaluated on an ongoing basis based on cumulative experience. All spontaneous reports are considered suspected for reporting purposes".

C2 Suspect Medication Dose #1:
A DAY, SUBCUTANEOUS;

C10 Concomitant medical products:

- 5) Ranitidine
- 6) Simethicone
- 7) Metoclopramide
- 8) Nicardipine
- 9) Vancomycin
- 10) Tobramycin
- 11) Morphine sulfate

MAY 17 2000

MAY 18 2000

The patient was referred from the [redacted] [redacted] with the presumptive diagnosis of hyperinsulinism, most likely diffused type, SUR receptor mutation.

ADMISSION DIAGNOSIS:

1. [redacted]-week-old term infant.
2. Rule out hyperinsulinism SUR receptor deficiency, diffuse versus focal defect.
3. Hypoglycemia.
4. Mild fluid overload secondary to diazoxide therapy at the prior-hospital.

HISTORY OF PRESENT ILLNESS: [redacted] is now [redacted] days old, admitted to the [redacted]. His prenatal history: Born to a [redacted]-year-old gravida II, para I. The prenatal labs were unremarkable, hepatitis negative, RPR negative, HIV negative. [redacted] was delivered by stat C-section secondary to maternal pre-eclampsia which subsequently developed into HELLP syndrome. There was meconium present at delivery. Apgars were 7 and 8. Respiratory stress was initially diagnosed with mild RDS. Antibiotics were given for five days, although the blood cultures were negative. [redacted] continued to improve at [redacted]. He had excellent p.o. intake, but was observed to have low glucose values, which did persist. Endocrinology was ultimately involved in [redacted], and hyperinsulinism was expected. There was a partial work-up done at [redacted], which did appear to point toward hyperinsulinism with the level of insulin at 11.7. The baby was on continuous infusion of D-28, and was p.o. feeding. Diazoxide was also started prior to the [redacted] admission, and [redacted] was noted to have some fluid retention because of this, and required Lasix, multiple doses. The maternal blood type was A-positive, and the Coombs was negative. [redacted] blood type was also noted to be A-positive.

His hospitalization at the [redacted] consisted of the following events:

Again, he was admitted here at approximately day of life [redacted]. He was taken care of primarily by the Endocrinology Service at the [redacted]. Neonatology care was provided on a daily basis, in conjunction with Endocrinology. He was essentially on p.o. feedings ad lib, and an IV stock of

PO 3/31

[redacted]

[redacted]

[redacted]

D-20 at approximately 17 cc an hour on admission. He apparently failed a glucagon administration test, and was scheduled for an acute insulin response test under my care. He had the usual Endocrinology lab sent, ketones, insulin, free fatty acids, growth hormone, and cortisol. It was felt again, by the Endocrinology Team, that he did fit into the diffuse SUR receptor mutation. He was started on octreotide again after a glucagon infusion was tried at the [redacted], and this was started on 2/16/00. He was started at 0.2 mcg per kg per hour, continuing with IV dextrose of 20% and p.o. feeding. He did have the insulin response test. His medications did change somewhat because of this, and he ultimately ended up on D-20 infusion, as low as approximately 2 cc an hour with p.o. feedings at times, with glucose control in the adequate range above 60 mg per deciliter to 80 mg per deciliter, which was the desired level by Endocrinology. Dr. [redacted] was the primary endocrinologist who was involved in [redacted] care. At approximately [redacted] days of life, [redacted] was scheduled for a pancreatic arteriogram after a family meeting to discuss the information which was required, to document and prove a diffuse pancreatic process. He was made n.p.o., started on full IV fluids, and was intubated for the procedure. It was a long procedure, and he did have a central venous catheter placed also in the Interventional Radiology Suite. It was reported that he did have a bout of SVT, requiring fluid bolus and a blood transfusion, and was returned intubated, with only a partial result since the catheter was difficult to ascend into the pancreas. The sampling was limited, as per Endocrinology. At about [redacted] days of life, [redacted] was again started on octreotide at 0.2 mcg per kg per hour. As per Endocrinology, he was allowed to eat as he desired, and he was continued on IV glucose of D-20 at approximately 12 mg per kg per minute. His p.o. intake started to become poor, for no apparent obvious reason. He was initially tachypneic from the presumed diazoxide therapy. This did resolve, although he did remain slightly tachypneic, but it was much less. He did have one bout of post-extubation stridor, responding to racemic epinephrine without any sequelae. Since his visit to the IR, he did have two central lines placed, one in the right external jugular vein, and one previously that was placed here at the [redacted] in the right saphenous vein, upon which one lumen of that catheter was clotted as a result of the AIRS insulin test that was done. Again, there was much discussion about a possible subtotal pancreatectomy as a cure, but the parents were somewhat anxious about this therapy and requested more exploration of medical therapy prior to the actual procedure. Throughout this, [redacted] physical exam was essentially unchanged. He was approximately 5 kg. He had an intake of approximately 120 cc per kg per day, with excellent urine output of approximately 3 cc per kg per hour, depending on his intake. He was on medications which changed from octreotide, IV glucose, glucagon, and ultimately calcium channel blocker therapy as per Endocrinology. He had a clear chest, and had resolved edema from admission. He had no cardiac murmur. He was always well-perfused. His abdomen was

soft and flat without any bowel distension or dysfunction. Again, he did have two central lines placed as previously described. His tone and neurological exam were appropriate for gestational age. At one point, he had a right IV infiltrate, which was resolved. On [redacted], as per Endocrinology, octreotide was changed to subcutaneous dosing at 20 mcg per dose q.6h. [redacted] continued to feed poorly, q.3-4h., and to require NG feeds intermittently. He was also started on Reglan and Zantac for a perceived clinical reflux. His IV glucose requirements again remained anywhere from 4 cc to 7 cc an hour, depending on his p.o. intake. He was also holding his serum glucose level in the 60 to 80 range. He had occasional low glucoses below 30, and did receive IV glucose bolus for this, but this was not a common occurrence. At day of life [redacted] was started on nicardipine, which is a calcium channel blocker, as per Endocrinology, to augment the effect of the medical treatment. He was getting an IV infusion of this medication at the time. He was also on his subcutaneous octreotide, and this was ultimately increased to 25 mcg subcutaneous q.6h. Suddenly, on [redacted] in the early to late evening, he had hyperglycemia of an unusual range in the 200 to 400 level. He had not done this before. He became irritable, had a low grade fever, and at that time a full sepsis work-up was done. Antibiotics were started. Over the course of five to six hours, he showed definite signs of peritonitis, and acute abdominal distress, ultimately with abdominal x-rays showing portal venous gas and extensive pneumatosis intestinalis. This was an unexpected finding, without any provocation clinically. In fact, at 5:00 p.m. that evening, he did have an abdominal x-ray to evaluate placement of the initial PICC line, and his bowel gas pattern was totally within normal limits, with no portal venous gas noted. He did ultimately go to the Operating Room and, upon Dr. [redacted] opinion, had diffuse necrosis of the small bowel, part of the gastric stomach, and colonic area. He was therefore closed surgically without any resection, and brought back to the NICU, where he subsequently expired after approximately no chance of survival with this extensive disease. He was made comfortable, and extubated with the parent's consent and presence. He was pronounced dead at 9:57 a.m. on [redacted]. An autopsy will be performed, as per parental consent.

DISCHARGE/DEATH DIAGNOSIS:

1. [redacted]-day-old term infant with hypoglycemia, requiring multiple medications and failed medical therapy.
2. Acute fulminant necrotizing enterocolitis, involving the entire small bowel, part of the stomach, and part of the colon, with no resection done, as per extensive nature of the injury.
3. He was status post an AIRS test, predicting an SUR receptor mutation. He was also status post a partial pancreatic arteriogram with failed pancreatic sampling due to technical difficulties.

MEDICATIONS PRIOR TO DEATH: Octreotide infusion, and

LOCATION
NEONATE INTER CARE B

FILE COPY PAGE 1

PATIENT: [REDACTED]	ACCT: [REDACTED]	LOC: [REDACTED]	DE: [REDACTED]
REG DE: [REDACTED]	AGE/SX: [REDACTED]	ROOM: [REDACTED]	REQ: [REDACTED]
SERVICE: NRO	STATUS: DIS IN	BED: [REDACTED]	DIB: [REDACTED]

Received: [REDACTED]-1039 Status: [REDACTED] Req#: [REDACTED] SPEC# 00: [REDACTED]
 Spec Type: AUTOPSY Subm Dr: [REDACTED]

Procedures: PM ATTENDANT, SECT/PM/ADD CUT/12, SECT/PM/COMP/69, NP SECT/COMP/3,
 CASE REVIEW, DISP-CONT MATER, ELASTIC ST./GP1/2, EM-EMBED (LEFT)/4,
 EM-EMBED (RIGHT)/5, EM-PREPARATION/2, EM-THICKS (LEFT)/4, EM-THICKS (RT)/4,
 IRON ST./GP1/2, GOWN/CONT SPEC/2, PM-CLERICAL, MRI/GP2/2,
 OIL RED O/GP2, PAS STAIN/GP2/2, PATH CULT, PHOTO/GROSS/2,
 WASHING BENCH

PATIENT INFORMATION

1. DATE OF BIRTH: [REDACTED]
2. RACE: M/W
3. ADMITTED: [REDACTED]
4. EXPIRED: [REDACTED] @ 09:57
5. AUTOPSY: [REDACTED] @ 13:00
6. AUTOPSY RESTRICTION: NONE
7. SERVICE: DR. [REDACTED]
10. PROSECTOR: DRS. [REDACTED]
11. MEDICAL EXAMINER'S CASE: NO
13. HGR: NO
14. TUMOR BOARD: NO

FINAL AUTOPSY DIAGNOSIS

[REDACTED] old male infant, product of a term gestation, who was delivered by emergent C-section secondary to preeclampsia. The mother was a [REDACTED] year old G2, P0-1, hepatitis B negative, RPR negative, HIV negative female who subsequently developed HELLP syndrome. Meconium was present at delivery and Apgar scores were 7 and 8 at one and 5 minutes, respectively. The baby was transferred to [REDACTED] NICU. Birth weight was 4.1 kg. (2 standard deviations above normal for age).

Respiratory distress syndrome was initially suspected, but soon it was noted that the infant's blood glucose level was low at 57, NH4 43, insulin 30, and cortisol 11. Additional studies later showed glucose at 22 and insulin 11.7. The infant was reported to have failed glucagon, and weight gains were significant. IVF was given to keep glucose between 70-9- mg/dl.

LOCATION
NEONATE INTEN CARE B

PAGE 2

(Continued) PATIENT: [REDACTED]

SPEC: 00 [REDACTED]

FINAL AUTOPSY DIAGNOSIS (Continued)

[REDACTED] admission was on day [REDACTED], and weight was 4.9 kg. The infant was treated with Diazoxide, then Octreotide (level 10), lasix for fluid overload, and at [REDACTED] the working diagnosis was hyperinsulinism, resistant to diazoxide, probably sulfonylurea receptor mutation.

On [REDACTED], pancreatic arteriography was performed, with procedural difficulty in placement of catheter. Insulin challenge test on [REDACTED] showed significant hyperinsulinism. Diffuse beta-cell hyperplasia lesion was suspected. Supportive care and treatment of hypoglycemia continued and partial pancreatectomy surgery was considered. However, on [REDACTED], the baby showed signs of increasing abdominal girth and decreasing oxygen saturations, and imaging of abdomen showed marked pneumatosis, indicative of necrotizing enterocolitis (NEC). The infant was taken to the OR at 09:00 on [REDACTED] for exploratory laparotomy. Open lap showed necrosis of bowel from stomach to large bowel; cultures were obtained. NEC was far too extensive for resection. Multiple antibiotics were started. The patient died at 09:57 on [REDACTED]. An unrestricted autopsy was performed.

Underlying Problem:

Hyperinsulinemic hypoglycemia, with diffuse beta-cell islet lesion of pancreas.

Intermediate Problem:

Necrotizing enterocolitis.

Immediate Problem:

Intestinal pneumatosis and perforation.

AUTOPSY FINDINGS:

- I. Necrotizing enterocolitis with pneumatosis, severely affecting small bowel, moderately affecting stomach and large bowel, multiple perforations of proximal jejunum and mid-small bowel with resultant severe peritonitis and sepsis:
 - A. Clinical history of urine culture positive for *Enterobacter aerogenes* [REDACTED].
 - B. Intraoperative culture of peritoneum positive for *Enterococcus* sp. and lactose fermenting, gram negative rods [REDACTED].
 - C. Autopsy blood cultures positive for *Enterobacter aerogenes* and *Enterococcus* sp.

(Continued) PATIENT

SPEC: 00

FINAL AUTOPSY DIAGNOSIS (Continued)

- D. Autopsy spleen, lung cultures positive for *Enterobacter aerogenes*.
 - E. Autopsy cultures of duodenum, ileum, colon, peritoneum positive for *Enterococcus sp.* and lactose fermenting gram negative rods.
 - F. Clinical history of blood culture positive for *Staphylococcus, coagulase negative sp.*
 - G. Thromboembolic material, multiple small mesenteric vessels, including at least one vessel containing foreign material.
 - H. No evidence of thrombosis of abdominal aorta, celiac axis, main superior mesenteric artery, inferior mesenteric artery, splenic artery, inferior vena cava, inferior mesenteric vein, or portal vein.
- II. mural thrombus, right jugular vein extending into superior vena cava:
- A. Associated with intravenous catheter.
 - B. Partially organized and attached to venous wall.
 - C. Inflammation and organizing granulation tissue, perivenous connective tissue.
 - D. 90% occlusion of venous lumen.
 - E. Colonies of Cocci in the thrombus.
- III. Valvular competent patent foramen ovale.
- IV. Pulmonary congestion, edema and focal hemorrhage:
- A. Thromboembolic material and platelet fibrin thrombi in small intraparenchymal pulmonary arterial and venous vessels, diffuse, some organizing.
 - B. Hypersecretory changes, distal airways, with mucus in lumen of airways and airspaces.
 - C. Pigmented macrophages, possibly meconium and/or hemosiderin.
- V. Acute tubular necrosis, diffuse, and possible patchy cortical necrosis, kidneys, bilateral.
- VI. Acute hemorrhage with possible early necrosis, patchy, spleen, with rare small vessels containing thromboembolic material.
- VII. Patchy, non-zonal acute congestion and hemorrhage with focal early necrosis, liver, with thromboembolic material, sometimes organizing, in a few small arteries and veins.
- VIII. Mucosal erosions, patchy, tracheobronchial mucosa.

LOCATION
NEONATE INTEN CARE B

PAGE 4

(Continued) PATIENT: [REDACTED]

SPEC: 00 [REDACTED]

FINAL AUTOPSY DIAGNOSIS (Continued)

IX. Diffuse pancreatic islet cell nucleomegaly and hyperchromasia, consistent with neonatal hyperinsulinemic hypoglycemia.

CLINICAL HISTORY

[REDACTED] month old male infant, product of a term gestation, who was delivered by emergent C-section secondary to preeclampsia. The mother was a [REDACTED] year old G2, P0-1, hepatitis B negative, RPR negative, HIV negative female who subsequently developed HELLP syndrome. Meconium was present at delivery and Apgar scores were 7 and 8 at one and 5 minutes, respectively. The baby was transferred to [REDACTED] NICU. Birth weight was 4.1 kg. (2 standard deviations above normal for age).

Respiratory distress syndrome was initially suspected, but soon it was noted that the infant's blood glucose level was low at 67, NH4 43, insulin 30, and cortisol 11. Additional studies later showed glucose at 22 and insulin 11.7. The infant was reported to have failed glucagon, and weight gains were significant. IVF was given to keep glucose between 70-90 mg/dl.

[REDACTED] admission was on day [REDACTED], and weight was 4.9 kg. The infant was treated with Diazoxide, then Octreotide (level 10), lasix for fluid overload, and at CHOP, the working diagnosis was hyperinsulinism, resistant to diazoxide, probably sulfonylurea receptor mutation.

On [REDACTED] pancreatic arteriography was performed, with procedural difficulty in placement of catheter. Insulin challenge test on [REDACTED] showed significant hyperinsulinism. Diffuse beta-cell hyperplasia lesion was suspected. Supportive care and treatment of hypoglycemia continued and partial pancreatectomy surgery was considered. However, on [REDACTED], the baby showed signs of increasing abdominal girth and decreasing oxygen saturations, and imaging of abdomen showed marked pneumatosis, indicative of necrotizing enterocolitis (NEC). The infant was taken to the OR at 09:00 on [REDACTED] for exploratory laparotomy. Open lap showed necrosis of bowel from stomach to large bowel; cultures were obtained. NEC was far too extensive for resection. Multiple antibodies were started. The patient died at 09:57 on [REDACTED]. An unrestricted autopsy was performed.

LOCATION
NEONATE INTEN CARE B

PAGE 5

(Continued) PATIENT: [REDACTED]

SPEC: 00 [REDACTED]

GROSS EXAMINATION

The body is that of a [REDACTED] month old male infant, the product of a term gestation, who appears moderately edematous overall. Body weight is 5340 gm, up from a birth weight of 4060 gm. Crown-heel length is 57.5/51.4 cm; crown-rump length 41.5 cm, foot length bilaterally, 8.7 cm. Circumferences of the head, chest and abdomen are 38, 39 and 43 cm, respectively. The palpebral fissures are 2.7 cm in length bilaterally. The inner canthal, outer canthal and interpupillary distances are 2.5, 8.0 and 4.5 cm, respectively. The pupils are equal (0.3 cm each), surrounded by blue irides and white sclerae.

The nailbeds are slightly cyanotic. Lividity is mild, beginning to form over dependent locations in the back. Skin color is white, and the hair is brown.

Evidence of External Therapeutic Intervention: A central venous access line is present within the right jugular vein; the tip of which extends to the upper portion of the superior vena cava. Over the anterior abdominal wall, there is a recent surgical transverse incision, 11.0 cm in length, 1.5 cm above the umbilicus. An intravascular access line is noted within the left wrist area. Intravascular access is present within the right extensor surface of the hand, and the right extensor surface of the foot.

Examination of the head reveals edematous facies; otherwise, the head, face and neck are non-traumatic and normocephalic. No dysmorphic facies are identified. The ears are normally-positioned and the external auditory meatus are patent and without exudate. The nares are patent bilaterally, as are the choanae to the posterior portion of the nasopharynx. The filtrum is appropriately formed and there is no clefting of the lip. The soft and hard palates are unremarkable. The uvula is midline.

The hands and feet all have 5 digits. No dysmorphic palmar or plantar creases are identified. No dysraphisms of the dorsal midline are identified. The external genitalia are those of an uncircumcised male, with bilaterally descended testes. No abnormalities of the lower extremities are identified.

The body is opened with the standard Y-shaped incision, revealing a 0.5 cm thick panniculus. Five cc of blood-tinged pleural fluid are noted bilaterally. The peritoneal cavity contains 20 cc of blood-tinged fluid. Bilaterally, the lungs occupy 80 % of their respective pleural cavities. The pleural surfaces of the lungs are remarkable for multifocal petechiae, both on the visceral and parietal pleural. In *situ* examination of the thoracic organs

(Continued) PATIENT: [REDACTED]

SPEC: OD: [REDACTED]

GROSS EXAMINATION

(Continued)

reveals no further abnormalities. The thymus is prominent in the anterior mediastinum.

In situ examination of the abdominal organs reveals marked pneumatosis and hemorrhagic necrosis of the small bowel, and to a lesser extent, portions of the large bowel. The stomach appears to be moderately affected by this process as well. The bowel is appropriately rotated and fixed to the retroperitoneal wall. The spleen, liver, kidneys and other organs are appropriately associated.

Respiratory System: The right lung weighs 58 gm, and the left 52 gm (combined weight of 110/85 gm). Section reveals vascular congestion bilaterally.

Cardio-Vascular System: The heart weighs 39.4/30 gm; it is anatomically normal. The azygous vein enters into the superior vena cava, as does the brachiocephalic vein. However, in the superior portion of the superior vena cava, adherent thrombus to the venous wall is noted. Sectioning of the superior vena cava, and cross sectioning reveals this thrombus to be fairly well organized into the wall. The heart is remarkable for a rather patent foramen ovale that maintains valve competence. Right ventricular wall thickness is 0.4 cm; the left ventricular wall thickness is 0.8 cm.

Diaphragm: The diaphragm weighs 32 gm and is without lesion. Both the membranous and muscular portions of diaphragm are appropriately formed.

Gastro-Intestinal System: The gastro-intestinal system throughout its extent is affected, from the stomach to the large intestine, by necrotizing enterocolitis. This is evidenced by severe pneumatosis associated throughout portions of the bowel wall, being exceptionally noticeable in association with its mesenteric attachment. The stomach appears to be moderately affected by this process, and opening of the stomach reveals hemorrhage into the mucosal surface and associated necrosis. Several perforations are noted within the small bowel, predominantly in the proximal small bowel-jejunal segment, and in the midportion of the small bowel. To a milder extent, the large bowel is affected by this same process, as evidenced by patchy hemorrhagic foci of the serosal mucosal surfaces.

Examination of the vasculature associated with the bowel and pancreas reveals no evidence of gross thrombi. This examination includes examination of the abdominal aorta and associated branches, superior and inferior

LOCATION
NEONATE INTEN CARE B

PAGE 7

(Continued) PATIENT: [REDACTED]

SPEC: 05 [REDACTED]

GROSS EXAMINATION

(Continued)

mesenteric arteries, portal and splenic veins, and splenic artery. In addition, section of the pancreas reveals largely patent arterial vessels with the possibility of gross thrombi observed in smaller caliber vessels at the pancreatic head. However, the pancreatic parenchyma is intact and without necrosis or infarction.

The liver weighs 240/180 gm. Grossly, it is affected by intervening areas of congestion, fatty change and centrilobular hemorrhage.

Genito-Urinary System: The right kidney weighs 22.7 gm., and the left 23.3 gm. External and sectioned surface examination reveals the cortices to be thin and discolored tan-yellow, grossly indicating acute tubular necrosis and full thickness patchy cortical necrosis. The pelvic collecting systems are patent, and the ureters are patent to the bladder bilaterally. There is otherwise, good demarcation between the cortico-medullary junction bilaterally. Fetal lobulations of the kidneys are mildly evident.

Both testes are descended. The left testis measures 1.3 x 0.7 x 0.8 cm and has an associated appendix testis, measuring 0.2 cm. The right testis measures 1.4 x 0.8 x 0.75 cm. These are fixed in Bouin's and transferred to formalin.

Endocrine System: The left adrenal weighs 4.64 gm, and the right 3.33 gm, for a combined weight of 7.97/6.8 gm. Section reveals tan-yellow cortices, and no evidence of lesion. The thyroid is identified within the neck bloc, and consists of a tan-pink, lobulated, normally-formed organ. Section reveals tan-pink parenchyma free of lesions. The neck bloc demonstrates normal anatomic morphology.

Hematopoietic/Reticuloendothelial Systems: The spleen weighs 30/15 gm. It is remarkable for a 2.5 cm oval lesion on the capsular surface, which appears to represent a hemorrhagic infarction. Section reveals congested red pulp. No lymphadenopathy is identified.

Musculo-Skeletal System: The musculature is well-developed, and no skeletal abnormalities are noted.

Central Nervous System: The brain weighs 425.5/460 gm. No external gross lesions of the brain or pituitary are identified. Cortical and gyral development is within normal limits.

LOCATION
NEONATE INTEN CARE B

PAGE 8

(Continued) PATIENT: [REDACTED]

SPEC: 00: [REDACTED]

GROSS EXAMINATION

(Continued)

Photographs: Photographs of the in situ necrotic bowel are taken, as well as the small bowel perforations.

Cultures: Blood, lung, spleen, peritoneum, bile fluid, small bowel (including ileum and duodenum) are cultured for routine, aerobic and anaerobic organisms. The lung is also cultured for fungus. Middle ear culture is obtained.

MRM

Rec'd [REDACTED]

MICROSCOPIC EXAMINATION

Respiratory System: Sections of the right and left lungs demonstrate congested vasculature and multifocally, medium-sized, predominantly venous vessels demonstrating platelet fibrin thromboemboli. These intravascular emboli take the form of fibrinous material admixed with red blood cells and inflammatory cells. These emboli show various degrees of association with fibrinous elements, indicating various degrees of long standing. These foci appear to be of recent formation. However, this evidence is strongly suggestive of an intravascular phenomenon leading to a showering of thromboemboli particulate material.

Additionally within the airway spaces, predominantly the alveolar spaces, the shedding of pneumocytes into the alveolar space is identified, and there is a net-like, mucoid/proteinaceous material in many of the airways and alveolar spaces. Extramedullary hematopoiesis is identified multifocally within the lung parenchyma. Alveolar macrophages are also identified, many of which contain yellow-brown cytoplasmic pigment. Multifocally, within medium and small caliber airways, abundant macrophages, filled with fine brown pigment are identified. In areas, these macrophages merge to form multinucleated giant cells filled with this fine brown pigment. Abundant squames are not identified within the alveolar space and there is mild, patchy simplification of peripheral lobules.

Sections of the trachea and upper respiratory system demonstrate sloughed/eroded epithelium within the luminal aspects of the trachea, associated with mucoid material and bacterial cocci. The presence of bacterial cocci most likely represents postmortem overgrowth. Within sections of the neck block, unremarkable respiratory epithelium is identified; submucosal and cartilaginous development around the cricoid structures is normal.

LOCATION
NEONATE INTEN CARE 8

PAGE 9

(Continued) PATIENT: [REDACTED]

SPEC: 00 [REDACTED]

MICROSCOPIC EXAMINATION (Continued)

Cardio-Vascular System: Unremarkable myocardium, endocardium and epicardium is identified within the left and right ventricular sections.

Gastro-Intestinal System: Sections of the submandibular salivary glands are unremarkable.

The esophagus demonstrates ganglionation throughout the esophageal wall. Squamous mucosa is observed in the appropriate places. The transition from squamous to gastric epithelium is identified. The gastric wall and epithelium are congested. The gastric mucosa demonstrates marked necrosis. Additional sections of the gastric wall demonstrate intact muscular wall; however, the epithelial and mucosal surfaces are necrotic. The vasculature is dilated and congested. The stomach wall is ganglionated throughout; however, while associated satellite cells are intact, the ganglion cells are showing signs of cytolysis. The necrotic gastric epithelium is attributed to necrotizing enterocolitis (NEC).

Sections of the small bowel demonstrate again congested and dilated vasculature intermixed with dilated lymphatics. Luminal contents of the small bowel demonstrate sloughed epithelium intermixed with fecal material. A serositis is present. Several sections of small bowel demonstrate the histological changes of pneumatosis. These consist of dilated, coalescent, evacuated spaces within the muscular and fibrous wall of the small bowel, as well as dilated lymphovascular spaces. These are also prominent at the mesenteric border. Bacterial cocci are also identified within the necrotic epithelium of the small bowel mucosa.

Several sections of small bowel were submitted that were associated with bowel wall perforations. These regions demonstrate almost full thickness necrosis of the small bowel wall, with only an occasional viable cell within the muscularis propria identified.

Sections of the terminal ileum demonstrate necrotic epithelium, the presence of associated lymphoid structures within the submucosal region and pneumatosis throughout the ileal wall, associated with dilated lymphatics. The small bowel is severely affected throughout by NEC.

Sections of the large bowel demonstrate pneumatosis to a much lesser degree. The muscularis propria layers throughout the large bowel appear to be largely intact. However, there is pneumatosis within the submucosa and the

LOCATION

NEONATE INTEN CARE B

PAGE 10

(Continued) PATIENT: [REDACTED]

SPEC# 00 [REDACTED]

MICROSCOPIC EXAMINATION (Continued)

epithelial lining of the bowel lumen is necrotic and sloughing. The large bowel and stomach are involved with NEC to a lesser degree than the small bowel.

Sections of the rectal wall and mucosa demonstrate no involvement with the aforementioned necrotizing enterocolitis. The epithelial lining of the mucosa is intact, as are all sections of the bowel wall. Ganglionation is present.

Sections of the appendix demonstrate a necrotic epithelial lining, however, the bowel wall muscular layers are largely intact.

Liver: Sections demonstrate largely intact triads. There is multifocal congestion of the sinusoids, as well as multifocal extramedullary hematopoiesis. Bile ducts are readily identified, and the overall liver histological pattern is that of recent congestion. Several of the portal tracts demonstrate an abundant surrounding collar of red blood cells. Patchy, non-zonal necrosis is identified. Small amounts of thrombotic material, composed of fibrin and inflammatory cells are seen within some of the medium caliber venous structures within the liver.

Pancreas: Sections of the pancreas demonstrate histological features of diffuse nesidioblastosis (diffuse lesion of hyperinsulinemia). The exocrine pancreas is well-preserved and maintains its acinar architecture. However, the endocrine pancreas, in the form of islets of Langerhans, multifocally shows degeneration of islet cells with cellular dropout, apoptosis, and cytolysis. No areas of overt infarction are identified within the pancreatic parenchyma.

The lesion of hyperinsulinemia manifests itself histologically as multifocal islet cell anisonucleosis, accompanied by hyperchromasia of the enlarged nuclei. These regions of islet cell anisonucleosis and hyperchromasia are identified predominantly within tail block sections (Pan 2 and Pan 3), as well as sections from the head, predominantly in block Pan 11. Given that these features are found within 2 geographically different locations within the pancreas, this defines it as a diffuse lesion. A single thrombosed small arteriole is identified within pancreatic block Pan 9, however, no evidence of pancreatic infarction is identified.

Focal lymphoid heterotopias and extramedullary hematopoiesis are identified, as well as multifocal ductular mucus.

LOCATION
NEONATE INTEN CARE B

PAGE 11

(continued) PATIENT: [REDACTED]

SPECN: 00 [REDACTED]

MICROSCOPIC EXAMINATION (Continued)

Genito-Urinary System: Sections of the right and left kidneys demonstrate several small foci of immature nephrogenic-type tissue, located multifocally subcapsullary. These consist predominantly of underdeveloped glomerular structures. There is noticeable loss of cortical substance. This predominantly takes the form of atrophic and vanishing tubules, indicative of acute tubular necrosis and patchy cortical necrosis. This histology is most noticeable in the first low power field, subjacent to the renal capsule. The entire renal cortex is similarly affected. The urothelium of the pelvic system is unremarkable. Interstitial hemorrhage is also seen in the right and left kidney blocks in the atrophic cortical areas. Section of the prostate gland demonstrates unremarkable prepubescent prostatic parenchyma with prostatic urethra and vas deferentia lumen observable. Section of the bladder wall demonstrates unremarkable urothelium and bladder muscle development. A mild cystitis is present.

Reticuloendothelial System: Sections of thymus demonstrate good cortico-medullary thymic development. Hassall's corpuscles are seen within the medullary components. Abundant tingible body macrophages are also seen scattered throughout the thymus gland. Sections of the spleen demonstrate intact splenic capsule. There is markedly congested red pulp and remnants of white pulp follicles. Section of the discoloration of the splenic capsule reveals an intact, attenuated splenic capsule with hemorrhage into the red pulp region, suggestive of recent partial splenic hemorrhagic infarction. Venous thrombotic material in hilar vessels is identified. Sections of vertebral and rib bone marrow demonstrate trilineage marrow with maturation. Growth plate at the rib appears normal.

Endocrine System: The thyroid gland, with appropriate development of colloid follicles is identified, as is parathyroid tissue. Sections of the adrenal demonstrate appropriate development of the cortex and medullary components. Focal adrenal hemorrhage and necrosis is present. Adrenal vasculature is congested. Sections of the pituitary gland demonstrate unremarkable anterior and posterior pituitary. Bone marrow is normocellular, left shifted, trilinear (erythroid, granulocytic, megakaryocytic) with maturation.

Middle Ear: No lesion identified.

Musculo-Skeletal System: Sections of diaphragmatic and skeletal muscle demonstrate no myopathic or neurogenic pathology.

LOCATION
NEONATE INTEN CARE B

PAGE 12

(Continued) PATIENT

SPEC: 00: [REDACTED]

MICROSCOPIC EXAMINATION (Continued)

Thromboses in Superior Vena Cava: Sections of the superior vena cava demonstrate well-formed thrombus which is organized into the venous wall of the superior vena cava. This thrombus has multiple laminations, as well as what appears to be a canaliculization through it. At its disrupted attachment to the venous wall, venous wall fibroplasia is identified. The thrombus itself occupies the main extent of the vena caval lumen. However, it does not totally obliterate the lumen. The thrombus is composed of abundant fibrin material, intermixed with inflammatory cells. The periphery of the thrombus has particles of recent thrombotic material, composed of fibrin, red blood cells and inflammatory cells which appear capable of shedding into the circulatory system. Within a single portion of the thrombus, there are small cavitory spaces, occupied by bacterial cocci. Examination of several additional sections of the superior vena caval wall demonstrates the thrombus being organized into the caval wall. This organization of thrombus into the caval wall takes the form of granulation and inflammatory tissue, disrupting the entire extent of the caval wall thickness. Bacterial cocci colonies are additionally seen multifocally within the thrombus material.

Thromboses in Celiac and Mesenteric Vessels: Cross sections of the celiac axis reveal partial portions of the arterial wall which are entirely unassociated in a thrombotic material. Cross section and submission of the entire mesenteric tissue, including vessels, reveals the presence of thromboembolic type material within several of the arterial lumens. In particular, there is foreign, pigmented, suture-type material identified within the arterial lumen in the mesenteric sections. This material is usually associated with fibrinous material and inflammatory cells, indicative of a recent thrombotic event. Proceeding proximal to distal in the mesenteric tissue, multiple venous thrombotic foci are seen multifocally within venous vessels. Some of these are free-floating within luminal aspects, some are attached to the venous wall. The majority of these venous fibrin thrombi appear to be of recent onset and most likely are a secondary event and not the primary event leading to necrotic bowel. Additionally, there is thromboemboli material identified within arterial lumen, some of which are also associated with the vessel wall. Examination of the entirely-submitted mesenteric tissue reveals every single section demonstrating multiple venous and arterial vessels affected by partial luminal occlusion by thrombus and thromboembolic event. Small bowel associated with these mesenteric sections shows wall pneumatosis and full thickness necrosis of NEC.

Rec'd & Typed [REDACTED]

LOCATION
NEONATE INTEN CARE B

(Continued) PATIENT: [REDACTED]

SPEC#: 00: [REDACTED]

FINAL SUMMARY

There was no anatomic evidence at the time of autopsy to suggest Beckwith-Wiedemann syndrome, which might be suspected because of the clinical history of a birth weight at term of 4100 gm, with associated neonatal hypoglycemia. A forme fruste variant of the syndrome cannot be excluded with certainty.

The pigment within intrapulmonary macrophages is interpreted as being primarily meconium, which correlates with the perinatal history of maternal pre-eclampsia and HELLP syndrome, C-section and meconium. No unequivocal evidence of pulmonary arteriolar hypertensive changes were recognized.

The persistent neonatal hypoglycemia was associated with diffuse pancreatic islet cell nucleomegaly and hyperchromasia. A "focal lesion" of islet cells was not found.

The catheter in the right jugular superior vena cava system was associated with an organizing firmly attached, 90% obstructing propagating mural thrombus containing colonies of cocci and associated with perivenous inflammation and fibroplasia. This thrombus could be a source of pulmonary emboli. Paradoxical systemic arterial emboli could theoretically occur only if elevated right heart pressure were present to allow a right to left shunt through the valve-competent foramen ovale. The thromboembolic material present in a few arterioles in the liver, peripancreatic area, and mesentery could have arisen in situ from unidentified sources in the systemic circulation or paradoxically from the jugular thrombus.

An unequivocal anatomic cause for the necrotizing enterocolitis was not demonstrated. The extensive enterocolitis involved segments supplied by the celiac, superior mesenteric and inferior mesenteric arteries. No thrombi, emboli or other lesions were found in those arteries or their major branches; or in the abdominal aorta; or in the inferior vena cava, splenic, superior mesenteric, or portal veins. The majority of the vascular lesions in microscopic sections of the mesentery are interpreted as being the result of (not the cause of) the necrotizing enterocolitis. Complications of the necrotizing enterocolitis led to pneumatosis; perforation; peritonitis; sepsis; the acute pulmonary, hepatic, splenic and renal lesions; and to death.

LOCATION
NEONATE INTEN CARE B

PAGE 14

(Continued) PATIENT: [REDACTED]

SPEC: 00 [REDACTED]

GROSS BRAIN DX-MICRO PEND

The fresh brain weighs 425.5/460 gm, and is evaluated to be within normal limits. External examination reveals intact leptomeninges with no subarachnoid blood identified. The gyral pattern is age-appropriate and fully-developed. No areas of polymicrogyria or other cortical lesions are identified externally.

The frontal, temporal, parietal and occipital regions of the cortex are all evaluated to be normal on external examination. Examination of the basal structures reveals the presence of all cranial nerves, appropriate development and relationships of all basal vessels in the circle of Willis, including the basilar and vertebral arteries. No midline herniations of the cerebellar tonsils are identified. The brainstem, including pons and olivary structures are identified. Cerebellar development is age-appropriate.

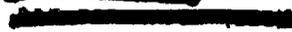
The brain is sectioned in coronal sections, with the cut surface demonstrating no gross abnormality. The periventricular white matter demonstrates no lesions. The cortical ribbons is of appropriate thickness, and throughout its extent demonstrates no cortical necrosis. No lesions of the basal ganglia or hippocampus are identified. The calcarine cortex is unremarkable.

The brainstem is sectioned, starting at the level of the medulla and red nucleus. Sectioning the brainstem from superior to inferior demonstrates no lesion of the grey or white matter. The aqueduct is patent. The cerebellar folia and nuclei are unremarkable.

The spinal cord is sectioned in the transverse plane, with the sectioned surface revealing no lesion.

Section Code:

1. Left hippocampus
2. Left parietal cortex
3. Brainstem and spinalcord



LOCATION
NEONATE INTEN CARE B

(Continued) PATIENT

APPC# 00

MICRO. BRAIN DESCRIPTION

Sections of the hippocampus from the left hemisphere demonstrate good preservation of pyramidal neurons within Ammon's horn, CA-4 and CA-3. However, pyramidal neurons within sections CA-2, CA-1 and the subiculum, all demonstrate early pyknotic nuclei, indicative of either hypoglycemic or hypoxic change. The cytoplasm of these associated cells is collapsed around the nucleus. Several small collections of mature lymphocytes are seen within the brain substance and adjacent to the ependyma in a paraventricular fashion. Very recent thrombotic material is seen within the luminal aspect of multiple vessels. Neuronal migration patterns appear to be age-appropriate.

Sections of the left cerebral cortex demonstrate normal neuronal layering, intact leptomeninges, and no lesions are identified.

Sections of the brainstem demonstrate periventricular ependymal rests at the level of the olive in the medulla. Sections of the lower brainstem and spinal cord demonstrate no abnormality.

Signed

