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Sudden Unexpected Unexplained Death in Infants*

A Comparative Clinicopathologic Study

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Plötzlicher, unerwarteter und ungeklärter Tod im Säuglingsalter

Eine vergleichende klinisch-pathologische Studie

Zusammenfassung. Makroskopische und mikroskopische Autopsiebefunde von 32 plötzlichen, unerwarteten und ungeklärten Todesfällen im Säuglingsalter (SUUD, „Krippentod")[1]. werden verglichen mit 1. 7 Fällen, bei denen sich morphologisch keine Todesursache fand, obwohl alarmierende klinische Symptome beobachtet worden waren (MUD, morphologisch ungeklärter Tod) und 2. 74 Fällen, bei denen die Todesursache autoptisch gesichert war [8 Kinder dieser Gruppe waren plötzlich und unerwartet gestorben (SUED), und 66 Kinder mit schweren klinischen Symptomen dienten als Kontrollen].

Laryngotracheitis war am häufigsten bei Krippentod (SUUD). Histologisch fanden sich keine Unterschiede zu den Infektionen der oberen Atemwege in den anderen Gruppen. Bronchitis, herdförmige Pankreatitis und geringgradige Pyelonephritis kamen ebenfalls als Primärinfektionen in Frage. Ähnliche Befunde wurden jedoch auch in Kontrollfällen mit anderer Todesursache erhoben.

Der Krippentod (SUUD) kann wahrscheinlich zu jeder beliebigen Zeit im Ablauf einer Infektion, besonders der oberen Atemwege, auftreten. Dafürd srechen die klinischen Vorgeschichten einiger Krippentodesfälle (SUUD) sowie einiger Fälle von morphologisch ungeklärtem Tod (MUD) und außerdem morphologische Veränderungen in der Milz, der Schilddrüse und der Nebennierenrinde.

Nach unseren Befunden müssen 2 Faktoren zusammentreffen, um den Krippentod auszulösen: 1. eine Infektion, gewöhnlich der oberen Atemwege, und 2. eine Disposition, z.B. als Folge einer Frühgeburt, oder Auslösemechanismen wie irritierende Hautschäden, Trauma oder Schmerz. Der Todesmechanismus scheint unabhängig von der auslösenden Krankheit zu sein. Die typischen Befunde des Endstadiums, hämorrhagisches Lungenödem und petechiale Schleimhautblutungen, finden sich auch bei tödlichen Krankheiten bekannter Ursache, wie Encephalitis oder Sepsis.

Summary. Gross and histologic findings at autopsy in 32 cases of sudden unexpected unexplained death (SUUD) in infants were compared with autopsy findings in (1) 7 cases in which alarming clinical symptoms had been observed but no cause of death was found pathologically (morphologically unexplained death, MUD) and (2) 74 cases in which the cause

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1. The abbreviations correspond to the English expression.

of death was clearly established [8 cases of sudden unexpected explained death (SUED) and 66 control cases]. Laryngotracheitis was found most often in SUUD cases but did not differ histologically from the upper respiratory infections in the other categories. Other infections in SUUD which may be considered primary were bronchitis, focal pancreatitis, and mild pyelonephritis. Similar lesions were also found in control cases in which death was due to unrelated causes. The history in some SUUD and MUD cases and the morphologic changes in the spleen, thyroid gland, and adrenal gland indicated that unexpected unexplained death may occur at any time during the course of an upper respiratory or other type of infection. Our findings suggest that 2 factors have to combine to initiate the lethal episode: (1) an infection, usually of the upper respiratory tract, and (2) a predisposing condition or a trigger mechanism such as irritating skin lesions, trauma, or pain. The final common pathway appeared to be independent of the underlying disease. The characteristic findings of the terminal episode — hemorrhagic pulmonary edema and petechial hemorrhages — may also be part of a known fatal disease such as encephalitis or sepsis.

Apparently healthy infants may die suddenly and unexpectedly. In some cases nothing can be found at autopsy to explain the cause and mechanism of death. Usually, these infants are between 2 weeks and 6 months old, and this phenomenon occurs more frequently in boys than in girls. The infants are usually found lying face down in the crib with brownish or pinkish foamy fluid running from their mouth and nose.

Among the more commonly reported autopsy findings are (1) frothy fluid and mucoid exudate in the upper part of the respiratory tract; (2) cloudy exudate in the middle ear; (3) hemorrhagic pulmonary edema; (4) petechial hemorrhages in the thymus and under the epicardium and pleura; and (5) severe acute passive congestion. Microscopic and microbiologic studies add little to these findings.

Theories on the cause of sudden unexpected unexplained death (SUUD), also called "crib death" or "cot death", have been based on postmortem findings (Werne and Garrow, 1953) or on bacteriologic (Arey and Sotos, 1956; Farber, 1934), virologic (Balduzzi and Greendyke, 1966; Gold, 1966; Valdes-Dapena and Hummeler, 1963), immunologic (Spain and co-workers, 1954; Valdes-Dapena and co-workers, 1963), epidemiologic (Carpenter and Shaddick, 1965; Coe and Hartman, 1960; Peterson, 1966), or experimental studies (Dawes, 1966; Handforth, 1959; Müller, 1963), or on combinations of these (Adelson and Kinney, 1956; Cooke and Welch, 1964). The problem is still unsolved. Therefore, we have attempted to reevaluate the significance of the gross and histologic findings at autopsy in SUUD by comparing them with the findings in cases in which (1) alarming clinical symptoms had been observed and no cause of death was found pathologically or (2) the cause of death was clearly established.

Material and Methods

Case Material and Definitions

These cases occurred in residents of Olmsted County, Minnesota, during a 20-year period from 1946 through 1965. They were described in an epidemiologic study on SUUD in this community, to be published elsewhere (Fitzgibbons, J. P., Jr., Nobrega, F. T., Ludwig, J., Kurland, L. T., and Harris, L. E., manuscript in preparation). Four categories were established (consisting of 32 cases of sudden unexpected unexplained death, 7 cases of morphologically unexplained death, 8 cases of sudden unexpected explained death, and 66 control cases).

1. Sudden unexpected unexplained death (SUUD). In the 32 cases, no cause could be found, clinically or pathologically, to explain the death of these infants. In this study, sudden unexpected death was defined as described by ADELSON and KINNEY (1956): "The death of a child who was thought to be in good health or whose terminal illness appeared to be so mild that the possibility of a fatal outcome was not anticipated." There were 18 boys and 14 girls. The age range was 2 weeks to 10 months, but only 2 were more than 6 months old (7 and 10 months, respectively).

2. Morphologically unexplained death (MUD). In 7 cases the clinical history revealed that the death was by no means sudden or unexpected. These infants had had alarming symptoms, of 1 day to 3 weeks' duration, which caused the parents to call the physician or bring the infant to the hospital emergency room. Although the cause of death was suspected clinically, no pathologic evidence of a cause could be found. The 7 infants (3 boys and 4 girls) were $2^1/_2$ to $11^1/_4$ months old.

3. Sudden unexpected explained death (SUED). In 8 cases, autopsy protocols and histologic findings clearly established the cause of death (Table 1). However, these cases differed from the control cases in that the death was sudden and unexpected. This group included 3 boys and 5 girls of ages ranging from 2 weeks to 6 months.

4. Control cases. For comparison, 66 cases (36 boys and 30 girls) were studied. In these cases the cause of death was apparent clinically and pathologically (Table 1). The age range in this group was 2 weeks to 12 months.

Table 1. *Causes of death in sudden unexpected explained death* (SUED) *and control cases*

Disease category	SUED (no.)	Control cases (no.)
Respiratory tract infections	1[a]	19
Congenital heart disease	3	10
Other congenital malformations (including central nervous system)	1	11
Inflammatory diseases of central nervous system	1[b]	8
Accidents; trauma	0	2
Gastrointestinal tract disease	1	6
Miscellaneous (birth injury, malignant tumor, renal vein thrombosis, etc.)	0	6
Septicemia	1[c]	4
Total	8	66

[a] Bronchopneumonia.
[b] *Toxoplasma* encephalitis.
[c] Secondary to otitis media.

Autopsy Studies

A complete autopsy examination was performed in all cases except 11 of the control group in which removal of the brain was not permitted. The autopsies were performed on unembalmed bodies within 24 hours after death. We did not inflate the lungs prior to sectioning.

An average of 25 tissue blocks and various wet tissues were available in each case. All tissues were fixed in 10% formalin and were stained with hematoxylin and eosin. Sudan IV, Brown's Gram stain, Gomori's reticulum stain, and Giemsa's stain were used when indicated.

All tissue sections of all cases, including the control cases, were studied by one of us (J.L.) without any other information. The histologic descriptions and diagnoses were later supplemented by the gross findings listed in the pathologic anatomic diagnoses and the autopsy protocols.

The standards of reference for body weight and recumbent length were taken from the anthropometric charts compiled by the Harvard School of Public Health (Stuart and associates). The limits of normal of the thymic and splenic weights of all infants were judged by the appropriate standards suggested by Sunderman and Boerner (1949) and Schulz and associates (1962).

Microbiologic Studies

Limited bacteriologic studies were carried out on various tissues in some cases. These included cultures of lung (28 cases), upper respiratory tract (4 cases), heart blood (25 cases), central nervous system (11 cases), intestinal contents (7 cases), spleen (5 cases), liver (2 cases), thymus (1 case), kidney (1 case), and urine (1 case).

Limited virologic studies were done on lung (6 cases), blood (2 cases), bowel content (2 cases), and brain (1 case).

Results

Clinical Data in Morphologically Unexplained Death (MUD)

Two infants had had loose stools or diarrhea and vomiting for 10 days and 3 weeks, respectively. The 5 other infants had had respiratory infection with running nose, coughing, pulmonary rhonchi, and rales for 1 to 3 days, in 2 cases complicated by convulsions, vomiting, and cyanosis. Terminally, gasping respiration was noted. All 5 of these infants had temperatures between 102 and 108 F. Septicemia was suspected in 3 of these infants. In 1 case, 2 siblings in the family had measles.

Comparison of Pathologic Findings

In this comparison, congestive changes will not be considered.

Weights and Lengths. Table 2 shows the percentages of cases with abnormal weights and recumbent lengths. In about one fourth of the SUUD cases and about one half of the control cases the infants were below the 10th percentile.

Table 2. *Abnormal weight and recumbent length*

Category	Weight					Length				
	Cases with available data	Below 10th percentile		Above 90th percentile		Cases with available data	Below 10th percentile		Above 90th percentile	
		No.	%	No.	%		No.	%	No.	%
SUUD	27	6	22	3	11	29	8	28	2	7
MUD	4	2	50	0	—	4	2	50	0	—
SUED	4	1	25	1	25	6	2	33	0	—
Control cases	50	27	54	5	10	52	23	44	3	6

Serosal Surfaces, Upper and Lower Respiratory Tracts, and Middle Ear. Table 3 shows that mucus and frothy hemorrhagic fluid in the tracheobronchial tree and around the mouth were found 3 to 4 times more often in unexplained death

Table 3. *Characteristic findings involving upper and lower respiratory tracts and serosal surfaces*

Findings	SUUD		MUD		SUED		Control	
	No.	%	No.	%	No.	%	No.	%
Frothy fluid and mucus in upper respiratory tract and around mouth and nostrils; perioral and perinasal crusts	17/32[a]	53	5/7	71	2/8	25	8/66	12
Epiglottitis, laryngitis, and tracheitis (microscopically only)	18/23	78	2/3	67	3/4	75	16/27	59
Bronchitis	8/32	25	0/7	0	1/8	13	21/66	32
"Typical" SUUD findings[b] in lung	21/32	66	3/7	43	4/7[c]	57	19/35[c]	54
Petechial hemorrhages in pleura, thymus capsule, and pericardium (Tardieu's spots)	20/23	87	2/7	29	1/8	13	13/66	20
Total cases	32		7		8		66	

[a] Denominator indicates number of cases in which information was available.
[b] See text.
[c] But without bronchopneumonia.

(SUUD and MUD) than in explained death. Frothy fluid and mucoid exudate running from the nose and mouth usually seemed to represent a mixture of pulmonary edema fluid and mucus from hyperactive laryngeal and probably nasopharyngeal glands. In many cases, brownish stomach content was also present.

Aphthae in the mouth and pharynx and cloudy exudate in the middle ear were found in one case each. There were no SUUD cases with evidence of aspiration.

Epiglottitis, laryngitis, and tracheitis were found in 18 of 23 SUUD cases. Infiltrates consisting of lymphocytes, plasma cells, histiocytes, and a few polymorphonuclear leukocytes were found in the epithelial and subepithelial layers and between the seromucous or mucoserous glands. In 3 cases a follicular laryngitis and epiglottitis was found (Fig. 1). Occasionally, small regions of necrosis were present in the edematous stroma of the larynx (Fig. 2). Distended, apparently hyperactive, mucus-producing glands were another characteristic finding. There were no ulcerations or inflammatory membranes. Edema and hyalinization of the basement membranes were frequently present, in some cases even in the absence of significant inflammatory infiltrates.

The laryngotracheitis in the other categories was similar in type except that there were occasionally denser and more widespread inflammatory infiltrates or follicles between deep laryngeal glands.

The pulmonary changes of the SUUD cases were characterized by edema with patchy intra-alveolar hemorrhages and phagocytic pneumocytes in the alveoli, focal alveolar distention ("focal emphysema"), and atelectasis. The interalveolar septa were slender in the overdistended regions and appeared broadened and hypercellular in some regions with edema and hemorrhages. The interlobular septa were edematous. The septal lymphatic vessels were markedly dilated. The lymph was

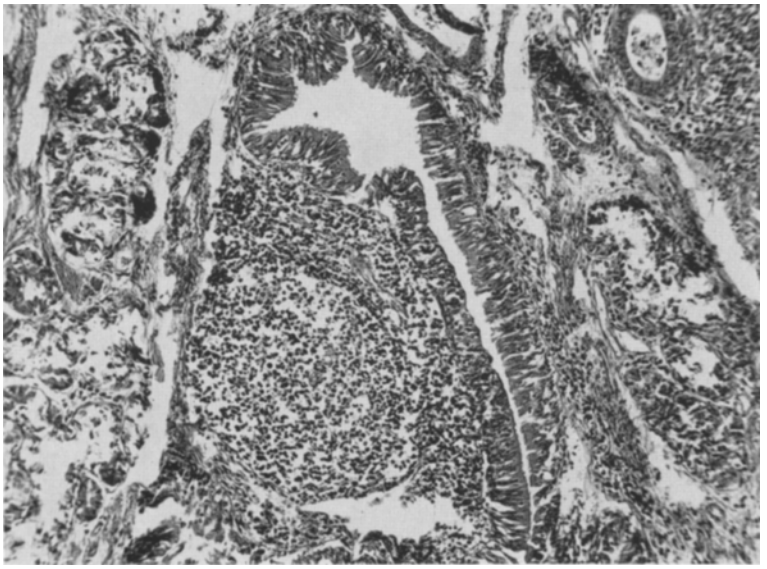

Fig. 1. Follicular laryngitis with predominantly lymphocyte and plasma cell infiltrate between laryngeal glands. Numerous lymph follicles were present. SUUD in 7-month-old girl with history of repeated colds. (Hematoxylin and eosin; × 95)

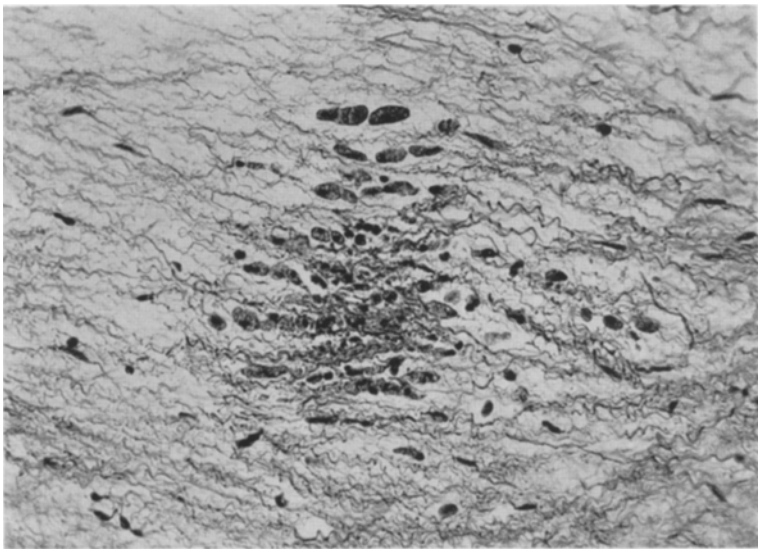

Fig. 2. Laryngitis with laryngeal edema and focal necrosis with cluster of large macrophages. SUUD in $6^1/_2$-week-old girl with no history of respiratory infection. (Hematoxylin and eosin; × 110)

hemorrhagic in various degrees. Inflammatory cells were scarce except around small bronchi in 8 SUUD cases in which they formed small cuffs. Bronchi and bronchioli were usually filled with hemorrhagic edema fluid.

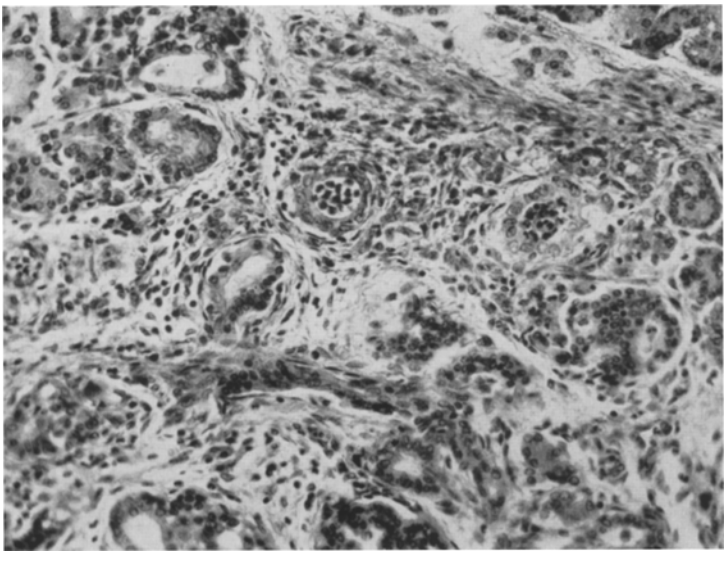

Fig. 3. Focal interstitial and intratubular purulent pancreatitis. SUUD in 2-month-old boy with 5-day history of coughing. (Hematoxylin and eosin; × 225)

We called these pulmonary changes "*typical*" (Table 3). They were found in $^2/_3$ of our SUUD cases and in the majority of SUUD cases described by other authors (Adelson and Kinney, 1956; Cooke and Welch, 1964). One third of our SUUD cases had only slight pulmonary congestion with or without edema. The "typical" pulmonary changes of SUUD were also found in more than half of the SUED and control cases.

Gastrointestinal Tract. Only 1 MUD case had histologic evidence of a mild gastroenteritis. Mucosal hemorrhages were found in 1 SUUD case and in 1 MUD case.

Liver. Inflammatory infiltrates in the portal fields were found in 25% of the SUUD cases and in 11 to 14% of the cases in the other categories. Hemosiderosis in hepatic and Kupffer cells was more frequent in SUUD (19%) and MUD cases (14%) than in control cases (8%). No hemosiderosis was present in SUED cases.

Extramedullary hematopoiesis, marked Kupffer cell proliferation, scattered hepatic cell necrosis, and mild intrahepatic bile stasis were found in some SUUD, MUD, and control cases but not in any SUED case. Fatty changes of the liver were present in some instances in all 4 categories. Congestion of blood and lymph vessels was a frequent finding in SUUD and SUED.

Pancreas. In 1 SUUD case, in which there had been a mild cold with coughing for 5 days before death, a focal and partly purulent pancreatitis was found (Fig. 3). The remainder of the gland was normal.

Lymph Nodes. In all 4 groups there were cases in which lymph nodes were enlarged and inflammatory. These nodes came from various sites. They are known to reflect mainly changes in their tributary regions. Therefore, no detailed comparison of the morphologic findings will be presented.

Spleen. The spleen weight was greater than normal in 4 of 30 SUUD cases (13%), in no MUD case, in 1 of 6 SUED cases (17%), and in 5 of 52 control cases (10%). Spleen weights below normal were only found in 1 of 6 MUD cases (17%) and 4 of 52 control cases (8%). Dilatation and engorgement of the sinuses occurred to various degrees in all 4 categories. The variation in numbers and types of pulpar cells was not significant enough to permit a comparison of the 4 groups. Other morphologic findings are listed in Table 4.

Table 4. *Morphologic findings in spleen*

Findings	SUUD		MUD		SUED		Control	
	No.	%	No.	%	No.	%	No.	%
Small and ill-defined primary and no or few secondary follicles	21	66	3	43	5	62	36	54
Large primary and secondary follicles without necrosis and without large central reticular cells	7	22	0	—	1	13	14	21
Follicular necrosis	2	6	1	14	2	25	9	14
Secondary follicles with large central reticular cells resembling epithelioid cells	2	6	3	43	0	—	7	11
Pulpal hemorrhages	10	31	3	43	1	13	13	20
Hemosiderosis	15	47	2	29	4	50	19	29
Extramedullary hematopoiesis	1	3	0	—	0	—	2	3
Total cases	32		7		8		66	

Thymus. In 6 of 18 SUUD cases (33%) the thymus weighed between 45 and 50 gm; normal for the first 9 months of life, according to Sunderman and Boerner (1949), is 6.05 to 34.10 gm. In the MUD group, no thymus weight more than 23 gm was recorded. In 1 SUED case (3-month-old girl with volvulus and gangrene of the ileum and lower jejunum) the thymus weighed 40 gm. None of the control cases had a thymus weight more than 30 gm. A thymus weight of less than 6.05 gm was recorded in 3 control cases.

The main morphologic findings in the thymus are listed in Table 5. In addition, interlobular edema, congestion, and interlobular inflammatory infiltrates were found in 3 SUUD cases, intermingled with numerous eosinophilic leukocytes in one of them. Calcifications were found in 1 MUD case.

Kidneys. Peripelvic and interstitial parenchymal round cell infiltrates were found in all 4 categories, including 4 SUUD cases. In another SUUD case, autopsy revealed hemorrhagic pulmonary edema and stenosis of the left ureteropelvic junction with moderate hydronephrosis and mild pyelonephritis, but, in our opinion, these lesions alone could not have caused the death of the infant.

In 1 SUUD case (2-month-old boy), 2 foci of cytomegalic inclusion body infection were found in the left kidney (Fig. 4). The autopsy also revealed a few

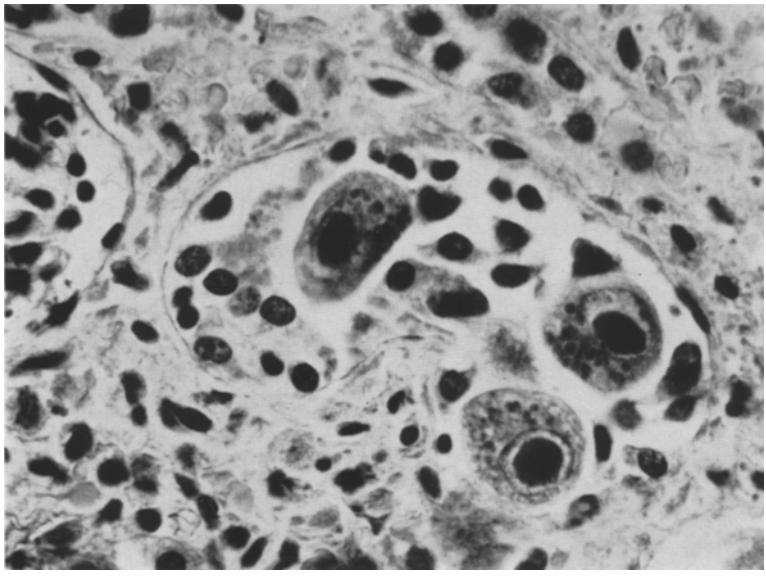

Fig. 4. Focus of cytomegalic inclusion body infection in left kidney. SUUD in 2-month-old boy with 3-day history of mild cold. (Hematoxylin and eosin; × 540)

Table 5. *Morphologic findings in thymus*

Findings	SUUD		MUD		SUED		Control	
	No.	%	No.	%	No.	%	No.	%
Cortical and medullary hemorrhages	20	65	3	43	4	67	9	20
Increase in number of large cortical reticular cells	8	26	1	14	1	17	10	23
Cortical lymphocytic depletion	1	3	2	29	1	17	24	55
Total with abnormal findings	25/31[a]	81	5/7	71	6/6	100	36/44	82

[a] Denominator indicates number of cases which were studied.

patchy intra-alveolar pulmonary hemorrhages with interstitial round cell infiltrates. There were no other signs of cytomegalic inclusion body disease. There were no such cases in the other 3 groups.

Congestion, intraglomerular hemorrhages, all grades of subcapsular congenital glomerulosclerosis (HEPTINSTALL, 1966), and focal tubular calcification were found in all 4 categories.

Adrenals. Minimal lipid depletion in segments of the cortex was found in 4 of 32 SUUD cases (13%). These cases showed also an early pseudotubular transformation in the zona glomerulosa and band-like zones with dark cortical cells and pyknotic nuclei in the zona fasciculata (Fig. 5). Cortical lipid depletion was also found in 1 MUD and in 1 SUED case. Lipid depletion (with or without

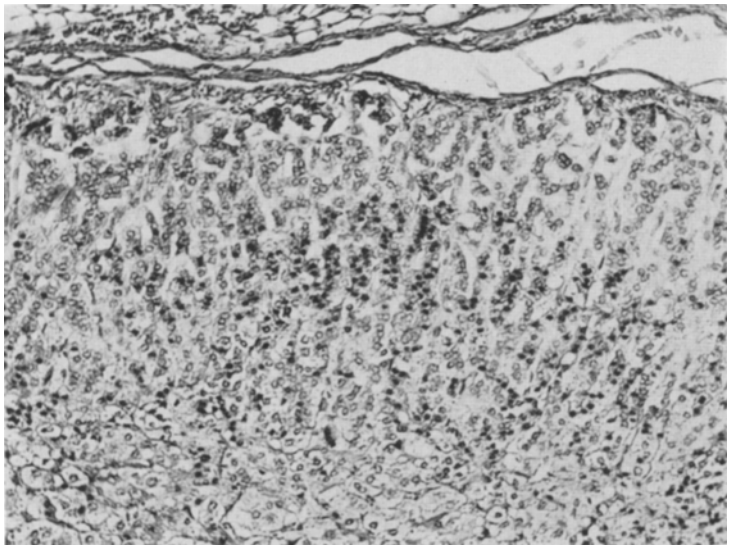

Fig. 5. Adrenal cortex with mild lipid depletion, early pseudotubular transformation of zona glomerulosa, and band-like zones of pyknotic nuclei and necrosis in zona fasciculata. SUUD in 2-month-old boy with history of recent recovery from respiratory infection. (Hematoxylin and eosin; × 140)

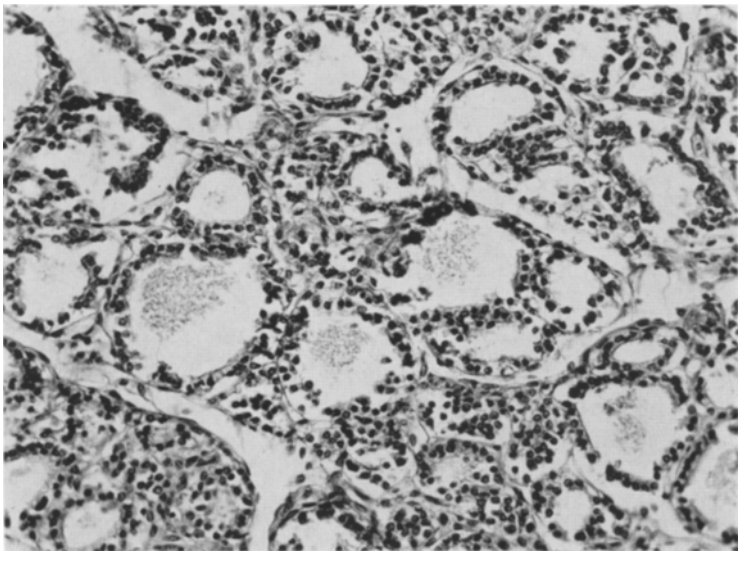

Fig. 6. Thyroid with colloid depletion and collapse of vesicles. SUUD in 1-month-old boy who had severe diaper dermatitis. (Hematoxylin and eosin; × 200)

pseudotubular transformation), focal pyknosis, and necrosis were found in about 1/3 of the control cases. Adrenal hemorrhages were present in 1 SUUD case (left side only) and 5 control cases.

Thyroid Gland. The thyroid gland was studied in 16 SUUD and 3 MUD cases. In 6 SUUD cases and 1 MUD case, colloid depletion of the thyroid with or without collapse of vesicles was found (Fig. 6). Interstitial inflammatory infiltrates were present in the thyroid gland in another SUUD case. Seven thyroid glands in the MUD and SUED groups were normal. Marked colloid loss was found in only 1 control thyroid gland, and focal inflammatory infiltrates were found in another.

Skin. In 5 SUUD cases (16%), skin lesions were found which were described as diaper rash, excoriations of the scrotum and buttocks, erythema, and pyoderma of the lower abdominal and diaper areas. No such lesions were found in the MUD, SUED, and control groups. The skin lesions were not available for histologic study.

Microbiologic Findings. The results from the limited number of specimens from SUUD and MUD cases submitted for microbiologic studies were not of significance in any instance.

Discussion

The upper part of the respiratory tract was the most frequent site of infection in SUUD. This is in agreement with results of other studies (Adelson and Kinney, 1956; Coe and Hartman, 1960; Segard and Koneman, 1968; Werne and Garrow, 1953). Other possibly significant infections were bronchitis, gastroenteritis, pancreatitis, pyelonephritis, and cytomegalic inclusion body disease. The histologic changes in these cases were mild. Furthermore, there was a coexisting upper respiratory infection, so the significance of these lesions was difficult to evaluate. Gastroenteritis may be a complication of respiratory infections. Similarly, focal pancreatitis was found in 1 SUUD case and also in control cases with bronchopneumonia, purulent otitis media, and congenital tracheoesophageal fistula.

Evidence of mild and focal pyelonephritis was also present in the SUUD cases reported by Cooke and Welch (1964) although less frequently (4%, compared to 16% in our series). We did not think that the focal pyelonephritis alone could have caused the death of these infants.

Histologic evidence of a virus infection was found in only 1 SUUD case, but the significance of the 2 foci of cytomegalic inclusion body infection in this case remains doubtful. Other authors (Balduzzi and Greendyke, 1966; Valdes-Dapena and Hummeler, 1963) also have had only slight success in demonstrating virus infections.

Shaw (1968) recently suggested that nasal obstruction in infants with upper respiratory infections may cause apnea and fatal asphyxia. Shaw found that, when the nares of newborns were gently occluded, some of these infants struggled violently to reestablish nasal breathing. Not all seemed to be able to breathe through their mouths, and laryngospasm appeared to occur during their violent efforts. Asphyxia would explain most of the morphologic findings in SUUD. Unfortunately, the nasal cavity is usually poorly studied at autopsy. In the few cases of SUUD in which the infant was under observation when it died, failure to breathe through the mouth was not noticed (Gold, 1968; Werne and Garrow, 1953). However, if SUUD results from different causes or a combination of events

(Gold, 1968), nasal obstruction might be an important factor particularly because it would be amenable to prophylactic measures.

Beckwith and Bergman (1967) also postulated that SUUD may be caused by various interrelated factors, such as upper respiratory infections, sleep, and constitutional autonomic reactivity. None of these factors alone would initiate the lethal episode. Infection would merely act as a trigger mechanism (Adelson and Kinney, 1956). A similar effect might result from the irritation of a diaper rash, which we found in 5 of our SUUD cases, or trauma and pain as we found in 2 other cases[2]. Other predisposing factors have been suggested, such as subnormal weight and prematurity (Coe and Hartman, 1960) and hypogammaglobulinemia (Spain et al., 1954).

Adelson and Kinney (1956) discussed the possibility that the "typical" pulmonary changes in SUUD represent a preinflammatory state, and that these infants might be incapable of producing frank pneumonia. We found that the pulmonary changes in SUUD were indistinguishable from similar changes in control cases, particularly those with central nervous system diseases such as leptomeningitis, *Toxoplasma* encephalitis, subdural hygroma secondary to birth trauma, and fracture of the skull. The "typical" hemorrhagic pulmonary edema was also found after strangulation, sepsis, gastrointestinal disorders, and atresia of the tricuspid valve.

We examined, as "unknowns", typical lung sections of 16 SUUD cases, 1 SUED case, and 15 control cases to determine whether or not the lungs of the SUUD cases could be differentiated from those of the other groups. It was not possible to do this. The lung sections of 8 SUUD cases and 7 control cases were classified incorrectly.

Thus, the hemorrhagic pulmonary edema seemed to reflect the mode of dying — sudden circulatory failure — rather than the underlying disease. The same holds true for the congestive changes which we found in all SUUD cases.

Petechial hemorrhages (Tardieu's spots) in the chest organs were the most characteristic changes in SUUD (Table 3). They were more than 4 times as frequent as in the control cases. It is our opinion that they must be intimately related to the mode of dying in SUUD. In the control cases with petechial hemorrhages, meningitis, *Toxoplasma* encephalitis, trauma to the head, strangulation, sepsis, congenital heart disease, bronchopneumonia, mucoviscidosis, or neuroblastoma was also present.

The changes in the thymus, spleen, and adrenal gland seemed to reflect mainly the varying severity and duration of the underlying infection. Thus, in the thymus, cortical lymphocytic depletion was found in more than half of the control cases and in only 1 SUUD case. The increase in number of large reticular cells in all 4 categories gave a starry-sky appearance to the cortex of the thymus. This might indicate increased activity (Stowens, 1966).

The thymus weight was greater than normal in about 1/5 of our SUUD cases. However, in view of the normal histologic appearance, these organs should probably be regarded as normal.

2. One infant had suffered for 1 day from a very painful abrasion of the cornea; the other infant was found at autopsy to have had numerous bruises and abrasions of the skin.

Reactive changes in the adrenal gland, probably secondary to an infection, were mild lipid depletion, increased dark cortical cells and pyknotic cortical cells (particularly in the zona fasciculata), and early pseudotubular transformation (DHOM, 1965). However, these changes were early and it was often difficult to distinguish between normal and abnormal.

Unaltered splenic follicles, large secondary follicles, follicular necrosis, and follicles with large central reticular cells resembling epithelioid cells occur at various stages of infections (ALBERTINI, 1936). The follicular changes supported the clinical impression that SUUD may occur at any time during the course of an infectious disease. Indeed, it is not rare for SUUD cases to include a history of improvement or apparent recovery from a previous infectious disease. This was found in 4 of our SUUD cases and 1 MUD case. Other authors (COOKE and WELCH, 1964) have made similar observations. This also suggested that infection is unlikely to be the only cause of SUUD.

More than 1/3 of our SUUD cases showed a colloid depletion of the thyroid follicles. This seemed to be a fairly characteristic finding in SUUD and could not be explained by the normal difference in maturation between central and peripheral follicles (KISSANE and SMITH, 1967). WERNE and GARROW (1953) made a similar observation. The significance of the finding remains unknown.

GEERTINGER (1967) considered fusion of thymus and parathyroid glands to be important in SUUD. We had no such case in our series. On the other hand, during the last 6 months we have seen this phenomenon in 3 children (1 month, 2 years, and 4 years of age) in whom the cause of death was known. There were no histologic signs of rickets or other metabolic bone diseases among our SUUD and MUD cases.

TOWBIN (1967) observed spinal epidural hemorrhages in 4 SUUD cases. We had no such case.

The numbers of patients in the MUD and SUED groups are insufficient for detailed comparisons. However, the existence of cases intermediate between SUUD and control cases showed that SUUD cannot be altogether separated from other categories.

We suggest the following hypothetic conclusion. SUUD in infants is the result of an infectious disease, usually of the upper respiratory tract, which may be complicated by a latent virus infection, gastrointestinal disorder, pyelonephritis, or other disease. The lethal episode may be initiated when infections coincide with certain predisposing factors — for example, factors related to sleep, subnormal weight, or prematurity — or trigger mechanisms such as nasal obstruction, excessive irritation from a diaper dermatitis, trauma, or pain. The coincidence of an infection with a predisposing condition or trigger mechanism may lead to the final common pathway. This terminal episode may occur at any time during the course of the disease.

The final common pathway described by BECKWITH and BERGMAN (1967) appears to be independent of the underlying disease. The manner of death in some SUED cases is probably the same as in SUUD cases. Severe hemorrhagic pulmonary edema and petechial hemorrhages in the chest seem to be manifestations of the final common pathway. They were found in some instances in all categories.

This mechanism of death might also be part of a known fatal disease such as encephalitis or some types of congenital heart disease.

The mechanism of the final common pathway is unknown and probably cannot be clarified by morphologic means (autonomous reactivity?).

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