s

PETITIONER'S EXHIBIT #82

Pediatric and Developmental Pathology 6, 142–155, 2003
DOI: 10.1007/s10024-002-0016-y

Incidence of Autopsy Findings in Unexpected Deaths of Children and Adolescents

DAVID M. PARHAM,[1,2,5*] VAN H. SAVELL,[1,2] CHARLES P. KOKES,[1,2,3] STEPHEN A. ERICKSON,[2,3] FRANK J. PERETTI,[2,3] JAMES B. GIBSON,[1,4,5] AND WILLIAM Q. STURNER[1,2,3]

[1]Department of Pediatric Pathology, Slot 820, Arkansas Children's Hospital, 800 Marshall Street, Little Rock, AR 72202, USA
[2]Department of Pathology, University of Arkansas for Medical Sciences, 4301 West Markham, Little Rock, AR 72205, USA
[3]Office of the Medical Examiner, Arkansas State Crime Laboratory, 3 Natural Resources Drive, Little Rock, AR 72215, USA
[4]Department of Genetics, Arkansas Children's Hospital, 800 Marshall Street, Little Rock, AR 72202, USA
[5]Department of Pediatrics, University of Arkansas for Medical Sciences, 4301 West Markham, Little Rock, AR 72205, USA

Received January 30, 2002; accepted March 30, 2002; published online December 17, 2002.

ABSTRACT

Studies in various settings reveal that a significant percentage of autopsies demonstrate findings that were not previously clinically diagnosed. In the pediatric and adolescent age group, forensic examinations comprise a large percentage of total autopsies performed. We hypothesized that a similar number of previously undiagnosed findings would be present in this population and thus reviewed a series of autopsy reports from the Medical Examiners Office in the Arkansas Crime Laboratory. During 1997 through 1999, we performed 439 complete forensic autopsies on children and adolescents (age range 1 day to 19 years; median 18 months). Previously undiagnosed lesions were found in 173 (39%). Of these subjects, 68 (39%) had clinically significant pathology, 60 (35%) had insignificant pathology, and 45 (26%) had pathology of undetermined significance. Thirty-six subjects had lesions expected from a previously diagnosed condition. Of the total number of lesions found, 168 were inflammatory, 58 were congenital anomalies (48 unexpected), and 88 comprised miscellaneous other conditions. Infants < 6 months of age were significantly more likely to have a previously undiagnosed lesion than children > 6 months ($P < 0.0001$). Previously undiagnosed findings, mostly inflammatory, occur relatively frequently in pediatric and adolescent forensic autopsies and are more likely to occur in infants.

Key words: autopsy, forensic medicine, infant, pathology, pediatrics, sudden infant death

INTRODUCTION

A striking decline in autopsy rates has occurred during the past several decades [1,2]. Reasons perceived for this decline include the availability of new imaging technology and laboratory testing that obviates the need for additional studies, the possibility of postmortem findings that confirm malpractice culpability, and the need to limit burgeoning medical expenditures that threaten hospital budgets. Public perceptions about the distaste-

This work was presented in part at the Interim Meeting of the Society for Pediatric Pathology, Vancouver, British Columbia, Canada, September 2000.
*Corresponding author, e-mail: parhamdavidm@uams.edu

ful aspects of autopsies were heightened by the recent Alder-Hey controversy, which surrounded highly questionable practices involving organ retention [3].

In spite of such perceptions and technological advances, the autopsy has retained its preeminence as a learning tool and quality assurance instrument [4–6]. Previously undiagnosed autopsy findings continue to be recognized at a high rate in various settings that include pediatric oncology wards [7], adult medical-surgical units [8], general hospitals [9], and adult vascular surgery wards [10]. A high discordance rate still exists between premortem and postmortem cancer diagnoses [11]. Some authors have questioned the validity of these assertions, as there is an obvious selection bias towards postmortem examination of cases with diagnostic uncertainty [12], whereas overall diagnostic accuracy has improved [13]. Nevertheless, the autopsy continues to be an integral component of clinical research, teaching, and improved patient care [6].

In contrast to the decline in hospital autopsies, pediatric and adolescent postmortem examinations performed by medical examiners have increased in some areas, particularly when communication among investigating agencies improves [14–16]. Pediatric and adolescent cases present a particular challenge to clinical forensic medicine, as the premortem diagnosis of child abuse can be difficult [17] and significant underreporting persists [18]. Suffocation cases, which generally mimic sudden infant death syndrome (SIDS), pose particular challenges [19]. Although it remains an elusive entity, the incidence of SIDS has declined as forensic investigators uncover more definitive reasons for infantile demise [20] and as the public acts upon "back-to-sleep" education programs [21,22]. The investigation of accidental childhood death plays a key role in recall of dangerous products and education of parents and teachers about child safety [23]. Genetic causes for sudden childhood demise abound and often present as rather subtle lesions at autopsy, yet their discovery may prevent future recurrences leading to additional parental grief and financial burdening [24]. For all of these reasons, pediatric and adolescent autopsies have attained prominence in medicolegal death investigation.

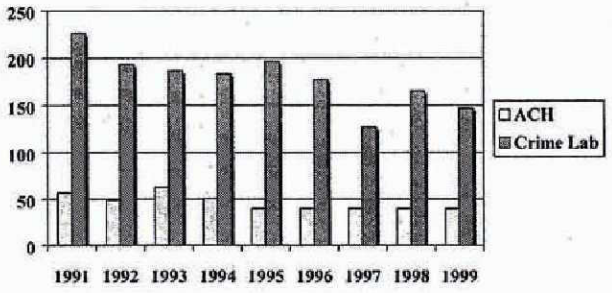


Figure 1. Incidence of pediatric autopsies in Arkansas, comparing number per year for the Arkansas Crime Laboratory (Crime Lab) and Arkansas Children's Hospital (ACH).

Our medical center has witnessed a decline in autopsy numbers similar to those seen nationwide. During the past decade, however, in-house pediatric and adolescent autopsies have reached a plateau, whereas those performed at forensic centers have declined (Fig. 1). Nevertheless, forensic pediatric and adolescent autopsies have consistently exceeded hospital autopsies. We hypothesized that forensic pediatric and adolescent autopsies would show an incidence of previously undiagnosed findings similar to those seen in other settings, as described above. Our results indicate that this is particularly true for infant deaths, and they likewise confirm the potential value of training at a forensic center for pathology residents and pediatric pathology fellows. Our findings also underscore the value of close consultation between pathologists trained in forensic medicine and those trained in pediatrics.

METHODS

During January 1997 through December 1999, 439 complete forensic autopsies on children and adolescents (age range 1 day to 19 years; median 18 months) were performed at the Medical Examiner's Office in the Arkansas State Crime Laboratory by forensic pathologists. These cases were the subject of a retrospective review that included all files with complete autopsy reports, excluding those with only skeletal remains. All cases involving unexpected deaths included bacteriological, toxicological, and postmortem chemical studies, as per a standard protocol [25]. Other studies such as neuropathology, radiology, and consultation with pediatric pathologists were performed as appropri-

Table 1. Indications for postmortem forensic examination

Indication	Age range	Number of cases
Sudden unexplained infant death	0–8 months	186
Gunshot wounds	4–19 years	92
Unexplained demise from presumed natural causes[a]	0–18 years	48
Child abuse/physical trauma	2 months–18 years	37
Drowning/submersion	11 months–18 years	19
Burns/smoke inhalation	8 months–8 years	12
Vehicular accident	0–18 years	12
Stab wounds	11–18 years	9
Hanging	10–18 years	7
Intoxication	2–18 years	7
Birth complications, including stillborn and premature infants	0–1 wk	7
Electrocution	8–18 years	3
Total	0–19 years	439

[a]Deaths with no evidence of foul play.

ate. Postmortem radiographs and photographs were routinely obtained. Retrospective review of histologic sections was performed on selected cases with unusual findings. In general, these deaths occurred outside of the hospital setting, except for cases that might have been dead on arrival or survived for a brief time after admission. Usually the latter were potential child abuse cases.

The categorical indications for postmortem examination are listed on Table 1. Of note is the large proportion of cases with sudden unexplained infant death or gunshot wounds, the former affecting very young children by definition and the latter usually affecting adolescents. Because the Medical Examiner's Office at the Arkansas Crime Laboratory functions as a referral office for the state coroner system, not all cases from every category, such as accidental fatalities, are submitted for autopsy.

In our review of the cases, we subdivided anatomic findings into four major categories: A) previously undiagnosed findings that were deemed to be of medical significance; B) those without serious medical significance; C) those of uncertain significance; and D) findings that were expected for a previously diagnosed medical condition. We used the following definitions for these findings: Significant lesions were those that we felt caused substantial morbidity and contributed to the subject's demise; insignificant lesions were those that we felt had minimal morbidity and did not contribute to demise; uncertain lesions were those in which the degree of morbidity and its contribution to demise was unclear, based on the available information. We also subdivided the findings into three major etiologies: 1) inflammatory lesions (usually of an infectious nature); 2) congenital anomalies; and 3) a miscellaneous category not easily included in the other two. Because of the possibility of one child having multiple lesions, the numbers documented in these categories exceed the total number of subjects.

RESULTS

Of the 439 pediatric and adolescent forensic autopsies, 173 (39%) revealed previously undiagnosed lesions. Sixty-eight of the 173 (39%) autopsies revealed significant lesions, and 59 (34%) of these noted lesions that were directly related to the demise of the subject. Sixty of the 173 (35%) had clinically insignificant lesions, and 45 (26%) had lesions that were judged to be of indeterminate significance. In contrast, only 36 of the 439 autopsies (8%) revealed lesions expected from a previously diagnosed medical condition, as listed in Table 2.

Inflammatory lesions comprised the largest category of previously undiagnosed lesions and

Table 2. Autopsy findings in subjects with previously diagnosed conditions

Case no.	Cause of death	Expected finding(s)	Unexpected findings
1	Acute narcotic intoxication	Hemorrhagic gastritis; pneumonia, early; splenic fibrosis, focal	
2	Airway obstruction with asphyxia	Down syndrome with associated findings	
3	Aspiration pneumonia secondary to malnutrition	Pneumonia	
4	Blunt trauma, head (twin)	Pneumonia	
5	Blunt trauma, head (twin)	Pneumonia	
6	Blunt trauma, head	Fractures, rib and arm; bronchopneumonia	
7	Blunt trauma, head	Pneumonia; hypoxic lesions	
8	Blunt trauma, head, recent	Healing fractures, arm and chest; pneumonia; thymic involution	
9	Bronchopneumonia	Epidural hematoma; cerebral edema; skull fracture	
10	Child abuse	Subdural hematoma; small bowel scarring/blood	
11	Congenital heart disease	ASD; hypertrophy; PDA; pneumonia	
12	Dehydration, hypothermia	Aortic thrombosis	Meckel diverticulum
13	Drowning	Absent corpus callosum	
14	Empyema	Down syndrome with associated findings, including glomerular cysts	Hepatic fibrosis and cholestasis; myositis and necrotizing fasciitis, epigastrium; empyema
15	Fungal pneumonia secondary to idiopathic immunodeficiency	Thymic atrophy; fungal pneumonia	Chronic myocarditis; accessory spleen; hepatic-steatosis, mild; cerebral calcification
16	GSW	Pneumonia	
17	Hanging	Hypoxic lesions in various organs	
18	Hanging	Pneumonia	
19	Hydrocephalus	Hydrocephalus; talipes	
20	Ischemic encephalopathy	Polygyria; intraventricular hemorrhage	Splenomegaly
21	Seizure-related apnea	Contusions; superficial injuries	
22	Suffocation, hyperthermia	Aspiration pneumonia, mild	
23	Trauma to head	Pneumonia; retroperitoneal abscess	
24	Trauma to head	Pneumonia	
25	Trauma to head	Bronchopneumonia; gliosis	
26	Trauma to head	Pyloric stenosis repair	
27	Trauma to head	Generalized hypoxic lesions	
28	Trauma to head (twin)	Pneumonia	
29	Trauma to head (twin)	Pneumonia	
30	Trauma to head	Fractures, rib and arm; bronchopneumonia	
31	Trauma to head	Pneumonia; hypoxic lesions	

(continued)

Table 2. *(Continued)*

Case no.	Cause of death	Expected finding(s)	Unexpected findings
32	Trauma to head	Healing fractures, arm and chest; pneumonia; thymic involution	
33	Trauma to head	Sagittal craniosynososis repair	Subacute myocarditis
34	Trauma to neck, with quadriplegia	Pneumonia	
35	Undetermined	Bronchiolitis; myocardial necrosis; cerebral anoxic lesions; acute tubular necrosis	
36	Undetermined	Hypoxic lesions, diffuse (3 d post-cardiac arrest)	

ASD, atrial septal defect; PDA, patent ductus arteriosus; GSW, gunshot wound.

were found in 168 instances. Ninety-nine of these 168 lesions were solitary, whereas the remainder affected multiple organs. Of the 168 lesions, 65 appearing to be clinically significant were found in 45 subjects, as listed in Table 3. The insignificant lesions primarily consisted of the usual catarrhal inflammation of an upper respiratory condition (Fig. 2); these were deemed significant if associated with lesions in other critical sites, such as the lungs (Fig. 3). The tracheopulmonary system was the most common site for significant previously undiagnosed inflammatory lesions, as might be expected. Of note was the relatively high number of myocardial lesions that represented either active myocarditis or old, fibrotic lesions with varying degrees of chronic inflammation (Fig. 4). Leptomeningitis and hepatitis were other recurring inflammatory conditions of interest.

Previously undiagnosed congenital anomalies were found in 48 instances and were primarily of an insignificant or indeterminate nature, as listed in Table 4. Significant previously undiagnosed anomalies were found in nine instances and comprised one example of cystic renal dysplasia and eight various cardiovascular lesions, including a dysfunctional prosthesis secondary to repair of a congenitally malformed mitral valve. We included the dysfunctional valvular prosthesis in the congenital category, as the original, expected lesion was congenital in nature. Note that cardiovascular lesions were the most common previously undiagnosed congenital abnormalities, a finding that should be of particular importance to pediatric cardiologists. Previously diagnosed anomalies included hydrocephalus (three cases), Down syndrome (two cases), synostosis, and absent corpus callosum (one case each).

The final category, miscellaneous lesions, comprised an eclectic group of 88 diverse conditions that included hepatic steatosis, cysts, neoplasms, ischemic/anoxic lesions, hemorrhagic lesions, noninflammatory hemodynamic lesions, and undiagnosed traumatic lesions. These are listed in Table 5. Note the presence of some rather unusual lesions seen in forensic practice, such as acute lymphoblastic leukemia and acute glottic edema. The glottic edema was caused by apparent anaphylaxis and was not due to intubation attempts. Cases of hepatic steatosis were of particular interest because of the association of this lesion with metabolic diseases that cause sudden death (Fig. 5). In our cases, the causes of death associated with steatosis were unexplained (five cases), cardiomyopathy, drowning, fungal pneumonia, myocarditis, seizure-related apnea, and SIDS (one case each); metabolic studies performed on two cases were negative. Of note is that no death in this series was caused by previously unrecognized trauma, e.g., a lacerated liver or head injury.

Finally, we compared the likelihood of finding previously undiagnosed lesions in infants < 6 months of age vs. older children. This age was chosen because of the probability of clinical diagnosis of lesions at routine well-baby examinations. A chi-square table is found in Table 6. Computation of significance using a two-sided relative devi-

Table 3. Significant inflammatory lesions

Case no.	Age	Cause of death	Other previously undiagnosed findings
1	3 y	Adrenal hemorrhage (enterococcus isolated from blood)	Asplenia syndrome; congenital heart disease
2	3 m	Adrenal hypoplasia (combined weight 1.5 g)	Aspiration pneumonia
3	1 m	Appendicitis, acute	Peritonitis
4	13 y	Asthma	
5	4 m	Bronchiolitis	Malrotation
6	5 m	Bronchiolitis (*Hemophilus influenzae* isolated from ear)	
7	3 m	Bronchiolitis	Atrial septal defect
8	8 m	Bronchiolitis	Laryngitis, acute; hydrocephalus
9	6 m	Bronchitis	
10	2 m	Bronchitis, acute and chronic (*Streptococcus mitis* isolated from blood)	Otitis media
11	2 m	Bronchopneumonia (staphylococci and streptococci isolated from lungs and blood)	Epiglottitis
12	2 m	Bronchopneumonia	
13	4 m	Bronchopneumonia	
14	3 m	Bronchopneumonia (*Hemophilus influenzae* isolated from lung)	Lymphadenitis
15	1 m	Bronchopneumonia	
16	2 m	Bronchopneumonia, acute; chronic bronchitis; prematurity	
17	3 m	Bronchopneumonia, acute (*H. influenzae* isolated from lung)	Thymic involution; laryngotracheitis, lymphocytic
18	9 y	Diabetic ketoacidosis	Fungal tonsillitis; acute pancreatitis with insulitis
19	17 y	Dilated cardiomyopathy, with old myocarditis	
20	8 y	Electrocution	Chronic lymphocytic thyroiditis; hepatitis; bronchiectasis, focal
21	3 m	Empyema	Down syndrome; hepatic fibrosis and cholestasis; myositis and necrotizing fasciitis, epigastrium
22	10 y	Endocarditis	Bicuspid aortic valve; fenestrated right coronary ostium; pneumonia
23	17 y	Hypertrophic cardiomyopathy, associated with old myocarditis	
24	16 y	Hypertrophic cardiomyopathy, associated with old myocarditis	Pleural effusions; pneumonia
25	6 m	Laryngotracheobronchitis, lymphocytic	Reflux esophagitis; left otitis media
26	1 m	Meningitis (Salmonella isolated from cerebrospinal fluid and blood)	Pulmonary fibrin clots
27	13 y	Meningitis, acute	Otitis media; adrenal hemorrhage
28	11 y	Meningitis, acute; adrenal hemorrhage	Sinusitis, mucopurulent
29	2 m	Metabolic disease?	Hepatic steatosis; bronchitis; myocardial vacuolization (fat?)
30	17 m	Myocarditis	

(continued)

Table 3. *(Continued)*

Case no.	Age	Cause of death	Other previously undiagnosed findings
31	4 m	Myocarditis	Steatosis
32	18 y	Myocarditis, acute	
33	14 y	Myocarditis, healed	
34	9 m	Myocarditis, lymphocytic	Bronchiolitis
35	6 m	Pneumonia	Aspiration; macrosomia
36	3 m	Pneumonia	
37	1 y	Pneumonia	Otitis media
38	2 m	Pneumonia	Patent ductus arteriosus
39	5 m	Pneumonitis	Otitis media
40	3 m	Pneumonitis	
41	15 y	Pulmonary hemorrhage; bronchitis; abscesses (secondary to Job syndrome)	Fasciitis, eosinophilic
42	3 m	Undetermined	Hydroceles, bilateral; chronic aspiration pneumonitis
43	5 m	Undetermined	Granulomatous inflammation, lungs and liver
44	3 m	Undetermined	Alveolitis
45	2 m	Undetermined	Cleft palate; bronchopneumonia

m, months; y, years.

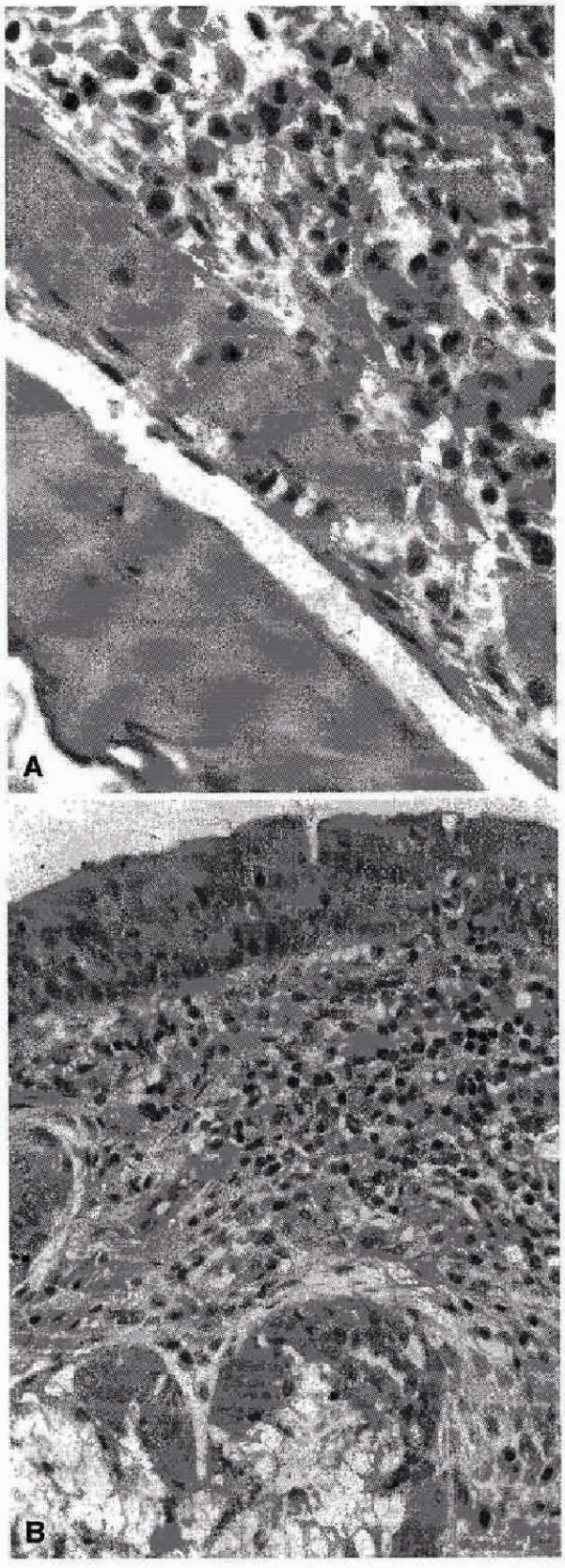
ate test yielded a P value of < 0.0001, indicating that there is a significantly greater chance of discovering previously undiagnosed lesions in infants < 6 months of age. Of these infantile deaths, 68 were certified as undetermined and 58 as SIDS. Table 7 compares the unexpected lesions found in infants vs. those found in older children.

DISCUSSION

Previously undiagnosed lesions occur at a significant rate in most published autopsy series [26], and postmortem findings continue to offer the ultimate means for quality assurance in medical care [5]. In the main, these observations have proceeded from hospital studies and have included a variety of pediatric and adult specialties. It was our goal in the current review to test whether a substantial number of significant previously undiagnosed findings might occur in a pediatric and adolescent forensic series. Our results indicate that autopsies performed on children dying unexpectedly yield a surprisingly high rate of significant and otherwise undetected lesions, particularly in infants. Specifically, we note that infectious/inflammatory lesions are commonly found in forensic autopsies of children (particularly younger ones), that congenital heart lesions are surprisingly frequent but other congenital lesions are usually insignificant, and that a wide array of other findings of varying clinical significance occur in children and adolescents who are autopsied in a forensic setting.

As in other series [9], inflammatory/infectious lesions constituted the single most common category in our autopsy population. This observation should not be surprising, given the tendency of young children to acquire infections in the community. However a large percentage of these lesions, mostly pneumonias, were clinically significant in our series. Pneumonias have also been identified as the most common immediate cause of

Figure 2. Insignificant lesions. **A.** Otitis media, with infiltrate of neutrophils and mononuclear cells in mucosa adjacent to ossicle. **B.** Associated chronic laryngitis, with mononuclear cell infiltrate in submucosal and mucus secretions in adjacent glands.



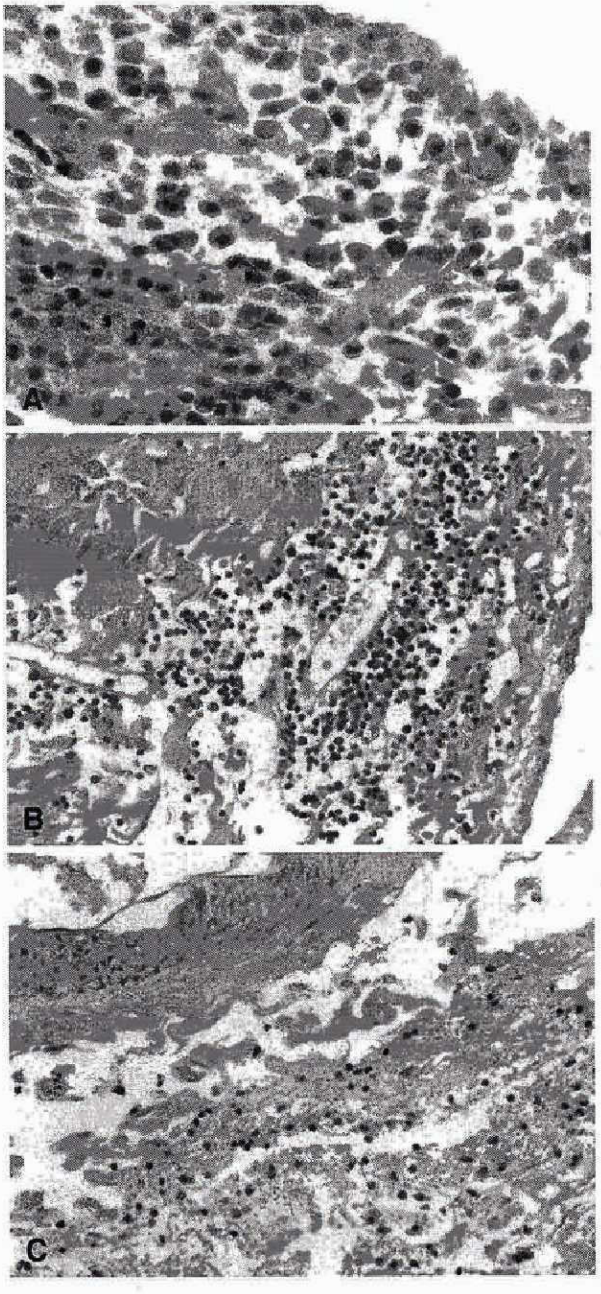


Figure 3. Significant lesions. **A.** Otitis media with infiltrate of mononuclear cells and granulocytes in mucosa adjacent to attenuated epithelial surface. **B.** Associated pachymeningitis, with infiltrate of lymphocytes in dura mater. **C.** Associated leptomeningitis, with infiltrate of mononuclear cells and fibrin adjacent to basilar artery.

death in one large series of neonatal autopsies [27]. Of particular note in our inflammatory/infectious category are several cases of active and healing forms of myocarditis, a well-known cause of unexpected death [28]. This condition can be caused by either infectious or allergic etiologies and cannot be reliably diagnosed without histologic examination. Old, fibrotic myocardial disease presents a diagnostic challenge, as it may be due to either

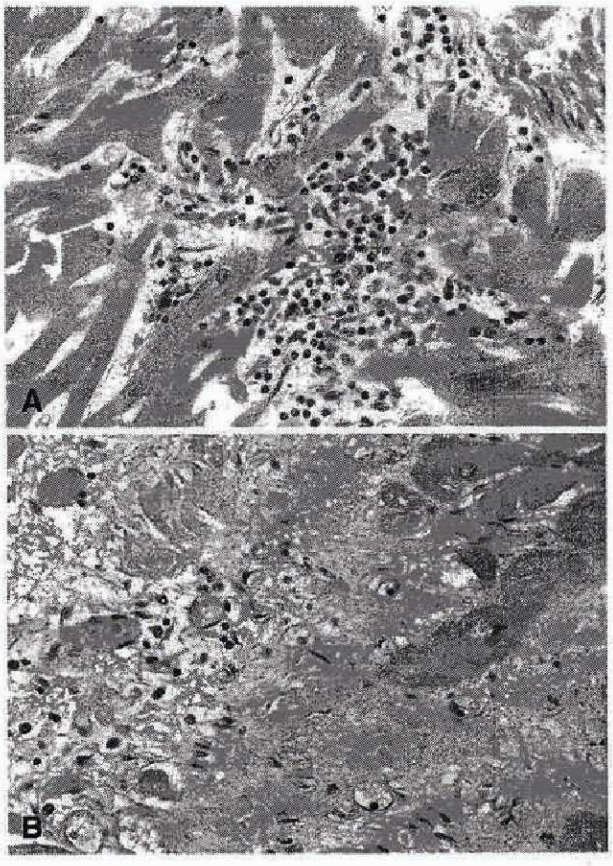


Figure 4. Myocarditis. **A.** Active lesion, with focal interstitial lymphocytic infiltrate in myocardium. **B.** Old lesion, with fibrosis, sparse lymphocytic infiltrate, and loss of myocytes.

prior myocarditis or possible genetic causes, e.g., arrhymogenic right ventricular dysplasia or familial hypertrophic cardiomyopathy. Tissue sampling renders other problems with the diagnosis of myocarditis, because the frequent occurrence of focal myocardial inflammation in patients with ischemic, genetic, and even no apparent clinical disease dictates caution in its interpretation [28].

Cardiovascular disease also figures prominently in our category of previously undiagnosed congenital anomalies. The young ages of many of these subjects suggests a possible role of ductus arteriosus closure in their precipitous demise [29]. One of our subjects had a previously diagnosed and repaired mitral valve lesion, with demise secondary to mechanical failure of the valve replacement. An autopsy study of patients dying in an adult vascular surgery ward [10] yielded a high rate of missed clinical diagnoses, reinforcing the importance of postmortem examination in cardiovascular surgery patients of all ages.

Cardiovascular lesions also occur as a result of metabolic or genetic errors, as seen in a small proportion of our findings in this category. Hypertrophic cardiomyopathy often results from muta-

Table 4. Previously undiagnosed congenital anomalies

Cardiovascular system
Atrial septal defect (4 cases)
Patent ductus arteriosus (4 cases)
Double right coronary artery
Hypoplastic right coronary artery
Aneurysm of ductus arteriosus
Anomalous coronary arteries
Aortic coarctation
Bicuspid aortic valve with a fenestrated coronary ostium
Asplenia syndrome
Hypoplastic left heart syndrome
Hemorrhagic cerebral arteriovenous malformation
Pulmonary venous stenosis with pulmonary lymphangiectasia
Dysfunctioning prothesis secondary to repair of a congenitally malformed mitral valve
Gastrointestinal system
Umbilical hernia (2 cases)
Meckel diverticulum (2 cases)
Cleft palate
Intestinal malrotation
Atrophic pancreas (by weight)
Genitourinary system
Hydrocele (4 cases)
Absent testicle
Hypoplastic kidney
Hydronephrosis
Cystic renal dysplasia
Lymphatic system
Accessory spleen (8 cases)
Heterotopic thymus
Thymic hypoplasia
Skeletomuscular system and soft tissue
Choristoma
Unilateral hip dysplasia
Hemangioma
Central nervous system
Polymicrogyria

Table 5. Miscellaneous lesions

Lesions	Probable etiologies
Ischemic/anoxic lesions (10 cases)	Undetermined (3 cases); birth/pregnancy complications (3 cases); head trauma (3 cases); hanging (1 case)
Hemorrhagic lesions (10 cases)	
Intracranial (7 cases)	Birth trauma (2 cases); ischemic encephalopathy; arteriovenous malformation; child abuse (2 cases); blunt trauma
Hepatic (1 case)	Birth trauma
Adrenal (2 cases)	Asplenia syndrome with sepsis; acute meningitis
Neoplasms (3 cases)	
Adrenal cortical adenoma	
Gastric leiomyoma	
Acute lymphoblastic leukemia	
Respiratory system	
Prematurity (unaerated lungs; 7 cases)	
Serous effusions/adhesion (4 cases)	Previous pneumonia vs. trauma
Pulmonary edema	Undetermined
Aspiration of gastric contents	
Alveolar hemosiderosis	Undetermined
Pulmonary arterial fibroplasia	Bronchopulmonary dysplasia
Glottic edema	Anaphylaxis (presumed)
Bronchial muscular hyperplasia	Undetermined
Gastrointestinal system	
Pyloric stenosis	
Intussusception	
Neonatal icterus	
Cholelithiasis	
Hepatic fibrosis and cholestasis	Down syndrome
Hepatic glycogenation and fibrosis	Undetermined (metabolic?)
Hepatic steatosis (7 cases)	Undetermined (6 cases—metabolic studies negative in 2); myocarditis (1 case)
Cardiovascular system	
Isolated right ventricular hypertrophy (2 cases)	Undetermined (1 case); bronchopulmonary dysplasia (1 case)
Aortic thrombosis	Dehydration
Hypertrophic cardiomyopathy and atherosclerosis	Idiopathic hypertrophic cardiomyopathy
Dilated/hypertrophic cardiomyopathy (5 cases)	Myocarditis, old, vs. idiopathic cardiomyopathy
Noninflammatory coronary thrombosis	Undetermined
Central nervous system	
Cerebral calcification	Immunodeficiency
Cerebral edema	Child abuse
Cerebral contusions	Abuse; blunt trauma
Lymphatic system	
Thymic involution (6 cases)	Infection (2 cases); undetermined (4 cases)
Splenomegaly	Undetermined
Splenic fibrosis	Drug abuse

(continued)

Table 5. (*Continued*)

Lesions	Probable etiologies
Musculoskeletal system and soft tissues	
Healed fractures (2 cases)	Child abuse
Macrosomia	Undetermined
Diffuse interstitial fibrosis of soft tissues and viscera	Undetermined
Muscular atrophy	Undetermined
Genitourinary system	
Hydronephrosis	Undetermined
Ovarian cysts	
Endocrine system	
Adrenal hypoplasia (2 cases; combined weights of each case; 1.5 g/4.8 g mean expected)	Undetermined
Islet cell hyperplasia (2 cases)	Maternal diabetes mellitus (1 case); presumed infantile diabetes mellitus (1 case; vitreous glucose = 289 mg/dL)
Ovarian hypoplasia	Undetermined
Uterine hypoplasia	Encephalitis, old
Absence of secondary sex characteristics in an adolescent	Encephalitis, old

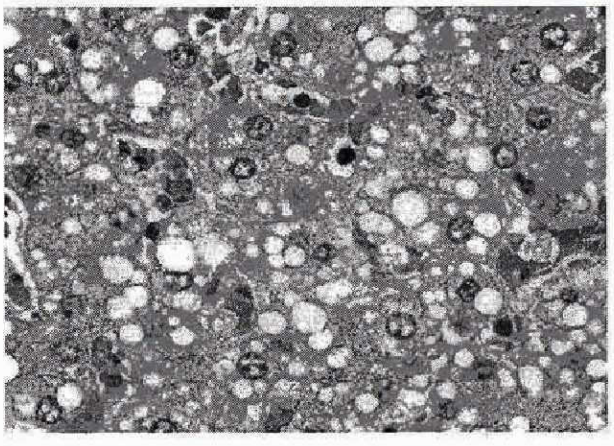


Figure 5. Hepatic steatosis, with prominent vacuolization of hepatocytes.

Table 6. Age vs. previously undiagnosed lesions*

Age (months)	Number of subjects	Number with lesions
< 6	196	113
> 6	243	60
Total	439	173

*$P < 0.0001$.

tions in genes encoding myofibrillary contractile proteins and leads to sudden death in a significant proportion of affected patients [28]. Mutations affecting cardiac ion channels result in the prolonged Q-T syndrome, which predisposes to fatal arrhythmias during exertion, particularly drowning [30]. Recent data indicate a role for this lesion in some cases of SIDS [31]. Our single case of coronary thrombosis may have resulted from a hypercoagulability syndrome [32]. Alternatively, Kawasaki disease has been known to cause this lesion and lead to sudden death [33], although there was no evidence of vasculitis in our example.

Metabolic diseases in general cause a significant proportion of unexpected childhood deaths. In one tandem mass spectroscopy study of 7058 putative SIDS cases [34], blood samples of 66 subjects suggested metabolic lesions, most commonly involving acyl-CoA dehydrogenase enzymes. The presence of hepatic steatosis in a number of our cases suggests a similar disorder, but the finding is nonspecific [29]. Postmortem metabolic studies performed on selected cases showed no evidence of a fatty acid oxidation disorder. Nevertheless, fatty acid oxidation defects are known to account for a

Table 7. Previously undiagnosed lesions found in infants vs. those found in older children and adolescents

Lesions in infants	Lesions in older children and adolescents
Chorioamnionitis, placental infarct (stillborns)	Hepatic glycogenation and fibrosis
Anoxic lesions	Splenomegaly
Congenital heart disease	Hepatic steatosis
Birth trauma-related lesions	Cerebral calcification
Meningitis	Accessory spleen
Aspiration	Pneumonia
Pneumonia	Child abuse-related injuries
Hepatitis	Asplenia
Hepatic steatosis	Congenital heart disease
Glottic edema	Myocarditis
Appendicitis	Cystic renal disease
Otitis media	Dilated/hypertrophic cardiomyopathy
Laryngotracheitis and epiglottitis	Hepatitis
Accessory spleens	Thyroiditis, lymphocytic
Pancreatic islet hyperplasia	Pancreatitis
Heterotopic thymus	Meningitis
Choristoma	Pleural adhesions
Gastroesophagitis	Leiomyoma
Acute lymphoblastic leukemia	Arteriovenous malformation
Hydroceles	Cholelithiasis
Empyema	Splenic fibrosis
Sialadenitis	Gastritis
Intestinal malrotation	Crohn ileitus
Hypoplasia of various organs	Adrenal cortical adenoma
Hydronephrosis	Meckel diverticulum
Congenital hip dysplasia	Granulomatous inflammation
Cardiomegaly	
Umbilical hernia	
Intussusception	
Bronchopulmonary dysplasia	
Pulmonary hemosiderosis	
Hydrocephalus	

substantial proportion of sudden deaths in infants [24,35–37].

We were intrigued by one case with a diffuse fibrosis affecting the interstices of multiple organs. This finding has previously been described in a patient with renal dysplasia and situs inversus totalis [38]. However, it occurred as an isolated phenomenon in our case.

Intraalveolar hemosiderosis, noted in one of our cases, has been described as a marker for previous suffocation [39], and pulmonary hemorrhage is observed in infants dying from presumed overlaying or smothering [40]. Accidental suffocation and purposeful smothering doubtlessly comprise a portion of SIDS cases. However, use of alveolar hemorrhage as a sole marker of upper airway obstruction in infants is controversial [19]. Nevertheless, recent data by Delaney et al. [41,42] indicate that high pulmonary hemosiderin scores suggest a cause of death other than SIDS.

Infantile autopsies in general are more apt to contain previously undiagnosed lesions, as illus-

trated by Table 6. To some degree, this reflects the fact that older children die more frequently from trauma, so that incidental lesions are apt to be rare. On the other hand, previously undiagnosed lesions more often tend to be the cause of death in young infants, as routine well-baby examinations do not generally occur until 6 months of age and unexpected perinatal, genetic, inflammatory, and congenital lesions would more likely occur in this age group. Table 7 compares the pathologic findings in these two major groups and confirms the relative frequency of these diseases in the younger group.

Pediatric neoplasms constituted an infrequent finding in our cases, as contrasted with adult autopsy series [11]. We found one malignant lesion (acute lymphoblastic leukemia) and two benign ones (adrenal cortical adenoma and gastric leiomyoma). Sudden deaths due to undiagnosed brain tumors appear to be decreasing in incidence, possibly due to improvements in imaging techniques [43].

In summary, a review of consecutive pediatric and adolescent forensic autopsies over a 3-year period revealed a high rate of previously undiagnosed and otherwise undetected pathological findings of variable significance. Infections/inflammatory lesions comprised the most common category of lesions in this series, with many clinically significant, whereas others were discovered only after microscopic examination. Of equal importance in this exercise was the collaboration established between pediatric and forensic pathologists in the recognition and evaluation of a variety of disease processes. It is hoped that studies of this kind may also prove helpful in bringing relevant data to clinicians in order to enhance diagnoses and improve the care of subsequent patients. Finally, as noted by Hanzlick and Parrish [15], forensic pediatric autopsies play a critical role in epidemiology, and their value in pediatric teaching and research underscores the importance of a good working relationship between forensic and pediatric pathologists [44].

ACKNOWLEDGMENTS

The authors are grateful to the administrative, investigational, and secretarial staffs at the Arkansas State Crime Laboratory and the Medical Examiner's Office, especially Rick Gallagher, Stephen Dillon, James Overton, Pat Calhoun, and Glenda Carr.

REFERENCES

1. AMA Council on Scientific Affairs. Autopsy. A comprehensive review of current issues. Council on Scientific Affairs. JAMA 1987;258:364–369.
2. Hill RB. College of American Pathologists Conference XXIX on Restructuring Autopsy Practice for Health Care Reform: summary. Arch Pathol Lab Med 1996;120:778–781.
3. Redfern M, Keeling JW, Powell E (2001) The Royal Liverpool Children's Inquiry Report; http://www.rlcinquiry.org.uk.
4. Kaufman SR. Autopsy. A crucial component of human clinical investigation. Arch Pathol Lab Med 1996;120:767–770.
5. Haque AK, Patterson RC, Grafe MR. High autopsy rates at a university medical center. What has gone right? Arch Pathol Lab Med 1996;120:727–732.
6. Nakhleh RE, Baker PB, Zarbo RJ. Autopsy result utilization: a College of American Pathologists Q-probes study of 256 laboratories. Arch Pathol Lab Med 1999;123:290–295.
7. Koszyca B, Moore L, Toogood I, Byard RW. Is postmortem examination useful in pediatric oncology? Pediatr Pathol 1993;13:709–715.
8. Landefeld CS, Chren M-M, Myers A, Geller R, Robbins S, Goldman L. Diagnostic yield of the autopsy in a university hospital and a community hospital. N Engl J Med 1988; 318:1249–1254.
9. Sarode VR, Datta BN, Banerjee AK, et al. Autopsy findings and clinical diagnoses: a review of 1,000 cases. Hum Pathol 1993;24:194–198.
10. Barendregt WB, Buskens FM, Kubat K, de Boer HH. Autopsy analysis in patients with vascular diseases. Hum Pathol 1992;23:178–182.
11. Burton EC, Troxclair DA, Newman WP III. Autopsy diagnoses of malignant neoplasms: how often are clinical diagnoses incorrect? JAMA 1998;280:1245–1248.
12. Dhar V, Perlman M, Vilela MI, Haque KN, Kirpalani H, Cutz E. Autopsy in a neonatal intensive care unit: utilization patterns and associations of clinicopathologic discordances. J Pediatr 1998;132:75–79.
13. Sonderegger-Iseli K, Burger S, Muntwyler J, Salomon F. Diagnostic errors in three medical eras: a necropsy study. Lancet 2000;355:2027–2031.
14. Maloney D, Keller SJ, Fierro MF. Child deaths in Virginia, 1996: a review of investigations of sudden, unexpected, or unnatural deaths of children less than age 13. Am J Forensic Med Pathol 2000;21:189–194.
15. Hanzlick RL, Parrish RG. Epidemiologic aspects of forensic pathology. Clin Lab Med 1998;18:23–37.
16. Wood MJ, Guha AK. Declining clinical autopsy rates versus increasing medicolegal autopsy rates in Halifax, Nova Scotia. Arch Pathol Lab Med 2001;125:924–930.
17. Jenny C, Hymel KP, Ritzen A, Reinert SE, Hay TC. Analysis of missed cases of abusive head trauma. JAMA 1999; 281:621–626.
18. Herman-Giddens ME, Brown G, Verbiest S, et al. Underascertainment of child abuse mortality in the United States. JAMA 1999;282:463–467.
19. Berry PJ. Intra-alveolar haemorrhage in sudden infant death syndrome: a cause for concern? J Clin Pathol 1999; 52:553–554.
20. Mitchell E, Krous HF, Donald T, Byard RW. Changing trends in the diagnosis of sudden infant death. Am J Forensic Med Pathol 2000;21:311–314.

21. Thogmartin JR, Siebert CF Jr, Pellan WA. Sleep position and bed-sharing in sudden infant deaths: an examination of autopsy findings. J Pediatr 2001;138:212–217.
22. Willinger M, Hoffman HJ, Hartford RB. Infant sleep position and risk for sudden infant death syndrome: report of meeting held January 13 and 14, 1994, National Institutes of Health, Bethesda, MD. Pediatrics 1994;93:814–819.
23. Byard RW. Accidental childhood death and the role of the pathologist. Pediatr Dev Pathol 2000;3:405–418.
24. Bennett MJ, Rinaldo P. The metabolic autopsy comes of age. Clin Chem 2001;47:1145–1146.
25. Sturner WQ. Sudden infant death syndrome—the medical examiner's viewpoint. Perspect Pediatr Pathol 1995;19:76–86.
26. Kaufman SR. Autopsy—a crucial component of human clinical investigation. Arch Pathol Lab Med 1996;120:767–770.
27. Moore GW, Berman JJ, Hanzlick RL, Buchino JJ, Hutchins GM. A prototype Internet autopsy database—1625 consecutive fetal and neonatal autopsy facesheets spanning 20 years. Arch Pathol Lab Med 1996;120:782–785.
28. Davies MJ. The investigation of sudden cardiac death. Histopathology 1999;34:93–98.
29. Wigglesworth JS. Perinatal Pathology. Philadelphia: W.B. Saunders, 1996.
30. Ackerman MJ, Tester DJ, Porter CJ, Edwards WD. Molecular diagnosis of the inherited long-QT syndrome in a woman who died after near-drowning. N Engl J Med 1999; 341:1121–1125.
31. Ackerman MJ, Siu BL, Sturner WQ, et al. Postmortem molecular analysis of SCN5A defects in sudden infant death syndrome. JAMA 2001;286:2264–2269.
32. Marz W, Nauck M, Wieland H. The molecular mechanisms of inherited thrombophilia. Z Kardiol 2000;89:575–586.
33. Burns JC, Kushner HI, Bastian JF, et al. Kawasaki disease: a brief history. Pediatrics 2000;106:E27.
34. Chace DH, DiPerna JC, Mitchell BL, Sgroi B, Hofman LF, Naylor EW. Electrospray tandem mass spectrometry for analysis of acylcarnitines in dried postmortem blood specimens collected at autopsy from infants with unexplained cause of death. Clin Chem 2001;47:1166–1182.
35. Brackett JC, Sims HF, Steiner RD, et al. A novel mutation in medium chain acyl-CoA dehydrogenase causes sudden neonatal death. J Clin Invest 1994;94:1477–1483.
36. Rinaldo P, Yoon HR, Yu C, Raymond K, Tiozzo C, Giordano G. Sudden and unexpected neonatal death: a protocol for the postmortem diagnosis of fatty acid oxidation disorders. Semin Perinatol 1999;23:204–210.
37. Wood JC, Magera MJ, Rinaldo P, Seashore MR, Strauss AW, Friedman A. Diagnosis of very long chain acyl-dehydrogenase deficiency from an infant's newborn screening card. Pediatrics 2001;108:E19.
38. Pinar H, Rogers BB. Renal dysplasia, situs inversus totalis, and multisystem fibrosis: a new syndrome. Pediatr Pathol 1992;12:215–221.
39. Becroft DM, Lockett BK. Intra-alveolar pulmonary siderophages in sudden infant death: a marker for previous imposed suffocation. Pathology 1997;29:60–63.
40. Yukawa N, Carter N, Rutty G, Green MA. Intra-alveolar haemorrhage in sudden infant death syndrome: a cause for concern? J Clin Pathol 1999;52:581–587.
41. Delaney K, Hanzlick R, Wolfe M. Pulmonary macrophage counts in deceased infants: baseline data for further study of infant mortality. Am J Forensic Med Pathol 2000;21: 315–318.
42. Hanzlick R, Delaney K. Pulmonary hemosiderin in deceased infants: baseline data for further study of infant mortality. Am J Forensic Med Pathol 2000;21:319–322.
43. Eberhart CG, Morrison A, Gyure KA, Frazier J, Smialek JE, Troncoso JC. Decreasing incidence of sudden death due to undiagnosed primary central nervous system tumors. Arch Pathol Lab Med 2001;125:1024–1030.
44. Sturner WQ. Pediatric autopsy in the forensic setting (Letter). Pediatr Dev Pathol 2000; 3: 111–112.