United States and Canadian Academy of Pathology

Annual Meeting, San Antonio, Texas February 26 - March 4, 2005

PLATFORM and POSTER PRESENTATIONS

Autopsy

1 Novel Association of Waterhouse-Friderichsen Syndrome with Severe *Staphylococcus aureus* Sepsis

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Background: Waterhouse-Friderichsen syndrome (WFS) was first described in 1911 by Rupert Waterhouse and is characterized by petechial rash, coagulopathy, cardiovascular collapse, and bilateral adrenal hemorrhage. This syndrome is generally associated with meningococcemia, all cases of purpura fulminans where the culture data is unknown or unavailable are classified as probable meningococcemia by the Centers for Disease Control. In a review of 250 cases Friderichsen found that about 20% of cases were caused by other organisms, usually *Streptococcus pneumoniae*. A recent report of non-meningococcal WFS cited two cases of *Streptococcus pneumoniae* and one case of beta-hemolytic streptococcus as the occasional cause of WFS. *Staphylococcus aureus* has never been closely associated with WFS. However this species has been increasingly identified as a cause of severe sepsis, necrotizing bronchopneumonia and death.

Design: Gross and microscopic examination of tissues was performed. Ante-mortem cultures were analyzed for clonality by pulsed-field gel electrophoresis and multi-locus species typing.

Results: We describe three cases of *S. aureus* sepsis in infants (9 – 15 months) all with WFS. All three had rash, coagulopathy, and cardiovascular collapse. The etiology was established with antemortem respiratory cultures. All three cases were clonal by pulsed-field gel electrophoresis and multi-locus species typing, two DNA fingerprinting techniques. Two of the isolates were methicillin resistant. Bilateral adrenal hemorrhage was documented in all cases at post mortem. Two were receiving extracorporeal membrane oxygenation (ECMO) at death.

Conclusions: Although hemorrhagic phenomena are documented ECMO complications, bilateral adrenal hemorrhage is not associated with ECMO anticoagulation. The hemorrhage in all three present cases was isolated to the adrenal glands, including the one case not on ECMO. These cases emphasize that WFS is not restricted to its historical association with meningococcemia. Specifically, *Staphylococcus aureus* strains endemic to the midwest are a newly recognized cause of fatal WFS.

2 The Final Consultation

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Background: The autopsy is an important tool for education, maintaining quality of patient care and, the final consultation. Among other benefits, the autopsy has helped define new diseases (SARS in 2003!), modify treatments, train young physicians and provide answers about treatments administered. Its acceptance has declined because of a number of misconceptions, apprehensions and perceptions. Nevertheless, the autopsy is a critical tool for any academic hospital . We undertook this study to correlate morphological diagnoses with clinical diagnosis and determine the clinical relevance of post-mortem diagnosis.

Design: The clinical diagnoses were compared with post mortem findings of 108 consecutive patients from1998. Diagnostic discrepancies were categorized according to Goldman et al[1]**.** If the autopsy revealed a new diagnosis that had not been established ante mortem, this was considered a missed diagnosis. We further divided Class I into Subclasses Ia and Ib. Subclass Ib: a new missed primary diagnosis causing death but not related to the ante mortem cause of death, subclass Ia: a missed diagnosis that results from, is a complication of or due to the primary cause of death. Class III & IV were lumped together as "Missed minor diagnoses".

Results: In the 108 autopsies studied, 44 (40.7%) major missed diagnoses were identified (Class I and II). Twelve, (11.1%) were Class II and not clinically significant; 32 (29.6%) were Class I discrepancies, and in 21(19.4%) of these cases, the missed cause of death was a result of the primary (previously diagnosed) disease - subclass Ia, while in 11 (10.2%) of the 108 patients the discrepancy was due to an entirely new diagnosis - subclass Ib. These findings are significant and are in keeping with findings from other large centers. We identified 32 (29.6%) missed minor diagnoses.

Conclusions: 1. The autopsy continues to provide new information which is relevant and potentially lifesaving.
2. The autopsy is a signficant learning tool.
3. All major clinical services must have regular, pathology based, mortality rounds, on a regular basis.
4. Medical management should not be considered complete without a postmortem examination, "The Final Consultation".
5. The autopsy continues to be an unrivaled tool for quality of case assessment and quality improvement.

References

1) Goldman L, Sayson R, Robbins S, Cohn LH, Bettmann M, Weisberg M. The value of the autopsy in three medical eras. N Engl J Med. 1983;308:1000-1005

3 Causes of Death in Posttransplant Lymphoproliferative Disorders in Solid-Organ Transplant Patients. An Autopsy Study

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Background: Posttransplant lymphoproliferative disorder (PTLD) is a relatively infrequent but serious complication occurring in 1-19% of solid-organ transplant (SOT) recipients. There are few previous studies of PTLD at autopsy. We have reviewed our long-term experience with autopises of patients with PTLD in a large transplant center.

Design: Our institution's autopsy records were searched for lymphoproliferative disorders in SOT recipients from 1988 to 2004. The following features were extracted: Age, sex, transplant type and reason, interval to diagnosis and type of PTLD, Epstein Bar Virus (EBV) status, rejection episodes, treatment of and interval from diagnosis of PTLD to death, residual PTLD and distribution at autopsy, and proximate cause of death (PCOD). When available, slides were reviewed to confirm presence/ classification of PTLD.

Results: In 16 years 22 autopsies were performed on patients with a diagnosis of PTLD (17) or in whom PTLD was diagnosed at autopsy (5). These represent approximately 7.6% (22/288) of all autopsies performed on transplant patients in our institution. Included were 22 adults (15 M/ 7 F, mean age 50) who received 8 lung, 5 kidney, 4 heart, 4 pancreas and kidney-pancreas and 1 liver transplant respectively. PTLD occurred after a median interval of 1.5 years. 18 were B-cell PTLD, mostly monomorphous PTLD/diffuse B-cell lymphoma, 3 were T-cell PTLD (kidney recipients diagnosed by bone marrow biopsy) and 1 an early lesion. 8/8 tested were EBV+. The organs most involved by PTLD were lymph nodes (14), liver (9), gastrointestinal tract (8), kidney (7), bone marrow (7), lung (6), spleen (5), and heart (3). The allograft was involved in 11 cases.

PTLD was the PCOD in 40% of patients in whom it was diagnosed at autopsy and the PCOD in 59% of the allograft recipients. The remaining patients PCOD were sepsis 18%, transplant failure 9% and other 14%. Of the patients in whom PTLD was diagnosed in vivo and were treated by antivirals (1) and chemotherapy (9), 72.7% had residual PTLD at autopsy, which constituted the cause of death in 100%.

Conclusions: Our study confirms the utility of autopsy in the study of PCOD in transplant patients. The diagnosis and true extent of PTLD were established at autopsy in a large proportion of our cases. The incidence of PTLD initially diagnosed at autopsy has not significantly decreased during the study period, suggesting that the value of autopsy in providing additional critical information is maintained.

4 Adipose Metaplasia (AM) in Healed Myocardial Infarction: A Study of 13 Autopsy Patients with End Stage Ischemic Cardiomyopathy (IC) Treated by Left Ventricular Assist Device (LVAD) and 21 Autopsy Patients with Healed Myocardial Infarcts

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Background: Adipose tissue within healed myocardial infarcts (HMI) has received little attention and has only been encountered after 1997. AM has gained increased importance with stem cell therapy for cardiac disease. We recently encountered 2 patients with LVADs whose HMI were almost totally replaced by AM that stimulated us to undertake this study.

Design: All patients with IC and LVAD autopsied from 1997 until August 2004 were studied. Two control groups comprised: (a) 11 consecutive autopsy patients with HMI encountered in 1991 and (b) 10 consecutive HMI autopsy patients from 1999. The following was noted in each case: age, sex, site of infarct, presence of coronary arterial bypass grafting (CABG). The amount of mature adipose tissue within each HMI was quantified: 0=no fat, 1= 1-5% fat, 2= 6-25% fat, 3= 26-50% fat, 4= 51-75% fat and 5= 76-100% fat.

Results: Thirteen patients (11 males and 2 females) with LVADs (Table 1) had a mean age of 65 years (range 56-75, SD=6.3); CABG was present in 11/13 and infarct distribution was posterior 2, anterior 6 and circumferential 5. The 11 pre-1997 control patients (9 males and 2 females) had a mean age of 67 years (range 51- 81, SD=9.8); CABG was present in 5/11 and infarct distribution was posterior 6, anterior 4 and lateral 1. The 10 post-1997 controls (5 males, 5 females) had a mean age of 66 years (range 46-85, SD=15.2); 5/10 had CABG and infarct distribution was posterior 6 and anterior 4. Mean duration of LVAD implants was 276.3 days (range 1-1095, SD=436.1); mean duration of LVAD <1 mth group was 9.7 days (range 1-26, SD=9.7); mean duration of LVAD >1 mth was 505 days (range 53-1095, SD= 498).

Conclusions: HMI in hearts with LVADs showed greater AM than did hearts with HMI and no LVAD. Likewise post-1997 HMI showed more AM than was seen in pre-1997 infarcts. However, AM was observed prior to 1997. No correlation between duration of LVAD and AM scores was noted.

Table 1: Adipose Metaplasia (Fat Scores) in 34 Healed Infarcts

CASES	FAT SCORE	RANGE	SD	p value
LVAD (n=13)	1.95	0-4	1.47	* , ** , ***
LVAD <1 mth (n=6)	1.83	0-3	1.17	a
LVAD >1mth (n=7)	2.06	0-4	1.78	a
Pre-1997 Controls (n=11)	0.09	0-1	0.30	* b
Post-1997 Controls (n=10)	0.65	0-2	0.82	** b
Pooled Controls (n=21)	0.33	0-2	0.66	***

*<0.001, ** <0.05, *** 0.0001, a NS, b <0.05

5 Androgen Receptor Expression in Hormone Refractory Prostate Cancer from a Rapid Autopsy Series: Quantitative Subcellular Localization Using AQUA

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Background: Recent studies in prostate cancer (PCA) cell lines suggest that an increase in Androgen Receptor (AR) mRNA and protein expression are both necessary and sufficient to convert PCA cells to a hormone refractory (HR) state. The goal of the current study is to access the expression of AR in tumor samples taken from men with HR Metastatic PCA.

Design: AR protein expression was the evaluated using the AQUA imaging system on high-density TMA composed of HR metastatic PCA samples from 30 Rapid Autopsies. The AQUA system is a molecular-based method of quantitative assessment of protein expression. This system integrates a set of algorithms that allows the rapid, automated, continuous and quantitative evaluation of tissue samples, including the sub-cellular localization of signals. In addition to AR, we also evaluated Ki-67, and AMACR expression. AR amplification was evaluated by FISH.

Results: There is significant correlation between increasing total AR expression and Ki67 expression (R2=0.5 (p=0.008, 2-tailed). Shorter survival time from time of initial diagnosis to death was observed with higher Ki-67 expression (p=0.029). AR protein expression was measured in the nuclear and cytoplasmic compartments for all tumors. Interestingly, there was significant correlation between nuclear and cytoplasmic AR (cAR) expression (R2=0.94, P<0.001). The N/C ratio of AR expression varied with time of effective hormone therapy. Longer hormone responsiveness was associated with the higher N/C AR ratio (ANOVA p=0.035). We examined for AR expression between individual multiple tumors and observed that 67% of the patients demonstrate uniform AR expression throughout all tumors. Large variations in AR expression from tumor to tumor were seen in 33% of the cases. Heterogeneous AR expression was significantly associated with tumor proliferation as determined by Ki67 (p=0.031). AR amplification and AMACR expression was not associated with survival time (p=0.588).

Conclusions: Using the AQUA system, we were able to identify significant AR expression in the cytoplasm that has not previously been measured. Interestingly, the higher concentration of AR in the nucleus (higher N/C AR) was associated with longer response to hormonal treatment.

6 How Many Blocks Are Needed To Diagnose a Transmural Acute Myocardial Infarction?

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Background: Ischemic heart disease is a highly prevalent disease and a common cause of death in developed countries. However, current autopsy protocols do not include standarized methods for identifying a transmural acute myocardial infarction (AMI). Once defined in a previous study (*abstract #3, USCAP 2003*) the most efficient heart sampling for diagnosing AMI in any clinical setting, we now investigate what could be the minimal heart sampling needed to detect it with reliability in daily practice.

Design: The series includes 202 AMIs that were diagnosed at autopsy between 1978 and 2000 following the same protocol. The myocardium between 1,5 cm below the atrioventricular sulcus (AVS) and 2 cm above the apex was sliced into 3 equivalent pieces, and the resulting 4 upper surfaces, from base to apex, were histologically evaluated (slices A, B, C, and D, respectively). AMIs were classified in 5 groups depending on the affected vessel and its related myocardial area: Type 1 (anteroseptal, LDA occlusion), type 2 (posterior, with/without right ventricle lesion, RCA or Cx occlusion in left dominancy), type 3 (lateral, Cx or OM occlusion), type 4 (anterior + lateral), and type 5 (anterior + posterior). Main arteries were sectioned every 3 mm to detect the exact site and level of the occlusion in every case. We selected and analyzed the myocardial block in the territory of each artery (anterior, posterior, lateral) in every slice.

Results: Most relevant results are summarized as follows:

AMI type	artery	slice	block	positive/total cases
1 (AS)	LDA	C	anterior	91/91
2 (Post)	RCA or Cx (left dom)	B	posterior	57/57
3 (Lat)	Cx or OM	B,C	lateral	27/27
4 (AS+Lat)	LDA+Cx or OM	B	lateral	18/18
5 (AS+Post)	LDA+RC	B,C	ant/post	9/9

AS: anteroseptal, LDA: left descending artery, RCA: right coronary artery, Cx: circumflex, OM: obtusa marginalis, dom: dominancy

If the affected vessel is unknown, three blocks are needed to diagnose the AMI in 100% of cases. These blocks are: block 1, anterior block-slice C, block 2, posterior block-slice B, and block 3, lateral block-slice B. Otherwise, only one block is needed if the affected artery is known (see slice and block in the Table).

Conclusions: At autopsy, any AMI can be detected following a simple sampling protocol that recapitulates the anatomy of the coronary tree. So, just three paraffin blocks are needed to diagnose an AMI if the occluded artery is unknown and only one if it is known.

7 Posttransplant Lymphoproliferative Disorders in Bone Marrow Transplant Recipients. An Autopsy Study of 16 Cases

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Background: Posttransplant lymphoproliferative disorder (PTLD) is a relatively uncommon but serious complication occurring in 1-2% of bone marrow transplant (BMT) recipients. Few studies investigating autopsy pathology of PTLD in BMT recipients exist. We reviewed our long-term experience with PTLD autopises in a large BMT transplant center.

Design: Our institution's autopsy records were searched for PTLD occurring in BMT recipients from 1988 to 2004. The following features were extracted: Age; sex, BMT type, pretransplant disease, PTLD interval and type, EBV status, rejection episodes, PTLD treatment, time from PTLD diagnosis to death, residual PTLD at autopsy and its distribution and the proximate cause of death (PCOD). When available, slides were reviewed to confirm the presence and classification of the PTLD.

Results: During the 16 year period, about 3,000 autopsies were performed. 16% (174) of the autopsies were BMT recipients, of which 3.4% (16) were performed on BMT patients who either had a diagnosis of PTLD (6) or in whom PTLD was diagnosed postmortem (10). This included 7 adults and 9 children (11 M and 5 F, ages 2-50, median 14 years), who received 12 bone marrow, 3 umbilical cord blood and 1 peripheral blood stem cell transplant. PTLD occurred after a median interval of 115 days after transplant (65- 620 days). The interval was shorter earlier in the study time period. There were 13 B-cell PTLD, mostly monomorphous PTLD/diffuse B-cell lymphoma and 3 unspecified types. 13/13 tested were EBV+ (10 IHC, 3 serology). The organs most involved by PTLD were lymph nodes:10; liver: 8; lung: 8; kidney: 8; GI tract: 7; spleen: 6; adrenal: 4; thyroid: 2; and CNS: 2. The average time to PTLD diagnosis was 201 days in the pediatric group and 147 days in the adult group. Of the patients in whom PTLD was diagnosed and treated antemortem a majority had extensive residual PTLD at autopsy. PTLD was the PCOD in all patients in whom it was diagnosed at autopsy. The remaining patients PCOD included respiratory failure, infection and other.

Conclusions: Autopsy studies of BMT patients are essential in documenting the diagnosis and distribution of PTLD as well as uncovering the causes for organ failure. PTLD was established at autopsy in the majority of our pateints and revealed widespread disease. Cases initially diagnosed at autopsy did not decrease with time, suggesting that autopsy maintains its value even with advanced serologic monitoring and imaging techniques.

8 Nature of the Dysplastic Rossettes in Trisomy 13 with Cyclopia and Holoprosencephaly

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Background: Dysplastic rossettes are seen in a variety of genetic syndromes that lead to ocular malformations. Although a common finding, the histogenesis of these structures is not understood. Cell-type specific markers can characterize the cellular composition of these structures.

Design: Our study focuses on an autopsy 37-week-old with Patau syndromes. A complete autopsy also includes immunohistochemical analysis of the eyes. ABC immunohistochemistry was performed on the paraffin-embedded ocular tissue. The antibodies used included: rod and cone opsins; interphotoreceptor retinoid-binding protein (IRBP); cellular retinaldehyde-binding protein (CRALBP), Muller cell and retinal pigment epithelial cells (RPE).

Results: Autopsy showed transposition of great vessels; interventricular and interatrial septal defects; alobar holoprosencephal; absence of the olfactory bulbs and tracts, and basal ganglia. One thalamus is present. Eye lids with partial fusion are inferior to a proboscis; fused globes with separate well formed lens, and a single posterior chamber; corneal and iris hypoplasia; single fused optic nerve. Although the RPE was well formed, the neural retina was separated from the RPE in most areas. The retina showed a typical laminar structure in some areas. However, most neural retina was replaced by rosette structures, admixed in some areas with foci of cartilage and brain tissue. Immunohistochemistry showed that the majority of the cells from the rosettes express rod opsin and IRBP. A second population of Muller glia like cells were observed sending CRALBP-positive processes between the opsin positive cells. The processes extend the full thickness of the rosette ending abruptly at the external limiting membrane like structure at the rosette lumen. The inclusion of retinal interneurons in the rosettes was variable and depended on the size of the specific rosette.

Conclusions: Unlike the neoplastic rosettes of retinoblastoma, which show cone opsin differentiation, the dysplastic rosettes described here are composed of multiple cells types including photoreceptor Muller cell glia in a topographic arrangement reminiscent of the normal fetal retinal architecture. These observations suggest a fundamental difference between Flexner-Wintersteiner rosettes, and the dysplastic rosettes. Our findings suggest that ongoing studies should consider the organizing influence of factors expressed by the RPE in establishing the normal linear topography of the developing neural retina.

9 Histologic and Molecular Correlates of Neonatal Mortality Due to In Utero Infection

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Background: It is well documented that the histologic findings in the placenta may be nonspecific in cases of neonatal mortality due to an infectious agent. However, the frequency of an infectious cause of idopathic neonatal mortality is not clear, nor are the histologic correlates in the placentas. The purpose of this study was to analyze the placenta and neonatal tissues for a wide variety of infectious agents and to correlate this with the histologic findings and cytokine expression.

Design: We examined placentas and corresponding neonatal tissues in 18 cases of neonatal mortality (stillborn or death within 48 hours of birth) for an infectious agent. Five cases of fetal and placental tissues from therapeutic abortions were used as controls. The tissues were analyzed by RT in situ PCR for bacterial infection (using a consensus rRNA primer set) and for infection by enterovirus/coxsackie virus, parvovirus, RSV, and varicella zoster as well as by in situ hybridization for adenovirus, CMV, EBV, and herpes simplex virus. All tissues were tested for TNFα expression by RT in situ PCR and immunohistochemistry.

Results: An intrauterine infection was noted in 13/18 (72%) of the placentas in the cases of neonatal mortality and in none of the therapeutic abortions. The gestational ages ranged from 18 to 40 weeks (30 mean) and in all but two cases the child was not intrauterine growth retarded. The infectious agents were as follows: enterovirus/coxsackie virus (9 cases), bacterial infection (2 cases), parvovirus (1 case), CMV (1 case). The histologic findings in the placenta in the cases of intrauterine infection were non-specific, except for the parvovirus and CMV cases where the characteristic inclusions were present. In each of the 13 cases of placental infection, the same infectious agent was evident in the spleen and, for the enteroviral cases, in the CNS. In each case of enteroviral infection, the viral protein was evident by immunohistochemistry in all but one of the 9 cases. There was strong expression of TNFα in the placenta and spleen of each of the cases of intrauterine infection, and in none of the 5 controls.

Conclusions: It is concluded that the majority of cases of "idiopathic" neonatal deaths are due to an intrauterine infection and that the histologic changes in the placenta in such cases are usually nonspecific. However, such placentas show marked up-regulation of TNFα expression compared to controls. The mechanism of neonatal death includes direct infection and, importantly, increased cytokine expression both in the placenta and in the neonatal/fetal tissues.

10 Cause of Death in Hepatitis C Cirrhotic Patients: An Autopsy Study

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Background: Individuals with chronic hepatitis C virus (HCV) infection may develop cirrhosis, which predisposes them to the development of hepatocellular carcinoma (HCC) at an annual rate of 3-5%. Reports from other countries have indicated that HCC is the leading cause of death among HCV associated cirrhotics, even more than complications of cirrhosis, such as portal hypertension, infection, liver failure and hepatorenal syndrome, to name a few. Our aim was to determine the principal cause(s) of death based on post-mortem findings in patients diagnosed with chronic HCV cirrhosis.

Design: The Mount Sinai Pathology autopsy database covering the period of January 1991 up to May 2004 was reviewed. All deaths where the deceased was HCV infected and cirrhotic were reviewed for 1) patient demographics, 2) the presence of HCC, 3) the primary mode of death: cirrhosis, HCC or "other factors" (defined as any cause not related to cirrhosis or HCC), 4) the grade and the stage of disease, 5) liver transplantation, and 6) concurrent liver disease. Patients who had received a liver transplant were excluded from the study. Slides were reviewed to ensure established cirrhosis was present in cases where the autopsy histology report was absent/deficient.

Results: 114 cases were examined; 64% were male and 36% were female. The mean age was 50.4 years. HCC was present in 25 cases. The mode of death was a direct complication of cirrhosis in 51, a complication of HCC in 13, and a result of "other factors" in 50 cases. Of the 12 patients with HCC who did not die as a direct result of their tumor, 8 died of a complication of cirrhosis, and 4 from "other factors". The most common concurrent disease was HIV/AIDS (36 cases); all except two cases in this group died of "other factors".

Conclusions: The mode of death in the HCV cirrhotic patient population, investigated through review of the autopsy charts was more often a direct complication of cirrhosis, and "other factors" and less often as a direct complication of HCC. Half of the cases with HCC died from their tumor, and the other half from either complications of cirrhosis or "other factors". This patient population had a high rate of HIV infection, and almost all of these cases died of "other factors", which explains the overall high rate of patients dying from "other factors" in this autopsy cohort.

11 Demographics and Co-Morbidities Associated with Pulmonary Embolism at Autopsy in a Community Hospital

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Background: Pulmonary embolism (PE) is a significant cause of morbidity and mortality in the United States with >250,000 hospitalizations resulting in >150,000 deaths annually. Patients with increased risk of developing PE include those with malignancy, chronic illness, trauma, recent surgery, immobility and obesity. The purpose of this study was to examine the demographics and co-morbidities associated with death of individuals who were found to have PE at autopsy.

Design: Studied were 47 autopsy cases, from January 2002 to May 2004, in which PE was identified as either the primary cause of death or a contributory factor. Co-morbidities were stratified based on malignancy, trauma, recent surgery, immobility, obesity, genetic thrombophilia, and chronic illness (including diabetes, hypertension and atherosclerotic coronary artery disease (ASCAD)). Genetic testing to identify hereditary thrombophilias (i.e. Factor V Leiden and Prothrombin 20210a) is in progress.

Results: The mean age for development of PE in both men and women was 56 (men 23-79 and women 36-82), with 24 decedents male and 23 female. In addition, 46 (98%) of decedents were Caucasian and 1 (2%) was African-American. The 5 most frequent co-morbidities were chronic illness 37 (79%), obesity 22 (47%), immobility 9 (19%), recent surgery 8 (17%) and malignancy 7 (15%). The most common chronic illness identified was ASCAD 27 (73%), followed by diabetes 5 (13.5%) and hypertension 5 (13.5%). Ten of 23 women (43%) and 17 of 24 men (71%) had ASCAD. Of those with ASCAD, 15 (56%) had advanced disease and 10 (37%) showed evidence of a previous myocardial infarction. Advanced ASCAD was more frequently associated with male gender 10 (37%) than female 5 (19%), with evidence of previous myocardial infarction seen more often in men 6 (22%) than women 4 (15%). Obesity was more common in women 12 (52%) than men 10 (42%). The most frequent presenting symptoms prior to death were dyspnea 19 (40%) and malaise 9 (19%), with a significant proportion being asymptomatic 13 (28%).

Conclusions: The most frequent co-morbidities in this study of PE were chronic illness and obesity, with ASCAD being the most common chronic illness. Advanced ASCAD was nearly twice as common in men than women, with a predominance of previous myocardial infarction in the male population. Obesity was 10% more common among women than men. The most common presenting symptom prior to death was dyspnea, however, many were asymptomatic.

12 Tattoos Association with Age, High Risk Behavior, and Death

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Background: Tattoos have been classically associated with negative behavior (criminal activity, drug use, etc.), but in recent years they have become more popular with mainstream Americans (15-16% incidence, overall, and 35% of Americans 25-29 y/o). With the increased popularity of tattoos, one would expect their presence to be relatively less significant as an indicator of high risk behavior in young adults. This study examines the association of age and tattoos with high-risk behavior in deaths at the Arkansas Crime Lab.

Design: A retrospective case control study of autopsy records from 2003 was performed to analyze the incidence of tattoos and the association between age and high risk behavior in adults with tattoos. Each case was evaluated for the presence of high-risk behavior and tattoo presence. Exclusionary criteria were set to limit bias, and the data was compared to both an internal low-risk behavior control and Harris poll data of age distributed tattoo incidence, from which odds ratios were calculated.

Results: 467 cases were analyzed, and the results are listed in the following table:

Conclusions: Tattoos are significantly associated with deaths involving high risk behavior. This risk is higher in younger victims when compared to age controlled data, which is contradictory to expectations. These findings are most significant with homicides and accidents involving high risk behavior. Prospective studies are needed to evaluate the impact of socioeconomic status and types of tattoos in this risk profile.

Risk of Death Associated with Tattoos

	N	Tattoo Incidence	Odds Ratio	P-Value	18-24 y/o (N=72)	25-29 y/o (N=57)	30-39 y/o (N=93)
All Crime Lab Subjects	467	34.9%	2.9	0.002	9.92	2.83	2.12
Low Risk Deaths	64	15.6%	—	—	0	0.59	1.71
Suicides	186	31.7%	2.1	0.0075	7.52	2.07	2.14
Homicides	191	47.1%	4.8	0.0001	16.5	3.91	2.36
High Risk Accident Deaths	35	42.9%	4.1	0.004	6.69	2.66	1.54

13 Prevalence of Steatohepatitis and Its Association with Splenomegaly and Abdominal Subcutaneous Adipose Thickness: An Autopsy Study

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Background: Obesity, diabetes and hyperlipidemia are associated with increased risk for developing steatosis or steatohepatitis (SH). It has been noted that patients with SH even in the absence of portal hypertension may have splenomegaly. This is a retrospective study that aims to determine the prevalence of steatosis and SH, to correlate the abdominal subcutaneous adipose tissue (ASAT) with steatosis and SH, and to correlate degree of steatosis and SH to spleen and liver weight in an autopsy cohort. There has been no autopsy study addressing the prevalence of SH since 1991 when Wanless and Lentz showed a frequency of 18.5%

Design: There were 214 consecutive adult autopsy cases selected from 340 post-mortem studies performed at our institution over an 18-month period. Inclusion criteria were: complete (unlimited) autopsies with available non-autolyzed representative liver sections. Spleen and liver weight and ASAT were noted. H&E and Trichrome (if available) stained slides were assessed and graded for steatosis (0= none, 1= <30%, 2= >30 <60%, 3->60% hepatocytes affected) and steatohepatitis (Brunt classification). Liver and spleen weights >1800g and 400g, respectively were considered as hepatomegaly and splenomegaly.
Results: There were 118 males, 96 females, mean age 63 years. 113 patients showed either steatosis or SH (62 of 214 or 29% showed pure steatosis and 51 of 214 or 24% showed SH ranging from mild to severe). The presence of steatosis alone does not correlate with ASAT ($p = 0.37$). SH is associated with a greater ASAT (non-SH = 2.12 cm, SH = 3.23cm, $p = 0.002$). 19 of 51 (38%)SH cases had splenomegaly. Liver weight does not correlate with SH or steatosis. Presence of ballooning, Mallorys hyalines, pericellular fibrosis, portal fibrosis, and lobular inflammation were each independently associated with splenomegaly (p values 0.02, 0.006, 0.0003, 0.001,0.003) but not with hepatomegaly.
Conclusions: The high prevalence of steatohepatitis in this study reflects the dramatic increase of this entity in the general population. Increased abdominal subcutaneous fat is strongly associated with an increased incidence of SH but not steatosis. Splenomegaly even in the absence of cirrhosis is seen in SH but not steatosis.

14 Torsion of the Umbilical Cord: An Explanation for the Unexplained

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Background: Only recently in the literature have cord accidents become increasingly recognized as an important cause of birth asphyxia and intra-uterine death. The aim of this retrospective study was to record an incidence figure for torsion of the umbilical cord (TUC) as a cause of intra-uterine death in foetuses >500g and to determine the specificity of histological features in assisting this diagnosis.
Design: Autopsy records over a seven-year period (1995-2001) inclusive were examined for cases of unexplained hypoxic intra-uterine deaths (UHIUD). Exclusion criteria included: birth weight < 500 g, malformations and intra-uterine death from known causes. Formalin fixed placentae of these cases were retrieved and a coiling index of the umbilical cord recorded. Umbilical cord torsion were defined as a combination of umbilical cord stricture or/and an increased coiling index, combined with histological evidence of thrombosis. Coiling index (CI) was defined as the number of vascular coils in the umbilical cord divided by the length of umbilical cord. Subsequently, the cord was serially blocked and processed into paraffin in the routine fashion. H&E slides were examined for histological evidence of thrombosis.Positive and negative controls were used to assess specificity and sensitivity of certain histological parameters to TUC i.e. thrombosis, medial muscle layer disruption/ thinning, number of vessels, presence of inflammation, arterial hypoplasia, decrease in Wharton's Jelly or change in rbc colour.Positive controls(n=12) were known nuchal(asphyxiated) cords; negative controls consisted of two groups(n=12 each): umbilical cords from normal livebirths, and IUD cases of known causes(multifocal infarction;fetomaternal haemorrhage, chronic villtis,abruptio placentae).
Results: 30 cases of UHIUD were identified. Twelve (40%) had evidence of torsion of the UC. Three (10%) had evidence of uncoiled cords (low CI) and histological evidence of thrombosis. This corresponds to 26.97 cases of TUC per 1000 perinatal deaths over 500g and 0.28 cases per 1000 livebirths. Thrombosis had a specificity of 83.3% and sensitivity of 62.5% for torsion cases (p=0.014). Logistic regression showed that tests were 8.3 times more likely to have thrombus compared to controls. None of the remaining histological parameters were statistically significant.
Conclusions: The importance of umbilical cord torsion as a cause of intra-uterine death has been understated.This also highlights the need for exploring possible preventative strategies.

15 DNA Sequencing of 16S rDNA for Identification of Microbial Pathogens from Autopsy Formalin-Fixed Paraffin Embedded Tissue in Neonates with Necrotizing Enterocolitis

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Background: Necrotizing enterocolitis (NEC) is a devastating gastrointestinal disease occurring in 1% to 5% of all neonatal intensive care unit admissions. The etiology of necrotizing enterocolitis is controversial**.** Bacterial invasion of the neonatal intestine has been theorized to be a key component in the etiology of NEC. Because the microorganisms commonly associated with NEC are difficult to culture, an effective means of characterization has yet to be established. We have developed a technique for microbial characterization using 16S rDNA sequencing and comparative analysis via GenBank nucleotide-nucleotide search to all known sequenced 16s rDNA genus and species of bacteria.
Design: The autopsy specimens of four patients identified histologically as necrotizing enterocolitis were used for bacterial detection studies. For this purpose DNA was extracted and amplification of 16S rDNA was done using universal primers. A negative control lacking DNA and a positive control with *Staphylococcus aureus* DNA was also run with all samples. PCR conditions were after the initial DNA denaturation at 94°C for 10 min, 35 cycles of denaturation at 94°C for 1 min, annealing at 50°C for 1 min, and elongation at 72°C for 1 min, and a final elongation at 72°C for 10 min. PCR products were purified and sequenced. The sequences were compared to GenBank using the nucleotide-nucleotide BLAST program of the National Center of Biotechnology Information at http://www.ncbi.nlm.nih.gov.
Results: Of the four cases identified histologically as NEC four had identifiable amplicons. One sample had a significant homology (>97%) with the 16S rDNA sequence of *Clostridium perfringens*. The remaining three amplicons failed to result in a significant sequence match, possibly reflecting a polymicrobial process. The positive control had a 99% match with *Staphylococcus aureus*.
Conclusions: Our study demonstrated that the sequencing of 16S rDNA amplicon obtained from autopsy tissue has the potential to be an effective and novel method to characterize specific microorganisms in patients with necrotizing enterocolitis, as well as having possible applications in other infectious disease processes.

16 Over-Twisting of Umbilical Cord as a Cause of Intrauterine Fetal Demise: A Frequent but Underrecognized Abnormality

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Background: Over-twisting of the umbilical cord (over-coiling, over-spiraling, torsion, coarctation) as a primary cause of intrauterine fetal demise (IUFD) has been a subject of dispute. It has been argued that cord over-twisting is the result rather than cause of IUFD. Umbilical cord over-twisting is a rarely reported event, and large systemic studies are almost non-existent.
Design: We collected 13 cases of IUFD involving an over-twisted cord at various gestational ages occurring over a two and half year period (Jan. 2002 to Jun 2004). For each case the maternal and gestational ages were compared along with other placental and fetal findings.
Results: Six of these IUFD's were submitted as surgical pathology specimens under the gestational age of 20 weeks. Five of the 13 cases were at a gestational age of 17 to 19 weeks, and 8 cases were over 20 weeks. Ten of the 13 cases were between 17 and 24 weeks. All these cases were found to have over-twisting of the cord within 5.0 cm of the fetal abdominal ends. None of these fetuses were found to have other developmental abnormalities. One case was a dichorionic twin with the co-twin subsequently delivered normally at term. Maternal ages ranged from 19 to 40 with seven under 30 years and six over 30 years.
Conclusions: Over-twisting of the cord in vitro in normal pregnancy is impossible due to the thickness and elastic nature of Wharton's Jelly. This leads us to believe that over-twisting of the umbilical cord is more likely to occur in those with defective development of Wharton's jelly, and it is our belief that over-twisting of the cord is the primary cause of IUFD. Although rare in reported studies, it is a relatively frequent observation in our institution. It is possible that close to the fetal end, the cord has a different or more variable composition of Wharton's jelly. We speculate that over-twisting of cords with defective Wharton's jelly may relate to the socio-economic status of the mother, and further investigation in this direction is needed. Furthermore, a thorough knowledge and awareness by the pathologist of this condition in examining both the fetus and the placenta is important for accurate diagnosis and patient counseling.

Cases of cord over-twisting by specimen type, maternal and gestational ages

Case Number	Maternal Age (years)	Gestational Age (weeks)	Specimen Type
1	25	19	Surgical
2	35	17	Surgical
3	23	21	Surgical
4	36	17	Surgical
5	39	19	Surgical
6	23	19	Surgical
7	23	37	Autopsy
8	27	36	Autopsy
9	27	38	Autopsy
10	33	22	Autopsy
11	36	24	Autopsy
12	40	25	Autopsy
13	19	22	Autopsy

17 Lymphoplasmacytic Sclerosing Pancreatitis Is Not an Occult Disease in the Autopsy Population

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Background: Lymphoplasmacytic sclerosing pancreatitis (LSP) is a rare cause of benign pancreatic disease, occurring in 1-2% of cases of chronic pancreatitis, and may clinically mimic pancreatic carcinoma. Characteristic histologic features include diffuse lymphoplasmacytic infiltration, marked interstitial fibrosis and prominent periductal inflammation. Given its rarity and relatively recent full description in the literature, we hypothesized that cases of LSP may have been histologically confused with the more common "usual" causes of chronic pancreatitis in the autopsy population.
Design: All completed reports of autopsies performed at the Hospital of the University of Pennsylvania from 1979 to 2003 were reviewed. H & E-stained sections of pancreas with microscopic descriptions consistent with chronic pancreatitis or possible LSP (fibrosis, chronic inflammation, prominent plasma cell infiltrates) were selected for microscopic review by the authors.
Results: 6444 autopsy reports were reviewed. Fetal and brain-only autopsies, as well as 64 cases of pancreatic adenocarcinoma were excluded from our study. 2915 reports remained with microscopic descriptions of the pancreas. Of these, 1703 (58.4%) were described as having no pathologic change, complete autolysis or both. The most commonly described pathologic microscopic features were fibrosis (491, 16.8%), fat necrosis (300, 10.3%), chronic inflammation (146, 5.0%), chronic pancreatitis (129, 4.4%) and metastatic disease (127, 4.4 %). Of these 1212 cases with pathologic diagnoses, 601 cases (49.6%) had microscopic descriptions suspicious for chronic pancreatitis and/or LSP, and were selected for further review. The median age of these patients was 53.6 years (range 21-87 years), with a male predominance (64%). Despite sharing multiple histologic features with LSP (chronic inflammation with plasma cells, extensive fibrosis), none of these sections exhibited sufficient histologic criteria for the diagnosis of LSP.

Conclusions: Had one case of LSP been diagnosed, prevalences of <0.03%, 0.775%, and 0.166% would have been obtained within the populations of pancreases with microscopic descriptions, "chronic pancreatitis," and the suspicious category, respectively. Given the complete absence of any pancreatic sections displaying histologic features consistent with LSP in the 2915 autopsy cases with pancreatic microscopic descriptions, it seems highly unlikely LSP occurs in an occult form.

18 Phenotype-Genotype Correlations in Chromosome 4q Deletion with Involvement of c-KIT and PDGFRA Genes

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Background: Constitutional deletion of material from chromosome 4q is a rare disorder. 4q is the location of c-KIT, a gene in which mutations are associated with "piebaldism" due to defective melanocyte migration, and PDGFRA, which is expressed on the surface of oligodendrocyte progenitors and is important for their proliferation. Phenotypic-genotypic investigation may provide insight into function of specific human genes.

Design: A complete autopsy was performed on a 4-year-old boy with interstitial 4q deletion. DNA was isolated and array CGH was performed to precisely determine the boundaries of the deleted region.

Results: Clinical history included dysmorphic features, developmental delay, seizure disorder, anemia, chronic constipation, and recurrent aspiration pneumonia. Autopsy revealed a striking pattern of predominantly midline ventral skin hypopigmentation. c-KIT immunostaining showed decreased melanocytes in these areas. There were also low-set abnormally formed ears, a short smooth philtrum, hypertelorism, upturned nose, and absent left kidney. The brain showed hydrocephalus ex vacuo, foreshortened frontal poles, and inferior olive asymmetry. Myelination was well developed. The deleted region extended 24 Mb from the centromere and contained approximately 40 genes, including c-KIT and PDGFRA.

Conclusions: Several clinicopathologic findings, including the striking piebaldism trait, can be traced to c-KIT deletion. The brain findings suggest that PDGFRA deletion is compensated for in human oligodendrocyte development and myelination.

19 Autopsy Findings, Manner and Cause of Death in Nursing Home Deaths Investigated by the Allegheny County Coroner's Office (ACCO), Pennsylvania: A Five Year Retrospective Review

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Background: Although approximately twenty percent of deaths in the United States occur in nursing homes, relatively little has been reported on the manner and cause of death in this population. The current investigation analyzed age, sex, race, manner and cause of death and major autopsy findings in an autopsied nursing home population.

Design: All cases from nursing homes autopsied by the ACCO, Pennsylvania from 1998 to 2003 were electronically identified from the official database. In each case the age, sex, race, manner and cause of death were extracted. Statistical analyses for the abstracted variables were performed using descriptive statistics and Chi Square analysis. Autopsy and clinical findings were separated into twelve major categories by careful review of the final autopsy and death investigation reports by two of the authors (DNI and GJN).

Results: A total of 116 cases were identified**.** The age ranged between 19 and 99. Fourteen cases were under the age of 60 (12%). Women represented 62% of cases and men 38%. 74 deaths were ruled accidental (A) (64%) and 40 natural (N) (34%). There was one homicide and was one undetermined case. 85% were white (W), 14% African-American (AA) and 1 was Hispanic. The manner of death was significantly different between W and AA, with 69.4% of A deaths in W and 33.3% in AA (Chi-square = 7.39, $p<0.01$). In the 40 cases of N deaths the most common autopsy findings were: Arteriosclerotic Cardiovascular and Cerebrovascular Diseases (ASCVCD) (n=30) and non ASCVCD (n=20), Broncho-lobar pneumonia (n=14), COPD (n=11), Dementia/Parkinson (n=9), Malignancies (n=6) and Pulmonary emboli/Deep venous thrombosis (n=6).

In the 74 cases of A deaths blunt force trauma (BFT) was the single most commonly identified traumatic event with trauma to the head and neck, trunk and extremities identified in 40, 13 and 26 cases, respectively. Other autopsy findings included: food aspiration (n=4), drug overdose (n=3), burns (n=2) and hypothermia (n=2). In A deaths common chronic and acute diseases were similar to those seen in N deaths.

Conclusions: These data suggest that A deaths might be more common in W as compared to AA nursing home residents. Acute and chronic diseases documented at autopsy are similar irrespective of manner of death. BFT is a major autopsy finding in accidental nursing home deaths.

20 Acutely Angled Left Main Coronary Artery, Mitral Valve Prolapse and Sudden Cardiac Death

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Background: Three cases of sudden cardiac death with acutely angulated left main coronary arteries and mitral valve prolapse are described. Sudden cardiac death is recognized in cases with angulated coronary arteries as well as in cases with mitral valve prolapse. The coexistence of angulated coronary arteries and mitral valve prolapse has not been previously reported.

Design: Three cases of sudden cardiac death with complete autopsies are described. The first case is a 41-years-old hospital employee found collapsed at work. The second is a 16-years-old motorcycle racer who stopped in mid race, stepped off and collapsed. Both resuscitations were unsuccessful. The third is a 14-years-old girl who collapsed after viewing a fireworks display. Initial resuscitation was successful with circulatory support by extra-corporeal membrane oxygenation but she died 36 hours later. Drug screens for all cases were noncontributory.

Results: All three hearts have left main coronary ostia arising in the usual position within the left sinus of Valsalva. However the artery takeoffs are acutely angled with respect to the aortic wall and are associated with distinct inferior ridges. The ventricles of the first two cases were grossly normal with minor histologic changes. The third case with prolonged survival showed hemorrhagic subendocardial infarction of the entire left coronary watershed, sparing the right coronary territory. The mitral valves showed varying myxoid degeneration. All three had recognizable friction lesions on the mural endocardium beneath the posterior leaflets. The first mitral valve had a thickened firm free margin and mild, not uniformly thickened or spongy valve spongiosa. The second mitral valve had a thick posterior leaflet zone with prominently hooding and a focal friction lesion in the atrium as well. The third mitral valve had diffusely myxomatous leaflets with marked posterior leaflet hooding.

Conclusions: Close examination of proximal coronary arteries and their ostia for angulation and obstruction and examination of the left heart subvalvular and supravalvular endocardium for friction lesions is recommended in subjects with sudden cardiac death who on initial exam seem to have normal hearts except for possibly mildly altered mitral valves. The relationship of coronary ostial abnormalities to mitral valve prolapse is unclear but may not be merely coincidental.

21 AIDS and Infection in Mexican Children. A Survey of 35 Autopsies

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Background: An immunosuppressed individual is susceptible to infections caused by those microorganisms present in the environment and the particular patterns of infection are dependent on ecological, geographical and socio-economic factors. Knowledge of the microorganisms infecting susceptible individuals in a given context generates management guidelines and creates an awareness of possible etiologies in individuals entering that particular context.

Design: We reviewed 35 autopsy records and materials of 17 girls and 18 boys with AIDS. Infectious agents were identified based on morphology and culture.

Results: In 33 patients infection was a major determinant of death. Organisms involved were: Bacteria (17), Cytomegalovirus (13), Pneumocystis (8), Histoplasmosis (5), Herpes virus (6), Candida sp. (4), Non tuberculous mycobateria (3), Adenovirus (2) and Toxoplasma (1).

Conclusions: In contrast with other series of childhood AIDS, Histoplasmosis was a significant presence in our material. These five children had systemic infection which remained undiagnosed and did not receive specific treatment. Tuberculosis, frequent in Mexico, was notably absent in our population. Other microorganisms identified were similar to those in other series. Infections in immunosuppressed patients reflect particular ecologic contexts; results of one series are not necessarily applicable to other populations

22 Histological Changes in Lupus Nephritis According to the Improvement of Immunotherapy: An Autopsy Study

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Background: Our clinical study examining 1,125 systemic lupus erythematosus (SLE) patients demonstrated that the outcome in the patients diagnosed after 1986 was better than that in the patients diagnosed before 1985 (J Jpn Soc Intern Med 92:30-41, 2003). The improvement of the prognosis was considered to be due to the improved immunotherapy for lupus nephritis. The aim of the present study was to examine the histological changes in lupus nephritis according to the improvement of the immunotherapy.

Design: The kidneys in 36 autopsy patients with SLE (20 autopsies before 1985 and 16 autopsies after 1986) were examined pathologically. The histological sections from the kidneys were stained with HE, PAS, PAM and Azan stains. The histological evaluation of lupus nephritis was performed according to the classification of glomerulonephritis in SLE revised (Kidney Int 65:521-530, 2004).

Results: The glomerular lesions in the examined cases were diffuse lupus nephritis, Class IV (32 cases) and advanced sclerotic lupus nephritis, Class VI (4 cases), and there were no differences in the classes between 2 groups (Before 1985 and After 1986). Although the occurence of wireloops did not differ in both groups, the occurence of fibrinoid necrosis ($P=0.03$), hyaline thrombi ($P=0.01$) and cellular crescents ($P<0.01$) in the After 1986 group was significantly lower than that in the Before 1985 group (Table 1).

Conclusions: The presence of fibrinoid necrosis, hyaline thrombi and cellular crescents in the glomeruli leads to the poor prognosis in SLE, and the improvement of the immunotherapy for lupus nephritis produces the disappearances of such glomerular lesions.

Table 1. Active glomerular lesions in 36 autopsies with SLE

Group	Wireloops	Fibrinoid necrosis	Cellular crescents	Hyaline thrombi
Before 1985	80% (16/20)	35% (7/20)	65% (13/20)	85% (17/20)
After 1986	63% (10/16)	6% (1/16)	0% (0/16)	31% (5/16)

23 Unexpected Significant Autopsy Findings: A Quality Assurance Tool

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Background: There has been a steady decline in the hospital autopsy rate nationwide over the years. Pathological information, obtained at autopsy, has consistently proved to be useful in providing answers to unresolved clinical questions. Using autopsy findings as a quality assurance tool at Westchester Medical Center (WMC), a tertiary care University Hospital, we investigated significant autopsy findings not anticipated clinically.

Design: Consecutive autopsies performed from Jan. 2001 to Dec. 2003 were analyzed and findings were compared with clinical diagnosis at the time of death. The autopsy findings were classified as expected and unexpected, the later being further subdivided into significant and incidental based on whether or not it contributed directly to patient's death. The unexpected significant findings were further categorized as infectious, neoplastic, cardiovascular, pulmonary, gastrointestinal, nervous system, congenital/metabolic and iatrogenic. The findings in adult and pediatric group were analyzed separately.

Results: Total numbers of deaths and autopsies performed at WMC from 2001 to 2003 were 2301 and 239 respectively. The average autopsy rate at WMC was 10.4 % which matches with the national statistics. A third of autopsies (33.9%) revealed significant unexpected findings contributing directly to patient's death; more in the neonatal/pediatric autopsy group (42%) than in the adult group (29.1%). Infectious diseases with unusual organisms were the most frequently encountered unexpected significant findings, followed by cardiovascular diseases, in both the groups.

Number of Autopsies and Unexpected Significant Findings from 2001 to 2003

Year	2001	2002	2003
No. of Autopsies	83	74	82
Unexpected Significant Findings	25	26	30
%	30.1	35.1	36.6

Unexpected Significant Findings in Adult and Neonatal/Pediatric Population

Category	Adult		Neonatal/Pediatric		Total	
No. of cases	46		35		81	
Infectious diseases	18	39.1%	13	37.1%	31	38.3%
Cardiovascular	12	26.1%	7	20.0%	19	23.5%
Pulmonary	6	13.0%	3	8.6%	9	11.1%
Gastrointestinal	4	8.7%	2	5.7%	6	7.4%
Nervous System	2	4.3%	3	8.6%	5	6.2%
Neoplasm	4	8.7%	-	-	4	4.9%
Iatrogenic	-	-	4	11.4%	4	4.9%
Congenital/Metabolic	-	-	3	8.6%	3	3.7%

The findings were discussed with focused physician groups every month to increase the awareness particularly of unusual infections and cardiovascular complications in our patients.

Conclusions: We underscore the importance of autopsies in not only providing the cause of death and answering unresolved clinical questions but also in serving as a tool for quality improvement in clinical medicine.

24 Autopsy Findings in Lung Allograft Recipients Stratified by Time Elapsed Post-Transplantation: An Update

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Background: The post-operative treatment and surgical technique of lung transplantation are rapidly evolving. Few autopsy series of lung allograft recipients have been reported; no complete series has been reported since 1996. We report here the single largest autopsy series of lung allografts recipients.

Design: We sought to determine whether or not a changing pattern in autopsy-proven cause of death in lung allograft recipients has emerged in the last decade. A total of 44 autopsies were reviewed, 22 from 1990 to 1999 and 22 from 2000 to 2004. Autopsies were divided into three groups based on the time interval between transplantation and death: 1) early (<1 month); 2) intermediate (1 month - 1 year); and 3) late (>1 year). Autopsy results were reviewed, summarized, and tabulated.

Results: Overall, as compared to earlier published autopsy series, there were fewer deaths in the early period (survival <1 mo), more subjects surviving into the late period (survival >1 year), and fewer patients dying of chronic rejection. In the group of 8 patients surviving less than one month, 7 of the deaths were due to postoperative complications such as pulmonary edema and thrombotic events, and one due to *Coccidioidomycosis* fungal pneumonia. In the group of 20 patients in the intermediate survival group, infection was the primary cause of death in 15 cases (75%). CMV was the single most commonly isolated infectious organism, but *Aspergillus* and various Gram-negative rod species also acounted for a significant fraction. Other causes of death in this intermediate period include chronic rejection and post-transplantation lymphoproliferative disorder (PTLD). In the group of 16 patients in the late survival group, the primary causes of death were infection (50%, 8 patients) and chronic rejection (25%, 4 patients). Of particular note, one death in this group was due to disseminated *Scedosporium* infection, a rare cause of human disease. Complications, PTLD, and unrelated causes accounted for the remainder of deaths in this group.

Conclusions: We suggest that a change in the pattern of autopsy-proven cause of death is emerging, with fewer deaths in the early post-transplant period and an overall decrease in the number of deaths due to chronic rejection, as compared to earlier published autopsy series. Infection remains the leading cause of death in the intermediate and late periods.

25 Autopsy Findings in Varicella. A Study in 34 Pediatric Cases

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Background: Chickenpox, the primary form of infection by Varicella/Zoster virus produces a benign, self limited disease, widespread in the pediatric population. Complications are infrequent and can result from systemic spread of the virus or from bacterial superinfection. Clinical distinction of these two types of complications is difficult and thus their frequency and risk factors involved are not known in detail. Varicella infection produces a characteristic cytopathic effect (intranuclear eosinophilic inclusions) which makes this differentiation possible in the examination of tissues from autopsy material.

Design: Thirty four cases of varicella infection in a series of 6800 consecutive autopsies performed between 1971 and mid 2004 were distributed in two groups: Group 1 with systemic viral disease and Group 2 with viral infection limited to the skin. Dependent variables analyzed were age, duration of clinical course, associated diseases, malnutrition and bacterial complications.

Results: Each group included 17 cases. Main organs involved by viral spread were: esophagus (17), liver (17), lung (9), adrenal (8), intestine (6) and lymph nodes (6). A significant underlying disease was present in 15/17 Group I and only in 3/17 Group 2 patients. Immunosuppression and bacterial superinfection emerged as the sole significant variables. Immunosuppression was present in 11/17 patients in Group 1 and only 2/17 in Group 2. Conversely bacterial superinfection was present in 10/17 of Group 1 and in 4/17 of Group 2. Organisms identified included Staph (8), Pseudomonas (4), Strep (3).

Conclusions: The autopsy is able to differentiate between different pathways to death in children with chicken pox. Primary forms die as a result of secondary infection with highly aggressive microorganisms and there is no evidence of widespread viral presence. On the other hand, the immunosuppressed child dies as a result of extensive viral dissemination and the resulting tissue damage, mainly in esophagus, liver and lung.

26 Development and Application of Geriatric Autopsy Database and Internet-Based Database of Japanese Single Nucleotide Polymorphisms for Geriatric Research (JG-SNP)

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Background: To facilitate geriatric research on the roles of genetic polymorphisms of candidate genes, two databases were developed based on data obtained from autopsy examinations of elderly subjects: the Geriatric autopsy database (GEAD), and the Japanese single nucleotide polymorphisms (SNP) database for geriatric research (JG-SNP) which is accessible on the Internet (http://www.tmgh.metro.tokyo.jp/jg-snp/english/E_top.html).

Design: The data for the GEAD were derived from 1,375 consecutive autopsy cases (744 male and 631 female) with an average age of 80 years. The average autopsy rate was 38%. Brain was obtained in 84% of the cases. The genotyping was performed by the DHPLC, PCR-RFLP, or Taqman method. The GEAD was installed on a stand-alone Windows server using Oracle 8i as the database application.

Results: The GEAD contains clinical diagnoses of 26 geriatric diseases, histories of smoking and alcohol consumption, pathological findings (720 items), severity of atherosclerosis and pulmonary emphysema, genetic polymorphism data, etc. The 26 geriatric diseases included ischemic heart disease, atrial fibrillation, dementia, cerebrovascular disorder, Parkinson's disease, osteoporosis, chronic obstructive pulmonary disease, lung cancer, and so on. Most frequent pathological findings were registered in the GEAD. In case of heart, 60 pathological findings were included, such as endocarditis, atrial thrombosis, mitral annular calcification, calcific aortic valvular stenosis, myocardial infarction, myocarditis, and amyloid depositions. The candidate genes for analysis included ACE, ALP, apoE, CYP2C, ERalpha, GGCX, IL6, Klotho, MTHFR, eNOS, PON1, PPARgamma, Werner, and ZNF147. On the JG-SNP website, case distribution corresponding to a specified SNP or disease can be searched or downloaded. Using this database, several papers have been published and cooperative researches are proceeding.

Conclusions: Although there are several Internet-based SNP databases such as dbSNP, no databases are available at present on the web that contains both SNP data and phenotypic data. As autopsy studies can provide large amounts of accurate medical information, including the presence of undiagnosed diseases such as latent cancers, the GEAD is a unique and excellent database for research on genetic polymorphisms.

27 Bone Marrow Transplant (BMT)-Associated Thrombotic Microangiopathy (TMA). A Retrospective Autopsy Study

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Background: Thrombotic microangiopathy has been a well-known complication in BMT patients, yet there is limited autopsy data available and the etiology remains unclear. The purpose of this retrospective autopsy study was to define the precise morphologic features of BMT-associated TMA and to seek for potential etiologic factors.

Design: The study included 21 consecutive allograft BMT patients autopsied at the Department of Pathology, University of Oklahoma, between 1994 and 2003. Applying strict clinical-laboratory criteria 7 patients carried the clinical diagnosis of TMA (TMA group) and 14 patients did not (non-TMA group). All clinical files, autopsy records and slides were reviewed and the relevant findings were keyed into a database. A number of morphologic findings and clinical variables including but not limited to absence/presence/severity of TMA, fungal, and angioinvasive fungal infection (AFI), primary diagnosis, induction chemotherapy, total body irradiation, plasmapheresis, and cyclosporine levels were compared statistically in the TMA and non-TMA groups.

Results: In the TMA group, morphologic features of TMA were identified most consistently in the kidney, while the non-TMA group did not show TMA in the majority of cases ($P = 0.002$). Three patients in the TMA group had features of TMA outside the kidney (heart and pancreas), while TMA was limited to the kidney in the non-TMA group (2 cases). No statistically significant differences in relevant clinical and morphologic variables were identified between the two groups.

Conclusions: Our findings provide compelling morphologic evidences that (a) the kidney is the primary target in BMT-associated TMA and (b) morphologic findings strongly correlate with the clinical diagnosis of TMA. Our study did not identify a significant etiologic relationship between BMT-TMA and AFI or other clinical variables. The findings are suggestive of multifactorial etiology and complex pathogenesis in BMT-associated TMA.

28 Myocarditis in the Autopsy Heart: Retrospective Analysis of a Major Urban Medical Examiner Case Population

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Background: The histologic pattern of myocarditis in cases of sudden death may be different from the histologic criteria used to diagnose myocarditis by endomyocardial biopsy in clinical practice. Much of the literature regarding the histologic diagnosis of myocarditis refers to findings on endomyocardial biopsy of symptomatic patients. The significance of focal and diffuse myocarditis discovered during the autopsy of individuals who die suddenly and unexpectedly has not been well defined. This study is a retrospective analysis of myocarditis identified at autopsy in an urban (Chicago) medical examiner's office.

Design: All cases with the autopsy diagnosis of myocarditis in the records of the Office of the Medical Examiner, Cook County, IL from 1998-2003 were identified. The medical examiners investigative report, autopsy protocol, toxicology and laboratory results and available medical records were reviewed. Cases were analyzed for the presence of co-morbidities such as significant disease, injury or drug intoxication and for a diagnosis of diffuse or focal myocarditis .

Results: Of 27,000 autopsies performed by the Cook County Medical Examiners Office in that period, there were 84 cases diagnosed with myocarditis. There were 52 adults (>18 years) with males equal to females and 32 were children with 17 males and 15 females. Eleven (11) of the children were under one year of age and 8 of these were male (p=0.001). Seventeen (17) of the 23 children with diffuse myocarditis had no co-morbidity while 2 of 9 with focal myocarditis had no co-morbidity (p=0.0147, Fishers exact test). Eleven (11) of 17 adults with diffuse myocarditis had no co-morbidity whereas only 1 of 34 with focal myocarditis was without a significant co-morbidity (p=0.0001 Fishers exact test). There was no statistical difference in co morbidity for age (children vs. adults) for diffuse (p=0.73) or focal (p=0.10) myocarditis.

Conclusions: Children dying with diffuse myocarditis were more likely to have no co-morbidities related to their deaths and those with focal myocarditis were more likely to have significant co-morbidities. In adults diffuse disease was associated more often with no co-morbidities but focal disease was almost exclusively associated with co-morbidities. These results question the significance of focal myocarditis in this autopsy population.

29 Differential Expression of INOS, VEGF and COX-2 in the Lungs Is Related to Pulmonary Hypertension in Sickle Cell Disease: An Autopsy Study of 23 Cases

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Background: Approximately 40% of patients with sickle cell disease (SCD) develop pulmonary hypertension (PH). The pathogenesis of SCD-associated pulmonary hypertension is unknown; hemolysis, chronic anemia, and frequent transfusions are significant predictors of PH. Reduction in NOS and increased expression of VEGF is reported in PH and in plexiform lesions. COX-2 is a mediator of angiogenesis. We investigated the expression of INOS, VEGF and COX-2 in the pulmonary arteries of autopsied patients with SCD to explore the pathogenesis of PH.

Design: Paraffin-embedded lungs from 23 autopsied adults (14 males and 9 females) were immunostained using enhanced sensitivity avidin-biotin peroxide method, and antibodies against nitric oxide synthase (INOS), vascular endothelial growth factor (VEGF), and cyclo-oxygenase -2 (COX-2). Clinical data were collected for correlation with pathologic data. Immunostained slides were graded: 0= 0, 1=weak, and 2= strong. Pulmonary vasculature endothelium and smooth muscle, and airway epithelium and smooth muscle were graded. Statistical analysis of the data was performed using Fisher's Exact test and Chi-Square.

Results: Mean age was 41 years (14 M=35, 9 F= 51). Hemoglobin S fraction percentages ranged from 23% to 98%; 9 patients had sickle cell trait (SCT) with HgbS fraction <40%;14 had SCD (HgbS >40%). All 23 cases showed PH grade I to grade IV (plexiform lesions in 57%). INOS expression was weak in the vascular endothelium (21%) but strong in smooth muscle (57%), and weak to moderate in the airways. VEGF expression was strong (85-100%) in vascular endothelium and smooth muscle (70-100%), but weak to moderate in the airways. COX-2 expression was absent to weak in both vessels and airways. In addition, more males had severe SCD compared to females; and more males than females had the diagnosis of sudden death (43% vs 11%). Cardiomegaly was present in 22 / 23 patients (mean weight=498 gms); mean weight of those with SCT (474 gms) was lower compared to SCD (514 gms).

Conclusions: Histologic changes of PH are present in all patients with SCH at autopsy. The weak expression of INOS in the endothelium and strong expression in the muscle suggests possible etiologic role of INOS in SCD-associated PH. The strong expression of VEGF in the vessels may be the cause of the muscular and endothelial hyperplasia and PH. Lack of COX-2 expression indicates that cytokines are not involved in the pathogenesis of PH in SCD.

Bone & Soft Tissue

30 The Prognostic Significance of Fibrosarcoma Arising in Dermatofibrosarcoma Protuberans

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Background: Dermatofibrosarcoma protuberans (DFSP) is a superficial tumor characterized by high rates of local recurrence and a low risk of metastases. Fibrosarcomatous (FS) areas rarely arise in DFSP and considerable controversy exists as to whether these tumors have a higher risk for metastases than typical DFSP. The aim of this study was to reappraise the prognostic significance of FS change in DFSP.

Design: The consultation files of our institution revealed 41 patients with fibrosarcoma arising in DFSP and the clinicopathologic features of each case were analyzed retrospectively. The tumors were examined for the proportion of FS areas, mitotic count, CD34 expression (0 to 3+), MIB-1 labeling index (LI), and p53 expression. Follow-up was obtained in 38 cases (median: 48 mo, range: 1-300 mo). Prognostic variables for predicting local recurrence were evaluated using a univariate Cox model.

Results: The study included 23 females and 18 males with a median age of 48 yrs (range: 16-100). Eighteen lesions were seen on the trunk, 16 on the extremities, and 7 on the head/neck. All tumors were treated with wide local excision and the surgical margins were considered positive in 22 of 39 cases (56%). Fibrosarcoma arose de novo in 38 cases and as a recurrence in 3 cases. All tumors involved the dermis and subcutis and the FS component comprised 5-95% of tumor area (median: 60%). Mitotic rates of the FS component (20/10hpf, range: 5-48) was considerably higher than neighboring DFSP (0-3/10hpf). CD34 expression was stronger and more extensive in the DFSP component (97%, median intensity 3+) than in the FS component (81%, median intensity 2+). Diminishment of CD34 staining was seen in the FS areas (median intensity 0/1+) in 15 cases. The MIB-1 LI of the FS regions was higher (median, 20%; range: 5-45%) than the DFSP areas (<3%). p53 expression was gained in the FS areas (92% positive) versus the adjacent DFSP (3% positive). Follow-up data revealed local recurrences in 8 patients (5-year local recurrence free survival, 68%), metastases in 4 patients (10%), and 3 patients died of disease. None of the variables evaluated (including margin status, FS area, or mitotic rate) correlated with disease progression.

Conclusions: Fibrosarcoma arising in DFSP is a form of tumor progression that carries a small, but definite risk for metastases. The pathogenesis of this progression can be partially explained by gains of *p53* mutations. In patients with FS transformation of DFSP, neither the extent of the FS area, mitotic rate, nor the margin status correlated with disease progression.

31 Deep-Seated Plexiform Schwannomas (PS). A Pathologic Study of 16 Cases and Comparative Analysis with the Superficial Variety

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Background: PS is the least common variant of schwannoma and typically occurs in the dermis and subcutaneus tissue. Morphologically, PS can display a conventional, cellular or mixed appearance. However, the frequent cellular morphology associated with hyperchromatic nuclei, increased mitoses, and plexiform growth can suggest a malignant process, mainly a high-grade malignant peripheral nerve sheath tumor (MPNST). Our objective was to study the clinicopathologic features of deep-seated PS, and compare them with the more common superficial variety.

Design: Clinicopathologic, immunohistochemical (IHC) and ultrastructural features from 16 deep PS were analyzed and compared with 8 superficial (5 dermal and 3 subcutaneous) PS. None had stigmata of neurofibromatosis.

Results: The deep PS occured in 12 females and 4 males. 15 PS were located in the deep somatic soft tissue (pelvis/retroperitoneum, 4; extremity, 8; trunk, 2; parotid, 1) and 1 in the viscera (thoracic esophagus). The largest tumor was 15 cm in size. The tumors frequently showed increased cellularity (68%), mild-moderate nuclear pleomorphism (50%) and mitotic activity (93%). Focal necrosis was seen in 12% and myxoid changes in 18% of cases. Verocay bodies were identified in 62% of cases. IHC (S100 protein, Laminin) and ultrastructural analysis were consistent with a well-differentiated schwannian proliferation in all cases analyzed. The 8 superficial PS occured in 5 males and 3 females and were located in the dermis and subcutis (lower extremity, 5; shoulder,1; perianal region,1). The tumors showed increased cellularity (62%), mild to moderate pleomorphism and mitotic activity (62%). No necrosis was identified. Verocay bodies were identified in 62% of cases.

Conclusions: Deep-seated PS is a rare, under-recognized PNST, typically not associated with neurofibromatosis. Although frequently occurring in the extremities, they can be seen in other locations such as viscera and can grow up to 15 cm in size. In contrast with the more common superficial tumors, deep PS have predilection for females, can occur in congenital settings, and can show necrosis and myxoid change. However worrisome histologic features were seen in both groups, including increased cellularity, mild to moderate pleomorphism and mitoses. It is important to differentiate these tumors from plexiform neurofibromas and MPNST, as they follow a benign clinical course, with complete surgical excision being curative.

32 A Simple and Reliable Method for the Molecular Diagnosis of Fibrous Dysplasia

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Background: Fibrous dysplasia (FD) is a benign intra-medullary fibro-osseous lesion, resulting from missense mutations in the GNAS1 gene. Distinguishing between FD and other pathological processes is not always easy and a robust molecular diagnosis would help in difficult cases. Known GNAS1 mutations occur in codons 201(C→T