

The Importance of the Autopsy in Medicine: Perspectives of Pathology Colleagues

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Louis Maximilian Buja, MD¹ , Rolf F. Barth, MD², Gerhard R. Krueger, MD¹, Sergey V. Brodsky, MD, PhD², and Robert L. Hunter, MD, PhD¹

Abstract

This article presents a perspective on the importance of the autopsy in medical practice and science based on experiences of the authors as physician-scientists involved in autopsy practice. Our perspectives are presented on the seminal contributions of the autopsy in the areas of cardiovascular disease, including congenital heart disease, atherosclerosis, coronary artery disease, and myocardial infarction, and infectious disease, including tuberculosis and viral infections. On the positive side of the future of the autopsy, we discuss the tremendous opportunities for important research to be done by application of advanced molecular biological techniques to formalin-fixed, paraffin-embedded tissue blocks obtained at autopsy. We also note with concern the countervailing forces impacting the influence of pathology in education and clinical practice at our academic medical centers, which also present impediments to increasing autopsy rates. Our challenge as academic pathologists, whose careers have been molded by involvement in the autopsy, is to counter these trends. The challenges are great but the benefits for medicine and society are enormous.

Keywords

autopsy, cardiovascular disease, graduate medical education, pathology, tuberculosis, undergraduate medical education, viral infections

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Introduction

Historically, the autopsy has fulfilled multiple purposes including those pertinent to medical care (diagnostic-related groups, quality assurance, and total patient care), body of medical science (research, education, transplantation, and prostheses), society (public health, vital statistics, forensic issues), and the family (counseling and understanding the life cycle).^{1–3} Furthermore, autopsies are the most important parts of forensic pathology, where establishing the exact cause and manner of death has important medical–legal implications.^{4,5} The importance of the autopsy remains unchanged in spite of the decline in autopsy rates in American medical institutions outside of the jurisdiction of medical examiners due to the multiple factors impacting on medical practice today.^{6,7} In other countries including England, the situation is worse.⁸ Multifaceted factors contributing to low autopsy rates include attitudes (of clinicians, pathologists, families, administrators, politicians), time

constraints, and competing responsibilities of pathologists, physicians' fears of legal liability and of being wrong, costs (professional, overhead), modern medical technology building false confidence, lack of Joint Commission autopsy requirements (since 1971), lack of inclusion of autopsy findings in death certificate documentation, as well as in published clinical

¹ Department of Pathology and Laboratory Medicine, McGovern Medical School, The University of Texas Health Science Center at Houston (UTHealth), Houston, TX, USA

² Department of Pathology, The Ohio State University, Columbus, OH, USA

Corresponding Author:

Louis Maximilian Buja, Department of Pathology and Laboratory Medicine, McGovern Medical School, The University of Texas Health Science Center at Houston (UTHealth), 6431 Fannin St, MSB 2.276, Houston, TX 77030, USA. Email: l.maximilian.buja@uth.tmc.edu



case reports, and frequent inability of clinicians to request permission from bereaved families appropriately.^{1-3,6,7}

With this perspective in mind, we would like to make the case for autopsies based on its importance in our own academic careers dating back for 4 of us (L.M.B., R.F.B., G.R.K., and R.L.H.) to our own personal experiences in training at the National Institutes of Health in Bethesda, Maryland.⁹⁻¹³ Over the years, we have functioned as physician-scientists and attending pathologists on the autopsy services of our respective institutions, and over the intervening years, we have been joined by other pathology colleagues.¹⁴⁻¹⁷ During the course of our academic careers, we have utilized autopsy cases to advance our research and scholarly activities in a variety of ways. Our experience as autopsy attending pathologists has been essential for the development of 2 teaching atlases of pathology, one with radiological correlation, and a textbook of cardiovascular pathology.¹⁸⁻²⁰ We have also utilized our autopsy experience to correlate with clinical and experimental findings to develop computer-based simulation of disease.²¹

It is often stated that advances in basic medical science and imaging have reduced the need for autopsies. Although these advances have been great, the need for autopsies continues in multiple areas, including teaching, quality assurance, and determination of the exact cause of death.^{1-3,6,7} Autopsies for the advantage of physicians and families of the deceased provide the unique opportunity to study the pathogenesis of different human disease processes and their influence on other organs in the human body such as how end-stage renal disease may lead to pericarditis and to malignant hypertension that could lead to thrombotic microangiopathy and strokes.

Hill and Anderson have documented that autopsies have led to discovery or critical clarification of many medical disorders (87 over a 46-year span), and this process of discovery has continued to the present day.^{1,2} We present here our personal experiences showing how the autopsy has contributed significantly to our expertise as pathologists and to our scholarly contributions to biomedical science in the areas of cardiovascular and infectious diseases.

Specific Entities

Cardiovascular Diseases

Congenital heart disease. One of the glories of 20th century medicine is the advancement made in the diagnosis and surgical correction of congenital heart defects. This achievement can be attributed to the contributions of pathologists whose expertise provided in-depth characterization of the anatomic changes that were associated with the pathophysiologic consequences of the congenital heart defects that were observed by studying autopsy specimens.²² First, Maude Abbott and then Maurice Lev and Jesse Edwards were important early contributors to publications documenting the pathology and pathophysiology of congenital heart disease.²² A specific example of the importance of their contributions is as follows. Abbott had discussions with Helen Taussig that led to the development of

the concept that a shunt could be created between the pulmonary artery and aorta to relieve the pulmonary hypoperfusion in “blue” babies with the tetralogy of Fallot, which resulted in the Blalock-Taussig shunt to correct this defect.²³ Subsequently, other investigators, including Stella and Richard van Praagh, have provided insights that have advanced knowledge of the pathogenesis and pathology of CHD.²⁴ William Manion developed an outstanding collection of hearts with a wide variety of congenital defects at the Armed Forces Institute of Pathology (AFIP).²² Following his untimely death, Dr Manion was succeeded by Dr Hugh (Chip) McAllister, Jr, as Chief of the Cardiovascular Pathology Branch at the AFIP. One of us (L.M.B.) developed expertise in evaluating congenital heart disease from Dr McAllister, who generously provided his time to pathologists and clinicians with a serious interest in understanding the pathologic physiology of congenital heart disease using the outstanding collection at the AFIP.²⁵

Atherosclerosis. Autopsy studies have documented the fundamental nature and stages in the progression of atherosclerotic disease of the aorta and great vessels. Autopsy studies documenting significant coronary atherosclerotic lesions in soldiers from the Korean war and young trauma victims were important in focusing attention on the early development of disease in predisposed populations.^{26,27} These autopsy studies led to 3 large population-based autopsy studies which greatly influenced understanding of atherosclerosis and atherogenesis. The first was the Geographic Pathology of Atherosclerosis, the second was the Bogalusa Heart Study, and the third was the Pathological Determinants of Atherosclerosis in Youth.²⁸⁻³⁵ These studies documented differences in type, extent, and severity of atherosclerotic lesions in high and low prevalence populations. They further defined the relationship of risk factors to burden of atherosclerotic disease. Two of us (S.V.B. and R.F.B.) have taken the lead to understand what were anecdotal observations that, more frequently than not, morbidly obese decedents had either no or minimal atherosclerosis involving their aortas.¹⁴⁻¹⁷ This study has challenged the conventional wisdom regarding atherogenesis by carrying out a carefully designed study that confirmed the paradoxical observation that morbidly obese decedents, the vast majority of whom had the comorbidities of hypertension, diabetes, and dyslipidemias, had either no or minimal atherosclerosis compared to nonobese individuals.¹⁴⁻¹⁷ This is a prime example of how the autopsy can uncover findings that challenge conventional wisdom and hopefully will stimulate research to understand this totally counterintuitive observation.

Coronary artery disease, coronary thrombosis, sudden cardiac death, and myocardial infarction. Autopsy studies have been essential for advancing our knowledge and understanding of coronary and ischemic heart disease and have yielded important insights that have had important clinical implications. Autopsy studies loom large in the long and convoluted history leading to the elucidation of the complex interactions of coronary artery disease, coronary thrombosis, sudden cardiac death, and

myocardial infarction.³⁶⁻⁴⁵ In the early 20th century, the entity that we now know as myocardial infarction was considered a form of inflammation (chronic myocarditis) of the myocardium without any relationship to coronary artery lesions that incidentally may have been present. J. B. Herrick, a cardiologist, and his colleague, Ludvig Hektoen, a pathologist, first proposed that coronary arterial thrombosis was the cause of clinical acute myocardial infarctions, as evidenced pathologically by ischemic necrosis of the myocardium.² Later, some pathologists questioned whether coronary thrombosis was a primary or secondary event in myocardial infarction.⁴¹ This issue was settled in favor of the primacy of coronary thrombosis in acute coronary syndromes (ACSs) as the concept of the vulnerable plaque was elucidated.^{42,43} Confirmatory support was provided by the retrieval of coronary thrombi from culprit arteries early in the course of acute myocardial infarction.⁴⁴ Sudden cardiac death was clarified to be a syndrome due to ventricular dysrhythmia, often induced by an ischemic event.⁴⁵

Pathobiology of myocardial infarction. Two seminal autopsy studies confirmed a quantitative relationship between the extent of myocardial infarction and the severity of symptoms and prognosis in patients with ACSs.^{46,47} Specifically, loss of 40% or more of left ventricular myocardium due to a single large infarct or the cumulative effects of multiple small infarcts correlated with the development of intractable ventricular arrhythmias and/or cardiogenic shock with an associated high mortality rate.^{47,48} Survival after relatively large infarcts was found to initiate a process of sustained pathological remodeling in the surviving myocardium leading to progressive cardiac dysfunction and heart failure, as manifested clinically by ischemic cardiomyopathy.³⁸

Based on these seminal autopsy findings regarding the importance of infarct size in the morbidity and mortality associated with myocardial infarction, an influential call was made to accelerate research to develop approaches to limit infarct size.⁴⁸ This led to a flurry of experimental studies in the 1970s and 1980s aimed at developing pharmacological therapies to limit myocardial infarct size.³⁸ Although limitation of infarct size by purely pharmacological means proved difficult to achieve, certain pharmacological agents, including aspirin and β adrenergic blockers, were shown to have positive effects on morbidity and mortality and have become standard of care in patients with ACS.³⁸

Subsequently, percutaneous interventions, including coronary balloon angioplasty and coronary stenting, were developed and shown to influence the course of progression of myocardial infarction. Autopsy studies documented the changed pathological features of myocardial infarction following coronary recanalization.⁴⁹ Autopsy studies also have contributed to an understanding of clinically important phenomena including reperfusion injury, stunning, preconditioning, and hibernation of the myocardium.³⁸

Infectious Diseases

Pathology and pathogenesis of pulmonary tuberculosis. Tuberculosis (TB) provides an excellent example of the important

contributions that autopsy pathology has made to the understanding of this devastating disease, which is the leading cause of death among infectious diseases. It ranks among the top 10 causes of death worldwide, killing around 5000 people per day.^{50,51} Over the past 2 centuries, TB has killed more people than malaria, smallpox, HIV, cholera, plague, Ebola, and influenza combined. Today, more than 2 billion people are estimated to be latently infected.⁵¹ Tuberculosis is exceedingly difficult to study because it occurs fully developed only in human lungs and there is no ethical justification for doing biopsies or resections of developing lesions. Although we are making great progress in defining the cells, molecules, and pathways by which *Mycobacterium tuberculosis* (MTB) establishes itself, we are still unable to put the proverbial pieces together to understand its pathogenesis because animal models do not replicate the human disease, which is a major impediment to the development of vaccines and new therapies.⁵⁰⁻⁵⁵ Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases, expressed a nearly universal opinion with the statement that “We need to better understand the delicate balance between the host and pathogen in the context of the entire biological system and this requires a “radical and transformational approach.” “Our goal should be to transform the entire field.”^{51,56}

Prior to the advent of molecular biology, investigators understood the pathologic, radiologic, and clinical course of each stage of TB but could not understand the biological processes. They had a “guiding vision” of TB but lacked “technological advances.” Today, although we have many powerful molecular techniques, we have forgotten the “guiding vision (overview)” and replaced it with a convenient but erroneous notion that granulomas are the only key lesion of TB.⁵⁷ The result is that research on the pathogenesis of TB describes increasing numbers of mechanisms and molecular components, but with an inaccurate guiding vision of pathology, these pieces cannot be assembled to form a coherent explanation.⁵⁸

It has long been recognized that TB induces both protective and tissue-damaging immune responses. Nearly 2 centuries of evidence, primarily from autopsies, has demonstrated that protection and tissue damage are mediated by separate disease entities in humans.⁵¹ Primary TB modulates protective immunity to disseminated infection, while post-primary TB causes tissue damage that results in formation of cavities. Both are necessary for continued survival of MTB.

Research on TB today is dominated by application of powerful technology to animal models, none of which reproduce the disease as it occurs in man.⁵⁹ Knowledge of the pathology of human pulmonary TB gained by 150 years of autopsy studies by many investigators has been replaced by the erroneous notion that granulomas are the key lesion of all TB. Primary TB has been extensively studied in humans and animals. Post-primary TB, in contrast, is seldom recognized or studied. It begins as an asymptomatic early infiltrate that may resolve or progress by bronchogenic spread to caseous pneumonia that either fragments to produce cavities or is retained to produce post-primary granulomas and fibrocaseous disease. Primary and post-primary TB differ in typical age of onset,

histopathology, organ distribution, radiologic appearance, genetic predisposition, immune status of the host, clinical course, and susceptibility to protection by *Bacillus Calmette-Guérin* (BCG). *Mycobacterium tuberculosis* is a highly successful human pathogen because it produces both primary and post-primary TB as distinct disease entities in humans. No animal reproduces this sequence of lesions documented by autopsy studies in humans.^{59,60} However, knowledge of the pathology of human TB makes it possible to manipulate animals to produce models of particular lesions. It appears that many mammals have the basic mechanisms of human TB but fail to replicate them as humans.⁶¹ We are optimistic that coordinated study of human tuberculous lung tissue with such models can be used with modern technologies to finally address long-standing questions about host/bacterium relationships in TB.

Viral infections. Over a long period of time, autopsies also have been a cornerstone for the detection of infectious diseases other than TB. Some 20% to 30% of infections in hospital patients remain undetected until a postmortem is performed.⁶²⁻⁶⁴ In recent years, autopsies have significantly contributed to the clarification of such infectious diseases caused by HIV, SARS, Hantavirus, West Nile Virus, and others. Especially important are postmortem examinations including detailed immunological and molecular techniques for the detection of diseases caused by reactivation of persistent infections with the herpes viruses varicella zoster, cytomegalovirus, Epstein-Barr virus, and human herpesviruses 6 and 7.⁶⁵⁻⁶⁸ Since many herpesviruses persist lifelong after primary infection, serology and some molecular techniques are insufficient to clearly define their causative role in individual diseases occurring later. Also, it is difficult, and sometimes impossible, to distinguish their causative and their opportunistic roles in such cases. Only a careful microscopic study assisted by immunohistological and molecular techniques can reveal the pathogenic activity of the infection. Detection of virus at the site of characteristically damaged cells and tissues as opposed to their presence in associated cells may elucidate the process. Only such combined efforts, including biopsy and autopsy studies, have allowed us to identify the causative roles of some herpesviruses in the individual patient.⁶⁹⁻⁷²

Another outstanding contribution was the AFIP studies of the 1917 influenza pandemic.^{73,74} In 2005, the entire genome sequence of the 1918 H1N1 pandemic influenza virus was completed from recovered remains of flu victims. This provided the breakthrough to study the virus in vitro and in vivo to better understand its properties, pathogenicity, transmissibility, and elicitation of host responses, with major implications for future prevention of subsequent influenza epidemics.

Ongoing Risks and Opportunities for the Autopsy

Into the Future

In 2009, the US National Academy of Sciences published a monograph entitled "A New Biology for the 21st Century"

stating that molecular biology of the 20th century was too narrowly focused to successfully address problems in areas such as evolution, morphogenesis, and infectious diseases.⁷⁵ As stated in the monograph, "Advancing from identifying parts to defining complex systems is well beyond its present capabilities." Carl Woese, a thought-provoking leader in this area, put it differently: "Science is impelled by 2 main factors, technological advance and a guiding vision (overview). A properly balanced relationship between the two is key to the successful development of a science. Without the proper technological advances the road ahead is blocked. Without a guiding vision there is no road ahead."⁷⁶ Biology hits the "wall of biocomplexity," meaning that simply defining molecular components is insufficient to understand higher levels of biologic functions.⁷⁶ Molecular and cellular biology have resulted in remarkable advances in areas such as the gene and complex cellular functions. However, they have been unable to successfully address questions of complex interactions such as evolution and the nature of biological form that are fundamentally not understandable as collections of parts.⁷⁶

Understanding such higher level functions requires a guiding vision to organize the technological advances. In the 19th and early 20th centuries, autopsies provided many guiding visions. For example, investigators understood the sequence of morbid changes that lead from infection to established pulmonary TB. They knew the clinical presentation, pathology, and radiologic appearance of each of the stages of TB very well, but the technical advances of their day were unable to address the biologic questions effectively. This ended in the late 1950s with the development of molecular biologic techniques and the decline in autopsies. Research interest shifted away from morphologic pathology to new areas of immunology, molecular microbiology, and genetics. Much of this research was carried out with in vitro and in vivo models.

The situation now has changed again. It has become increasingly apparent that many animal models do not adequately reproduce the human disease and that studies on isolated cells cannot explain many interactions within the human body. Such studies provide "technological advances." They define the parts (cells, molecules, and pathways), but they cannot provide the "guiding vision" required to put them together to understand complex biologic processes. We now recognize that formalin-fixed paraffin-embedded tissue (FFPET) blocks preserve the actual human disease with the entire microenvironment and regulatory molecules intact. We just need to learn to read them. In many situations, they can provide the guiding vision that is required to understand how the components work together.

We now can determine the DNA sequence and gene expression in FFPET blocks of any cell in any human organ.⁷⁷ As proof of principle, next-generation sequencing of FFPET from 4 phenotype-positive/genotype unknown cases all revealed putative disease-causing variants, including 2 cases of hypertrophic cardiomyopathy, 1 case of Noonan syndrome, and 1 case of Marfan syndrome.⁷⁸ We also can conduct 8 color immunofluorescence studies on FFPET with intact morphology allowing the

characterization of multiple markers on many types of individual cells in their native environment.⁷⁹ Three-dimensional microscopic images with multiplexed platform combining immunofluorescent and immunohistochemical markers are now being done.⁸⁰ With recent advances in the immunotherapy of cancer, the methods for studying mutations, cell maturation and differentiation, immune parameters, inflammation and healing on slides have advanced dramatically and will continue to increase.⁸¹ Thousands of studies can be done on single paraffin-embedded samples over a period of years. Enhanced imaging can monitor the lesions over time. This is providing new opportunities for studying human tissues and for developing animal models to be used in a coordinated fashion to address previously unanswerable questions. Although some human tissues, such as blood, skin, and many cancers, are readily available for research, tissues from many other diseases are seldom available by any means except autopsies.

The entire June 19 to 26, 2018, issue of the American Heart Association journal, *Circulation*, was devoted to the role of the autopsy in contemporary clinical and basic research in cardiovascular medicine, including genetic studies.⁸²⁻⁸⁵ Guidelines for contemporary autopsy studies of sudden cardiac death have been published.⁸⁶ Postmortem genetic testing (the so-called molecular autopsy) is now scientifically feasible, although the financing of these studies is problematic.⁸⁷⁻⁸⁹ Blood or fresh tissue samples for DNA and RNA analysis are still preferable. But technological progress is making it increasingly feasible to perform genetic analyses on FFPE.^{77,78} This is opening up great new opportunities for pathologists to pursue cutting-edge studies from materials obtained during the clinical practice of pathology, including the autopsy.

A detailed analysis has been developed for best practices and future directions for the autopsy in the 21st century.⁹⁰ The contemporary autopsy can be placed in the context of larger health-care systems with the use of autopsy in quality improvement and a valuable professional activity, as well as a procedure that adapts new technology that affects practice models. Particularly for public health purposes, constructs have been designed for minimally invasive autopsies.^{91,92} There is also a growing field of utilization of autopsies to be performed on an urgent basis to sample both diseased and normal control tissue for research, optimally within 6 to 8 hours of death. These “rapid research autopsies” are especially crucial to cancer research and the growth of personalized medicine.⁹⁰ The science behind utilization of autopsy tissue is providing for a full template for designing and delivering a successful rapid autopsy program. The contemporary autopsy has an important role as a clinical outcome measure and valuable scientific resource. With the advent of “personalized medicine,” especially in the treatment of patients with cancer, the specialty of Pathology has assumed a key role in determining molecularly oriented, gene-specific cancer therapies.

Perhaps one of the most important studies utilizing the autopsy in this era of “personalized medicine” is one presently underway at The Ohio State University and at a number of other institutions comparing the genomic profile of the primary

cancer with those of metastases in different organ sites in the same patient.⁹³⁻⁹⁵ At the present time, the selection of specific cancer therapeutics is based on genomic profiling of the primary tumor, based on the assumption that metastases at various organ sites will have the same genomic profile, irrespective of the site of the metastases, which may be growing in different microenvironments. It is now becoming apparent that this is not the case and that the genomic profile of the primary tumor may not be the same as the metastases.⁹⁶ Therefore, in order to develop more effective, molecularly targeted therapies, it will be necessary to further “personalize” the treatment to target tumors in different microenvironments. Practically, what does this mean for patients with cancer? Very simply put, biopsies of metastatic tumors at different organ sites must also be subjected to genomic analysis since therapeutically targeted mutations in the primary tumor may be quite different from those in the metastases. Autopsy studies should be able to confirm or refute this hypothesis, which ultimately may have great clinical significance. Implementation of these contemporary approaches to autopsy has the potential to lead to an unexpected renaissance for autopsy as new and improved uses are found for postmortem examination in quality improvement, education, and research.

Role of Academic Pathologists in Advancement of the Autopsy

Yes, the future of the autopsy in research in the molecular and genetic age is great. Yet the problem remains of the very low autopsy rates, even in our academic institutions. Pathology educators have utilized a variety of approaches to attempt to put the importance of the autopsy into the consciousness of medical students (undergraduate medical education) and residents and fellows (Graduate Medical Education).⁹⁷⁻¹⁰² However, this task has been made much more difficult by the trends in modern undergraduate medical education where the perception of needed curriculum reform has led to an integrated curriculum with a focus on patient-centered approach through which problem-based learning has replaced the traditional subject-based curriculum.^{7,97-99} This has resulted in the discontinuation of pathology courses and their replacement by elements of pathology scattered throughout the preclinical years which, not surprisingly, has contributed to a reduced understanding and interest in pathology.⁷ This problem is compounded by generally minimal interaction with pathology and pathologists in the clinical clerkship years.¹⁰⁰ Exposure of medical students to the autopsy is a casualty of the process.

The removal of categorical pathology courses in the post-Flexnerian medical curricula has had negative effects both on the discipline of pathology and on the vast majority of medical students who pursue careers in clinical medicine.^{7,100-104} Because of minimal exposure to autopsy during medical school, clinical residents and faculty have a dearth of understanding of practical issues related to requesting an autopsy, including attitudes of family and how best to approach them to obtain permission for autopsy.¹⁰⁵⁻¹⁰⁷ Even within the ranks of

pathology, the importance of the autopsy in the pathology residency curriculum has been questioned. An Autopsy Working Group of the Association of Pathology Chairs recently has issued a report addressing the continued relevance of the autopsy in education of pathologists.¹⁰⁸

Our challenge as academic pathologists, whose careers have been molded by involvement in the autopsy, is to counter these trends. Academic pathologists need to work at the local, national, and international levels to be proactive advocates of the autopsy to medical students in the preclinical and clinical years, residents, fellows, pathology faculty colleagues, faculty in other departments, medical school leaders, hospital administrators, nursing staff, and when the opportunity arises, the general public. The challenges are great but the benefits for medicine and society are enormous.

Authors' Note (Post Review)

We also have demonstrated the importance of the autopsy in setting straight the historical record regarding the cause of death of important personages: adenocarcinoma of the gallbladder (not the liver) in the case of Sun Yat-sen and hypertensive cerebral hemorrhage in the case of Joseph Stalin.^{109,110}

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ORCID iD

Louis Maximilian Buja, MD  <https://orcid.org/0000-0001-8386-7029>

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