ISBN: 978-93-342-1790-2

Pathoinsights: Dissecting Disease Mechanisms

Authors:

Dr. Titlee Majumder
Dr. Rajen Dey
Mr. Manojit Bysack
Dr. Oly Banerjee
Mr. Rupak Bera,

Vol I

PATHOINSIGHTS: DISEASE DISSECTING MECHANISMS

Volume 1

AUTHORS:

DR. TITLEE MAJUMDER

DR. RAJEN DEY

MR. MANOJIT BYSACK

DR. OLY BANERJEE

MR. RUPAK BERA

SWAMI VIVEKANANDA UNIVERSITY

Published by Swami Vivekananda University (Institutional Publishers), Kolkata-700121

ISBN: Third Edition: January, 2025

Publisher: Swami Vivekananda University (Institutional Publisher), Kolkata-700121, India
Contact us: hod.mlt@svu.ac.in

Preface

The human body is a marvel of intricate biological processes, functioning in a delicate balance to sustain life. However, when this equilibrium is disrupted, diseases arise, leading to a cascade of pathological events that can significantly impact health. Understanding the underlying mechanisms of these diseases is fundamental to developing effective diagnostics, treatments, and preventive strategies.

Pathoinsights: Disease-Dissecting Mechanisms is an endeavor to bridge the gap between complex pathological processes and their real-world implications. This book delves deep into the molecular, cellular, and systemic alterations that drive various diseases, unraveling the intricate pathways that govern their onset and progression. Each chapter presents a thorough analysis of a specific pathological condition, exploring its etiology, pathogenesis, and the biochemical and physiological disruptions that define it.

Designed for students, researchers, and healthcare professionals, this book provides a structured approach to disease mechanisms, supported by the latest scientific research and illustrative explanations. Whether you are a medical student seeking clarity on disease pathology, a researcher aiming to explore novel therapeutic targets, or a clinician striving for a deeper understanding of disease processes, **Pathoinsights** serves as a valuable resource to enhance your knowledge and clinical acumen.

Scientific advancements continue to reshape our understanding of diseases, and this book aspires to provide a solid foundation while encouraging curiosity and further exploration. As we dissect these mechanisms, we move one step closer to unraveling the mysteries of pathology, ultimately paving the way for better medical interventions and improved patient outcomes.

With this in mind, I invite you to embark on this journey through the fascinating world of disease mechanisms, where science meets pathology in its most profound form.

(Dr. Oly Banerjee)
Assistant Professor
Swami Vivekananda University
Kolkata, West Bengal, India

Acknowledgement

I am writing to show my sincere gratitude for the support and encouragement to Swami Vivekananda University, Kolkata, India provided in the creation of this book, **" Pathoinsights: Disease-Dissecting Mechanisms".** The commitment from university to fostering education and research has played a pivotal role in shaping the content and direction of this publication. We are extremely thankful of the collaborative spirit and resources offered by Swami Vivekananda University, Kolkata which have allowed us to exploreand share the latest innovations and technologies across various fields. We hope that this book serves as a valuable resource for this esteemed institution and the broader academic community, reflecting our shared dedication to knowledge, progress, and the pursuit of excellence.

With sincere appreciation,

(Dr. Oly Banerjee)
Assistant Professor
Swami Vivekananda University
Kolkata, West Bengal, India

Authors' conflict

We state to declare that no authors have shown any misjudgment and confliction of decisions during the time of preparing contents of book & no such data have been manipulated of falsified during writing.

The traditional concept of hematological disorders has been catered and the cytological alteration in the volume of the blood is the primary area of emitting knowledge, which is a cumulative decision of the authors.

Thank you
Dr. Oly Banerjee
Assistant Professor, Swami Vivekananda University
Barrackpore, Kolkata, West Bengal, India

List of Authors

1. Dr. Oly Banerjee, Assistant Professor & Head, Department of Medical Laboratory Technology, Swami Vivekananda University.
2. Dr. Rajen Dey, Assistant Professor, Department of Medical Laboratory Technology, Swami Vivekananda University.
3. Mr. Manojit Bysack, Assistant Professor, Department of Medical Laboratory Technology, Swami Vivekananda University.
4. Mr. Rupak Bera, Laboratory Assistant, Department of Medical Laboratory Technology, Swami Vivekananda University.
5. Dr. Titlee Majumder, Assistant Professor, Department of Medical Laboratory Technology, Swami Vivekananda University.

Table of Contents:

Chapter 1

PATHOLOGY: AN INTRODUCTION & OVERVIEW

Chapter 2

AN IN-DEPTH EXPLORATION OF CELLULAR INJURY, THE ASSOCIATED RESPONSES, AND MECHANISMS OF CELLULAR ADAPTATION

Chapter 3

INFLAMMATORY PERSPECTIVE OF DISEASE: FROM MOLECULES TO ORGANS

Chapter 4

WHEN DEFENSE TURNS DESTRUCTIVE: THE SCIENCE OF HYPERSENSITIVITY

Chapter 5

Understanding Hemorrhage- A life threatening emergency: Mechanisms, Management and Mitigation strategies

Chapter 1

PATHOLOGY: AN INTRODUCTION & OVERVIEW

Dr. Titlee Majumder

Assistant Professor, Department of Medical Laboratory Technology, School of Allied Health Sciences, Swami Vivekananda University, Telinipara, Barasat-Barrackpore Rd, Bara Kanthalia, West Bengal- 700121, India

Email: titleem@svu.ac.in

1.1 Introduction

Definition: Pathology is the study of diseases, focusing on their causes, processes, development, and consequences.

It's a crucial field in medicine that bridges basic science with clinical practice, helping doctors understand the mechanisms behind diseases and how they affect the body. The science of knowing a human body said as human physiology in a state of homeostasis, where as alterations or abnormalities in the physiological system leads to clinical manifestations or pathophysiology (1, 2).

1.1 a) Various aspects of pathology:

1. Etiology (Cause of Disease):

Pathology investigates the origin of diseases, identifying factors like infections, genetic mutations, environmental influences, and lifestyle choices that can lead to illness.

2. Pathogenesis (Development of Disease):

This area explores how diseases progress from the initial cause to the manifestation of symptoms. It looks at the cellular and molecular changes that occur during this process (3).

3. Morphology (Structural Changes):

Pathologists study the structural changes in cells, tissues, and organs that result from disease. These changes can be observed through various techniques, including microscopy, which allows for the examination of tissue samples.

4. Clinical Manifestations:

This involves understanding how the structural and functional changes in tissues lead to symptoms and signs of disease. Pathologists help correlate these findings with clinical outcomes (4).

5. Diagnosis:

Pathology plays a central role in diagnosing diseases. Pathologists analyze tissue samples, blood, and other body fluids to identify abnormalities. Their findings guide clinicians in choosing appropriate treatments.

6. Prognosis and Treatment:

Based on pathological findings, doctors can predict the likely course of a disease (prognosis) and determine the best treatment options. Pathology also helps monitor the effectiveness of treatments.

1.2 History

The history of pathology is rich and spans centuries, evolving alongside advances in medicine, science, and technology. Here's a broad overview:

Ancient and Classical Periods:

1.2 a) Early Observations:

Pathology, as a concept, dates back to ancient civilizations, where early physicians observed and documented disease symptoms. The Egyptians, for instance, recorded medical knowledge on papyrus, and the famous Edwin Smith Papyrus (around 1600 BCE) contains descriptions of injuries, infections, and diseases. In the theory of Hippocrates and Humoral it is said as in ancient Greece, Hippocrates (circa 460-370 BCE), often called the "Father of Medicine," proposed the humoral theory. He believed that disease was caused by imbalances in the body's four humors: blood, phlegm, black bile, and yellow bile. Although incorrect, this theory dominated medical thought for centuries. As per Galen's (129-216 CE)

Contributions it is stated various improvements on expanding the ideas of Hippocrates' and made significant contributions to anatomy by understanding the kind of disease. His writings influenced medical practice in Europe and the Middle East for over a millennium (5,6,7).

1.2 b) In Medieval Period:

1. Islamic Golden Age:

During the Islamic Golden Age (8th-14th centuries), scholars like Avicenna (Ibn Sina) (980-1037) made crucial advancements in medical knowledge. Avicenna's "Canon of Medicine" synthesized earlier knowledge and included descriptions of diseases and their treatments, influencing both Eastern and Western medicine (8).

2. Autopsies and Dissections:

Although human dissections were rare in the medieval period due to religious and cultural taboos, some were performed in Europe, leading to a better understanding of anatomy and disease.

1.2 c) Renaissance and Early Modern Period:

1. Rise of Anatomical Pathology:

The Renaissance saw a revival of interest in human anatomy and dissection. Andreas Vesalius (1514-1564) published "De humani corporis fabrica" (On the Fabric of the Human Body), challenging Galen's anatomical errors and laying the groundwork for modern anatomy (9).

2. Giovanni Morgagni and the Birth of Modern Pathology:

Giovanni Battista Morgagni (1682-1771) is often considered the "Father of Modern Pathology." In his seminal work "De Sedibus et Causis Morborum per Anatomen Indagatis" (1761), Morgagni correlated clinical symptoms with post-mortem anatomical findings, establishing the foundation of pathological anatomy.

1.2 d) During 19th Century:

1. Cell Theory and Rudolf Virchow:

The 19th century was transformative for pathology. Rudolf Virchow (1821-1902), a German physician and pathologist, introduced the concept that diseases arise from cellular abnormalities. His famous statement, "Omnis cellula e cellula" (every cell arises from another cell), laid the groundwork for cellular pathology (10).

2. Advances in Microscopy:

The development of the microscope allowed pathologists to examine tissues and cells in greater detail. This led to the identification of microorganisms as the cause of infectious diseases, advancing the germ theory of disease (11,12).

3. Emergence of Bacteriology:

Scientists like Louis Pasteur (1822-1895) and Robert Koch (1843-1910) made groundbreaking discoveries in bacteriology, linking specific pathogens to diseases. Koch's postulates provided a framework for identifying causative agents of infectious diseases.

1.2 e) 20th Century to Present:

1. Molecular Pathology:

The discovery of DNA's structure in 1953 by James Watson and Francis Crick revolutionized biology and pathology. The field of molecular pathology emerged, allowing for the study of diseases at the genetic and molecular levels. Techniques such as PCR, gene sequencing, and the identification of biomarkers have become standard tools (13).

2. Immunohistochemistry and Advanced Imaging:

The development of immunohistochemistry in the late 20th century enabled pathologists to identify specific proteins in tissues, aiding in the diagnosis of various cancers and other diseases. Advanced imaging technologies, such as electron microscopy and digital pathology, have further enhanced diagnostic capabilities.

3. Personalized Medicine:

Today, pathology plays a critical role in personalized medicine, where treatments are tailored to the individual based on their genetic makeup. Advances in molecular pathology have led to targeted therapies for conditions like cancer, improving outcomes and reducing side effects (14).

4. Digital and Computational Pathology:

The advent of digital pathology and artificial intelligence (AI) is transforming the field, allowing for more accurate diagnoses and faster processing of large datasets. AI algorithms are increasingly

being used to assist pathologists in analyzing complex images and identifying patterns indicative of specific diseases.

1.3 Classification of Pathology:

1. Anatomical Pathology: Anatomical pathology is a branch of pathology that focuses on the study of the structural and morphological changes in tissues and organs associated with disease. It is a crucial field in medicine that provides essential insights into the diagnosis, understanding, and treatment of various conditions, particularly cancers and other complex diseases (15,16).

The components of anatomical pathologies are as follows

• Histopathology:

Definition: Histopathology involves the microscopic examination of tissues to study the manifestations of disease. This is often done by analyzing biopsy samples or surgical specimens.

Process: Tissue samples are processed, embedded in paraffin, sliced into thin sections, stained with dyes (like hematoxylin and eosin), and examined under a microscope (17,18).

Applications: Histopathology is essential for diagnosing cancers, inflammatory conditions, infections, and other diseases. The examination of tissue architecture, cell morphology, and patterns of disease are central to making accurate diagnoses.

• Cytopathology:

Definition: Cytopathology is the study of individual cells or clusters of cells to diagnose diseases. It is commonly used for cancer screening and diagnosis.

Common Techniques:

Pap Smear: Used in screening for cervical cancer.

Fine Needle Aspiration (FNA): A technique where cells are aspirated from a lump or mass and examined under a microscope.

Applications: Cytopathology is crucial in the early detection of cancers, particularly in accessible tissues like the cervix, lungs, and thyroid. It is also used to diagnose infectious diseases and inflammatory conditions (20,21).

- Autopsy Pathology:

Definition: Autopsy pathology involves the examination of the body after death (postmortem) to determine the cause of death, understand the extent of disease, and evaluate the effects of treatments.

Process: A thorough external and internal examination of the body is conducted, often including the dissection of organs and tissues, followed by microscopic analysis.

Applications: Autopsies are important for understanding disease processes, confirming clinical diagnoses, and providing information for public health and legal investigations (22,23).

- Forensic Pathology:

Definition: Forensic pathology is a subspecialty of anatomical pathology focused on determining the cause of death in cases of sudden, unexpected, or suspicious deaths.

Role: Forensic pathologists perform autopsies and analyze tissue samples, toxicology reports, and other evidence to help establish the cause and manner of death (natural, accidental, homicide, or suicide).

Applications: Forensic pathology is critical in legal investigations and criminal cases, helping to provide crucial evidence in court (24,25).

- Neuropathology:

Definition: Neuropathology specializes in the study of diseases of the nervous system, including the brain, spinal cord, and nerves.

Role: Neuropathologists examine brain tissue in cases of neurodegenerative diseases (like Alzheimer's disease), brain tumors, and trauma.

Applications: Neuropathology plays a key role in diagnosing central nervous system disorders and guiding treatment decisions (26).

- Surgical Pathology:

Definition: Surgical pathology involves the examination of tissues removed during surgery to diagnose disease and determine the next steps in patient care.

Role: Surgical pathologists provide rapid intraoperative consultations (often through frozen section analysis) to assist surgeons in making immediate decisions during surgery.

Applications: It is crucial in determining the margins of tumors, staging cancer, and identifying other pathological conditions that may affect surgical outcomes (27, 28).

- Clinical Pathology:

Clinical pathology, also known as laboratory medicine, is a branch of pathology that focuses on the analysis of blood, urine, tissues, and other body fluids to diagnose diseases, monitor treatment, and promote overall health. It plays a critical role in patient care, providing essential information for diagnosing and managing various conditions, from infections and anemia to metabolic

disorders and cancers. It deals with the analysis of blood, urine, and other body fluids. It includes areas like hematology, microbiology, insertion techniques, immunology, serology, clinical biochemistry and chemical pathology (29).

Clinical pathology is integral to modern healthcare, providing the data necessary for accurate diagnosis, treatment planning, and disease prevention. Through a combination of advanced technology and skilled interpretation, clinical pathologists ensure that patients receive precise and timely medical care (30).

• Molecular Pathology:

Molecular pathology is a specialized branch of pathology that focuses on the study and diagnosis of disease through the examination of molecules within organs, tissues, or bodily fluids. It combines aspects of traditional pathology with molecular biology to provide a deeper understanding of disease mechanisms at the genetic and molecular levels. Molecular pathology plays a crucial role in modern medicine, particularly in the fields of oncology, genetic disorders, and infectious diseases. This modern branch of pathology involves the study of disease at the molecular level, including genetic testing and biomarker identification (31).

1.4 Importance of Pathology:

Pathology is of immense importance in medicine and healthcare for several reasons, contributing to almost every aspect of patient care, from diagnosis to treatment and prevention. Role of pathology is not only limited within this it is also extremely important in the research to identify newer frontiers. The drug delivery system is also dependent upon the growth and development of the pathological aspects, even in terms of dose dependent aspects (33).

Here's an overview of the key roles that pathology plays:

a. Accurate Diagnosis:

• Core Function: Pathology is crucial for diagnosing diseases. Through the analysis of tissues, cells, and body fluids, pathologists can identify the nature of a disease, whether it's infectious, inflammatory, neoplastic (related to tumors), or genetic.

• Example: In cancer, pathology determines the type, grade, and stage of the tumor, which are essential for deciding the best course of treatment.

b. Guiding Treatment Decisions:

• Tailored Therapy: Pathology provides detailed information that helps physicians choose the most appropriate treatments. For instance, molecular pathology can identify specific genetic mutations in a tumor that may respond to targeted therapies.

• Monitoring Effectiveness: Pathologists also monitor the effectiveness of treatments through follow-up tests, ensuring that therapies are working as intended.

c. Prognosis:

• Predicting Outcomes: Pathological findings help in predicting the likely course of a disease (prognosis). This information is crucial for planning treatment strategies, setting patient expectations, and providing the most appropriate care.

• Risk Stratification: Pathology helps identify high-risk patients who may need more aggressive treatment or closer monitoring.

d. Public Health:

• Disease Surveillance: Pathologists play a key role in tracking the spread of infectious diseases, identifying new pathogens, and understanding epidemiological trends. This is vital for public health responses, including vaccination strategies and outbreak control.

• Population Health: Through autopsies and studies of population health trends, pathology provides insights into the causes of death and disease patterns, informing public health policies and preventive measures.

e. Medical Research:

• Advancing Knowledge: Pathology is at the forefront of medical research, contributing to the understanding of disease mechanisms. Research in pathology leads to the discovery of new diseases, biomarkers, and therapeutic targets.

• Development of Treatments: Many medical advances, such as the development of new drugs or vaccines, are based on findings from pathological research (34).

f. Education and Training:

• Teaching: Pathology is a fundamental part of medical education, helping students and healthcare professionals understand disease mechanisms, interpret laboratory results, and make informed clinical decisions.

• Training Specialists: Pathology departments in hospitals and academic institutions are essential for training the next generation of pathologists and researchers (35).

g. Forensic Investigations:

• Legal Medicine: Forensic pathology is crucial in determining the cause of death in cases of sudden, unexplained, or suspicious deaths. The findings can have significant legal implications and provide closure for families.

• Public Safety: Forensic pathologists contribute to criminal investigations, helping law enforcement understand circumstances surrounding deaths, which is vital for justice and public safety.

h. Quality Assurance in Healthcare (36):

• Diagnostic Standards: Pathology labs establish and maintain high standards for diagnostic accuracy, ensuring that patients receive reliable and timely results. This quality control is vital for the overall functioning of healthcare systems.

• Accreditation and Compliance: Pathology departments are often involved in maintaining compliance with healthcare regulations and standards, contributing to patient safety and care quality.

i. Innovation and Technology Integration:

• Digital Pathology: The integration of digital tools and artificial intelligence in pathology is transforming the field, enabling more precise and rapid diagnoses, as well as enhancing research capabilities.

• Personalized Medicine: Pathology is essential in the era of personalized medicine, where treatments are customized based on individual patient characteristics, such as genetic profiles.

j. Global Health:

• Addressing Global Challenges: Pathologists contribute to global health by researching and addressing diseases that affect populations worldwide, such as HIV/AIDS, malaria, and emerging infectious diseases. Their work is critical in developing global health strategies and interventions.

l. Importance in Medicine:

• Diagnosis: Pathology is essential for accurate diagnosis, guiding treatment decisions, and improving patient outcomes.

• Research: It contributes to medical research by providing insights into the mechanisms of diseases, leading to the development of new treatments and therapies.

• Public Health: Pathologists play a vital role in identifying and controlling disease outbreaks and contributing to public health policies.

1.5 Futuristic approaches in Pathology

The future of pathology is being shaped by several cutting-edge technologies and methodologies that promise to enhance diagnostic accuracy, efficiency, and patient outcomes (37, 38, 39). Here are some key trends and approaches expected to play a significant role:

Digital Pathology and AI Integration:

Whole Slide Imaging (WSI): The digitization of pathology slides allows for the creation of high-resolution digital images, which can be stored, shared, and analyzed more efficiently than traditional glass slides.

Artificial Intelligence (AI) and Machine Learning (ML): AI algorithms can assist pathologists by quickly identifying patterns, detecting anomalies, and even predicting disease progression. This can reduce human error and improve diagnostic precision.

Molecular Pathology and Genomics:

Next-Generation Sequencing (NGS): NGS enables detailed analysis of genetic mutations and alterations at a molecular level. This is crucial for personalized medicine, where treatment is tailored to the genetic profile of an individual's disease.

Liquid Biopsy: This minimally invasive method allows for the detection of circulating tumor DNA (ctDNA) and other biomarkers in blood samples, offering a way to monitor cancer and other diseases in real-time.

Personalized and Precision Medicine

Targeted Therapies: Pathology is increasingly involved in identifying specific biomarkers that can guide the use of targeted therapies, especially in oncology.

Pharmacogenomics: This involves studying how an individual's genetic makeup affects their response to drugs, leading to more personalized treatment plans.

Advanced Imaging Techniques :

Multiplex Immunohistochemistry (IHC) and Imaging Mass Cytometry: These techniques allow for the simultaneous visualization of multiple biomarkers in a single tissue section, providing deeper insights into the tumor microenvironment.

3D Imaging: Advances in 3D reconstruction of tissues from serial sections are providing more detailed spatial context, which is crucial for understanding complex disease processes.

Telepathology

Remote Diagnosis: Telepathology allows pathologists to consult and diagnose cases remotely using digital slides. This is particularly beneficial in regions with a shortage of specialized pathologists.

Collaboration and Second Opinions: Digital platforms enable easier collaboration between experts globally, ensuring that complex cases receive the best possible interpretation.

Integration of Multi-Omics Data

Comprehensive Analysis: The integration of genomics, transcriptomics, proteomics, and metabolomics data with traditional pathology is leading to a more holistic understanding of diseases.

Bioinformatics Tools: Advanced bioinformatics platforms are being developed to handle and interpret the vast amounts of data generated from multi-omics approaches, aiding in more accurate diagnoses.

Automation and Robotics: Automated Slide Preparation and Staining:** Robotics is increasingly being used to automate labor-intensive processes like slide preparation and staining, reducing human error and increasing efficiency.

Automated Image Analysis: AI-driven tools are increasingly capable of analyzing digital pathology images, identifying regions of interest, and providing preliminary diagnoses, which pathologists can then review.

Ethical and Regulatory Considerations -

Data Privacy and Security: With the increasing digitization of patient data, ensuring the privacy and security of this information is paramount.

Regulatory Approvals for AI Tools: As AI tools become more prevalent, they will need to undergo rigorous validation and regulatory approval processes to ensure they are safe and effective.

Education and Training

Virtual and Augmented Reality (VR/AR): These technologies are being used to enhance the training of future pathologists, allowing for immersive and interactive learning experiences.

Continuous Learning: With rapid advancements in technology, continuous education will be essential for pathologists to stay updated with the latest tools and techniques.

Sustainability and Global Health

Accessible Diagnostics: Efforts are underway to develop low-cost, easy-to-use diagnostic tools that can be deployed in resource-limited settings, addressing global health disparities.

Sustainable Practices: As the field evolves, there is a growing emphasis on adopting environmentally sustainable practices in laboratory operations.

Pathology is a dynamic and evolving field, integrating new technologies and scientific discoveries to improve healthcare. Pathology has been instrumental in advancing medical knowledge, improving diagnostic accuracy, and developing effective treatments. It remains a dynamic field that continues to evolve with new scientific discoveries and technological innovations, playing a crucial role in modern healthcare. These advances collectively point to a future where pathology becomes more integrated with other disciplines, more reliant on technology, and more focused on personalized patient care (40).

References

1. Kierszenbaum, A. L., & Tres, L. (2015). Histology and Cell Biology: an introduction to pathology E-Book. Elsevier Health Sciences.

2. Ainsworth, G. C. (1981). Introduction to the history of plant pathology. Cambridge University Press.

3. Cheville, N. (1994). Ultrastructural pathology. An introduction to interpretation, 946.

4. Crowley, L. V. (2013). An introduction to human disease: pathology and pathophysiology correlations. Jones & Bartlett Publishers.

5. Pardridge, W. M. (Ed.). (1998). Introduction to the blood-brain barrier: methodology, biology and pathology. Cambridge University Press.

6. Rosai, J. (2011). Rosai and Ackerman's surgical pathology e-book. Elsevier Health Sciences.

7. MacCallum, W. G. (1924). A Text-book of Pathology. WB Saunders.

8. Finkbeiner, W. E., Connolly, A. J., Ursell, P. C., & Davis, R. L. (2009). Autopsy Pathology: A Manual and Atlas E-Book. Elsevier Health Sciences.

9. Bowen, I. (2012). Cell death in biology and pathology. Springer Science & Business Media.

10. Wallig, M. A., Bolon, B., Haschek, W. M., & Rousseaux, C. G. (Eds.). (2017). Fundamentals of toxicologic pathology. Academic press.

11. Hornick, J. L. (2017). Practical soft tissue pathology: a diagnostic approach: a volume in the pattern recognition series. Elsevier Health Sciences.

12. Broom, D. M. (2006). Behaviour and welfare in relation to pathology. Applied Animal Behaviour Science, 97(1), 73-83.

13. Kertesz, A., McMonagle, P., Blair, M., Davidson, W., & Munoz, D. G. (2005). The evolution and pathology of frontotemporal dementia. Brain, 128(9), 1996-2005.

14. Hoerder-Suabedissen, A., & Molnár, Z. (2015). Development, evolution and pathology of neocortical subplate neurons. Nature Reviews Neuroscience, 16(3), 133-146.

15. Diogo, R., Smith, C. M., & Ziermann, J. M. (2015). Evolutionary developmental pathology and anthropology: A new field linking development, comparative anatomy, human evolution, morphological variations and defects, and medicine. Developmental Dynamics, 244(11), 1357-1374.

16. Hermanek, P. (1982). Evolution and pathology of rectal cancer. World journal of surgery, 6(5), 502-509.

17. Cooper, D. N. (2002). Human gene mutation in pathology and evolution. Journal of inherited metabolic disease, 25(3), 157-182.

18. Judelson, H. S. (2012). Dynamics and innovations within oomycete genomes: insights into biology, pathology, and evolution. Eukaryotic Cell, 11(11), 1304-1312.

19. Yano, M., Kumada, H., Kage, M., Ikeda, K., Shimamatsu, K., Inoue, O., ... & Okuda, K. (1996). The long-term pathological evolution of chronic hepatitis C. Hepatology, 23(6), 1334-1340.

20. Peters, C. M., Jimenez-Andrade, J. M., Kuskowski, M. A., Ghilardi, J. R., & Mantyh, P. W. (2007). An evolving cellular pathology occurs in dorsal root ganglia, peripheral nerve and spinal cord following intravenous administration of paclitaxel in the rat. Brain research, 1168, 46-59.

21. Nankivell, B. J., Renthawa, J., Sharma, R. N., Kable, K., O'Connell, P. J., & Chapman, J. R. (2017). BK virus nephropathy: histological evolution by sequential pathology. American Journal of Transplantation, 17(8), 2065-2077.

22. Kishimoto, C., Hung, G. L., Ishibashi, M., Khaw, B. A., Kolodny, G. M., Abelmann, W. H., & Yasuda, T. (1991). Natural evolution of cardiac function, cardiac pathology and antimyosin scan in a murine myocarditis model. Journal of the American College of Cardiology, 17(3), 821-827.

23. McDonald, W. I., Miller, D. H., & Barnes, D. (1992). The pathological evolution of multiple sclerosis. Neuropathology and applied neurobiology, 18(4), 319-334.

24. Beaver, J. T., Lelutiu, N., Habib, R., & Skountzou, I. (2018). Evolution of two major Zika virus lineages: implications for pathology, immune response, and vaccine development. Frontiers in immunology, 9, 1640.

25. Metchnikoff, E. (1893). Lectures on the comparative pathology of inflammation delivered at the Pasteur Institute in 1891. Рипол Классик.

26. Marenholz, I., Heizmann, C. W., & Fritz, G. (2004). S100 proteins in mouse and man: from evolution to function and pathology (including an update of the nomenclature). Biochemical and biophysical research communications, 322(4), 1111-1122.

27. Matthews, P. M., & Arnold, D. L. (2001). Magnetic resonance imaging of multiple sclerosis: new insights linking pathology to clinical evolution. Current opinion in neurology, 14(3), 279-287.

28. García-Cabezas, M. Á., Zikopoulos, B., & Barbas, H. (2019). The Structural Model: a theory linking connections, plasticity, pathology, development and evolution of the cerebral cortex. Brain Structure and Function, 224(3), 985-1008.

29. Malik, D., Mahendiratta, S., Kaur, H., & Medhi, B. (2021). Futuristic approach to cancer treatment. Gene, 805, 145906.

30. Kulkarni, S. P. (2024). Therapeutic Pathology-The Pathology of Tomorrow. Journal of Experimental Pathology, 5(1), 1-5.

31. Gupta, S., & Parveen, S. (2024). Potential role of microRNAs in personalized medicine against hepatitis: a futuristic approach. Archives of Virology, 169(2), 33.

32. Ferreira-Silva, J., Medas, R., Girotra, M., Barakat, M., Tabibian, J. H., & Rodrigues-Pinto, E. (2022). Futuristic developments and applications in endoluminal stenting. Gastroenterology Research and Practice, 2022(1), 6774925.

33. Miree, O., Srivastava, S. K., Dasgupta, S., Singh, S., Rocconi, R., & Singh, A. P. (2021). Current and futuristic roadmap of ovarian cancer management: an overview. Ovarian Cancer: Molecular & Diagnostic Imaging and Treatment Strategies, 1-19.

34. Rahman, M. A., Yilmaz, I., Albadri, S. T., Salem, F. E., Dangott, B. J., Taner, C. B., ... & Akkus, Z. (2023). Artificial intelligence advances in transplant pathology. Bioengineering, 10(9), 1041.

35. Rakha, E. A., & Pareja, F. G. (2021, July). New advances in molecular breast cancer pathology. In Seminars in cancer biology (Vol. 72, pp. 102-113). Academic Press.

36. Hutchins, G. G. A., & Grabsch, H. I. (2009). Molecular pathology—the future?. The Surgeon, 7(6), 366-377.

37. Schumacher, V. L., Aeffner, F., Barale-Thomas, E., Botteron, C., Carter, J., Elies, L., ... & Williams, B. (2021). The application, challenges, and advancement toward regulatory acceptance of digital toxicologic pathology: results of the 7th ESTP international expert workshop (September 20-21, 2019). Toxicologic Pathology, 49(4), 720-737.

38. Caie, P. D., & Harrison, D. J. (2018). Digital pathology: path into the future. In Tissue Phenomics: Profiling Cancer Patients for Treatment Decisions (pp. 185-198). Jenny Stanford Publishing.

39. Niazi, M. K. K., Parwani, A. V., & Gurcan, M. N. (2019). Digital pathology and artificial intelligence. The lancet oncology, 20(5), e253-e261.

40. Hassell, L. A., Absar, S. F., Chauhan, C., Dintzis, S., Farver, C. F., Fathima, S., ... & Bui, M. (2023). Pathology education powered by virtual and digital transformation: now and the future. Archives of Pathology & Laboratory Medicine, 147(4), 474-491.

Chapter 2

AN IN-DEPTH EXPLORATION OF CELLULAR INJURY, THE ASSOCIATED RESPONSES, AND MECHANISMS OF CELLULAR ADAPTATION

Mr. Manojit Bysack

Department of Medical Laboratory Technology, School of Allied Health Sciences, Swami Vivekananda University, Telinipara, Barasat-Barrackpore Rd, Bara Kanthalia, West Bengal-700121, India

Email: monojitb@svu.ac.in

2.1. INTRODUTION:

The term "cell injury" describes how different stressors, or causative agents, affect a cell and cause changes to both its internal and exterior environment. The two primary elements that affect the extent of cell injury are (i) host factors, which include the kind of cell and tissue involved, and (ii) factors connected to the injurious agent, which include the type and intensity of cell injury. Depending on the properties of the cells, their metabolism, blood supply, and nutritional state, damage may be reversible or irreparable. The ideas of reversible and irreversible injury originate from the capacity of a cell to heal after suffering a harm. The kind, extent, and length of the damage may determine whether the cell survives. Even though cells can heal themselves remarkably well by adjusting to their surroundings, if an injury is too great for them to heal or adapt, they may die. An irreversible cell injury known as necrosis, which can be brought on by external sources like infections, ischemia, or the environment, causes a portion or all of the cell to die. In contrast,

apoptosis, also known as programmed cell death (PCD), is a process that is triggered by internal factors such as genetic impulses [1]. Injuries include ischemia, which is reduced blood flow, heat exhaustion, toxic exposure, and physical trauma can all lead to necrosis. In order to get rid of cellular debris, cells going through apoptosis may also undergo secondary necrosis, or apoptotic necrosis [2]. Necrosis is now understood to be a process that can be stopped and regulated rather than a random or uncontrollable occurrence. This finding creates new opportunities for the development of treatments aimed at necrotic disorders [3].

2.2. OVERVIEW OF CELLULAR RESPONSES TO STIMULI:

- Cells function within a narrow range of physiological conditions, maintaining a state of homeostasis.

- Homeostasis refers to the balance in the cell's microenvironment, encompassing both chemical factors (like electrolytes, glucose, and pH) and physical factors (such as temperature).

- In order to adjust to changes in their surroundings, cells constantly alter their structure and function.

- To preserve a cell's viability and functionality, adaptation entails changing to new circumstances.

- Any strain on the cell that necessitates adaptation is referred to be stress in a pathological environment.

- A cell's integrity is weakened when it is unable to adapt, which may result in harm or death.

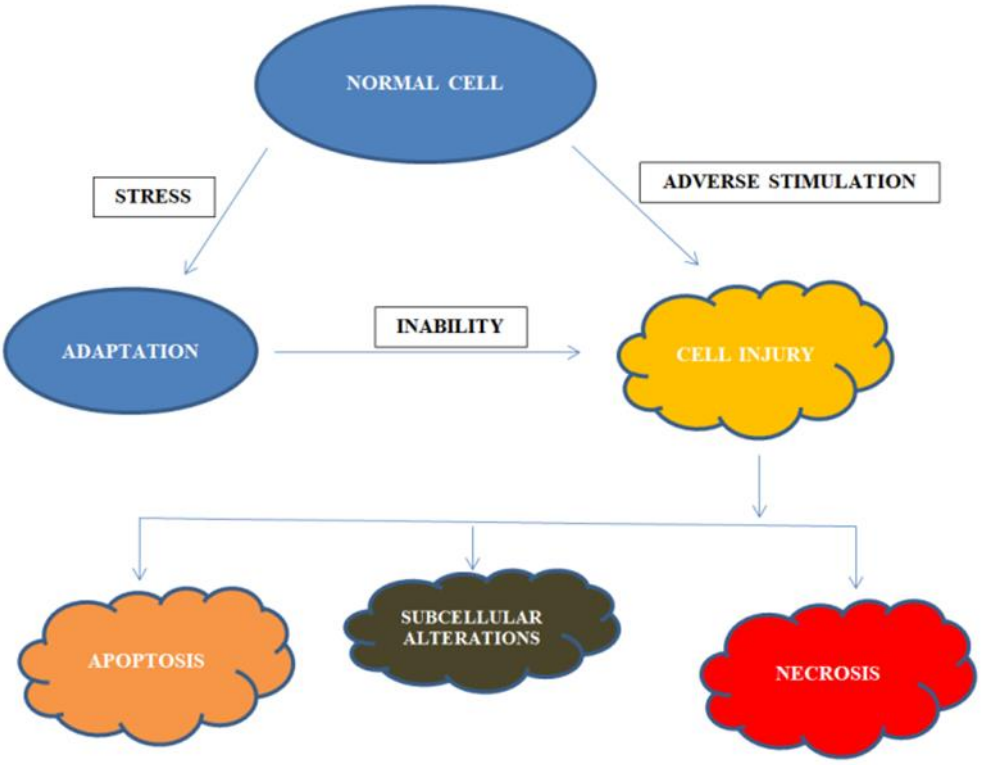
- Atrophy, metaplasia, hypertrophy, and hyperplasia are important adaptive responses.

- When a cell's ability to adapt is compromised or the stress is harmful in and of itself, cell damage results. Damage can be irreversible, resulting in cell death from substances like ischemia,

infections, toxins, or immunological reactions, or it can be reversible, enabling the cell to return to its initial state. Additionally, cell death may be a necessary and natural process.

- Reperfusion damage is a critical factor in myocardial and cerebral infarctions, significantly affecting clinical outcomes.

2.3. SCHEME OF RESPONSE:



2.4. TYPES OF CELL INJURY:

2.4.1. REVERSIBLE CELL INJURY – When the stress is mild to moderate, an injured cell has the potential to recover, a process referred to as reversible cell injury.

2.4.1.1. Hydropic Swelling- When a cell is first injured, it retains fluid because the cell membrane, sodium pump, and adenosine triphosphate (ATP) supply are disrupted, which causes the cell to accumulate fluid. Under a microscope, this condition — known as hydropic swelling — appear as

swollen, pale cells with otherwise normal nuclei. The endoplasmic reticulum (ER) has enlarged, fluid-filled cisternae visible under electron microscopy, and polysomes have the ability to separate from the rough ER. Additionally, swelling may be seen in mitochondria, and blebbing, or protrusions in the cell membrane, may be seen. This is frequently the earliest detectable indication of cell damage and is usually curable. The cell usually recovers to normal if the injury's cause is eliminated. But if the wound is serious and continues, it may result in

necrosis [4].

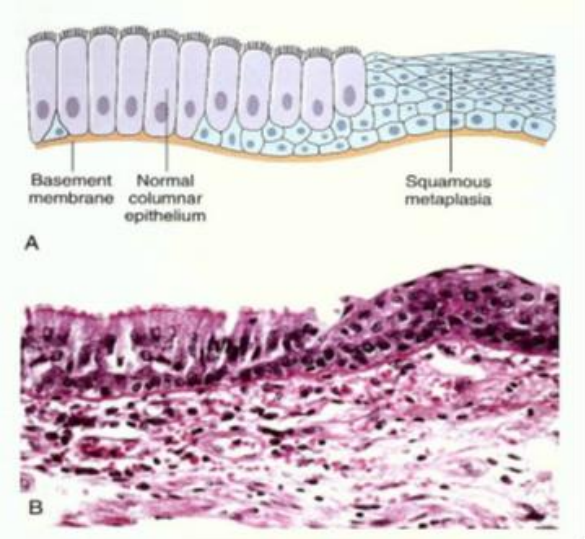


FIGURE 1: METAPLASIA OF COLUMNAR TO SQUAMOUS EPITHELIUM [COLLECTED FROM GOOGLE IMAGES]

2.4.1.2. Atrophy- Atrophy, or a reduction in cell size, is among the simplest types of cellular adaptation. Reduced cell function or utilization, which might be brought on by insufficient blood or nutrition, weakened hormone signals that would normally activate the cell, or persistent inflammation, is what usually causes atrophy. For example, the muscles in an arm that has been broken and is immobilized in a cast for a few weeks in order to heal are not as active as the muscles

in the arm that is not damaged. The patient may notice that the healed arm has a much smaller diameter after taking off the cast. The shrinkage of myocytes, or muscle cells, brought on by inactivity is the cause of this decrease in muscle mass; this condition is referred to as "disuse atrophy" [5].

2.4.1.3. Hypertrophy and Hyperplasia- When cells experience increased demands, they may adapt by enlarging in size (hypertrophy), increasing in number (hyperplasia), or both. Hypertrophy and hyperplasia are typically driven by heightened functional needs, loss of functional tissue, or elevated hormonal signals. Additionally, they can arise as a response to chronic inflammation.

Certain cells, known as "permanent tissues," are incapable of further division, such as neural and muscular tissues. In contrast, "stable tissues" can proliferate in response to injury, including glands, liver, and kidney tissues. "Labile tissues" are constantly reproducing and regenerating, such as skin, mucosa, and bone marrow.

In tissues that are still capable of proliferating, such as labile and stable tissues, hyperplasia develops. For example, hormonal signals cause the uterine endometrium to hyperplasia during the proliferative phase of the menstrual cycle [6]. Hormonal signaling alterations cause benign prostatic hyperplasia, or an expansion of the prostate gland, in older men. Comparably, a person's bone marrow may create more erythrocytes, or red blood cells, when they relocate to a higher altitude in order to make up for the decreased oxygen levels.

Permanent tissues, on the other hand, adapt through hypertrophy, or an increase in cell size, rather than proliferation. For example, strength training results in muscle hypertrophy, where each muscle cell (myocyte) enlarges [5]. In cases of severe obesity, cardiac hypertrophy can occur, where cardiac myocytes increase in size due to the additional workload.

Often, hypertrophy and hyperplasia occur together to meet increased functional demands. For instance, during pregnancy, the uterus enlarges through both hypertrophy of the uterine muscle and hyperplasia of the endometrial lining [6].

Hyperplasia typically arises from normal cellular signaling, but when cell proliferation occurs without such signals, it is called neoplasia. Neoplastic cell proliferation can eventually lead to cancer [5].

2.4.1.4. Metaplasia- Injured cells change from one mature type to another that is more suited to the new surroundings in a process known as metaplasia. For instance, the specialized respiratory epithelium that lines the respiratory system is often made up of tall, vertically aligned cells with small cilia that aid in clearing mucus and irritants. This epithelium may shift into a more durable type made up of several layers of horizontal cells called stratified squamous epithelium when exposed to a chronic irritant such as cigarette smoke.

Like hyperplasia, metaplasia can occasionally result in neoplasia in specific circumstances. Barrett's esophagus, for instance, develops when glandular epithelium replaces the esophageal epithelium, which is normally squamous or horizontally stratified. This illness greatly increases the chance of getting esophageal cancer [5].

2.4.1.5. Intracellular accumulations- In some instances, signs of previous injury can be observed microscopically through intracellular deposits of various cellular materials or pigments. These deposits may consist of normal cellular or tissue components, as well as blood products [5].

2.4.2 IRREVERSIBLE CELL INJURY – If the stimulus is severe or persists, the cell may reach a point of no return, leading to cell death. This condition is referred to as irreversible cell injury.

2.4.2.1 Nuclear changes in cell death- Pyknosis, karyorrhexis, and karyolysis are modifications to the nuclear material that occur after irreversible cell death [2]. Usually, during apoptosis, a cell experiences pyknosis, which is nuclear shrinkage, karyorrhexis, which is nuclear fragmentation, and finally "apoptotic necrosis" or karyolysis, which is the dissolution of nuclear material [2]. On the other hand, karyolysis typically occurs after cellular enlargement (oncosis) in necrotic cells [2,23]. These nuclear alterations, however, are visible in both processes and are not unique to any one type of cell death. For example, all three types of nuclear alterations may be present in cells receiving chemotherapy for cancer [24].

Pyknosis, characterized by the condensation of the nucleus, can occur in both necrosis and apoptosis. It is often seen in various clinical scenarios; for example, after a myocardial infarction, pyknotic nuclei of necrotic cardiac muscle cells are observed 24–48 hours post-ischemic event [25]. In cases of slow cell death, pyknosis may also be present [26].

Karyorrhexis involves the fragmentation of the cell nucleus into "nuclear dust" and typically follows pyknosis. After a myocardial infarction, karyorrhexis is commonly seen in cardiac muscle cells 3–5 days after the ischemic event [25].

Karyolysis is the dissolution of the cell nucleus due to the cell's automatic response to eliminate damaged structures and usually represents the final stage of nuclear change following cell death [27].

2.4.2.2 Tissue Patterns of Necrosis-

When cell death reaches a certain threshold, necrosis becomes apparent across a tissue rather than just in individual cells. Different patterns of tissue necrosis can indicate the underlying disease process. Unlike apoptosis, which generally does not provoke extensive inflammation, necrosis

typically triggers a strong inflammatory response [3]. This is significant because a robust immune response is crucial for addressing certain injuries, such as viral and bacterial infections [28]. For instance, small-intestine cells may use both apoptotic and necrotic mechanisms to renew themselves after viral infections [23]. Recent cancer therapies are exploring inducing necrosis in tumors to generate a stronger immune response that might eliminate more cancer cells, particularly when tumors have developed resistance to apoptosis [23] [29].

There are various types of necrosis:

- **Coagulative necrosis** often indicates a sudden loss of oxygen to tissues, such as in the cardiac muscle after a myocardial infarction. In this type, the cell outlines remain visible, but the nuclear material is lost from the destroyed cells [4].

- **Liquefactive necrosis** is typically associated with acute bacterial infections. It involves the enzymatic destruction of dead cells, resulting in cell fragments and neutrophils, which appear as pus (purulent exudate) [4].

- **Caseous necrosis** is seen in chronic bacterial infections, particularly those caused by mycobacteria like tuberculosis, and occasionally in deep fungal infections. The central necrotic zone has a cheese-like appearance and is surrounded by a granuloma, which includes macrophages and multinucleated giant cells, with lymphocytes at the periphery [30].

- **Gummatous necrosis** occurs in the late stage of syphilis and is a destructive form of coagulative necrosis seen in granuloma centers, surrounded by an inflamed fibrotic outer zone [4].

- **Fat necrosis** involves the destruction of fat tissue, often due to inflammation or infection in nearby glandular tissues that releases enzymes like lipases. This results in the breakdown of adipocytes and the formation of free fatty acids, which react with calcium and magnesium to

produce chalky deposits in a process called saponification [5]. This type of necrosis is common in conditions with extensive pancreatic inflammation and can lower serum calcium levels. In the breast, fat necrosis may be mistaken for malignancy on imaging and biopsy [31].

- **Fibrinoid necrosis** is characterized by the destruction of blood vessel walls due to inflammation. Plasma proteins deposit in the vessel walls, leading to a pink appearance under the microscope [4]. It is seen in conditions like temporal arteritis (giant-cell arteritis), which primarily affects the elderly and can result in vision loss if not treated [32].

Similar to how cells can accumulate deposits of external or internal materials after injury, tissues damaged by necrosis may also display deposits that indicate prior damage. One of the most common findings in this context is dystrophic calcification [5].

Different from systemic calcium imbalances, metastatic calcifications are localized deposits of calcium salts that happen in injured tissues. The size of these deposits can range from little sand grains to larger accumulations. They are especially abundant in the circulatory system and are frequently seen in

tuberculosis-affected areas, such as lymph nodes (scrofula). Dystrophic calcifications in the cardiovascular setting can worsen pre-existing diseases, such as aging or damaged heart valves, where they can limit the orifice of the valve and diminish valve flexibility, resulting in calcific aortic valve stenosis, a condition that is common in the elderly. Severe atherosclerosis frequently exhibits dystrophic calcification, and cardiac calcium-scoring CT scans are utilized to assess the risk of coronary artery disease.

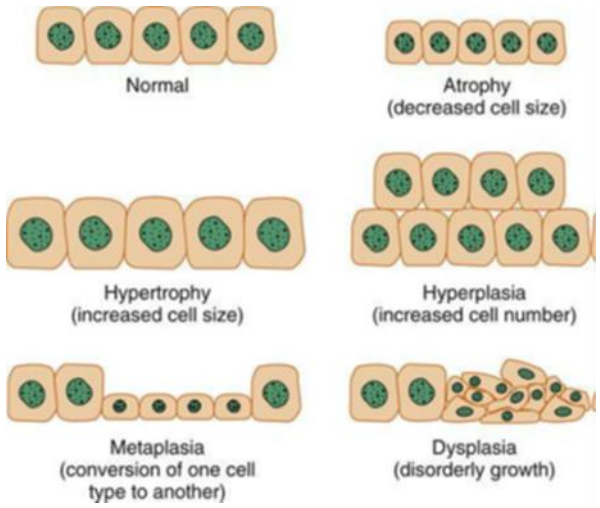


FIGURE 2: VARIOUSY TYPES OF DAMAGE MORPHOLOGY [COLLECTED FROM GOOGLE

Localized calcifications can also occur in tumors and cysts. In breast cancer, these calcifications are significant and form a key component of mammography, where clustered, linear, or segmental calcifications may suggest malignancy. However, such calcifications can also be associated with benign conditions, such as odontogenic cysts.

2.5. ETIOLOGY OF CELL INJURY:

A cell may be injured by two ways:

A. Genetic Causes

B. Acquired Causes

A. Genetic Causes-

Genetic causes of disorders and abnormalities include conditions resulting from specific genetic defects. These can be categorized as follows:

- Monogenic disorders: These result from alterations in a single gene or the genome, such as sickle cell disease, where red blood cells change shape, leading to their premature destruction and potential blockages in blood flow.

- Chromosomal abnormalities: Conditions like polyploidy and aneuploidy, which involve changes in the number of chromosomes. An example is Down syndrome, caused by an extra copy of chromosome 21 due to abnormal cell division.

B. Acquired Causes-

Conditions that cause cell injury and death can arise from various factors, including:

- Hypoxia: This is a major and common cause of cell injury and death, resulting from a loss of blood supply (ischemia), cardio-respiratory failure, or reduced oxygen-carrying capacity of blood due to anemia or carbon monoxide poisoning. Hypoxia impairs aerobic oxidative respiration.

- Physical agents: Extreme temperatures, radiation, and rapid changes in atmospheric pressure can cause cell damage.

- Chemical agents: Toxic substances such as cyanide, arsenic, environmental pollutants, insecticides, pesticides, alcohol, and narcotic drugs can lead to cell injury.

- Biological agents: Injuries caused by microbes, including bacteria, viruses, fungi, protozoa, and parasites, as well as hypersensitivity reactions.

- Nutritional factors: Deficiencies or excesses in nutrition, such as protein deficiency (marasmus) or mineral deficiencies (e.g., anemia), can also contribute to cell damage. Additionally, drug addiction, alcoholism, and smoking are significant contributors to cell injury and death.

2.6. CELL DEATH:

The ultimate result of cell injury is cell death, which can occur in two primary patterns:

i) Necrosis: This is an uncontrolled form of cell death that occurs in living tissues due to factors like infection or trauma. It leads to the premature death of cells and involves the unregulated digestion of cell components.

ii) Apoptosis: This more controlled type of cell death is intended to naturally remove undesirable cells during different physiological processes. Cells engage in a strictly regulated mechanism of self-destruction in which they release enzymes that break down their own nuclear DNA and cytoplasmic and nuclear proteins. The plasma membrane is unaltered but stays intact as the pieces of apoptotic cells break off.

2.7. PATHOGENESIS:

Pathologists employ a range of methods to comprehend the biochemical, structural, and functional alterations that take place in cells, tissues, and organs. They evaluate modifications in bodily fluids and examine changes in the microscopic structure (morphology) of cells and tissues. Significant alterations in cell damage were noted consist of:

- Damage to the Plasma Membrane: This is caused by insufficient ATP, which interferes with the production of phospholipids derived from fatty acids found in cells, which are vital for the healing

of membranes. Thus, membrane Pumps in charge of controlling calcium, potassium, and sodium malfunction.

- Mitochondrial Damage: An excessive calcium ion inflow causes a build-up of calcium in the

affecting the mitochondria's ability to operate. This damage is manifested as mitochondrial vacuoles

and calcium salt deposits that are amorphous.

- Nuclear Damage: Insufficient oxygen supply impairs aerobic respiration by mitochondria, leading to energy depletion. This results in rapid glycogen depletion and lactic acid accumulation, which lowers intracellular pH. The nuclear chromatin may clump as a consequence.

2.8. CELLULAR ADOPTATION:

Cellular adaptation is a reversible adjustment that allows cells to adjust to changes in their environment, which can involve modifications in cell function, morphology, or both. If the stimulus causing the adaptation is removed, the cell can return to its normal state. However, if the limits of the cell’s adaptive response are surpassed, adaptation becomes unfeasible, leading to cell injury.

2.9. MORPHOLOGY OF RESPONSES:

Pathologic adaptations are cellular responses to stress that enable cells to adjust their structure and function to avoid injury. Key adaptive responses include hypertrophy, hyperplasia, metaplasia, and autophagy:

- Hypertrophy: This refers to an increase in cell size, leading to an enlarged organ. It can result from hormonal support or increased functional demand. For instance, in response to chronic high blood pressure, the heart enlarges because the individual cardiac muscle cells increase in size.

- Hyperplasia: This is the enlargement of an organ or tissue as a result of a cell proliferation. Hormonal stimulation or an increase in functional demand might cause it. For instance, increased endometrial cell count during puberty is

caused by increasing estrogen levels. Comparably, in order to improve oxygen delivery, low oxygen levels can cause the bone marrow to create more red blood cells (RBCs). Hyperplasia can also be brought on by long-term stress or trauma. A reversible process known as metaplasia occurs when a mature cell type—either mesenchymal or epithelial—is replaced by a different mature cell type that is more adapted to the changing environment. By swapping out fragile cells for more resilient and related ones, this adaptation enables the cell to live in a harsher environment. For example, fibrous tissue can transform into bone under certain conditions.

-Autophagy involves the lysosomal digestion of a cell's own components, helping to recycle damaged or obsolete cellular materials. This process contrasts with **heterophagy**, where a cell, such as a macrophage, engulfs and destroys external substances. An example of autophagy is the degradation of excess peroxisomes. Cellular organelles called peroxisomes are involved in the metabolism of fatty acids and the removal of toxic chemicals from the body. When there is an accumulation of peroxisomes beyond the cell's needs or if they become damaged, autophagy helps by engulfing and breaking down these excess or damaged peroxisomes in lysosomes, thus maintaining cellular homeostasis.

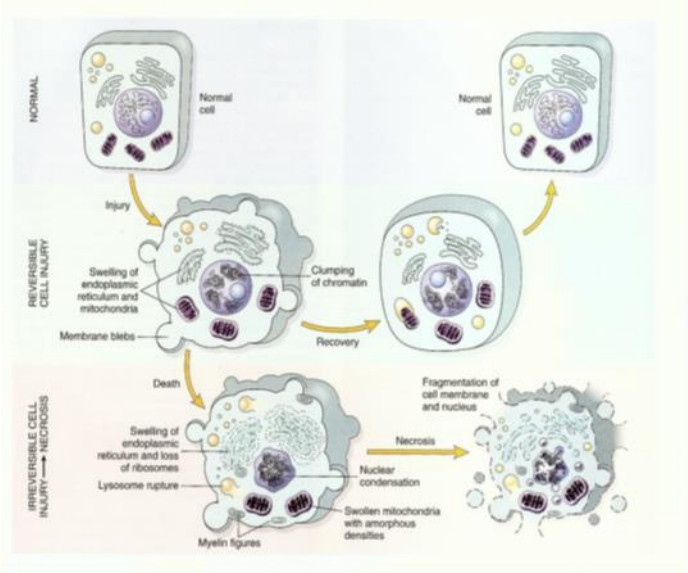


FIGURE 3: MORPHOLOGY OF CELL [COLLECTED FROM GOOGLE IMAGES]

2.10. HOMEOSTASIS:

The capacity of an organism to keep its internal environment largely constant in the face of external changes is known as homeostasis. This equilibrium condition, sometimes referred to as dynamic equilibrium, makes sure that the body's cellular requirements are satisfied and that functional activities run without a hitch. This internal equilibrium is maintained in part by each organ system.

2.11. FEEDBACK REGULATIONS:

A feedback mechanism is a physiological system that regulates the body's internal environment, either by restoring homeostasis or, less commonly, by moving the system further from it. This regulation occurs through nerve pathways (neurotransmitters) or chemicals like hormones, which can have stimulatory or inhibitory effects. A feedback system comprises three main components:

1. Receptors: These detect changes in a controlled condition and send this information to the control center via sensory receptors.

2. Control Center: This analyzes the incoming information and sends appropriate responses via motor receptors.

3. Effectors: These are cells or organs that respond to the commands from the control center, executing the necessary actions.

There are two main types of feedback systems:

- Negative Feedback: This response reduces the effect of the initial stimulus and helps maintain homeostasis. For example, the brain regulates body temperature through negative feedback, hormonal control manages various body functions, and blood glucose levels are controlled by negative feedback mechanisms.

- Positive Feedback: This response amplifies the initial stimulus, leading to an increased effect rather than a return to homeostasis. Positive feedback accelerates the process and can sometimes disrupt homeostasis. Examples include blood clotting, digestion, and labor during childbirth.

2.12. INTRACELLULAR ACCUMULATION:

Cells may collect aberrant concentrations of certain compounds under specific situations; these substances may be innocuous or associated with differing degrees of injury. These materials may originate externally or be formed by the afflicted cells. They can be discovered in the nucleus, cytoplasm, or inside organelles like lysosomes. Accumulation can occur due to several mechanisms:

1. Normal Substances: When a substance is produced at a normal or increased rate but cannot be removed efficiently, it may accumulate. For example, fatty change in the liver occurs when fat accumulates due to an imbalance in metabolism and removal processes.

2. Endogenous Substances: Abnormalities in genetic processes, such as defective protein folding, packaging, transport, or secretion, can lead to the accumulation of endogenous substances. For instance, alpha-1 antitrypsin deficiency results from mutations that affect protein folding and transport.

3. Storage Diseases: These arise from inherited enzyme defects that prevent the degradation of certain metabolites, leading to their accumulation in cells.

4. Exogenous Substances: When cells cannot degrade or transport foreign substances, these may accumulate. Examples include carbon or silica particles, which the cell cannot process or move.

Abnormal deposits in cells and tissues can result from excessive intake or defective transport and catabolism of various materials. These include:

Pathogenic Calcification Such as dystrophic calcification (deposition of calcium in damaged tissues) and metastatic calcification (calcium deposits due to abnormal calcium levels).

Lipid Deposition Includes fatty changes and cholesterol accumulation.

Protein Deposition Abnormal protein buildup in cells.

Glycogen Deposition Excessive glycogen storage.

Pigment Deposition Includes various pigments accumulated due to metabolic or external factors.

Acidosis Can result from disturbances in electrolyte balance, such as abnormal serum levels of sodium, potassium, calcium, and phosphate, often linked to metabolic syndrome and clinical symptoms.

2.13. MODE OF INFLAMMATION:

Self-defense is a fundamental characteristic of living organisms. Inflammation is a primary response of tissues to harmful or damaging external or internal stimuli. It can be triggered by various factors, including:

- Toxic Chemicals: Such as acids, alkalis, and other harmful substances.

- Physical Factors: Including heat, cold, electricity, radiation, and physical trauma.

- Microorganisms: Pathogens and their metabolic by-products.

- Immune Responses: Such as hypersensitivity reactions, immune complex formation, and autoimmune reactions.

Every organ or tissue can experience inflammation, and the extent and type of inflammatory response vary based on factors like overall health, nutrition, immunity, and the nature and severity of the harmful stimulus. The four main signs of inflammation are:

1. Redness~ (erythema): Increased blood flow to the affected area.

2. Swelling~ (edema): Accumulation of fluid in the tissues.

3. Heat: Elevated temperature in the inflamed area due to increased blood flow.

4. Pain: Discomfort caused by the release of chemicals that stimulate nerve endings.

5. Loss of Function: Impairment of the affected tissue's normal function.

Inflammation can be classified into three main types: latent, acute, and chronic. The inflammatory response involves several stages of vascular changes:

1. Initial Vascular Response:

- Transient Vasoconstriction: Immediately following an injury, arterioles undergo brief constriction. This response typically lasts a few seconds to minutes.

- Vasodilation: After the initial constriction, there is a prolonged dilation of arterioles and, to a lesser extent, venules and capillaries. This occurs within 30 minutes of the injury, leading to increased blood flow and contributing to redness and warmth at the site.

2. Progressive Changes:

- Increased Blood Volume: Vasodilation results in more blood in the microvascular bed, causing redness and warmth.

- Increased Hydrostatic Pressure: This pressure can cause fluid to move from the blood vessels into the extracellular space, resulting in swelling.

- Slowed Circulation: The slowing of blood flow increases blood viscosity and allows for leucocyte margination—white blood cells, primarily neutrophils, adhere to the endothelial lining of blood vessels.

3. Leucocyte Migration:

- Emigration: White blood cells migrate through gaps in the endothelial cells into the extravascular space. This process is crucial for the inflammatory response.

4. Fluid Accumulation:

- Transudate: In the initial stage, fluid leakage is due to vasodilation and increased hydrostatic pressure, resulting in transudate—a fluid with low protein content.

- Exudate: As inflammation progresses, increased vascular permeability leads to the escape of fluid with higher protein content, known as exudate.

5. Drainage:

- Lymphatic Drainage: Excess fluid in the interstitial space is normally drained by lymphatics. However, in inflamed tissues, increased vascular permeability leads to excessive fluid accumulation, resulting in exudative inflammatory edema.

Chemical Mediators of Inflammation:

These mediators are crucial for the inflammatory response and include:

Vasoactive Amines Histamine, 5-Hydroxytryptamine

Neuropeptides Various peptides that influence inflammation

Arachidonic Acid Metabolites Prostaglandins, leukotrienes

Lysosomal Components Enzymes released from leukocytes

Platelet Activating Factor (PAF) Influences platelet aggregation and inflammation

Cytokines Proteins such as interleukins and tumor necrosis factor (TNF)

The Kinin System Bradykinin, which increases vascular permeability

The Clotting System Coagulation factors that contribute to inflammation

The Fibrinolytic System Enzymes that break down fibrin clots

The Complement System Proteins that enhance the immune response

Each of these mediators plays a role in modulating the inflammatory response, influencing the extent and duration of inflammation.

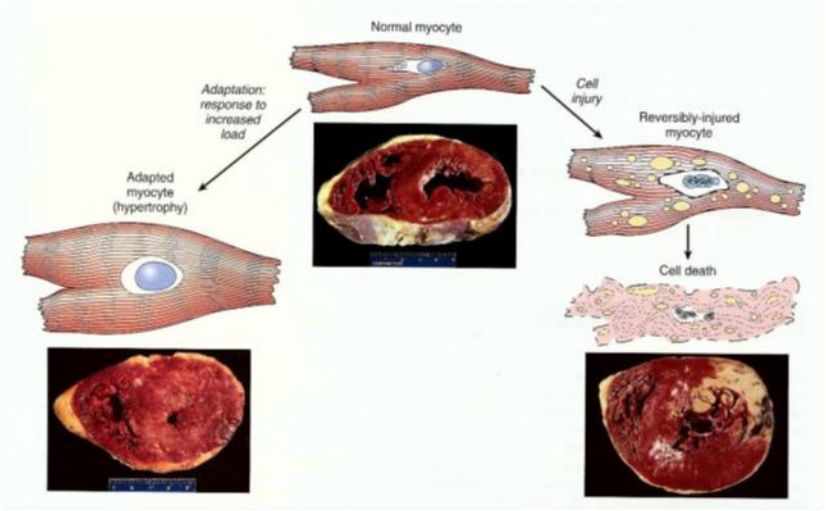


FIGURE 4: CELL REACTION TO STIMULI [COLLECTED FROM GOOGLE IMAGES]

2.14. POSSIBLE MODE OF HEALING:

Healing involves both regeneration and repair and can occur through two main processes: primary intention and secondary intention. Here's a detailed overview of each:

Primary Intention:

Primary intention refers to the healing of a clean, straight incision with opposed edges. This type of healing is characterized by [33]:

1. Immediate Response:

- Blood Clot Formation: Immediately after injury, blood fills the space between the approximated surfaces of the wound, forming a clot that seals the wound against dehydration and infection.

- Inflammatory Response: Within 24 hours, polymorphonuclear leukocytes (polymorphs) appear at the wound margins [34].

2. Early Healing:

- Macrophage Infiltration: By the 3rd day, polymorphs are replaced by macrophages that help clear debris.

- Epithelialization: Basal cells from the epidermal margins start to proliferate and migrate across the wound, forming epithelial spurs. By 48 hours, the wound is covered by a layer of epithelium [35].

3. Ongoing Repair:

- Formation of Scab: Migrated epidermal cells separate the viable dermis from the necrotic material and clot, forming a scab which eventually falls off.

- Fibroblast Activity: By the 5th day, fibroblasts invade the wound area, and new collagen fibrils start forming.

- Scar Formation: Over 4 weeks, scar tissue forms with scant cellular and vascular elements, and the epithelial surface becomes fully restored [37].

4. Suture Tracks:

- Healing: Each suture track follows a similar healing process, with blood clot formation, inflammatory cell reaction, and eventual epithelial and fibroblastic proliferation [36].

Secondary Intention:

Secondary intention involves healing of wounds with more extensive tissue loss, where the edges cannot be approximated [33]:

1. Initial Response:

- Blood Clot and Inflammation: Blood and fibrin clot form in the wound, followed by acute inflammation and macrophage infiltration to clear debris [34].

2. Granulation Tissue Formation:

- Granulation Tissue: Fibroblasts proliferate to form granulation tissue, which is crucial for wound repair. Myofibroblasts in the granulation tissue help in wound contraction, reducing the wound size by one-third to one-fourth [35].

3. Epithelialization:

- Epithelial Migration: As in primary intention, epithelial cells from the wound margins proliferate and migrate to cover the wound. However, this process is slower and less orderly compared to primary intention [37].

4. Delayed Healing:

- Bacterial Contamination: Open wounds may be delayed in healing due to bacterial contamination, which can provoke further necrosis, suppuration, and thrombosis [36].

Cellular Responses and Healing Mechanisms

1. Cellular Injury and Adaptation [33]:

- Adaptive Stress Response: Cells respond to injury by expressing adaptive stress response genes, including those for ischemic/hypoxic stress, oxidative stress, and heat shock. If these responses are overwhelmed, cell death may occur.

2. Cell Death Mechanisms [34]:

- Ischemic and Accidental Death: Typically associated with cytoplasmic swelling (oncosis).

- Suicidal Cell Death (Apoptosis): Characterized by cytoplasmic shrinkage.

3. Organ Dysfunction and Systemic Inflammatory Response Syndrome (SIRS) [35]:

- Multiorgan Dysfunction Syndrome (MODS): Often results from the body's response to a significant or widespread stimulus, such as endotoxins or cytokines, which can lead to organ dysfunction. Treatment strategies have shifted from targeting extracellular mediators to addressing intracellular responses to these signals.

Understanding these mechanisms helps in developing targeted treatments and improving management strategies for wound healing and systemic responses [36] [37].

2.15. DISCUSSION:

Your summary highlights the evolving understanding of the cellular basis of Multiorgan Dysfunction Syndrome (MODS), emphasizing a shift from focusing on extracellular factors to intracellular responses. Here’s a concise summary of the key points:

Cellular Basis of MODS

1. Intracellular Focus:

- Recent research suggests that MODS arises from distinct, prioritized genetic programs activated in response to cellular injury. These programs are specific to cell types and types of injury.

2. Gene Response Programs:

- Protective Mechanisms: Typically, stress response gene programs provide cytoprotection.

- Apoptosis Induction: When activated in sequence, these programs can lead to apoptotic cell death, which contributes to tissue damage.

3. Pharmacological Modulation:

- Recent advances have demonstrated that modulation of apoptotic pathways using reducing agents [38], antioxidants [39], inhibitors of protein synthesis [40], anti-TNF antibodies [41], and steroid antagonists [42] can be effective. This suggests potential for clinical pharmacological control.

4. Gene-Directed Therapy:

- Understanding the type, sequence, and interaction of stress response genes is crucial for developing gene-directed therapies aimed at treating and preventing MODS.

5. Diagnosis and Prognosis:

- When it comes to diagnosis and treatment, patterns of tissue damage and cell death seen in MODS might offer important information about the underlying etiology of the injury or illness.

In summary, focusing on intracellular responses to stress and injury opens new avenues for understanding and managing MODS, potentially leading to more effective treatments through targeted gene-based therapies.

2.16. VARIOUS VIEWS OF INJURIES:

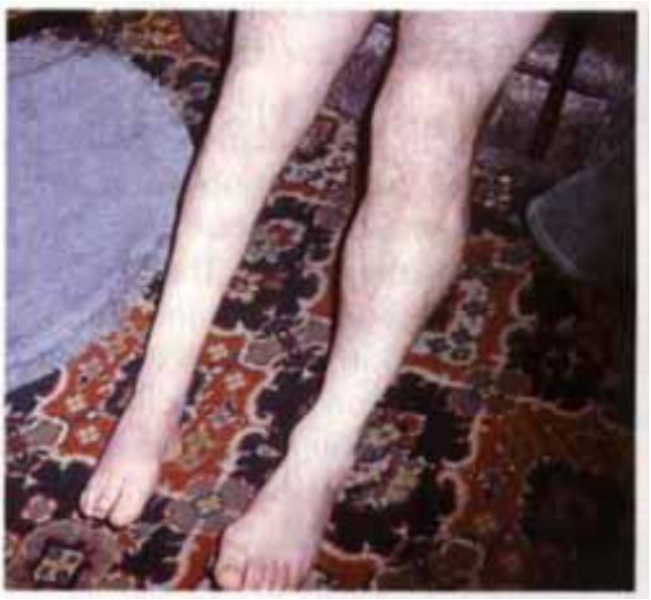


FIGURE 5: ATROPY [ADOPTED FROM GOOGLE IMAGES]

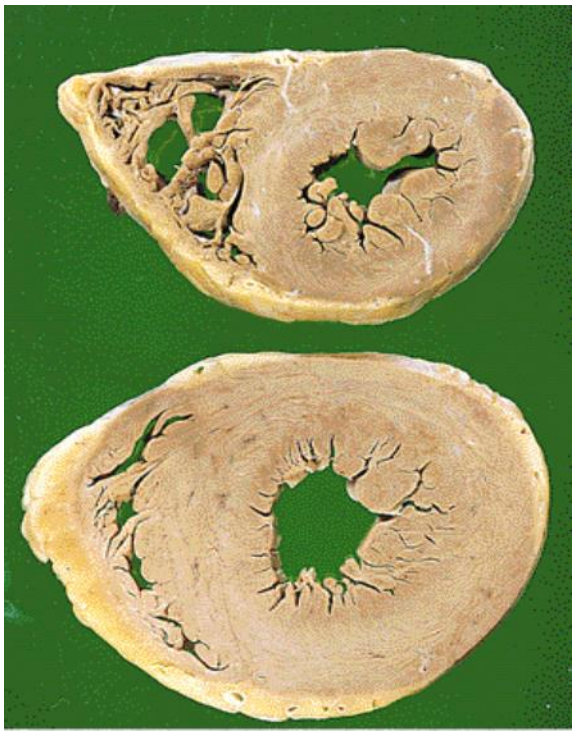


FIGURE 6: ATROPY [ADOPTED FROM GOOGLE IMAGES]

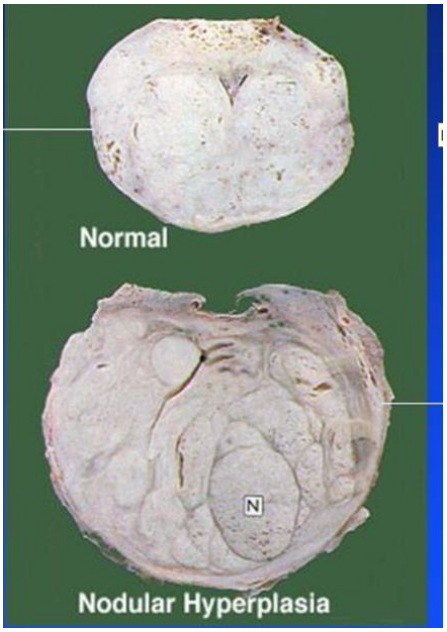


FIGURE 7: HYPERPLASIA [ADOPTED FROM GOOGLE IMGES]

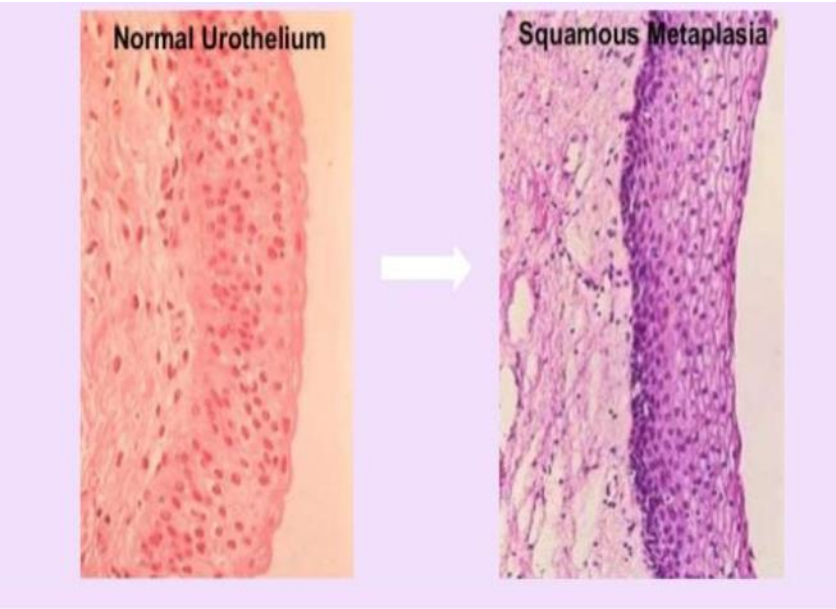


FIGURE 8: METAPLASIA [ADOPTED FROM GOOGLE IMAGES]

REFERENCES:

1. Gamrekelashvili J, Geten TF, Korangy F. Immunogenicity of necrotic cell death. Cell Mol Life Sci 2015; 72(2):273–83.

2. Majno G, Joris I. Apoptosis, oncosis, and necrosis, an overview of cell death. Am J Pathol 1995; 146(1):3–15.

3. McCall K. Genetic control of necrosis – another type of programmed cell death. Curr Opin Cell Biol 2010; 22:882–8.

4. Stevens A, Lowe J, Scott I. Core Pathology, 3rd edn. Marylands Heights, MO: Mosby Elsevier. 2009.

5. Kumar V, Cotran RS, Robbins SL. Robbins Basic Pathology, 9th edn. Philadelphia, PA: Saunders Elsevier. 2013.

6. Burkitt HG, Stevens A, Lowe JS,Young B. Wheater's Basic Histopathology, a Color Atlas and Text, 4th edn. Edinburgh: Churchill Livingstone. 2003.

7. Sears D. Fatty liver. Emedicine by Medscape. August 16, 2012. Available from http://emedicine.medscape.com/article/175472-overview (last accessed March 22, 2018).

8. Fair KP. Xanthomas. Emedicine by Medscape. October 23, 2014. Available from http://emedicine.medscape.com/article/1103971-overview (last accessed March 22, 2018).

9. Lambert CW. Verruciform xanthoma. Emedicine by Medscape. October 31, 2014. Available from http://emedicine.medscape.com/article/1061445-overview (last accessed March 22, 2018).

10. Cianciola NL, Carlin CR. Molecular pathways for intracellular cholesterol accumulation: common pathogenic mechanisms in Niemann–Pick disease type C and cystic fibrosis. Arch Biochem Biophys 2011: 515(1–2);54–63.

11. Zhang JR, Coleman T, Langmade SJ, Scherrer DE, Lane L, Lanier MH, et al. Niemann-Pick C1 protects against atherosclerosis in mice via regulation of macrophage intracellular cholesterol trafficking. J Clin Invest 2008;118(6):2281–90.

12. Ladich ER. Atherosclerosis pathology. Emedicine by Medscape. October 4, 2012. Available from http://reference.medscape.com/article/1612610-overview (last accessed March 22, 2018).

13. Holmes RO. Amyloidosis. Emedicine by Medscape. November 26, 2014. Available from http://emedicine.medscape.com/article/335414-overview (last accessed March 22, 2018).

14. Quarta CC, Kruger JL, Falk RH. Cardiac amyloidosis. Circulation 2012;126:e178–82.

15. Latta CH, Brothers HM, Wilcock DM. Neuroinflammation in Alzheimer's disease; a source of heterogeneity and target for personalized therapy. Neurosci 2014; pii:S03064522(14)00820-3.

16. Seidiu I, Torffvit O. Decreased urinary concentration of Tamm-Horsfall protein is associated with development of renal failure and cardiovascular death within 20 years in type1 but not in type2 diabetic patients. Scand J Urol Nephrol 2008;42(2):168–74.

17. Froissart R, Piraud M, Boudjemline AM, Viarey-Saban C, Petit F,Hubert-Buron A, et al. Glucose-6-phosphate deficiency. Orphanet J Rare Dis 2011;6:27.

18. Bali DS, Chen YT, Goldstein JL. Glycogen storage disease type I. April 19, 2006 [updated September 19, 2013]. Gene Reviews. Available from http://www.ncbi.nlm.nih.gov/books/NBK1312/ (last accessed March 22, 2018).

19. Leslie N, Tinkle BT. Glycogen storage disease type II (Pompe disease). August 31, 2007 [updated May 9, 2013]. Gene Reviews. Available from http://www.ncbi.nlm.nih.gov/books/NBK1261/ (last accessed March 22, 2018).

20. Khan FJ. Coal worker's pneumoconiosis. Emedicine by Medscape. March 27, 2014. Available from http://emedicine.medscape.com/article/297887-overview#a0104 (last accessed March 22, 2018).

21. Feller L, Masilana A, Khammissa RAG, Altini M, Jadwat Y, Lemmer J. Melanin: the biophysiology of oral melanocytes and physiological oral pigmentation. Head Face Med 2014;10:8.

22. Kroemer G, Galluzzi L,Vandenabeele P, Abrams J, Alnemri E, Baehrecke E, Melino G. Classification of cell death: recommendations of the Nomenclature Committee on Cell Death 2009. Cell Death Differ 2009;16(1);3–11.

23. Proskuryakov SY, Konoplyannikov AG, Gabai VL. Necrosis: a specific form of programmed cell death? Exp Cell Res 2003;283:1–16.

24. Sethi D, Sen R, Parshad S, Khetarpal S, Garg M, Sen J. Histopathologic changes following neoadjuvant chemotherapy in various malignancies. Int J App Basic Med Res 2012;2:111–16.

25. Burke AP. Pathology of acute myocardial infarction. Emedicine by Medscape. July 17, 2013. Available from http://emedicine.medscape.com/article/1960472-overview (last accessed March 22, 2018).

26. Burgoyne LA. The mechanisms of pyknosis: hypercondensation and death. Exp Cell Res 1999;248:214–22.

27. Trump BE, Berezesky IK, Chang SH, Phelps PC. The pathways of cell death: oncosis, apoptosis, and necrosis. Toxicol Pathol 1997;25:82–7.

28. Festjens N, Vanden Berghe T, Vandenabeele P. Necrosis, awell-orchestrated form of cell demise: signaling cascades, important mediators and concomitant immune response. Biochim Biophys Acta 2006;1757:1371–87.

29. Zhang J. Lou X, Jin L, Zhou R, Liu S, Xu N, Liao DJ. Necrosis, and then stress induced necrosis-like cell death, but not apoptosis, should be the preferred cell death mode for chemotherapy: clearance of a few misconceptions. Oncoscience 2014;1(6):407–22.

30. Yeldandi AV. Pathology of pulmonary infectious granulomas. Emedicine by Medscape. April 3, 2013. Available from http://emedicine.medscape.com/article/2078678-overview (last accessed March 22, 2018).

31. Amin AL, Purdy AC, Mattingly JD, Kong AL, Termuhlen PM. Benign breast disease. Surg Clin N Am 2013;93:299–308.

32. Flood TA. Temporal arteritis pathology. Emedicine by Medscape. May 9, 2013. Available from http://emedicine.medscape.com/article/1612591-overview (last accessed March 22, 2018).

33. Buchman TG, Zehnbauer BA. Molecular biology in the intensive care unit: a framework for interpretation. New Horizons 1995; 3: 139–145.

34. Hockenbery D. Defining apoptosis. American Journal of Pathology 1995; 146: 16–19.

35. Manjo G, Joris I. Apoptosis, oncosis and necrosis. American Journal of Pathology 1995; 146: 3–15.

36. Natanson C, Hoffinan WD, Suffredini AF, Eichacker PQ, Danner RL. Selected treatment strategies for septic shock based on proposed mechanisms of pathogenesis. Annals of Internal Medicine 1994; 120: 771–783.

37. Taveira Da Silva AM, Kaulbach HC, Chuidian FS, Lambert DR, Suffredini AF, Danner RL. Brief report: shock and multiple-organ dysfunction after self-administration of Sal- monella endotoxin. New England Journal of Medicine 1993; 328: 1457–1460.

38. Abello PA, Fidler SA, Buchman TG. Thiol reducing agents modulate induced apoptosis in porcine endothelial cells. Shock 1994; 2: 79–83.

39. Abello PA, Fidler SA, Bulkley GB, Buchman TG. Anti- oxidants modulate induction of programmed endothelial cell death (apoptosis) by endotoxin. Archives of Surgery 1994; 129: 134–140

40. Buchman TG, Abello PA, Smith EH, Buckley GB. Induction of heat shock response leads to apoptosis in endothelial cells previously exposed to endotoxin. American Journal of Physi- ology 1993; 265: H165–H170

41. Wang S-D, Huang KJ, Lin YS, Lei HY. Sepsis-induced apoptosis of the thymocytes in mice. Journal of Immunology 1994; 152: 5014–5023.

42. Ayala A, Herdon CD, Lehman DL, DeMaso CM, Ayala CA, Chaudry IH. The induction of accelerated thymic pro- grammed cell death during polymicrobial sepsis: control by corticosteroids but not tumour necrosis factor. Shock 1995; 3: 259–267.

Chapter 3

INFLAMMATORY PERSPECTIVE OF DISEASE: FROM MOLECULES TO ORGANS

Dr. Rajen Dey

Department of Medical Laboratory Technology, School of Allied Health Sciences, Swami Vivekananda University, Telinipara, Barasat-Barrackpore Rd, Bara Kanthalia, West Bengal - 700121, India.

Email: rajend@svu.ac.in

Overview:

An immune system's biological reaction, inflammation can be brought on by a number of things, such as infections, injured cells, and poisonous substances. In the heart, pancreas, liver, kidney, lung, brain, intestinal tract, and reproductive system, these variables may cause acute or chronic inflammatory reactions that could result in disease or tissue damage. Inflammatory cells are stimulated by both infectious and non-infectious stimuli, as well as by cell injury, which in turn activates inflammatory signaling pathways, most commonly the NF-κB, MAPK, and JAK-STAT pathways. In this review, we examine the inflammatory reactions that occur within different organs, with particular attention to the genesis, mechanisms, resolution, and organ-specific inflammatory responses.

3.1. Introduction

The immune system's reaction to dangerous stimuli, such as infections, injured cells, poisonous substances, or radiation, is inflammation [1]. Inflammation functions by eliminating harmful stimuli and starting the healing process [2]. Therefore, inflammation is an essential defense

mechanism for good health [3]. Typically, cellular and molecular processes and interactions effectively reduce the risk of harm or infection during acute inflammatory reactions. This mitigating procedure aids in the resolution of the acute inflammation and the return of tissue homeostasis. Unchecked acute inflammation, however, has the potential to develop into a chronic condition and fuel a range of chronic inflammatory illnesses [4].

Local immunological, vascular, and inflammatory cell responses to infection or injury cause inflammation at the tissue level, which is characterized by redness, swelling, heat, discomfort, and loss of tissue function [5]. Leukocyte recruitment and accumulation, inflammatory mediator release, and modifications in vascular permeability are all significant microcirculatory events that take place throughout the inflammatory process [2, 6]. Inflammation can be brought on by a number of pathogenic events that damage tissue, including infection, myocardial infarction, and tissue damage. Inflammation can have infectious or non-infectious etiologies. The body starts a chemical signaling cascade in reaction to tissue damage, which prompts reactions meant to repair damaged tissue. Leukocyte chemotaxis from the general circulation to injury sites is triggered by these signals. These leukocytes that have been stimulated release cytokines that cause inflammatory reactions [7].

3.2. Inflammatory mechanisms

The coordinated activation of signaling pathways that control the amounts of inflammatory mediators in both resident tissue cells and inflammatory cells drawn from the circulation is known as the inflammatory response [8]. Numerous chronic illnesses, including as cancer, diabetes, inflammatory bowel and cardiovascular disorders, and rheumatoid arthritis, are mostly attributed to inflammation [9]. All inflammatory response processes share a basic mechanism, which can be summed up as follows, albeit depending on the specifics of the original stimulus and where it

occurs in the body: 1) Detrimental stimuli are recognized by cell surface pattern receptors; 2) inflammatory pathways are triggered; 3) inflammatory markers are produced; and 4) inflammatory cells are drawn in.

3.3. Activation of pattern recognition receptor

Through the activation of germline-encoded pattern-recognition receptors (PRRs), which are expressed in both immune and nonimmune cells, microbial structures known as pathogen-associated molecular patterns (PAMPs) can initiate the inflammatory response [10, 11]. Some PRRs, referred to as danger associated molecular patterns (DAMPS) [11], are also capable of identifying a variety of endogenous signals that are triggered when tissue or cell damage occurs. Host biomolecules known as DAMPs have the ability to start and maintain a non-infectious inflammatory response [12]. By generating DAMPs, disrupted cells can also attract innate inflammatory cells when pathogens are not present [13]. Toll-like receptors (TLRs), C-type lectin receptors (CLRs), retinoic acid-inducible gene (RIG)-I-like receptors (RLRs), and NOD-like receptors (NLRs) are among the classes of PRR families [5]. TLRs are a class of mammalian PRRs that are highly conserved and involved in initiating the inflammatory response [14]. Of all the known PRRs, TLRs have been investigated the most, with over 10 members found so far [15]. Together with TLRs, myeloid differentiation factor-88 (MyD88) mediates the transmission of PAMPs and DAMPs. TLR-mediated signaling initiates an intracellular signaling cascade [16, 17], which results in the nuclear translocation of transcription factors, including NF-κB, interferon regulatory factor 3, and activator protein-1 (AP-1). Similar receptors, like TLR4, are shared by DAMPs and PAMPs, indicating that infectious and noninfectious inflammatory responses are similar [18, 19].

3.4. Pathways related to inflammation

Numerous chronic diseases are impacted by inflammatory pathways, which also involve common inflammatory mediators and regulatory processes. Intracellular signaling pathways are triggered by inflammatory stimuli, which in turn trigger the synthesis of inflammatory mediators. Through interactions with TLRs, IL-1 receptor (IL-1R), IL-6 receptor (IL-6R), and TNF receptor (TNFR), primary inflammatory stimuli, such as microbial products and cytokines including interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), mediate inflammation [20]. Important intracellular signaling pathways, such as the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway, nuclear factor kappa-B (NF-κB), and mitogen-activated protein kinase (MAPK) are triggered by receptor activation [21–23].

3.5. NF-κB pathway

The transcription factor NF-κB is involved in immunological response, survival, inflammation, and apoptosis [24]. P50, p52, RelA (p65), RelB, and c-Rel are the five related transcription factors that make up the NF-κB family [25, 26]. Several chemicals, including those originating from pathogens, intercellular inflammatory cytokines, and several enzymes, can all trigger NF-κB activation [27, 28]. IκB proteins found in the cytoplasm suppress NF-κB in physiological settings [29]. IκB kinase (IKK) is activated by PRRs by comparable signal transduction pathways. IKK is made up of two kinase subunits, IKKα and IKKβ, and one regulatory subunit, IKKγ. IKK controls the activation of the NF-κB pathway by phosphorylating IκB [8]. When IκB is phosphorylated, the proteasome degrades it, releasing NF-κB, which then activates gene transcription and nuclear translocation [30]. This route controls the recruitment of inflammatory cells and the synthesis of pro-inflammatory cytokines, both of which enhance the inflammatory response.

3.6. MAPK pathway

A family of serine/threonine protein kinases known as MAPKs controls how cells react to a range of stimuli, such as heat shock, mitogens, osmotic stress, and inflammatory cytokines like IL-1, TNF-α, and IL-6, which control apoptosis, survival, differentiation, and proliferation of cells [31, 32]. p38 MAP Kinase, c-Jun N-terminal kinases (JNK), and extracellular signal-regulated kinase (ERK1/2) are examples of mammalian MAPKs [33]. At least three elements make up each MAPK signaling pathway: a MAPK, a MAPK kinase (MAPKK), and a MAPK kinase kinase (MAPKKK). Following their phosphorylation and activation of MAPKs, MAPKKs are phosphorylated and activated by MAPKKKs [33, 34]. While inflammatory stimuli and stress activate JNK and p38, mitogens and differentiation signals typically activate ERKs [35]. ERK1/2 is activated by MKK1 and MKK2, JNK is activated by MKK4 and MKK7, while p38 is activated by MKK3 and MKK6. The inflammatory response is started when the MAPKs, such as Erk1/2 and JNK, are activated. This causes the p38 transcription factors that are found in the cytoplasm or nucleus to be phosphorylated and activated [32, 36].

3.7. JAK-STAT pathway

One signaling system that is used by exogenous molecules to influence gene expression is the highly conserved JAK-STAT pathway. Numerous cytokines, growth factors, interferons, and associated substances like leptin and growth hormone are involved [37]. Receptor-associated JAKs are activated by ligands, and they phosphorylate one another to create docking sites for latent STAT cytoplasmic transcription factors. Cytoplasmic STATs that are drawn to these sites phosphorylate and subsequently dimerize prior to being translocated to the nucleus [38]. Tyrosine phosphorylation is necessary for DNA binding and STAT dimerization [39]. Because of JAK/STAT signaling, extracellular cues can be converted straight into transcriptional responses. For example, when members of the IL-6 family attach themselves to receptors on the plasma membrane, the

JAK-STAT proteins get activated. In order to control the transcription of inflammatory genes, STAT proteins that have translocated into the nucleus bind target gene promoter regions [40]. Dysregulation of JAK-STAT, MAPK, or NF-κB activity is linked to cancer, autoimmune, and inflammatory illnesses [41]. Cytokine production is the outcome of signaling via transcription factors [42, 43]. Many inflammatory genes, including IL-1, TNF-α, IL-6 [44], interferons, transforming growth factor (TGF), colony stimulating factor (CSF), and chemokines, are regulated by multiple transcription factors.

3.8. Inflammatory markers

In clinical applications, markers are utilized to distinguish between diseased and normal biological processes and evaluate how well therapeutic interventions work. Inflammatory markers have been shown to correlate with endothelial dysfunction, infection, and cardiovascular disease, among other inflammatory disorders, and may be predictive of inflammatory diseases [45–50]. In addition to causing the production of inflammatory cytokines like TNF-α, IL-1β, and IL-6, as well as inflammatory proteins and enzymes, stimuli also activate inflammatory cells including macrophages and adipocytes. These compounds may be used as biomarkers for the diagnosis, prognosis, and selection of appropriate treatments [53–57].

3.9. Inflammatory cytokines

Immune cells such as lymphocytes, macrophages, and monocytes are the main sources of cytokines. Inflammation is facilitated and inhibited by pro- and anti-inflammatory cytokines, respectively. Cells produce inflammatory cytokines, which include ILs, colony stimulating factors (CSF), IFNs, TNFs, TGFs, and chemokines. Their primary function is to draw leukocytes to the site of injury or infection [58]. Through a complex web of interconnections, cytokines control

inflammation and the immune system's reaction to infection or inflammation. On the other hand, overproduction of inflammatory cytokines can result in organ failure, tissue damage, hemodynamic abnormalities, and eventually death [59, 60]. Treatment of inflammatory illnesses and more precise detection of agent-mediated inflammation would be made possible by a greater understanding of how to control cytokine pathways [58].

3.10. Inflammatory molecules and enzymes

During trauma, stress, or infection, inflammatory proteins in the blood, such as alpha 1-acid glycoprotein, haptoglobin, serum amyloid A, fibrinogen, and C-reactive protein (CRP) [61], help restore homeostasis and inhibit microbial development independently of antibodies [62]. High-mobility group box 1 (HMGB1), superoxide dismutase (SOD), glutathione peroxidase (GPx), NADPH oxidase (NOX), inducible nitric oxide synthase (iNOS), and cyclooxygenase (COX)-2 are just a few of the enzymes whose abnormal activation plays a major role in the development of inflammation-related diseases like cancer and cardiovascular disease [63–66]. For instance, TLR-coupled signaling pathways may be activated in order to mediate the effects of extracellular HMGB1 [67]. TLR4 is the principal target of extracellular HMGB1 [68], which initiates intracellular signaling cascades dependent on MyD88 that activate the NF-κB and MAPK pathways. As a result, pro-inflammatory cytokines such TNF-α and IL-1β are released [67]. In medicine, inflammatory proteins and enzymes have been employed as biomarkers for trauma, infection, and inflammation.

3.11. Other inflammatory markers

Oxidative stress is influenced by antioxidant defense mechanisms, which include antioxidant enzymes. Reactive oxygen species (ROS), malondialdehyde (MDA), 8-hydroxy-2-

deoxyguanosine (8-OHdG), and isoprostanes can all be produced in response to elevated oxidative stress [64, 69]. These compounds can then activate different transcription factors, such as NF-κB, AP-1, p53, and STAT. As a result, this cascade can enhance the expression of genes that code for chemokines, inflammatory cytokines, and growth factors [70]. Numerous diseases, including atherosclerosis, diabetes, cancer, cardiovascular disease, and hypertension, are linked to oxidative stress in their etiology. Thus, products of oxidative stress may potentially serve as indicators of the inflammatory response.

3.12. Cell involved in inflammatory responses

Numerous cell types interact together in a highly coordinated network during the inflammatory response. Local reactions to infection and tissue injury are mediated by activated monocytes, macrophages, and other cells. Damaged epithelium and endothelial cells release growth factors and chemokines, which draw neutrophils and monocytes, as well as substances that start the inflammatory cascade at the site of tissue injury. Neutrophils are the first cells drawn to an injured location, followed by monocytes, mast cells, lymphocytes (NK, T, and B cells), and natural killer cells [71–73]. Chemotaxis is the mechanism by which monocytes are drawn into injured tissues and develop into macrophages and dendritic cells. Numerous illnesses, such as asthma, cancer, chronic inflammatory disorders, atherosclerosis, diabetes, autoimmune and degenerative diseases, are linked to inflammation-mediated immune cell changes. In addition to attacking inside bacteria, neutrophils can harm host tissues and cells [74]. Important players in the inflammatory response, neutrophils produce localized factors that draw monocytes and dendritic cells and instruct antigen-presenting cells to activate T cells [7]. Macrophages play a crucial role in the development, maintenance, and resolution of inflammation and are an essential part of the mononuclear phagocyte system [75]. Macrophages present antigens, engage in phagocytosis, and produce

growth factors and cytokines to influence the immune response during inflammation. Effector cells called mast cells live in connective tissue matrices and on the surfaces of epithelial cells. They are responsible for inducing inflammatory reactions. Many inflammatory mediators, such as histamine, proteases, prostaglandins, leukotrienes, cytokines, chemokines, and serglycin proteoglycans, are released by activated mast cells [76]. Numerous studies have shown how platelets affect inflammatory processes, including infection and atherosclerosis. Pro-inflammatory effects could be mediated by platelet interactions with inflammatory cells. The first reaction to an illness or damage is known as the acute phase response (APR), and some research has shown that platelets can trigger the APR [77]. Immune cells are drawn in by inflammatory stimuli, and they release local inflammatory mediators at the site of inflammation to augment and maintain the APR.

3.13. Resolution of inflammatory responses

The suppression of the inflammatory response is necessary to stop further tissue damage and the evolution of acute inflammation into persistent, chronic inflammation. Chemokine gradients are gradually dissolved throughout the well-managed process of inflammation resolution, which involves the generation of mediators under controlled temporal and geographical conditions.

Eventually, circulating white blood cells lose their ability to detect these gradients and are not drawn to damage sites. Chronic inflammation that is out of control can result from this process' dysregulation [78]. Reduction or cessation of neutrophil tissue infiltration and apoptosis of spent neutrophils, counter-regulation of chemokines and cytokines, macrophage transformation from classically to alternatively activated cells, and the start of healing are examples of inflammation resolution processes that restore tissue homeostasis [79, 80]. Acute inflammatory mechanisms cannot completely heal tissue damage, which results in chronic inflammation [81]. Chronic inflammation can cause a variety of illnesses, including cancer, heart disease, atherosclerosis, type

2 diabetes, rheumatoid arthritis, and atherosclerosis [82]. Improved targeted medicines can be developed and produced by knowing the common processes that orchestrate malfunction in the different organ systems.

3.14. Organ-specific inflammation

It has long been known that one of the main causes of disease is inflammation. According to estimates, persistent inflammation and infection account for 15% of human malignancies [83]. Numerous organ systems, including the heart, pancreas, liver, kidney, lung, brain, digestive tract, and reproductive system, have been shown to be affected by acute and chronic inflammation-mediated tissue damage.

3.14.1. Heart

Globally, atherosclerosis, the underlying pathology of cardiovascular disease, is the leading cause of mortality and disability [84, 85]. It is estimated that cardiovascular illnesses will claim the lives of over 23.6 million individuals yearly by 2030 [86, 87]. From the first leukocyte recruitment to the rupture of the atherosclerotic plaque, inflammatory mediators are important players in atherosclerosis [88–91]. Another early occurrence in cardiac stress is inflammation. Affected cardiac tissues show increased production and release of inflammatory cytokines and chemokines, as well as elevated levels of endothelial adhesion molecules [92].

The main line of defense for the heart against infections and tissue damage is the innate immune system [93]. The most frequent cause of heart injury is myocardial infarction, which is typically caused by coronary atherosclerosis and involves the abrupt loss of a large number of myocardial cells [94]. An inflammatory cascade is started by necrotic cardiac cells in order to remove debris and dead cells from the infarct [95, 96]. An inflammatory reaction is triggered by the release of

intracellular components upon cell death, which in turn activates innate immune mechanisms. Cell surface receptors identify endogenous ligands generated after injury as danger signals, which trigger inflammation [97, 98]. Through the activation of NF-κB signaling, TLR-mediated pathways set off post-infarction inflammatory responses [98–103]. Leukocyte-endothelial cell adhesions are facilitated by cytokines, while chemokines draw inflammatory leukocytes to the infarct [104, 105]. Furthermore, by reducing inflammation, improving myofibroblast phenotypic regulation, and encouraging extracellular matrix deposition, TGF-β and IL-10 aid in cardiac repair [106, 107].

3.14.2. Pancreas

Pancreatitis is an inflammatory condition of the pancreas that can be brought on by drinking, trypsinogen gene mutation, or obstruction of the pancreatic duct [108]. In most developed nations, the incidence of acute pancreatitis (AP) varies from 4–45 per 100,000 patients annually and rises by roughly 1.3–4.0% annually. Chronic pancreatitis (CP) is less prevalent than acute pancreatitis (AP), which is one of the most common gastrointestinal reasons for hospitalization in the United States. On the other hand, exocrine and/or endocrine insufficiency, as well as persistent stomach pain, negatively impact the quality of life for CP patients [109]. The death of acinar cells and the activation of inflammatory cells, such as neutrophils, granulocytes, and macrophages, which release inflammatory cytokines, are the hallmarks of pancreatitis [110]. These cytokines activate pancreatic stellate cells (PSCs) to promote CP even more. A multitude of biochemical pathways, such as JAK-STAT, MAPK, and NF-κB, are required for the activation of inflammatory cells in pancreatitis and for the progression of the disease.

3.14.3. Liver

The liver is protected against infection and damage by inflammation, but too much inflammation can cause ischemia-reperfusion injury, hepatocyte loss, metabolic changes, and ultimately irreversible liver damage [111]. Hepatic parenchymal cells can be destroyed by inflammation, which raises the possibility of developing chronic liver illnesses such viral hepatitis or non-alcoholic fatty liver disease (NAFLD). In the United States, chronic liver disorders constitute a major cause of morbidity and mortality [112].

As the biggest solid organ in the body, the liver is a target for inflammatory diseases that are both infectious and non-infectious [113]. Microorganisms such as bacterial products, hepatitis B virus (HBV), or hepatitis C virus (HCV) are the main cause of infectious inflammation of the liver [114, 115]. In addition, sterile inflammation (SI) plays a significant role in the pathophysiology of numerous liver illnesses, including drug-induced liver injury, ischemia/reperfusion, and steatohepatitis, whether alcohol or nonalcoholic [116–118]. Endogenous DAMPs are released into damaged tissues during SI, where they stimulate immune cells [119]. Pathogen-driven inflammation and SI are not the same, but they do have certain functional similarities. PAMPs and DAMPs can both activate a wide variety of receptors and pathways [120].

3.14.4. Brain

A common factor in the abnormal development of organ disease is inflammation. Inflammation is primarily caused by three pathways: NF-κB, MAPK, and JAK-STAT. Dysregulation of one or more of these processes can result in diseases linked to inflammation. Improved prevention and treatment of inflammatory illnesses will surely result from a deeper comprehension of the molecular mechanisms and pathways underlying the inflammatory response. Endogenous ligands that TLRs identify can potentially cause inflammatory reactions in the central nervous system. DAMPs that cross the blood-brain barrier and reach the brain, such as heat-shock proteins and

extracellular matrix degradation molecules, have the potential to trigger inflammatory reactions. Both infectious agents and brain injury, such as tissue destruction following ischemia, traumatic, or excitotoxic brain injury, or seizure, trigger a robust CNS inflammatory response [125, 122, 126].

3.15. Conclusion

A common factor in the abnormal development of organ disease is inflammation. Inflammation is primarily caused by three pathways: NF-κB, MAPK, and JAK-STAT. Dysregulation of one or more of these processes can result in diseases linked to inflammation. Improved prevention and treatment of inflammatory illnesses will surely result from a deeper comprehension of the molecular mechanisms and pathways underlying the inflammatory response.

References

1. Medzhitov R. Inflammation 2010: new adventures of an old flame. Cell. 2010; 140:771–776.

2. Ferrero-Miliani L, Nielsen O, Andersen P, Girardin S. Chronic inflammation: importance of NOD2 and NALP3 in interleukin-1β generation. Clin Exp Immunol. 2007; 147:227–235.

3. Nathan C, Ding A. Nonresolving inflammation. Cell. 2010; 140:871–882.

4. Zhou Y, Hong Y, Huang H. Triptolide Attenuates Inflammatory Response in Membranous Glomerulo- Nephritis Rat via Downregulation of NF-κB Signaling Pathway. Kidney and Blood Pressure Res. 2016; 41:901–910.

5. Takeuchi O, Akira S. Pattern Recognition Receptors and Inflammation. Cell. 2010; 140:805–820.

6. Chertov O, Yang D, Howard O, Oppenheim JJ. Leukocyte granule proteins mobilize innate host defenses and adaptive immune responses. Immunol Rev. 2000; 177:68–78.

7. Jabbour HN, Sales KJ, Catalano RD, Norman JE. Inflammatory pathways in female reproductive health and disease. Reprod. 2009; 138:903–919.

8. Lawrence T. The Nuclear Factor NF-κB Pathway in Inflammation. CSH Perspect Biol. 2009; https://doi. org/10.1101/cshperspect.a001651.

9. Libby P. Inflammatory mechanisms: the molecular basis of inflammation and disease. Nutr Rev. 2007; 65:S140-S146.

10. Brusselle G, Bracke K. Targeting immune pathways for therapy in asthma and chronic obstructive pulmonary disease. Annals American Thoracic Society. 2014; 11:S322 -S328.

11. Gudkov AV, Komarova EA. p53 and the Carcinogenicity of Chronic Inflammation. CSH Perspect Med. 2016; https:// doi.org/10.1101/cshperspect.a026161.

12. Seong SY, Matzinger P. Hydrophobicity: an ancient damage-associated molecular pattern that initiates innate immune responses. Nat Rev Immunol. 2004; 4:469–478.

13. Ozinsky A, Underhill DM, Fontenot JD, Hajjar AM, Smith KD, Wilson CB, Schroeder L, Aderem A. The repertoire for pattern recognition of pathogens by the innate immune system is defined by cooperation between toll-like receptors. P Natl Acad Sci. 2000; 97:13766–13771.

14. Janeway CA Jr, Medzhitov R. Innate immune recognition. Annu rev of immunol. 2002; 20:197–216.

15. Yamamoto M, Takeda K. Current Views of Toll-Like Receptor Signaling Pathways. Gastroenterol Res Pract. 2010: https://doi.org/10.1155/2010/240365.

16. Czerkies M, Kwiatkowska K. Toll-Like Receptors and their Contribution to Innate Immunity: Focus on TLR4 Activation by Lipopolysaccharide. Adv Cell Biol. 2014; 4:1–23.

17. Akira S, Takeda K, Kaisho T. Toll-like receptors: critical proteins linking innate and acquired immunity. Nat Immunol. 2001; 2:675–680.

18. Adib-Conquy M, Cavaillon JM. Stress molecules in sepsis and systemic inflammatory response syndrome. FEBS let. 2007; 581:3723–3733.

19. Rubartelli A, Lotze MT. Inside, outside, upside down: damage-associated molecular-pattern molecules (DAMPs) and redox. Trends immunol. 2007; 28:429–436.

20. Kaminska B. MAPK signalling pathways as molecular targets for anti-inflammatory therapy--from molecular mechanisms to therapeutic benefits.BBA. 2005; 1754:253–262.

21. Hendrayani SF, Al-Harbi B, Al-Ansari MM, Silva G, Aboussekhra A. The inflammatory/cancer-related IL-6/ STAT3/NF-κB positive feedback loop includes AUF1 and maintains the active state of breast myofibroblasts. Oncotarget. 2016; 7:41974–41985. https://doi.org/10.18632/ oncotarget.9633.

22. Kyriakis JM, Avruch J. Mammalian mitogen-activated protein kinase signal transduction pathways activated by stress and inflammation. Physiol Rev 2001; 81:807–869.

23. Henríquez-Olguín C, Altamirano F, Valladares D, López JR, Allen PD, Jaimovich E. Altered ROS production, NF- κB activation and interleukin-6 gene expression induced by electrical stimulation in dystrophic mdx skeletal muscle cells. BBA-Mol Basis Disc. 2015; 1852:1410–1419.

24. Girard S, Kadhim H, Roy M, Lavoie K, Brochu ME, Larouche A, Sébire G. Role of perinatal inflammation in cerebral palsy. Pediatr neurol. 2009; 40:168–174.

25. Moynagh PN. The NF-kB pathway. J Cell Sci. 2005; 118:4585–4592.

26. Hoffmann A, Natoli G, Ghosh G. Transcriptional regulation via the NF-|[kappa]|B signaling module. Oncogene. 2006; 25:6706–6716.

27. Pasparakis M, Luedde T, Schmidt-Supprian M. Dissection of the NF-κB signalling cascade in transgenic and knockout mice. Cell Death Differ. 2006; 13:861–872.

28. Basak S, Kim H, Kearns JD, Tergaonkar V, O'Dea E, Werner SL, Benedict CA, Ware CF, Ghosh G, Verma IM. A fourth IκB protein within the NF-κB signaling module. Cell. 2007; 128:369–381.

29. Kadhim H, Tabarki B, Verellen G, De Prez C, Rona AM, Sebire G. Inflammatory cytokines in the pathogenesis of periventricular leukomalacia. Neurology. 2001; 56:1278– 1284.

30. Hayden MS, Ghosh S. NF-κB, the first quarter-century: remarkable progress and outstanding questions. Gene Dev. 2012; 26:203–234.

31. Kaminska B. MAPK signalling pathways as molecular targets for anti-inflammatory therapy--from molecularmechanisms to therapeutic benefits. Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics. 2005; 1754:253–262.

32. Pearson G, Robinson F, Beers GT, Xu BE, Karandikar M, Berman K, Cobb MH. Mitogen-activated protein (MAP) kinase pathways: regulation and physiological functions. Endocr Rev. 2001; 22:153–183.

33. Kim EK, Choi EJ. Pathological roles of MAPK signaling pathways in human diseases. BBA-Mol Basis. 2010; 1802:396–405.

34. Dhillon AS, Hagan S, Rath O, Kolch W. MAP kinase signalling pathways in cancer. Oncogene. 2007; 26:3279– 3290.

35. Sabio G, Davis RJ. TNF, MAP kinase signalling pathways. Semin in Immunol. 2014; 26:237–245.

36. Raingeaud J, Whitmarsh AJ, Barrett T, Dérijard B, Davis RJ. MKK3- and MKK6-regulated gene expression is mediated by the p38 mitogen-activated protein kinase signal transduction pathway. Mol Cell Biolog. 1996; 16:1247– 1255.

37. O'Shea JJ, Schwartz DM, Villarino AV, Gadina M, Mcinnes IB, Laurence A. The JAK-STAT pathway: impact on human disease and therapeutic intervention. Annu Rev Med. 2015; 66:311–328.

38. Walker JG, Smith MD. The Jak-STAT pathway in rheumatoid arthritis. J Rheumatol. 2005; 32:1650–1653.

39. Ivashkiv LB, Hu X. The JAK/STAT pathway in rheumatoid arthritis: pathogenic or protective? Arthritis Rheumatol. 2003; 48:2092–2096.

40. Boengler K, Hilfiker-Kleiner D, Drexler H, Heusch G, Schulz R. The myocardial JAK/STAT pathway: from protection to failure. Pharmacol Therapeut. 2008; 120:172–185.

41. Oeckinghaus A, Hayden MS, Ghosh S. Crosstalk in NF-κB signaling pathways. Nat Immunol. 2011; 12:695–708.

42. Iwasaki A, Medzhitov R. Toll-like receptor control of the adaptive immune responses. Nat Immunol. 2004; 5:987–995.

43. Opitz B, Van LV, Eitel J, Suttorp N. Innate immune recognition in infectious and noninfectious diseases of the lung. American J Resp Crit Care Med. 2010; 181:1294– 1309.

44. Rahman I, Adcock IM. Oxidative stress and redox regulation of lung inflammation in COPD. Eur Respir J. 2006; 28:219–242.

45. Cesari M, Penninx BW, Newman AB, Kritchevsky SB, Nicklas BJ, Sutton-Tyrrell K, Rubin SM, Ding J, Simonsick EM, Harris TB. Inflammatory markers and onset of cardiovascular events. Circulation. 2003;108: 2317–2322.

46. Bhowmik A, Seemungal TA, Sapsford RJ, Wedzicha JA. Relation of sputum inflammatory markers to symptoms and lung function changes in COPD exacerbations. Thorax. 2000; 55:114–120.

47. Pecoits-Filho R, Heimbürger O, Bárány P, Suliman M, Fehrman-Ekholm I, Lindholm B, Stenvinkel P. Associations between circulating inflammatory markers and residual renal function in CRF patients. Am J Kidney Dis. 2003; 41:1212–1218.

48. Ross AC. Relationship between Inflammatory Markers, Endothelial Activation Markers, and Carotid Intima-Media Thickness in HIV-Infected Patients Receiving Antiretroviral Therapy. Cli Infect Dis. 2009; 49:1119–1127.

49. Pai JK, Pischon T, Ma J, Manson JE, Hankinson SE, Joshipura K, Curhan GC, Rifai N, Cannuscio CC, Stampfer MJ. Inflammatory markers and the risk of coronary heart disease in men and women. New Engl J Med. 2004; 351:2599–2610.

50. Bautista LE, Vera LM, Arenas IA, Gamarra G. Independent association between inflammatory markers (C-reactive protein, interleukin-6, and TNF-alpha) and essential hypertension. J Hum Hypertens. 2005; 19:149–154.

51. Carrero JJ, Yilmaz MI, Lindholm B, Stenvinkel P. Cytokine Dysregulation in Chronic Kidney Disease: How Can We Treat It? Blood Purificat. 2008; 26:291–299.

52. Machowska A, Carrero JJ, Lindholm B, Stenvinkel P. Therapeutics targeting persistent inflammation in chronic kidney disease. Translat Res J La Clin Med. 2016; 167:204– 213.

53. Goldstein BI, Kemp DE, Soczynska JK, Mcintyre RS. Inflammation and the phenomenology, pathophysiology, comorbidity, and treatment of bipolar disorder: a systematic review of the literature. J Clin Psych. 2009; 70:1078–1090.

54. Miller AH, Maletic V, Raison CL. Inflammation and Its Discontents: The Role of Cytokines in the Pathophysiology of Major Depression. Biol Psych. 2009; 65:732–741.

55. Lindahl B, Toss H, Siegbahn A, Venge P Wallentin L. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. New Engl J Med. 2000; 343:1139–1147.

56. Shlipak MG, Fried LF, Crump C, Bleyer AJ, Manolio TA, Tracy RP, Furberg CD, Psaty BM. Elevations of inflammatory and procoagulant biomarkers in elderly persons with renal insufficiency. Circulation. 2003; 107: 87–92.

57. Gupta J, Mitra N, Kanetsky PA, Devaney J, Wing MR, Reilly M, Shah VO, Balakrishnan VS, Guzman NJ, Girndt M. Association between albuminuria, kidney function, and inflammatory biomarker profile in CKD in CRIC. Clin J Am Soc Nephrolog Cjasn. 2012; 7:1938–1946.

58. Turner MD, Nedjai B, Hurst T, Pennington DJ. Cytokines and chemokines: At the crossroads of cell signalling and inflammatory disease. BBA-Mol Cell Res.2014; 1843:2563–2582.

59. Czaja AJ. Hepatic inflammation and progressive liver fibrosis in chronic liver disease. World J Gastroenter. 2014; 20:2515–2532.

60. Liu Z, Wang Y, Wang Y, Ning Q, Zhang Y, Gong C, Zhao W, Jing G, Wang Q. Dexmedetomidine attenuates inflammatory reaction in the lung tissues of septic mice by activating cholinergic anti-inflammatory pathway. Int Immunopharmacol. 2016; 35:210–216.

61. Eckersall PD, Bell R. Acute phase proteins: Biomarkers of infection and inflammation in veterinary medicine. Vet J. 2010; 185:23–27.

62. Murata H, Shimada N, Yoshioka M. Current research on acute phase proteins in veterinary diagnosis: an overview. Vet J. 2004; 168:28–40.

63. Murakami A, Ohigashi H. Targeting NOX, INOS, COX- 2 in inflammatory cells: chemoprevention using food phytochemicals. Int J Cancer. 2007; 121:2357–2363.

64. Lopresti AL, Maker GL, Hood SD, Drummond PD. A review of peripheral biomarkers in major depression: the potential of inflammatory and oxidative stress biomarkers. Prog neuro-psychoph. 2014; 48:102–111.

65. Huang W, Tang Y, Li L. HMGB1, a potent proinflammatory cytokine in sepsis. Cytokine. 2010; 51:119–126.

66. Schierbeck H, Lundbäck P, Palmblad K, Klevenvall L, Erlandssonharris H, Andersson U, Ottosson L. Monoclonal anti-HMGB1 (high mobility group box chromosomal protein 1) antibody protection in two experimental arthritis models. Mol Med. 2011; 17:1039–1044.

67. Cheng Y, Wang D, Wang B, Li H, Xiong J, Xu S, Chen Q, Tao K, Yang X, Zhu Y. HMGB1 translocation and release mediate cigarette smoke–induced pulmonary inflammation in mice through a TLR4/MyD88-dependent signaling pathway. Mol Biol Cell. 2017; 28:201–209.

68. Asavarut P, Zhao H, Gu J, Ma D. The role of HMGB1 in inflammation-mediated organ injury. Acta Anaesthesiol Taiwanica. 2013; 51:28–33.

69. Park J, Min JS, Kim B, Chae UB, Yun JW, Choi MS, Kong IK, Chang KT, Lee DS. Mitochondrial ROS govern the LPS-induced pro-inflammatory response in microglia cells by regulating MAPK, NF-κB pathways. Neurosci Lett. 2015; 584:191–196.

70. Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB. Oxidative stress, inflammation, and cancer: how are they linked? Free Radical Biol Med. 2010; 49:1603–1616.

71. Stramer BM, Mori R, Martin P. The inflammation-fibrosis link? A Jekyll and Hyde role for blood cells during wound repair. J Invest Dermatol. 2007; 127:1009–1017.

72. Van LS, Miteva K, Tschöpe C. Crosstalk between fibroblasts and inflammatory cells. Cardiovasc Res. 2014; 102:258–269.

73. Robb CT, Regan KH, Dorward DA, Rossi AG. Key mechanisms governing resolution of lung inflammation. Semin Immunopathol. 2016; 38:425–448.

74. Nathan C. Neutrophils and immunity: challenges and opportunities. Nat Rev Immunol. 2006; 6:173–182.

75. Fujiwara N, Kobayashi K. Macrophages in inflammation. Current Drug Targets Inflam Allergy. 2005; 4:281–286.

76. Huang C, Šali A, Stevens RL. Regulation and Function of Mast Cell Proteases in Inflammation. J Clin Immunol. 1998; 18:169–183.

77. Aggrey AA, Srivastava K, Ture S, Field DJ, Morrell CN. Platelet induction of the acute-phase response is protective in murine experimental cerebral malaria. J Immunol. 2013; 190:4685–4691.

78. Headland SE, Norling LV. The resolution of inflammation: Principles and challenges. Semin Immunol. 2015; 27:149– 160.

79. Reville K, Crean JK, Vivers S, Dransfield I, Godson C. Lipoxin A4 redistributes myosin IIA, Cdc42 in macrophages: implications for phagocytosis of apoptotic leukocytes. Jof Immunol. 2006; 176:1878–1888.

80. Serhan CN, Savill J. Resolution of inflammation: the beginning programs the end. Nat Immunol. 2005; 6:1191– 1197.

81. Lintermans LL, Stegeman CA, Heeringa P, Abdulahad WH. T cells in vascular inflammatory diseases. Front Immunol. 2014; 5:504.

82. Sugimoto MA, Sousa LP, Pinho V, Perretti M, Teixeira MM. Resolution of Inflammation: What Controls Its Onset? Front Immuno. 2016; https://doi.org/10.3389/ fimmu.2016.00.00160.

83. He G, Karin M. NF-κB, STAT3 - key players in liver inflammation and cancer. Cell Res. 2011; 21:159–168.

84. Sofi F, Fabbri A, Casini A. Inflammation and Cardiovascular Disease and Protection by the Mediterranean Diet. Mediterranean Diet: Springer International publishing.2016; 89–96.

85. Khan N, Khymenets O, Urpísardà M, Tulipani S, Garciaaloy M, Monagas M, Moracubillos X, Llorach R, Andreslacueva C. Cocoa Polyphenols and Inflammatory Markers of Cardiovascular Disease. Nutrients. 2014; 6:844–880.

86. Lloydjones D, Adams RJ, Brown TM, Carnethon M, Dai S, Simone GD, Ferguson TB, Ford E, Furie K, Gillespie C. Heart Disease and Stroke Statistics—2010 Update A Report From the American Heart Association. Circulation. 2010; 115:e25-e146.

87. Mathers CD, Loncar D. Projections of Global Mortality and Burden of Disease from 2002 to 2030. Plos Med. 2006; 3:e442.

88. Packard RRS, Peter L. Inflammation in atherosclerosis: from vascular biology to biomarker discovery and risk prediction. Clin Chem. 2008; 54:24–38.

89. Libby P. History of Discovery: Inflammation in Atherosclerosis. Arteriosclerosis Thrombosis Vascular Biology. 2012; 32:2045–2051.

90. Libby P. Atherosclerosis in Inflammation. Nature. 2002; 420:868–874.

91. Libby P, Okamoto Y, Rocha VZ, Folco E. Inflammation in atherosclerosis: transition from theory to practice. Circulation J. 2010; 74:213–220.

92. Glezeva N, Baugh JA. Role of inflammation in the pathogenesis of heart failure with preserved ejection fraction and its potential as a therapeutic target. Heart Fail Rev. 2014; 19:681–694.

93. Askevold ET, Gullestad L, Dahl CP, Yndestad A, Ueland T, Aukrust P. Interleukin-6 signaling, soluble glycoprotein 130, and inflammation in heart failure. Curr Heart Fail Reports. 2014; 11:146–155.

94. Jennings RB, Murry CE, Steenbergen C Jr, Reimer KA. Development of cell injury in sustained acute ischemia. Circulation. 1990; 82:II2–12.

95. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. Circulation. 1990; 81:1161–1172.

96. Opie LH, Commerford PJ, Gersh BJ, Pfeffer MA. Controversies in ventricular remodelling. Lancet. 2006; 367:356–367.

97. Frangogiannis NG. The immune system and cardiac repair. Pharmacol Res. 2008; 58:88–111.

98. Beg AA. Endogenous ligands of Toll-like receptors: implications for regulating inflammatory and immune responses. Trends Immunol. 2002; 23:509–512.

99. Frantz S, Ertl G, Bauersachs J. Mechanisms of Disease: Toll-like receptors in cardiovascular disease. Nat Clin Pract Card. 2007; 4:444–454.

100. Nijmeijer R, Lagrand WK, Visser CA, Meijer CJ, Niessen HW, Hack CE. CRP, a major culprit in complement-mediated tissue damage in acute myocardial infarction? Int Immunopharmacol. 2001; 1:403–414.

101. Giordano FJ. Oxygen, oxidative stress, hypoxia, and heart failure. J Clin Invest. 2005; 115:500–508.

102. Griendling KK, Fitzgerald GA. Oxidative Stress and Cardiovascular Injury: Part I: Basic Mechanisms and In Vivo Monitoring of ROS. Circulation. 2003; 108:1912– 1916.

103. Hall G, Hasday JD, Rogers TB. Regulating the regulator: NF-κB signaling in heart. J Mol Cell Cardiol. 2006; 41:580–591.

104. Gerard C, Rollins BJ. Chemokines and disease. Nat Immunol. 2001; 2:108–115.

105. Moser B, Loetscher P. Lymphocyte traffic control by chemokines. Nat Immunol. 2001; 2:123–128.

106. Kaur K, Dhingra S, Slezak J, Sharma AK, Bajaj A, Singal PK. Biology of TNFα and IL-10, and their imbalance in heart failure. Heart Fail Rev. 2009; 14:113–123.

107. Frangogiannis NG. Targeting the transforming growth factor (TGF)-β cascade in the remodeling heart: Benefits and perils. J Mol Cell Cardiol. 2014; 76:169–171.

108. Manohar M, Verma AK, Venkateshaiah SU, Sanders NL, Mishra A. Pathogenic mechanisms of pancreatitis. World J Gastr Pharmacol Therapeut. 2017; 8:10–25.

109. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology. 2013; 144:1252– 1261.

110. Zheng L, Xue J, Jaffee EM, Habtezion A. Role of immune cells and immune-based therapies in pancreatitis and pancreatic ductal adenocarcinoma. Gastroenterology. 2013; 144:1230–1240.

111. Brenner C, Galluzzi L, Kepp O, Kroemer G. Decoding cell death signals in liver inflammation. J Hepatol. 2013; 59:583–594.

112. Leitão HS, Doblas S, Garteiser P, D'Assignies G, Paradis V, Mouri F, Geraldes CF, Ronot M, Van Beers BE. Hepatic Fibrosis, Inflammation, and Steatosis: Influence on the MR Viscoelastic and Diffusion Parameters in Patients with Chronic Liver Disease. Radiology. 2016: 283:98–1107.

113. Ramadori G, Moriconi F, Malik I, Dudas J. Physiology and pathophysiology of liver inflammation, damage and repair. J Physiol Pharmacol. 2008; 59:107–117.

114. Pawlotsky JM. Pathophysiology of hepatitis C virus infection and related liver disease. Trends in Microbiol. 2004; 12:96–102.

115. Dunn C, Brunetto M, Reynolds G, Christophides T, Kennedy PT, Lampertico P, Das A, Lopes AR, Borrow P, Williams K, Humphreys E, Afford S, Adams DH, et al. Cytokines induced during chronic hepatitis B virus infection promote a pathway for NK cell–mediated liver damage. J Exp Med. 2007; 204:667–680.

116. Gao B, Seki E, Brenner DA, Friedman S, Cohen JI, Nagy L, Szabo G, Zakhari S. Innate immunity in alcoholic liver disease. Am J Physiol Gastrointest Liver Physiol. 2011; 300:516–525.

117. Brenner DA, Seki E, Taura K, Kisseleva T, Deminicis S, Iwaisako K, Inokuchi S, Schnabl B, Oesterreicher CH, Yong HP. Non-alcoholic steatohepatitis-induced fibrosis: Toll-like receptors, reactive oxygen species and Jun N-terminal kinase. Hepatol Res. 2011; 41:683–686.

118. Maher JJ. DAMPs ramp up drug toxicity. J Clin Invest. 2009; 119:246–249.

119. Kubes P, Mehal WZ. Sterile Inflammation in the Liver. Gastroenterology. 2012; 143:1158–1172.

120. Poltorak A, He X, Smirnova I, Liu MY, Huffel CV, Du X, Birdwell D, Alejos E, Silva M, Galanos C. Defective LPS Signaling in C3H/HeJ and C57BL/10ScCr Mice: Mutations in Tlr4 Gene. science. 1998; 282:2085–2088.

121. Nelson PT, Soma LA, Lavi E. Microglia in diseases of the central nervous system. Annals Med. 2002; 34:491–500.

122. Vezzani A, Granata T. Brain Inflammation in Epilepsy: Experimental and Clinical Evidence. Epilepsia. 2005; 46:1724–1743.

123. Block ML, Zecca L, Hong JS. Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. Nat Rev Neuro. 2007; 8:57–69.

124. Ekdahl CT, Claasen JH, Bonde S, Kokaia Z, Lindvall O. Inflammation is detrimental for neurogenesis in adult brain. P Natl Acad of Sci USA. 2003; 100:13632–13637.

125. Koltsakis GC, Stamatelos AM. Cytokines and acute neurodegeneration. Nat Rev Neuro. 2001; 2:734–744.

126. Jankowsky JL, Patterson PH. The role of cytokines and growth factors in seizures and their sequelae. Prog Neurobio. 2001; 63:125–149.

Chapter 4

WHEN DEFENSE TURNS DESTRUCTIVE: THE SCIENCE OF HYPERSENSITIVITY

Dr. Oly Banerjee

Email: olyb@svu.ac.in

Department of Medical Laboratory Technology, School of Allied Health Sciences, Swami Vivekananda University, Telinipara, Barasat-Barrackpore Rd, Bara Kanthalia, West Bengal-700121, India

Overview

Hypersensitivity refers to an exaggerated or inappropriate immune response to a foreign substance or antigen that can lead to tissue damage and a variety of clinical symptoms. This phenomenon can be categorized into four primary types, each with distinct mechanisms and manifestations. Type I hypersensitivity, also known as immediate hypersensitivity, involves the rapid reaction of IgE antibodies to allergens, leading to conditions such as asthma, hay fever, and anaphylaxis. Type II hypersensitivity, or cytotoxic hypersensitivity, is characterized by antibody-mediated destruction of cells, often seen in autoimmune diseases like hemolytic anemia. Type III hypersensitivity involves immune complex deposition, causing inflammation and tissue damage as observed in conditions like systemic lupus erythematosus. Type IV hypersensitivity, or delayed-type hypersensitivity, is mediated by T-cells and is associated with conditions such as contact dermatitis and chronic transplant rejection. The complexity of hypersensitivity reactions underscores the delicate balance of the immune system and its role in maintaining health, with dysregulation potentially leading to significant morbidity. Understanding these mechanisms is crucial for

developing therapeutic strategies to mitigate the harmful effects of hypersensitivity and improve patient outcomes.

4. **Causes of Hypersensitivity:** Hypersensitivity diseases arise from immune responses that target specific antigens from various sources:

- Autoimmunity: reactions directed against the body's own antigens.
- Reactions against microbial antigens.
- Reactions against environmental antigens that are not microbial.

Hypersensitivity is an exaggerated or inappropriate immune response to an antigen or foreign substance, which can result in tissue damage and a range of clinical symptoms. It occurs when the immune system reacts more intensely than normal to a substance that is typically harmless or to which the body has become sensitized. Hypersensitivity reactions are classified into four main types based on their mechanisms and the timing of the response: Type I (immediate), Type II (cytotoxic), Type III (immune complex-mediated), and Type IV (delayed-type) hypersensitivity.

Hypersensitivity reactions are characterized by several distinct properties that help to define and differentiate them from normal immune responses. These properties include:

Exaggerated Immune Response:

- Hypersensitivity reactions involve an overactive immune response to a typically harmless substance (allergen) or an antigen. The intensity of the response is disproportionate to the threat posed by the antigen.

Antigen Specificity:

- Hypersensitivity reactions are triggered by specific antigens or allergens. The immune system mistakenly identifies these substances as harmful and mounts a targeted response against them.

Tissue Damage:

- Unlike protective immune responses, hypersensitivity can result in tissue damage. This damage occurs due to the immune system's attack on the body's own cells, tissues, or organs in response to the perceived threat.

Classification into Four Types:

Hypersensitivity reactions are classified into four main types based on their underlying mechanisms:

- **Type I (Immediate Hypersensitivity):** Involves IgE antibodies and mast cells, leading to rapid onset symptoms like allergies and anaphylaxis.
- **Type II (Cytotoxic Hypersensitivity):** Mediated by IgG or IgM antibodies targeting cells, leading to cell destruction, as seen in autoimmune hemolytic anemia.
- **Type III (Immune Complex-Mediated Hypersensitivity):** Involves the formation and deposition of immune complexes, leading to inflammation and tissue injury, such as in systemic lupus erythematosus.
- **Type IV (Delayed-Type Hypersensitivity):** Mediated by T-cells, leading to delayed inflammatory responses, commonly observed in contact dermatitis and tuberculosis.

Timing of the Reaction:

The timing of hypersensitivity reactions varies:

- **Immediate (Type I):** Occurs within minutes to hours after exposure to the antigen.
- **Delayed (Type IV):** Develops over hours to days after exposure.
- **Genetic Predisposition:**

  Individuals may have a genetic predisposition to hypersensitivity, particularly in cases of allergic reactions (Type I). Family history can influence the likelihood of developing conditions like asthma, hay fever, or eczema.
- **Chronicity and Recurrence:**
- Hypersensitivity reactions can be chronic and recurrent, particularly in conditions like asthma, eczema, or autoimmune diseases, where the immune response is continuously or repeatedly triggered.

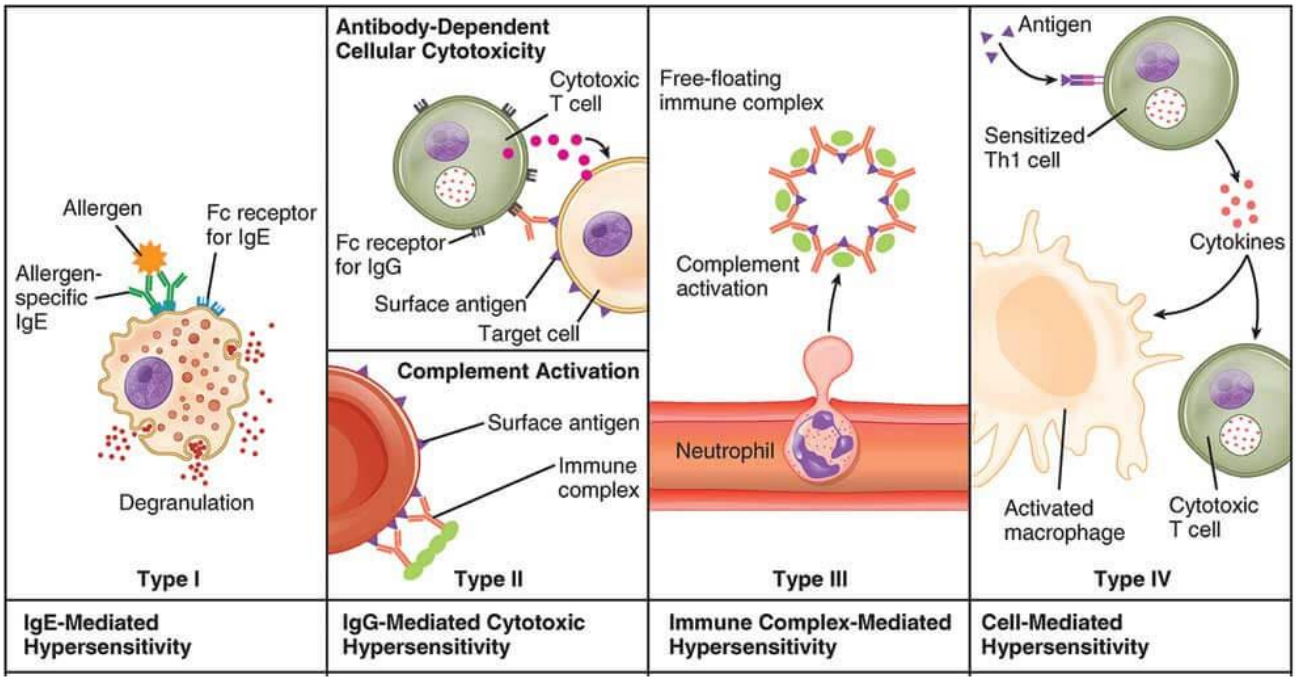
Variety of Clinical Manifestations:

The clinical manifestations of hypersensitivity vary widely, from mild allergic reactions like sneezing and itching to severe, life-threatening conditions such as anaphylaxis or organ failure in autoimmune diseases.

Understanding these properties is essential for diagnosing, managing, and treating hypersensitivity reactions effectively.

4.1 Hypersensitivity Diseases Classification: Hypersensitivity diseases are typically categorized based on the type of immune response and the mechanisms causing cell and tissue damage. These mechanisms can be either antibody-dependent or T cell-dependent, though many hypersensitivity conditions involve both humoral (antibody-mediated) and cell-mediated immunity.

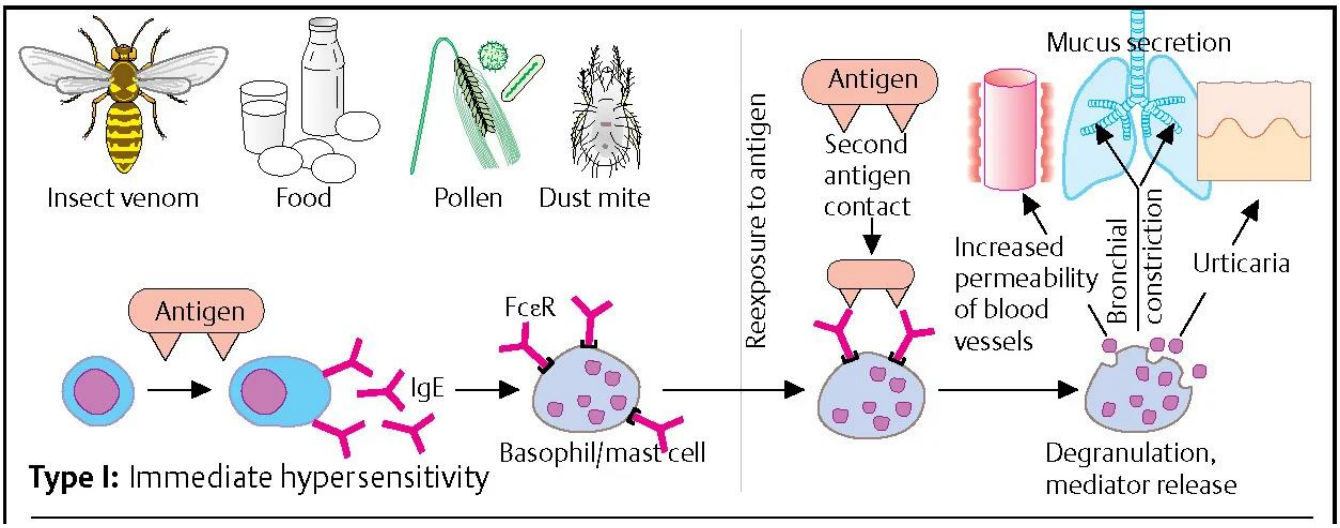
- **Immediate (Type I) Hypersensitivity:** This type is triggered by IgE antibodies specific to environmental antigens and is the most common hypersensitivity condition. Often associated with allergies or atopy, it results from the activation of Th2 cells that produce interleukin-4 (IL-4), IL-5, and IL-13, leading to the production of IgE antibodies. These antibodies activate mast cells and eosinophils, which contribute to inflammation.
- **Antibody-Mediated (Type II) Hypersensitivity:** IgG and IgM antibodies targeting cell surface or extracellular matrix antigens can cause tissue damage through complement activation, recruitment of inflammatory cells, and disruption of normal cellular functions.
- **Immune Complex-Mediated (Type III) Hypersensitivity:** In this type, IgM and IgG antibodies form complexes with soluble antigens in the blood. These immune complexes can deposit in the walls of blood vessels in various tissues, leading to inflammation, thrombosis, and tissue damage.
- **T Cell-Mediated (Type IV) Hypersensitivity:** This form of hypersensitivity involves T lymphocytes that either induce inflammation or directly damage target cells. The primary mechanism usually involves CD4+ helper T cells, which release cytokines that drive inflammation and activate leukocytes like neutrophils and macrophages. In some cases, cytotoxic T lymphocytes (CTLs) also play a role in tissue injury.



4.2 Type I Hypersensitivity (Immediate Hypersensitivity)

4.2.1 Mechanism:

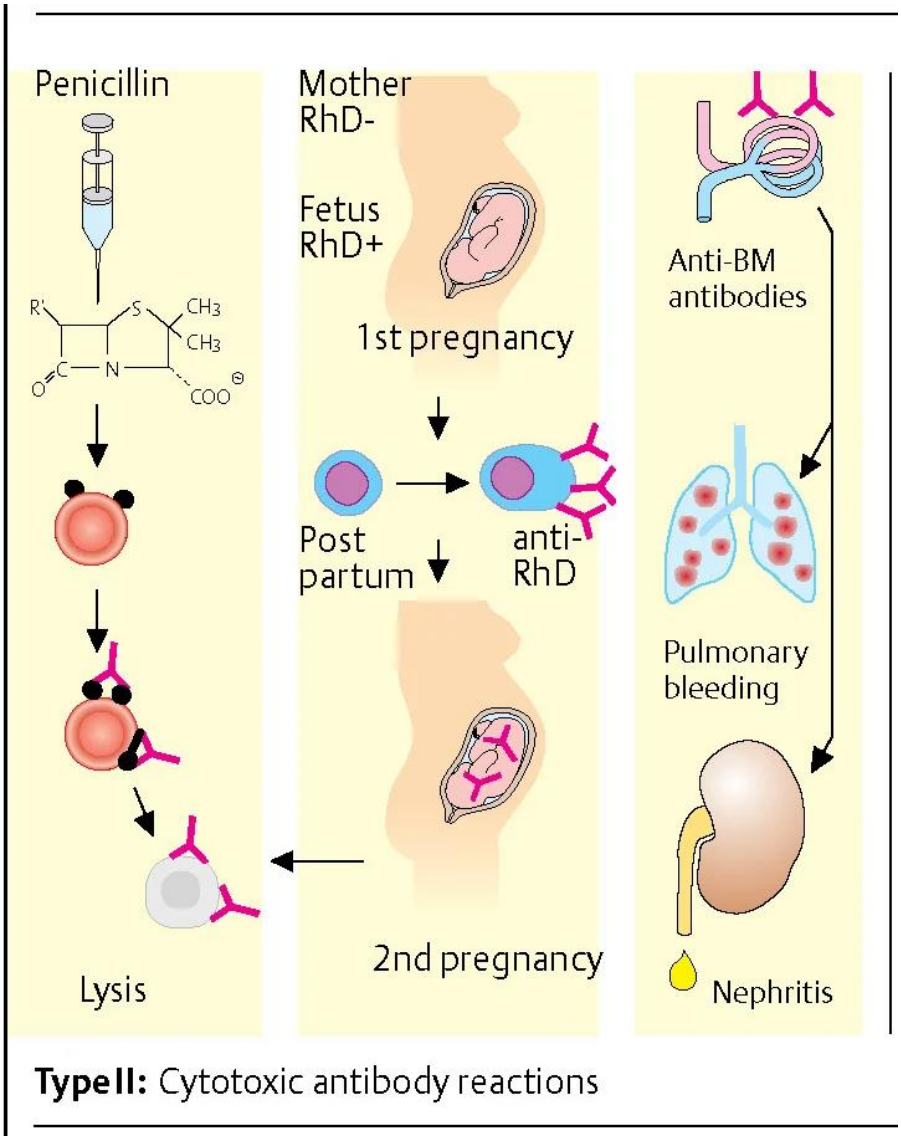
- **Sensitization Phase:** Upon first exposure to an allergen (e.g., pollen, pet dander), the body produces IgE antibodies specific to that allergen. These IgE antibodies bind to Fc receptors on the surface of mast cells and basophils, "sensitizing" them.
- **Effector Phase:** On subsequent exposure to the same allergen, it binds to the IgE antibodies on mast cells and basophils, leading to their degranulation. This releases various mediators such as histamine, prostaglandins, and leukotrienes.
- **Result:** These mediators cause vasodilation, increased vascular permeability, smooth muscle contraction, and mucus secretion, leading to symptoms like itching, swelling, bronchoconstriction, and, in severe cases, anaphylaxis.



4.3 Type II Hypersensitivity (Cytotoxic Hypersensitivity)

4.3.1. Mechanism:

- **Antibody-Mediated Response:** IgG or IgM antibodies are produced against antigens on the surface of cells, such as red blood cells or tissue cells. These antigens can be intrinsic (normal cell components) or extrinsic (attached to the cell surface, such as drugs).
- **Cell Destruction:** The antibodies bind to the cell surface antigens, leading to cell destruction through:
    - **Complement Activation:** The classical complement pathway is activated, leading to the formation of the membrane attack complex (MAC) and cell lysis.
    - **Antibody-Dependent Cellular Cytotoxicity (ADCC):** Immune cells like NK cells recognize antibody-coated cells and destroy them.
    - **Phagocytosis:** Macrophages engulf and digest the antibody-coated cells.
- **Result:** This leads to conditions such as hemolytic anemia, thrombocytopenia, or transfusion reactions.

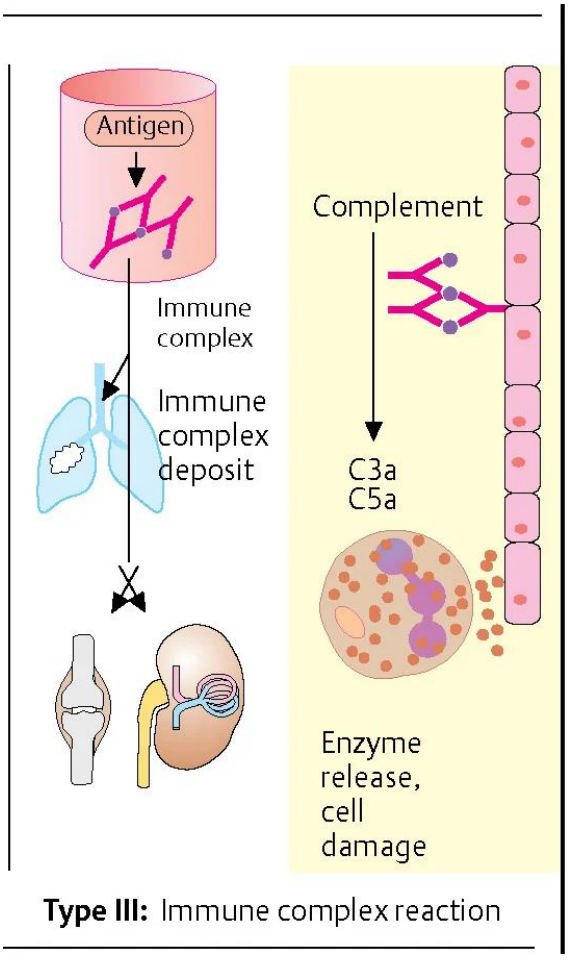


4.4 Type III Hypersensitivity (Immune Complex-Mediated Hypersensitivity)

4.4.1 Mechanism:

- **Formation of Immune Complexes:** Antigen-antibody complexes (mainly IgG) form in the circulation when there is an excess of antigens. These immune complexes are typically soluble and circulate in the bloodstream.

- **Deposition in Tissues:** These immune complexes can deposit in various tissues, such as blood vessel walls, kidneys, and joints.
- **Inflammation and Tissue Damage:** The deposited immune complexes activate the complement system, leading to the recruitment of neutrophils and other inflammatory cells. The inflammatory response causes tissue damage through the release of enzymes and reactive oxygen species.
- **Result:** This mechanism is involved in conditions like systemic lupus erythematosus (SLE), rheumatoid arthritis, and post-streptococcal glomerulonephritis.

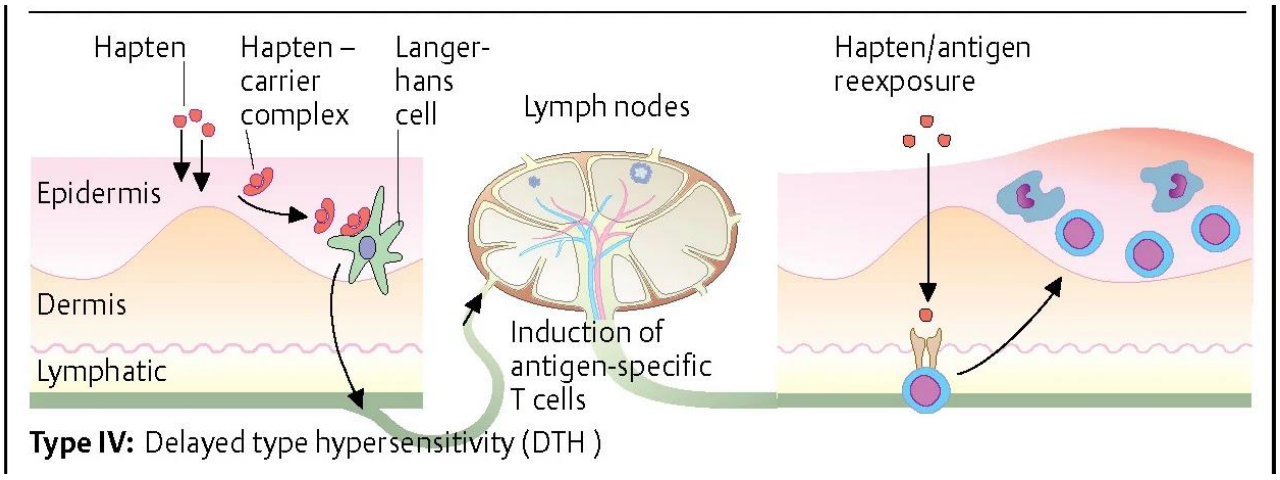


Type III: Immune complex reaction

4.5 Type IV Hypersensitivity (Delayed-Type Hypersensitivity)

4.5.1 Mechanism:

- **T-Cell Mediated Response:** Unlike the other types, Type IV hypersensitivity is mediated by T-cells, not antibodies. Upon first exposure to an antigen (e.g., poison ivy, tuberculin), the antigen is processed and presented by antigen-presenting cells (APCs) to T-helper cells (CD4+).
- **Sensitization Phase:** The T-helper cells become sensitized and differentiate into Th1 cells, which produce cytokines like IFN-γ.
- **Effector Phase:** On subsequent exposure, the sensitized Th1 cells recognize the antigen and release cytokines that activate macrophages and cytotoxic T-cells (CD8+). These activated cells mediate inflammation and tissue destruction.
- **Result:** The response typically peaks 48-72 hours after exposure, leading to conditions such as contact dermatitis, tuberculin reactions, and chronic transplant rejection.



Type I hypersensitivity, also known as immediate hypersensitivity or allergic hypersensitivity, is an immune response that occurs rapidly after exposure to an allergen. It is primarily mediated by

IgE antibodies and mast cells, leading to a range of allergic reactions, from mild symptoms like itching and hives to severe reactions such as anaphylaxis.

4.10. Key Characteristics of Type I Hypersensitivity

- **Rapid Onset:**
    - The reaction occurs within minutes to hours after exposure to the allergen. This rapid onset is why it is called "immediate" hypersensitivity.
- **IgE-Mediated:**
    - The hallmark of Type I hypersensitivity is the involvement of IgE antibodies. These antibodies are produced in response to allergens and play a central role in triggering the allergic response.
- **Allergen Specificity:**
    - The reaction is specific to certain allergens, which can include pollen, dust mites, pet dander, insect venom, certain foods (e.g., peanuts, shellfish), and medications (e.g., penicillin).
- **Mast Cell and Basophil Activation:**
    - Mast cells and basophils, which are abundant in tissues like the skin, respiratory tract, and gastrointestinal tract, are key effector cells in this response. They become sensitized after IgE binds to their surface receptors.
- **Release of Inflammatory Mediators:**

- Upon activation by the allergen, sensitized mast cells and basophils degranulate, releasing a variety of inflammatory mediators, including histamine, prostaglandins, leukotrienes, and cytokines.
- **Clinical Manifestations:**
- The release of these mediators leads to the characteristic symptoms of allergic reactions, such as:
    - **Local Reactions:** Itching, redness, swelling, hives (urticaria), rhinitis, conjunctivitis, asthma.
    - **Systemic Reactions:** Anaphylaxis, which is a severe, potentially life-threatening reaction characterized by widespread vasodilation, drop in blood pressure (shock), bronchoconstriction, and airway obstruction.

4.6.1 Mechanism of Type I Hypersensitivity

- **Sensitization Phase:**
    - **Exposure to Allergen:** The individual is exposed to an allergen, which is recognized by antigen-presenting cells (APCs) like dendritic cells.
    - **Presentation to T-helper Cells:** The APCs process the allergen and present it to naïve T-helper cells (Th0). These cells differentiate into Th2 cells under the influence of cytokines like IL-4.
    - **B-cell Activation:** Th2 cells release cytokines (e.g., IL-4, IL-13) that stimulate B-cells to undergo class switching and produce IgE antibodies specific to the allergen.
    - **IgE Binding:** The IgE antibodies bind to high-affinity FcεRI receptors on the surface of mast cells and basophils, sensitizing these cells to the allergen.

- **Effector Phase:**
    - **Re-exposure to Allergen:** Upon subsequent exposure to the same allergen, it binds to the IgE antibodies on the surface of sensitized mast cells and basophils.
    - **Cross-linking of IgE:** The allergen cross-links the IgE molecules, triggering the activation of the mast cells and basophils.
    - **Degranulation:** Activated mast cells and basophils undergo degranulation, releasing pre-formed mediators like histamine, as well as newly synthesized mediators such as prostaglandins, leukotrienes, and cytokines.
- **Clinical Effects:**
    - **Vasodilation and Increased Vascular Permeability:** Histamine and other mediators cause blood vessels to dilate and become more permeable, leading to redness, swelling, and fluid leakage into tissues (edema).
    - **Smooth Muscle Contraction:** Mediators like leukotrienes cause contraction of smooth muscle, leading to bronchoconstriction in the lungs, which manifests as asthma.
    - **Mucus Secretion:** Increased mucus production in the respiratory tract leads to symptoms like a runny nose (rhinitis) and coughing.
    - **Anaphylaxis:** In severe cases, the widespread release of mediators leads to systemic effects, including a dramatic drop in blood pressure, airway constriction, and potentially fatal shock.
- **Clinical Management**

- **Avoidance of Allergens:** Identifying and avoiding the trigger allergen is the most effective preventive measure.
- **Pharmacotherapy:**
    - **Antihistamines:** Block the effects of histamine, reducing symptoms like itching and swelling.
    - **Corticosteroids:** Reduce inflammation and are used in more severe cases or chronic allergic conditions like asthma.
    - **Epinephrine:** Administered during anaphylaxis to rapidly reverse severe symptoms by constricting blood vessels and relaxing airway muscles.
    - **Leukotriene Modifiers:** Inhibit the action of leukotrienes to reduce bronchoconstriction and inflammation in asthma.
- **Immunotherapy:** Allergy shots or sublingual tablets can be used to gradually desensitize the immune system to the allergen over time, reducing the severity of reactions.

Summary

Type I hypersensitivity is a rapid and IgE-mediated immune response that can result in a wide range of allergic reactions, from mild to life-threatening. Understanding the mechanisms behind this hypersensitivity is crucial for the diagnosis, treatment, and management of allergic conditions.

Type II hypersensitivity, also known as cytotoxic or antibody-dependent hypersensitivity, is an immune response in which antibodies target antigens on the surface of cells or extracellular matrix components, leading to cell destruction or dysfunction. This type of hypersensitivity can result in a variety of autoimmune and alloimmune conditions, where the immune system mistakenly attacks the body's own cells or tissues.

4.11. Key Characteristics of Type II Hypersensitivity

- **Antibody-Mediated Response:**

    - Type II hypersensitivity is primarily mediated by IgG and IgM antibodies. These antibodies specifically target antigens that are either intrinsic (naturally present on cell surfaces) or extrinsic (foreign antigens that have adhered to cell surfaces).

- **Target Cells or Tissues:**

  The antigens targeted by these antibodies are usually located on the surface of cells, such as red blood cells (RBCs), white blood cells, or platelets, but can also be found on basement membranes or other components of the extracellular matrix.

- **Direct Cell Damage:**

    - The immune response in Type II hypersensitivity leads to the direct damage or destruction of the target cells or tissues, which distinguishes it from other hypersensitivity types.

- **Complement System Activation:**

    - The binding of antibodies to antigens on the cell surface can activate the classical complement pathway, leading to the formation of the membrane attack complex (MAC) and subsequent lysis of the cell.

- **Effector Cells Involvement:**

    - Immune cells, such as macrophages, neutrophils, and natural killer (NK) cells, play a role in mediating cell damage through mechanisms like phagocytosis and antibody-dependent cellular cytotoxicity (ADCC).

- **Clinical Manifestations:**

- The clinical outcomes of Type II hypersensitivity include conditions like hemolytic anemia, thrombocytopenia, and tissue-specific autoimmune diseases (e.g., Graves' disease, myasthenia gravis).

4.7.1 Mechanism of Type II Hypersensitivity

- **Antigen Recognition:**
  - **Intrinsic Antigens:** These are self-antigens that are normally present on the cell surface or tissue. In autoimmune diseases, the immune system loses tolerance to these antigens, leading to the production of autoantibodies.
  - **Extrinsic Antigens:** These include foreign antigens that may bind to the surface of cells, such as certain drugs or microbial proteins, making the cells targets for the immune response.
- **Antibody Binding:**
  - IgG or IgM antibodies produced in response to these antigens bind to the antigenic targets on the cell surface. This binding is the first step in the immune response.
- **Effector Mechanisms Leading to Cell Damage:**
  - **Complement Activation:**
    - The binding of antibodies to the antigen on the cell surface activates the classical complement pathway.
    - Activation of the complement cascade results in the formation of the membrane attack complex (MAC), which creates pores in the cell membrane, leading to osmotic lysis and cell death.
  - **Opsonization and Phagocytosis:**

        - Antibody-coated cells are recognized by phagocytes (e.g., macrophages and neutrophils) through Fc receptors and complement receptors.
        - The opsonized cells are engulfed and digested by phagocytes.
    - **Antibody-Dependent Cellular Cytotoxicity (ADCC):**
        - NK cells and other cytotoxic cells recognize and bind to the Fc region of antibodies attached to target cells.
        - These effector cells then release cytotoxic granules that induce apoptosis in the target cell.
- **Clinical Consequences:**
    - **Hemolytic Anemia:**
        - In autoimmune hemolytic anemia, antibodies target antigens on red blood cells, leading to their destruction by complement-mediated lysis or phagocytosis, resulting in anemia.
    - **Thrombocytopenia:**
        - In immune thrombocytopenic purpura (ITP), antibodies target platelets, leading to their destruction and causing bleeding disorders.
    - **Autoimmune Diseases:**
        - **Graves' Disease:** Antibodies target the thyroid-stimulating hormone (TSH) receptor on thyroid cells, leading to hyperthyroidism.
        - **Myasthenia Gravis:** Antibodies target acetylcholine receptors on muscle cells, impairing neuromuscular transmission and leading to muscle weakness.

4.7.2 Clinical Management

- **Immunosuppressive Therapy:**
    - Corticosteroids and other immunosuppressive drugs are used to reduce the production of autoantibodies and the immune-mediated destruction of cells.
- **Plasmapheresis:**
    - In severe cases, plasmapheresis may be used to remove circulating autoantibodies from the bloodstream.
- **Management of Underlying Conditions:**
    - Treating the underlying cause, such as discontinuing an offending drug in drug-induced hemolytic anemia, is crucial.
- **Supportive Care:**
    - Blood transfusions may be necessary in cases of severe hemolytic anemia or thrombocytopenia.

Summary

Type II hypersensitivity is a form of antibody-mediated immune response that results in the direct destruction or dysfunction of cells and tissues. It plays a significant role in a variety of autoimmune and alloimmune diseases, where the body's immune system mistakenly targets its own cells or tissues, leading to clinical conditions that range from mild to life-threatening. Understanding the mechanisms behind Type II hypersensitivity is essential for the effective management and treatment of these conditions.

Type III hypersensitivity, also known as immune complex-mediated hypersensitivity, is an immune response that occurs when immune complexes (aggregates of antigens and antibodies) are

formed in excess and deposit in various tissues, leading to inflammation and tissue damage. This type of hypersensitivity is implicated in a range of autoimmune and inflammatory diseases.

4.12. Key Characteristics of Type III Hypersensitivity

- **Immune Complex Formation:**
    - The hallmark of Type III hypersensitivity is the formation of immune complexes, which consist of antigens bound to antibodies, usually IgG or IgM. These complexes can circulate in the bloodstream or form directly in tissues.
- **Excessive Immune Complexes:**
    - Normally, immune complexes are cleared by the immune system, particularly by phagocytes in the spleen and liver. However, when immune complexes are produced in large quantities or are not efficiently cleared, they can deposit in tissues.
- **Deposition in Tissues:**
    - The immune complexes tend to deposit in tissues where filtration occurs, such as blood vessel walls, kidneys (glomeruli), joints, and serous membranes, leading to localized inflammation.
- **Complement Activation:**
    - The deposited immune complexes activate the classical complement pathway, leading to the generation of complement components like C3a and C5a, which are potent inflammatory mediators.
- **Inflammation and Tissue Damage:**

- The complement activation and the recruitment of inflammatory cells, primarily neutrophils, result in an inflammatory response that causes tissue damage. The inflammation can become chronic and lead to fibrosis.

- **Systemic vs. Localized Reactions:**
  - Depending on the distribution of immune complexes, Type III hypersensitivity can cause systemic diseases, like systemic lupus erythematosus (SLE), or localized conditions, such as post-streptococcal glomerulonephritis.

4.8 Mechanism of Type III Hypersensitivity

- **Formation of Immune Complexes:**
  - **Antigen-Antibody Binding:** When an individual is exposed to an antigen, antibodies (IgG or IgM) are produced in response. These antibodies bind to the antigens, forming immune complexes.
  - **Circulation in Blood:** The immune complexes can remain soluble and circulate in the bloodstream, particularly when there is an excess of antigen.
- **Deposition of Immune Complexes:**
  - **Tissue Deposition:** When these immune complexes are not adequately cleared, they deposit in various tissues. The most common sites of deposition are areas with high blood filtration, such as the kidneys, joints, and small blood vessels.
  - **Factors Influencing Deposition:** The size of the immune complexes, charge, and the presence of certain vascular features influence where and how immune complexes deposit.
- **Complement Activation:**

- **Classical Pathway Activation:** The immune complexes activate the classical complement pathway, starting with the binding of C1q to the Fc region of the antibodies in the immune complex.
- **Generation of Inflammatory Mediators:** Complement activation leads to the formation of C3a and C5a, which are anaphylatoxins that increase vascular permeability and recruit neutrophils and other inflammatory cells to the site of immune complex deposition.

- **Inflammatory Response:**
  - **Neutrophil Recruitment and Activation:** Neutrophils are attracted to the site of immune complex deposition by C5a. However, neutrophils often cannot efficiently phagocytose the deposited complexes, leading to frustration and the release of toxic substances like proteolytic enzymes and reactive oxygen species.
  - **Tissue Damage:** The enzymes and reactive oxygen species released by neutrophils cause local tissue damage, leading to inflammation, necrosis, and in chronic cases, fibrosis.
- **Clinical Manifestations:**
  - **Systemic Lupus Erythematosus (SLE):** Immune complexes formed against nuclear antigens deposit in various tissues, leading to symptoms like a butterfly-shaped rash, arthritis, and kidney damage (lupus nephritis).
  - **Post-Streptococcal Glomerulonephritis:** After a streptococcal infection, immune complexes deposit in the glomeruli of the kidneys, causing inflammation and hematuria (blood in the urine).

- **Rheumatoid Arthritis:** Immune complexes deposit in the synovial joints, leading to chronic inflammation, joint pain, and deformity.
- **Serum Sickness:** Occurs after administration of foreign proteins (e.g., antitoxins) and is characterized by fever, rash, joint pain, and kidney damage due to immune complex deposition.

4.8.1 Clinical Management

- **Anti-inflammatory Agents:**
  - Nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are commonly used to reduce inflammation and alleviate symptoms.
- **Immunosuppressive Therapy:**
  - Drugs like cyclophosphamide, methotrexate, or mycophenolate are used to suppress the immune system, reducing the formation of immune complexes and preventing further tissue damage.
- **Plasmapheresis:**
  - In severe cases, plasmapheresis may be used to remove circulating immune complexes from the blood.
- **Management of Underlying Causes:**
  - Treating the underlying cause, such as eradicating a streptococcal infection in post-streptococcal glomerulonephritis, can help prevent further immune complex formation.

Summary

Type III hypersensitivity is characterized by the formation and deposition of immune complexes in tissues, leading to complement activation, inflammation, and tissue damage. This type of hypersensitivity is associated with various systemic and localized autoimmune and inflammatory diseases. Understanding the underlying mechanisms is crucial for developing effective treatments to manage and mitigate the tissue damage associated with these immune responses.

Type IV hypersensitivity, also known as delayed-type hypersensitivity, is a T-cell-mediated immune response that typically manifests 24 to 72 hours after exposure to an antigen. Unlike other hypersensitivity types, Type IV hypersensitivity does not involve antibodies but is driven by T-cells and macrophages. It is characterized by its delayed onset and the involvement of cellular immune responses.

4.9 Key Characteristics of Type IV Hypersensitivity

- **Cell-Mediated Response:**
    - Type IV hypersensitivity is primarily mediated by T-cells, particularly CD4+ T-helper 1 (Th1) cells and CD8+ cytotoxic T-cells, rather than antibodies.
- **Delayed Onset:**
    - The reaction usually takes 24 to 72 hours to develop after antigen exposure. This delayed response is why it is termed “delayed-type hypersensitivity.”
- **Antigen Specificity:**
    - The response is specific to particular antigens, which can be either environmental (e.g., contact allergens) or self-antigens in autoimmune diseases.
- **Inflammatory Response:**

- The response involves the activation of macrophages and other inflammatory cells, leading to a localized inflammatory reaction and tissue damage.

- **No Antibody Involvement:**
  - Unlike Types I, II, and III hypersensitivity, Type IV does not involve antibodies in the effector phase. Instead, it relies on cellular immune mechanisms.
- **Clinical Manifestations:**
  - The clinical manifestations of Type IV hypersensitivity include conditions like contact dermatitis, tuberculin skin test reactions, and chronic transplant rejection.

4.9.1 Mechanism of Type IV Hypersensitivity

- **Sensitization Phase:**
  - **Antigen Exposure and Processing:**
    - The initial exposure to the antigen leads to its processing by antigen-presenting cells (APCs) such as dendritic cells or macrophages.
    - APCs present the processed antigen peptides to naïve T-helper cells (Th0) in the context of Major Histocompatibility Complex (MHC) molecules.
  - **Activation and Differentiation:**
    - Th0 cells are activated and differentiate into Th1 cells under the influence of cytokines like IL-12 and IFN-γ. These Th1 cells produce cytokines like IFN-γ that help activate macrophages and cytotoxic T-cells.
    - In some cases, CD8+ T-cells are also activated and can directly attack antigen-expressing cells.
- **Effector Phase:**

- **Re-exposure to Antigen:**
    - Upon subsequent exposure to the same antigen, the sensitized Th1 cells and/or CD8+ T-cells recognize the antigen presented by APCs or on the surface of target cells.
- **Activation of Macrophages and Cytotoxic T-Cells:**
    - Th1 cells release cytokines (e.g., IFN-γ, TNF-α) that activate macrophages, enhancing their ability to phagocytose and kill antigen-expressing cells.
    - Activated macrophages release inflammatory mediators such as cytokines, prostaglandins, and reactive oxygen species, which contribute to tissue damage and inflammation.
    - CD8+ cytotoxic T-cells can directly kill antigen-expressing cells through the release of perforin and granzymes, leading to cell apoptosis.
- **Inflammatory Response:**
    - The recruitment of additional inflammatory cells, including neutrophils, and the release of pro-inflammatory cytokines lead to localized inflammation and tissue damage.
    - Chronic exposure to the antigen can result in prolonged inflammation and tissue fibrosis.

4.9.2 Clinical Manifestations:

- **Contact Dermatitis:**

        - Caused by allergens such as nickel, poison ivy, or certain chemicals. The skin reacts with redness, itching, and swelling at the site of contact, usually 24-48 hours after exposure.
    - **Tuberculin Skin Test (Mantoux Test):**
        - Used to test for tuberculosis exposure. The test involves intradermal injection of purified protein derivative (PPD) from Mycobacterium tuberculosis. A positive reaction (induration) occurs 48-72 hours later if the individual has been sensitized to tuberculosis.
    - **Chronic Transplant Rejection:**
        - Involves an ongoing immune response against transplanted tissue or organs, leading to inflammation, fibrosis, and eventual loss of function.
- **Other Examples:**
    - **Autoimmune Diseases:** Conditions like rheumatoid arthritis and multiple sclerosis involve T-cell-mediated inflammation and damage to self-tissues.

4.9.3 Clinical Management

- **Corticosteroids:**
    - Used to reduce inflammation and suppress the immune response in conditions like contact dermatitis and chronic transplant rejection.
- **Topical Immunomodulators:**
    - For localized conditions like eczema or contact dermatitis, topical calcineurin inhibitors (e.g., tacrolimus, pimecrolimus) can be used to modulate the immune response without systemic side effects.

- **Avoidance of Antigen:**
    - Identifying and avoiding the offending antigen is crucial in managing contact dermatitis and other allergic reactions.
- **Immunosuppressive Therapy:**
    - In chronic conditions such as autoimmune diseases or severe transplant rejection, systemic immunosuppressive drugs (e.g., methotrexate, azathioprine) may be used.

Summary

Type IV hypersensitivity is a T-cell-mediated immune response that leads to delayed inflammation and tissue damage. It is characterized by its reliance on cellular immune mechanisms rather than antibodies and is involved in a range of conditions from contact dermatitis to chronic transplant rejection. Understanding the underlying mechanisms is essential for the effective management and treatment of these conditions.

References

1. Lydyard, P.M., Whelan,A.,& Fanger,M.W. (2005).Immunology (2 ed.).London: BIOS Scientific Publishers.
2. Owen, J. A., Punt, J., & Stranford, S. A. (2013). Kuby Immunology (7 ed.). New York: W.H. Freeman and Company.
3. http://semmelweis.hu/mikrobiologia/files/2014/05/hypersensitivity.pdf
4. https://basicmedicalkey.com/streptococcus-enterococcus-and-similar-organisms/
5. https://www.researchgate.net/publication/16984737_Immune_complexes_Characteristics_clinical_correlations_and_interpretive_approaches_in_the_clinical_laboratory
6. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3597223/
7. https://quizlet.com/228679925/week-vi-flash-cards/
8. https://quizlet.com/12054435/cytokines-flash-cards/
9. https://en.wikipedia.org/wiki/Red_blood_cell
10. http://site.iugaza.edu.ps/asilmi/files/2017/09/14.pptx
11. https://courses.lumenlearning.com/microbiology/chapter/hypersensitivities/
12. http://www.biologydiscussion.com/immunology/4-main-types-of-hypersensitivity-immunology/61851
13. https://www.slideshare.net/drsomeshwaranamsana/hypersensitivity-reactions-dr-somesh-microbiology
14. http://www.yourarticlelibrary.com/immunology/type-iii-hypersensitivity-and-its-mechanism-human-immunology/28081

Chapter 5

Understanding Haemorrhage- A life threatening emergency: Mechanisms, Management and Mitigation strategies

Mr. Rupak Bera.

Email: rupakb@svu.ac.in

Department of Medical Laboratory Technology, School of Allied Health Sciences, Swami Vivekananda University, Telinipara, Barasat-Barrackpore Rd, Bara Kanthalia, West Bengal - 700121, India.

5.1 Overview:

Haemorrhage- escape of blood from blood vessel.

Synonymous- bleeding

Loss of blood- Life threatening

It is the blood that either escapes the circulatory system or is lost. In order to decrease the intensity and duration of shock, prevent mortality and/or multiple organ failure, it needs to be identified and treated quickly. The goal of controlling haemorrhage is to stop the bleeding, not to give blood or resuscitate fluids; however, resuscitation is required as a supportive step to keep organ perfusion. After a haemorrhage, blood volume recovers quickly by removing fluid from the tissues and circulating it (a process known as hemodilution); red cell recovery, on the other hand, takes approximately five-six weeks to recovery. [1]

5.2 Definition of Haemorrhage:

The excessive blood loss followed on by blood vessel rupture is known as haemorrhage.

Blood loss from a damaged blood vessel is called a haemorrhage. Internal bleeding occurs when blood is "trapped" inside your body. Alternatively, it may come from a wound or other orifice in your body and flow outside of it (external bleeding). A small or large amount of blood can be lost.

5.3 Mechanism of Haemorrhage:

Hypovolaemic shock is the result of haemorrhage. It is the major effect shows by haemorrhage. Hemorrhage's pathophysiological effects include coagulopathy, acidosis, and hypothermia.

- **Acidosis:** is caused by tissue hypoperfusion-induced lactic acidosis and anaerobic metabolism in cells.
- **Coagulopathy:** Occurs as a result of acidosis-induced reduced coagulation protease function, which exacerbates hemorrhage. This is made worse by endothelial cell ischaemia, which triggers anticoagulant pathways.
- **Hypothermia:** Hypothermia results from underperfused muscle's inability to produce heat. At low temperatures, there is deteriorating acidosis and hypothermia, increased bleeding, hypoperfusion, and poor coagulation. [2]

5.4 TYPES AND CAUSES OF HEMORRHAGE:

There are several reasons why there is hemorrhage.

Based on the cause, hemorrhage is classified into five categories:

5.4.1 ACCIDENTAL HEMORRHAGE

Road and industrial accidents, which are frequent in both industrialized and developing nations, can result in accidental bleeding. There are two categories of unintentional bleeding: There are two types of bleeding that happen after an accident:

i. Primary hemorrhage which happens right away after the accident, and

ii. Secondary hemorrhage which happens a few hours later after the accident. [3]

5.4.2 CAPILLARY HEMORRHAGE

The bleeding that results from the rupture of blood vessels, especially capillaries, is known as capillary hemorrhage. Cerebral hemorrhage, which occurs in the brain, and heart during cardiovascular illnesses are highly common capillary hemorrhage. Following the capillary rupture, blood leaks into the surrounding surroundings.

5.4.3 INTERNAL HEMORRHAGE

The bleeding in the viscera is called internal hemorrhage. It is brought on by the visceral blood vessels rupturing. Blood accumulates in the viscera. [4]

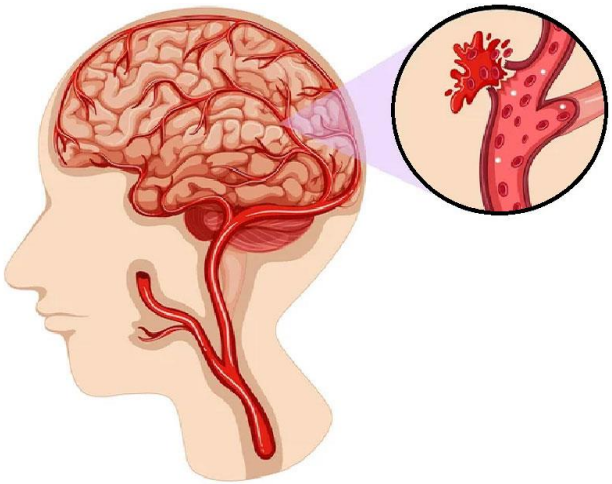


Fig : **Cerebral Hemorrhage (adopted from https://www.turquiesante.com/en/blog/cerebral-hemorrhage-causes-treament-201.html)**

5.4.4 POSTPARTUM HEMORRHAGE

Postpartum hemorrhage is the term used to describe excessive bleeding that happens right after labor (baby delivery). It can sometimes be extremely severe and cause serious problems.

5.4.5 HEMORRHAGE DUE TO PREMATURE DETACHMENT OF PLACENTA

Sometimes the placenta separates from the mother's uterus before the scheduled birth date, leading to heavy bleeding. [6]

5.5 COMPENSATORY EFFECTS OF HEMORRHAGE

There are multiple effects both during and following a hemorrhage. Acute and chronic hemorrhages have various effects. [7]

- **Acute Hemorrhage**

  Acute hemorrhage is the significant volume of blood lost suddenly. It happens in circumstances similar to accidents. In an acute hemorrhage, decreased blood volume results in hypovolemic shock.

- **Chronic Hemorrhage**

  A prolonged period of internal or external bleeding results in blood loss known as chronic haemorrhage. Conditions such as ulcers can cause internal bleeding. Conditions such as haemophilia and menorrhagia, or excessive vaginal bleeding, can cause external bleeding. There are several repercussions of chronic bleeding, including anaemia. [8]

5.5.1 Compensatory Effects

After hemorrhage, series of compensatory reactions arise in the body to adjust with the blood loss. Compensatory effects of hemorrhage are of two categories. A. Immediate compensatory effects B. Delayed compensatory effects. [9]

- **IMMEDIATE COMPENSATORY EFFECTS OF HEMORRHAGE**

1. Effects on Cardiovascular System

Following a hemorrhage, less blood volume reduces cardiac output, ventricular filling, and venous return. Severe bleeding also causes a drop in blood pressure. On the other hand, arterial blood pressure is not significantly impacted by gradual or minimal blood loss. If it is impacted, it is promptly restored. [10]

<u>During mild haemorrhage</u>

When there is a minor blood loss of 350 to 500 mL during a slow or mild hemorrhage, the blood pressure drops slightly and quickly returns to normal. [11]

Mechanism by which blood pressure is maintained:

i. The carotid and aortic baroreceptors are typically triggered when arterial blood pressure rises, sending impulses to the brain that cause the blood pressure to drop. When arterial blood pressure drops during bleeding, baroreceptors inactivate and cease to release impulses.
ii. Vasoconstriction results from an increase in vasomotor tone. Every part of the body experiences this kind of reflex vasoconstriction, with the exception of the heart and brain.
iii. A rise in peripheral resistance is the outcome of vasoconstriction.

iv. Vein reflex constriction is another effect of blood loss. Venoconstriction improves stroke volume, ventricular filling, and venous return. Thus, the arterial blood pressure is restored as a result of increased peripheral resistance and stroke volume.

v. This mechanism involves an additional element. Organs with reservoir functions, such as the skin, liver, and spleen, experience vasoconstriction. These reserve organs' blood is sent into the general circulation. This could make up for the blood volume lost during bleeding. [12]

In cases of severe hemorrhage

An extensive hemorrhage resulting in a blood loss of 1,500–2,000 mL causes a significant drop in arterial blood pressure. It is brought on by a reduction in stroke volume and venous return. [13]

Reflex tachycardia in the heart raises the amount of metabolic products in the myocardium. Coronary vasodilatation is caused by these metabolic products.

2. Effects on Skin

Skin vasoconstriction, which follows a hemorrhage, lowers the blood flow to the skin. It causes a significant amount of decreased hemoglobin to collect in cutaneous blood vessels and accelerates blood deoxygenation. Skin turns pale and gray as a result of it.

There are instances where cyanosis appears in particular bodily parts. Less blood flow causes the skin to get cold as well. There is less perspiration. [14]

3. Effects on Tissue Fluid

Constriction of the arteries lowers the capillary pressure. Tissue fluid thus gets into capillaries. It aids in making up for lost blood. Additionally, it dilutes blood.

4. Effects on Kidneys

Following a hemorrhage, constriction of the kidney's afferent and efferent arterioles significantly lowers the glomerular filtration rate (GFR). Urinary output consequently declines. Uremia is caused by an increase in nitrogenous compounds in the blood, specifically urea. Acute renal failure is caused by severe bleeding, which also damages the renal tubules and lowers arterial blood pressure. [15]

5. Effects on Renin Secretion

The hypoxia that follows blood loss causes the kidneys to secrete more renin, which in turn causes the production of angiotensin II. Angiotensin II causes widespread vasoconstriction, which aids in raising blood pressure. Additionally, it causes the adrenal cortex to release more aldosterone. Because of its ability to retain salt, aldosterone contributes to elevated blood pressure. Blood pressure restoration also involves angiotensins III and IV. [16]

6. Effects on Secretion of Antidiuretic Hormone

Antidiuretic hormone (ADH) is released in large quantities immediately after the hemorrhage. It is probably due to increased osmolality of body fluid by aldosterone induced sodium retention. ADH promotes water retention and helps in restoring osmolality and volume of ECF.

7. Effects on Secretion of Catecholamines

Loss of blood causes an increase in sympathetic activity. Large amounts of catecholamines are secreted as a result, and these chemicals have the vasoconstrictor effect of raising blood pressure. [17]

8. Effects on Respiration

Static hypoxia is brought on by hemorrhage because it lowers cardiac output, venous return, and blood flow velocity. The chemoreceptors are stimulated by hypoxia, which raises the respiratory rate. Hemorrhage causes the body to release significant amounts of catecholamines, which stimulate breathing through the reticular activating system (RAS). [18]

9. Effects on Nervous System

i. On the brain: Although bleeding makes many organs in the body vasoconstricted, it causes vasodilatation in the brain due to increased sympathetic activity. Because of autoregulation, bleeding does not significantly affect brain blood flow.

ii. On reticular formation: Catecholamines stimulate the RAS, which results in restlessness, anxiety, and increased motor activity after bleeding. It also accelerates breathing movements.

iii. Passing Out Severe bleeding causes a drop in cardiac output and blood pressure. The brain's autoregulation is unable to handle the hypotension. Thus, fainting is caused by a decrease in blood supply to the brain.

iv. Ischemia cerebral Within five minutes, ischemia of the brain tissues occurs when hypoxia causes a significant reduction in blood flow to the brain. The brain tissues suffer permanent damage as a result.

- **DELAYED COMPENSATORY EFFECTS OF HEMORRHAGE**

There are several delayed compensatory reflexes that happen if the bleeding is not severe. These responses support the restoration of blood flow, blood pressure, and volume to various body parts.

The following are delayed reactions:

1. Plasma volume restoration

Because of the low capillary pressure during the actual bleeding, tissue fluid begins to enter the blood. Thus, the volume of plasma rises. Hemodilution happens as a result of an increase in plasma volume. Thus, there is a low concentration of hemoglobin and plasma proteins. After bleeding, there is a prolonged period of tissue fluid transport. [19]

2. Plasma protein restoration

   After a hemorrhage, the liver begins to synthesize plasma proteins and mobilize its reserve proteins within a few hours. Within three to four days, the plasma proteins are restored. The function of plasma proteins is to preserve the fluid that is transferred from tissues to blood.

3. 3. Hemoglobin content and red blood cell count are restored.

The hypoxia that follows a bleed causes the kidneys to secrete more erythropoietin. In turn, erythropoietin activates the red bone marrow, resulting in erythropoiesis. RBC count restoration, however, is a drawn-out procedure. It requires four to six weeks. Blood reticulocyte count rises.

If there is an adequate amount of iron and protein in the diet, the RBC count and hemoglobin content return to normal.

5.6 Clinical Classification

5.6.1 Based on the time pass after injury, hemorrhage is classified into three categories:- Primary, reactionary and secondary haemorrhage.

- Primary hemorrhage is defined as bleeding that starts as soon as an injury (or operation) occurs.

- Reactionary hemorrhage is defined as delayed hemorrhage that occurs within 24 hours (generally 4-6 hours) and is typically brought on by vasodilatation, blood pressure normalization, and resuscitation efforts with the objective of eliminating a clot. Technical errors like a ligature slipping might potentially cause reactionary hemorrhage.
- Vessel wall sloughing is the cause of secondary hemorrhage. It usually happens 7–14 days following the injury and can be caused by an infection, pressure necrosis (from a drain, for example), or cancer. [20]

5.6.2 Based on the source of hemorrhage, it is classified into Arterial, Venous and Capillary haemorrhage**:**

- **Arterial:** Blood in the arterial system is bright red and surges as a jet that rises and falls in time with the pulse. It may become watery if large amounts of fluid other than blood are given in prolonged bleeding.
- **Venous:** Blood in the venous system is darker red, flows steadily, and copiously. When blood loss is severe or occurs in respiratory failure or obstruction, the color darkens even further due to excessive oxygen desaturation.
- **Capillary:** Blood in the capillary system is bright red and frequently oozes quickly. If blood loss persists for several hours, it could become serious, as in hemophilia.

5. 6.3 Based on the site of hemorrhage, it is classified into Revealed and Concealed haemorrhage:

- **Revealed haemorrhage**: Clearly visible external hemorrhage that is revealed occurs when blood seeps through a skin break or a naturally occurring orifice like the vagina, mouth, nose, ear, or anus.

- **Concealed haemorrhage:** Since concealed bleeding occurs inside the body cavity, it needs to be suspected, looked into, and managed. Trauma-related hemorrhage can be hidden in the limbs, with contained vascular injury, or in the chest, belly, pelvis, or retroperitoneum. It can also be linked to long-bone fractures.

Examples of non-traumatic concealed haemorrhage include occult gastrointestinal bleeding or ruptured aortic aneurysm.

5. 6.4 Classification according to Degree of blood loss:

Blood loss assessment and treatment must take into account the pre-existing blood volume, which an adult human has about five liters of blood (70 ml/kg for adults and children, 80 ml/kg for neonates).

The amount of blood lost is difficult to estimate, prone to error, and typically underestimates the true figure. Nonetheless, a rough approximation might be acquired by:

• A blood clot of the size of a closed fist is equivalent to 500 milliliters.

• edema in a closed fracture: 500–1500 ml of blood loss corresponds to significant edema in a closed tibia fracture. A femur fracture with moderate edema results in 500–2000 milliliters of blood loss.

• Swab weight measurement: in the operating room, blood loss can be calculated by weighing the swabs and deducting the dry weight; the total that results (1 gm = 1 ml) is then added to the amount of blood collected in the drainage or suction bottles.

Since hemoglobin is a concentration rather than an absolute quantity, it is a poor indicator of the extent of hemorrhage. The hemoglobin concentration remains constant throughout the initial phases of severe bleeding (as whole blood is lost). Subsequently, the levels of hemoglobin and haematocrit will decrease as fluid moves from the intracellular and interstitial

regions into the vascular compartment. [21]

Based on the predicted blood loss necessary to cause specific physiological compensatory changes, the degree of hemorrhage is traditionally divided into classes 1-4 by the American College of Surgeons' Advanced Trauma Life Support (ATLS):

- Class I Hemorrhage: A Class I hemorrhage can cause a 15% volume loss in blood. Vital signs usually do not alter, and fluid resuscitation is not required.
- Class II Hemorrhage: Class II hemorrhage affects 15–30% of the total volume of blood. Patients frequently have a narrowing of the systolic and diastolic blood pressure differential and are tachycardic. The body uses peripheral vasoconstriction as a kind of compensation. The skin may become pallid and feel chilly to the touch. The patient's behavior can vary a little. Usually, all that is needed is volume resuscitation using crystalloids, such as saline solution or lactated Ringer's solution. Usually, no blood transfusion is necessary.
- Class III Hemorrhage: A class III hemorrhage results in a 30–40% reduction in the volume of blood in circulation. The patient experiences peripheral hypoperfusion (shock), which exacerbates capillary filling, a decrease in blood pressure, an increase in heart rate, and a worsening of mental status. Transfusions of blood and crystalloids are typically required for fluid resuscitation.
- Class IV Hemorrhage: Greater than 40% of the volume of blood in circulation is lost in a class IV hemorrhage. When the body can no longer compensate as much, intensive resuscitation is needed to keep the patient alive.

This classification, although conceptually beneficial there is variation across ages (the young compensate well, the old extremely badly), between individuals (athletes vs. the obese) and because of complicating circumstances (e.g. concomitant drugs, discomfort).

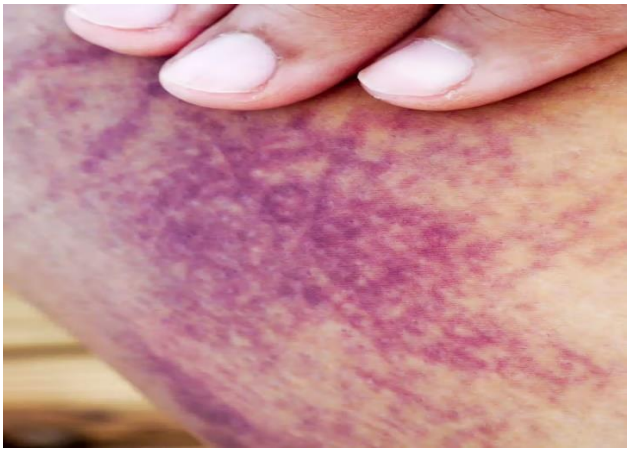


Fig : **Internal Haemorrhage (adopted from** https://www.google.com/url?sa=i&url=https%3A%2F%2Fwww.medicalnewstoday.com%2Farticles%2F320322&psig=AOvVaw1mUkZLB2E-PDwjJ_f_ypYG&ust=1738513816571000&source=images&cd=vfe&opi=89978449&ved=0CBUQjhxqFwoTCJD52eHyoosDFQAAAAAdAAAAABAE)

5.7 <u>Sign & Symptoms of Haemorrhage:</u>

Early signs & symptoms are-

- Restlessness & anxiety
- Feeling faint
- Coldness (temperature slightly sub-normal)
- Pallor
- Patients feels thirsty

Sign & Symptoms after severe hemorrhage-

- Extreme pallor
- Child sensation
- Air hunger
- Rapid thredy pulse
- Extremely low blood pressure

- Extreme thirst
- Diminished urine output
- Blindness & coma prior death [22]

5.8 Control of External Hemorrhage:

1. Pad and Bandage:

This is the most common and straightforward technique for directly providing pressure to a bleeding cut.

It works well and doesn't harm anything.

2. Digital pressure:

This is the force exerted on the artery point that supplies blood to the injured area. This is known as indirect pressure and it will control bleeding over time.

3. Elevating the affected limb: This will reduce venous bleeding.

This is a traditional way of treating an unexpected bleeding from a ruptured varicose vein in the leg.

4. Surgical ligation:

If the bleeding is not stopping, this procedure is required.

5. Coagulation:

Blood from tiny blood vessels can be coagulated using this technique.

6. Pack:

It will reduce acute bleeding for a while.

This technique is typically applied in the operating room to manage abrupt or transient bleeding.

7. Styptics:

These have astringent properties and are often used to stop bleeding. In certain situations, astringents like snake venom or adrenaline may be used topically. [23]

5.9 Control of Internal hemorrhage:

The following techniques for stopping bleeding can be applied:

• If there is significant bladder bleeding, a catheter is inserted and the bladder is emptied to clear the organ of blood clots.

• It is recommended that the vessels come into touch with large amounts of saline or sodium bicarbonate that have been mixed with a few drops of adrenaline solution. You can do this again every two hours.

• The use of medications: ergometrine, which stimulates the vascular to contact pitosin IV, may be useful in controlling bleeding following placenta delivery.

A surgical ligation may be necessary if the spleen ruptures. [24]

5.10 Management

- Determine the type of bleeding:

While bleeding from the outside may be easy to spot, bleeding that is hidden may be harder to diagnose.

Until proven otherwise, any shock should be considered hypovolaemic. Similarly, hypovolaemia should be thought to be caused by hemorrhage until that possibility has been ruled out. [25]

Quick resuscitation techniques

-The area of external hemorrhage needs to be directly compressed.

-Breathing and the airway should be examined and managed as needed.

It is recommended to implement large-bore intravenous access and get blood samples for cross-matching.

-If necessary, emergency blood should be obtained due to the severity of shock and ongoing bleeding. [26]

- Determine the location of the bleeding:

Following consideration of hemorrhage, the hemorrhage location needs to be quickly located. Keep in mind that the goal here is to specify the next step in hemorrhage control, not to pinpoint the precise spot (surgery, angioembolization, endoscopic control). The history (past incidents, known aneurysm, non-steroidal medication for gastrointestinal bleeding, etc.) or the fourth examination (kind of blood: fresh, melaena, abdominal soreness, etc.) may provide clues. The outward indications of injury in shocked trauma patients may indicate internal bleeding, but cavitary bleeding needs to be ruled out by quick examinations (diagnostic peritoneal aspiration, abdominal ultrasonography, and chest and pelvic radiography). [27]

Blood loss investigations need to be adapted to the patient's physiological state.

For profound shock and exsanguinating hemorrhage, rapid bedside diagnostics are more suited than lengthy investigations like computerized tomography, which make patient monitoring and treatment challenging. Individuals who are not bleeding profusely may benefit from a more thorough, conclusive work-up.

Control of bleeding:

Reduce the amount of blood lost by using packing and pressure, positioning, resting, and operating, as well as angioplasty or endoscopic management. [28]

Pressure and packing:

- Pressure dressing made of anything readily available that is clean and soft (used as first-aid treatment) is one example of how pressure is used to control bleeding.
- Digital pressure (using the thumb and forefinger)
- A Bouble balloon placed in the stomach and oesophagus to stop esophageal varices from bleeding.

  • Here are some instances of packing to stop bleeding:
- Wide gauze rolls. [29]

Position and rest:

Examples include:

- Elevating limbs (such as in the case of a ruptured varicose vein).
  o Some surgeries involve gravity, such as thyroidectomies, in which the patient is positioned with their feet slanted downward (reverse Trendelenburg position), or varicose vein stripping, which uses a head-down tilt (Trendelenburg position).
- Endoscopic control, angioembolization, and operation:
  The bleeding, shocked patient needs to be taken right away to a hemorrhage control facility. This will often take place in the operating room, however it could also happen in the hospital's angiography or endoscopy suites. [30]

After the bleeding has stopped, patients need to get vigorous resuscitation, warming, and correction of coagulopathy.

Reference:

1. Lee, S. U., Kim, T., Kwon, O. K., Bang, J. S., Ban, S. P., Byoun, H. S., & Oh, C. W. (2020). Trends in the Incidence and Treatment of Cerebrovascular Diseases in Korea : Part I. Intracranial Aneurysm, Intracerebral Hemorrhage, and Arteriovenous Malformation. *Journal of Korean Neurosurgical Society*, *63*(1), 56–68.
2. Gross, B. A., Jankowitz, B. T., & Friedlander, R. M. (2019). Cerebral Intraparenchymal Hemorrhage: A Review. *JAMA*, *321*(13), 1295–1303.
3. Agarwal, S., Zhou, T., & Frontera, J. (2019). Journal Club: Association between aspirin dose and subarachnoid hemorrhage from saccular aneurysms: A case-control study. *Neurology*, *92*(19), 920–922.
4. Pontius, E., & Vieth, J. T. (2019). Complications in Early Pregnancy. *Emergency medicine clinics of North America*, *37*(2), 219–237.
5. Baekgaard, J. S., Eskesen, T. G., Lee, J. M., Yeh, D. D., Kaafarani, H. M. A., Fagenholz, P. J., Avery, L., Saillant, N., King, D. R., & Velmahos, G. C. (2019). Spontaneous Retroperitoneal and Rectus Sheath Hemorrhage-Management, Risk Factors and Outcomes. *World journal of surgery*, *43*(8), 1890–1897.
6. Lazarev, A., Golokhvast, K., & Borozda, I. (2019). Review of the Problems of Diagnosis of Endopelvic Haemorrhage, Its Intensity, Volume, and Duration, and Treatment Methods of Circulatory Injuries and Surgical Hemostasis after Pelvic Fractures. *Emergency medicine international*, *2019*, 2514146.
7. Matano, F., Fujiki, Y., Mizunari, T., Koketsu, K., Tamaki, T., Murai, Y., Yokota, H., & Morita, A. (2019). Serum Glucose and Potassium Ratio as Risk Factors for Cerebral

Vasospasm after Aneurysmal Subarachnoid Hemorrhage. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association*, *28*(7), 1951–1957.

8. Kauvar, D. S., Lefering, R., & Wade, C. E. (2006). Impact of hemorrhage on trauma outcome: an overview of epidemiology, clinical presentations, and therapeutic considerations. *The Journal of trauma*, *60*(6 Suppl), S3–S11.
9. Carmichael, H., Steward, L., Peltz, E. D., Wright, F. L., & Velopulos, C. G. (2019). Preventable death and interpersonal violence in the United States: Who can be saved?. *The journal of trauma and acute care surgery*, *87*(1), 200–204.
10. Mackenzie, M. J., Hiranandani, R., Wang, D., Fung, T., & Lang, E. (2017). Determinants of Computed Tomography Head Scan Ordering for Patients with Low-Risk Headache in the Emergency Department. *Cureus*, *9*(10), e1760.
11. Kim, duS., Kong, M. H., Jang, S. Y., Kim, J. H., Kang, D. S., & Song, K. Y. (2013). The usefulness of brain magnetic resonance imaging with mild head injury and the negative findings of brain computed tomography. *Journal of Korean Neurosurgical Society*, *54*(2), 100–106.
12. Aboudara, M., & Maldonado, F. (2019). Update in the Management of Pleural Effusions. *The Medical clinics of North America*, *103*(3), 475–485.
13. Nixon, G., Blattner, K., Muirhead, J., Finnie, W., Lawrenson, R., & Kerse, N. (2018). Scope of point-of-care ultrasound practice in rural New Zealand. *Journal of primary health care*, *10*(3), 224–236.
14. Rubano, E., Mehta, N., Caputo, W., Paladino, L., & Sinert, R. (2013). Systematic review: emergency department bedside ultrasonography for diagnosing suspected abdominal aortic

aneurysm. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine*, *20*(2), 128–138.

15. Vulliamy, P., Thaventhiran, A. J., & Davenport, R. A. (2019). What's new for trauma haemorrhage management?. *British journal of hospital medicine (London, England : 2005)*, *80*(5), 268–273.
16. Palmer L. (2017). Fluid Management in Patients with Trauma: Restrictive Versus Liberal Approach. *The Veterinary clinics of North America. Small animal practice*, *47*(2), 397–410.
17. Dhakal, P., Wang, L., Gardiner, J., Shrotriya, S., Sharma, M., & Rayamajhi, S. (2019). Effectiveness of Sequential Compression Devices in Prevention of Venous Thromboembolism in Medically Ill Hospitalized Patients: A Retrospective Cohort Study. *Turkish journal of haematology : official journal of Turkish Society of Haematology*, *36*(3), 193–198.
18. Hegvik, J. R., Spilman, S. K., Olson, S. D., Gilchrist, C. A., & Sidwell, R. A. (2017). Effective Hospital-Wide Education in Hemorrhage Control. *Journal of the American College of Surgeons*, *224*(5), 796–799.e1.
19. Chambers, J. A., Seastedt, K., Krell, R., Caterson, E., Levy, M., & Turner, N. (2019). "Stop the Bleed": A U.S. Military Installation's Model for Implementation of a Rapid Hemorrhage Control Program. *Military medicine*, *184*(3-4), 67–71.
20. Spahn, D. R., Bouillon, B., Cerny, V., Coats, T. J., Duranteau, J., Fernández-Mondéjar, E., Filipescu, D., Hunt, B. J., Komadina, R., Nardi, G., Neugebauer, E., Ozier, Y., Riddez, L., Schultz, A., Vincent, J. L., & Rossaint, R. (2013). Management of bleeding and

coagulopathy following major trauma: an updated European guideline. *Critical care (London, England)*, *17*(2), R76.

21. Rossaint, R., Bouillon, B., Cerny, V., Coats, T. J., Duranteau, J., Fernández-Mondéjar, E., Filipescu, D., Hunt, B. J., Komadina, R., Maegele, M., Nardi, G., Neugebauer, E., Ozier, Y., Riddez, L., Schultz, A., Vincent, J. L., Spahn, D. R., & STOP Bleeding Campaign (2013). The STOP the Bleeding Campaign. *Critical care (London, England)*, *17*(2), 136.
22. Hoogenboom, B. J., & Smith, D. (2012). Management of bleeding and open wounds in athletes. *International journal of sports physical therapy*, *7*(3), 350–355.
23. Kragh, J. F., Jr, Walters, T. J., Baer, D. G., Fox, C. J., Wade, C. E., Salinas, J., & Holcomb, J. B. (2009). Survival with emergency tourniquet use to stop bleeding in major limb trauma. *Annals of surgery*, *249*(1), 1–7.
24. Johansson, P. I., Stensballe, J., & Ostrowski, S. R. (2012). Current management of massive hemorrhage in trauma. *Scandinavian journal of trauma, resuscitation and emergency medicine*, *20*, 47.
25. Bardes, J. M., Palmer, A., Con, J., Wilson, A., & Schaefer, G. (2017). Antifibrinolytics in a rural trauma state: assessing the opportunities. *Trauma surgery & acute care open*, *2*(1), e000107.
26. Kheirabadi B. (2011). Evaluation of topical hemostatic agents for combat wound treatment. *U.S. Army Medical Department journal*, 25–37.
27. Ribeiro Junior, M. A. F., Feng, C. Y. D., Nguyen, A. T. M., Rodrigues, V. C., Bechara, G. E. K., de-Moura, R. R., & Brenner, M. (2018). The complications associated with Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA). *World journal of emergency surgery : WJES*, *13*, 20.

28. Mahama, M. N., Kenu, E., Bandoh, D. A., & Zakariah, A. N. (2018). Emergency response time and pre-hospital trauma survival rate of the national ambulance service, Greater Accra (January - December 2014). *BMC emergency medicine*, *18*(1), 33.

29. Hedges, J. R., Adams, A. L., & Gunnels, M. D. (2002). ATLS practices and survival at rural level III trauma hospitals, 1995-1999. *Prehospital emergency care*, *6*(3), 299–305.

30. Parsons, S. E., Carter, E. A., Waterhouse, L. J., Fritzeen, J., Kelleher, D. C., O'connell, K. J., Sarcevic, A., Baker, K. M., Nelson, E., Werner, N. E., Boehm-Davis, D. A., & Burd, R. S. (2014). Improving ATLS performance in simulated pediatric trauma resuscitation using a checklist. *Annals of surgery*, *259*(4), 807–813.