INTRODUCTION TO GENERAL PATHOLOGY

AUTOPSY

INVESTIGATIVE PATHOLOGY

Biopsies
Surgical Pathology

MANIFESTATION OF DISEASE

Macroscopic
Microscopic
Ultrastructure
Autopsy means "see for yourself". It is a special surgical operation, performed by specially-trained physicians, on a dead body. Its purpose is to learn the truth about the person's health during life, and how the person really died, i.e. to determine the cause of death. Autopsy dealing with a body of our own species, a human body.

Necropsy dealing with other species.

Use of general Latin expression post mortem examination.
AUTOPSY anatomical pathology

Rembrandt 1632 Anatomy
Overall, according to research done in Britain by Cancer Research UK, a charity, 42% of cancer cases are tied to factors within an individual’s control. These include smoking (which, through the carcinogenic chemicals it creates, causes 86% of lung cancer, 65% of oesophageal cancer, 37% of bladder cancer and 29% of pancreatic cancer), poor diet (51% of stomach cancer and 56% of head and neck cancer), overexposure to sunlight (86% of malignant melanomas) and infection with papilloma virus (almost 100% of cervical cancer). Obesity, alcohol and lack of exercise are also in the frame. The best advice, then, remains: keep slathering on the sun cream, avoid tobacco smoke, eat and drink well, exercise regularly and, if you are a young woman, have an anti-papilloma vaccination.
we generally understand that pathology is used to explain the past

yet at times past organs were examined to predict the future
On one hand we have a clear example of .......

on the other hand......

Leads to discussion
clinical and *ante mortem* vs *post mortem*

- needle aspirates, biopsies
- clinical pathology: hematology, blood chemistry, cytology, cytoscan
- intra-operative surgical pathology
- in combination with ultrasound, x-ray, mri, nmr
autopsy and *post mortem*

- external examination
- samples of body fluids, body parts
- chemical, physical analysis, x-ray, tomography, mri etc.
- laboratory tests
- histopathology, immunology, histo-chemistry
- genetics
clinical and *ante mortem*

- needle aspirates, biopsies, smears
- frozen sections (e.g. during surgery)
the pathologist a generalist physician
always works together with other disciplines / specialists:
this makes the work a lot of fun
namely working with a large variety of other people, professions
the pleasure of sharing

(note Herve This)
PATHOLOGY and LABORATORY MEDICINE

clinical and *ante mortem*

- needle aspirates, biopsies
- clinical pathology: haematology, blood chemistry
- intra-operative surgical pathology
PATHOLOGY and LABORATORY MEDICINE

clinical and *ante mortem*

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clinical and *ante mortem*

- needle aspirates, biopsies
- clinical pathology: haematology, blood chemistry
- intra-operative surgical pathology
A medical pathologist is a **physician** with a specialty degree in the scientific study of the body and its parts. This always includes several years learning to do autopsies and ancillary investigations, and to work in Laboratory Medicine in combination with Clinical Medicine.

The pathologist is a very good example of a **generalist physician**, working with specialists the one who puts the **puzzle** together if only sometimes **at the end**
THE PATHOLOGIST

A pathologist can also be a veterinarian with a specialty degree in the scientific study of the body and its parts in many different animal species. This always includes several years learning to do autopsies, learning anatomy / physiology of various species, ancillary investigations, and to work in Laboratory Medicine. The veterinary pathologist will be working with specialists, biologists, zoologists trying to put the puzzle together.
If there is no story to be put together at the end................

where is the fun?

Pathology reporting is most satisfying when the conclusions make sense

Pathologist are by nature very curious, never quite satisfied with the answers, often distracted by serendipity

(Some are said to have started doing autopsies on their Teddy Bears.. Finding the source of the noise)
Stories need to be put together at the end...........

Pathologist are also working with Paleontologists trying to piece together the living history of specimens found for instance in excavations etc.

can have influence on history (e.g. Napoleon)

can describe diseases in mummies and skeletons
Pathologist are also working with Paleontologists trying to piece together the living history of specimens found for instance in excavations etc.

A 2011 study of 52 mummies in the Egyptian Museum in Cairo showed that almost half had clogged arteries, the kind of condition that can lead to a heart attack or stroke.

This perfectly preserved baby from Peru was born with a heart defect. NAT GEO
EXAMPLE OF AN AUTOPSY

a dead cat
(In case of a human corpse the body would have already been identified.)
Lawful consent needs to be obtained for an autopsy or necropsy to get started.
The procedure is done with respect and seriousness. The prevailing mood in the autopsy room is curiosity, scientific interest, and pleasure at being able to find the truth and share it. Most pathologists choose their specialty, at least in part, because they like finding answers and like to share their acquired knowledge, which might be useful to the living (e.g. side effects of therapies, exposure to dangerous workplaces, sports).

“hic locus est ubi mors gaudet succurrere vitae"

this is the place where death rejoices to teach those who live
The procedure is done with respect and seriousness. The prevailing mood in the autopsy room is *curiosity*, scientific interest, and *pleasure* at being able to find the truth and share it. Most pathologists choose their specialty, at least in part, because they like finding answers and like to share their acquired knowledge, which might be useful to the living (e.g. side effects of therapies, exposure to dangerous workplaces, sports).

"hic locus est ubi mors gaudet succurrere vitae"

this is the place where death rejoices to teach those who live
AUTOPSY

The pathologist first examines the outside of the body. A great deal can be learned in this way about the general health for instance.

dead dog

Observations
Measuring
Recording
Describing
To expose the internal organs the pathologist must open the body. The first cut known as the 'Y' incision, is made. The arms of the Y extend from the front of each shoulder to the bottom end of the breastbone. The tail of the Y extends from the sternum to the pubic bone and typically deviates to avoid the navel.

The incision is very deep, extending to the rib cage on the chest, and completely through the abdominal wall below that. The skin from this cut is peeled back, with the top flap pulled over the face.
The body is opened using a Y-shaped incision from shoulders to mid-chest and down to the pubic region. If the head is to be opened, the pathologist makes a second incision across the head, joining the bony prominences just below and behind the ears. When this is sewed back up, it will be concealed by the pillow on which the dead person's head rests. The pathologist uses a scalpel for these incisions. There is almost no bleeding, since a dead body has no blood pressure except that produced by gravity.
sometimes pathologists have to deal with curious bystanders who might not be respectful

L’image du martyr
AUTOPSY / NECROPSY

The pathologist first examines the outside of the body. A great deal can be learned in this way.

Observations
Measuring
Recording

on location
there would be
additional
information
available
Observations
Measuring
Recording
sometimes there is clear evidence
rarely
The pathologist first examines the outside of the body. A great deal can be learned in this way.

Observations
Measuring
Recording

clear evidence for the cause of death
Following the Y incision the ribs are sawn off to expose the internal organs.
Each pathology service has its own autopsy technique. The most common way to remove the organs is known as the Rokitansky method - removing the body organs all at once. That is, the heart, lungs, liver, kidneys and spleen etc are removed in one block and then dissected on the autopsy table.
The incisions are carried down to the rib cage and breastbone, and the cavity which contains the organs of the abdomen. The soft tissues in front of the chest are then reflected back. Again, the pathologist looks around for any abnormalities.

There is a great deal to be learned from touch also.
The soft tissues, skin in front of the chest are then reflected back. Again, the pathologist looks around for any abnormalities.

**COLOR is important**

discoloration of fat in subcutaneous tissue
AUTOPSY

When the breastbone and attached rib cartilages are removed, they are examined (sometimes they are fractured during cardiopulmonary resuscitation)

Freeing up the intestine takes some time.
opening the abdomen reveals not only organs but also fluids, colored or not
AUTOPSY

organs are laid out for further examination

intestines are opened
The chest organs, including the heart and lungs, are inspected. Sometimes the pathologist takes blood from the heart to check for bacteria, toxins etc. in the blood. Even the fluid in the eye can be analysed.
The chest organs, including the heart and lungs, are inspected. Sometimes the pathologist takes blood from the heart to check for bacteria, toxins etc. in the blood.
The chest organs, including the heart and lungs, and chest fluid are inspected.
investigating the source of blood in the chest cavity
AUTOPSY

opening the chest
AUTOPSY

fluid in chest
PATHOLOGY and LABORATORY MEDICINE

clinical and ante mortem post mortem

- needle aspirates, biopsies
- clinical pathology: haematology, blood chemistry
- intra-operative surgical pathology
AUTOPSY

The chest organs, including the heart and lungs, are inspected. Sometimes the pathologist takes blood from the heart to check for bacteria in the blood. For this, he uses a very large hypodermic needle and syringe. He may also find something else that will need to be sent to the microbiology lab to search for infection. Sometimes the pathologist will send blood, urine, bile, or even the fluid of the eye for chemical study and to look for medicine, street drugs, alcohols, and/or poisons.

Then the pathologist must decide in what order to perform the rest of the autopsy. The choice will be based on a variety of considerations.
The pathologist weighs the major solid organs (heart, lung, brain, kidney, liver, spleen, sometimes others) on a grocer's scale. The smaller organs (thyroid, adrenals) get weighed on a chemist's triple-beam balance. The next step in this abdominal dissection will be exploring the bile ducts and then freeing up the liver.

For humans there are tables with average weights of organs according to age, sex etc. There are some difficulties to find tables for animals.
Then the pathologist must decide in what order to perform the rest of the autopsy. The choice will be based on a variety of considerations.
AUTOPSY

To open the skull a special vibrating saw is used that cuts bone but not soft tissue. This is an important safety feature.
Inspecting the brain often reveals surprises. A good pathologist takes some time to do this.
Inspecting the brain often reveals surprises. A good pathologist takes some time to do this.

it is good sometimes to have a specimen to compare
AUTOPSY

The liver has been removed. The pathologist has found something important. It appears that this man had a fatty liver. It is too light, too orange, and a bit too big. Perhaps this man had been drinking heavily for a while.

Check notes / clinical observations / patient history
There are several ways in which heavy drinking, without any other disease, can kill a person. The pathologists will rule each of these in or out, and will probably be able to give a single answer to the police or family.
The pathologists will submit the tissue they saved to the histology lab tomorrow (after fixation), to be made into microscopic slides (within days). When these are ready, they will examine the sections (under the microscope), look at the results of any lab work, and draw their final conclusions.
AUTOPSY

The lungs are almost never normal at autopsy. The pathologist will inspect and feel them for areas of pneumonia and other abnormalities.

The pathologist weighs both sides of the lungs together, then each one separately. Afterwards, the lungs may get inflated with fixative.
Dissecting the lungs can be done in any of several ways. All methods reveal the surfaces of the large airways, and the great arteries of the lungs. Most pathologists use the long knife again while studying the lungs. The air spaces of the lungs will be evaluated based on their texture and appearance.
AUTOPSY

The lungs are almost never normal at autopsy. The pathologist will inspect and feel them for areas of pneumonia and other abnormalities.
The rest of the team is continuing with the removal of the other organs. They have decided to take the urinary system as one piece, and the digestive system down to the small intestine as another single piece. This will require careful dissection.
kidneys with cystic structures, fluid accumulation

Question: cause? acquired congenital
AUTOPSY

ante mortem X-Ray

X-RAY DEMONSTRATES DENSITIES
entire body laid out for study
AUTOPSY
When the internal organs, have been examined, the pathologist may return all but the portions they have saved to the body cavity. Or the organs may be cremated without being returned. The appropriate laws, and the wishes of the family, are obeyed. The breastbone and ribs are usually replaced in the body. The skull and trunk incisions are sewed shut ("baseball stitch"). The body is washed and is then ready to go to the funeral director.
A final report of a study pathologist is usually reviewed by other pathologists. Often this is called a peer review. Samples are kept to allow other pathologists to go back and look at specimens again.

Importance of review
Importance of good recording
Documentation
Justification of diagnosis (differential diagnosis)

Discussion with colleagues

this shows you the importance of being connected and not working alone
importance of critical differential diagnosis

pathologist should not work in isolation

always look for second opinion

and

do they ever have opinions!

here is an example for illustration
Man’s ‘nightmare’ ends after Crown finds pathologist erred

Charges dropped; wife wasn’t strangled, she drowned in pool

BY JAKE RUPERT

An Ottawa man’s 2½-year “nightmare” ended yesterday when the Crown abruptly halted its prosecution of him on charges of killing his wife.

New evidence showed that, 52, had accidentally drowned, and had not been strangled, as a pathologist had first declared. The move left 57, who has always maintained his innocence, emotional and speechless.

“He can’t talk right now,” said Mr.’s lawyer, Michael Edelson. “It’s been horrific for him and his family. It’s really been a nightmare.”

On Aug. 13, 2003, at about 9 p.m., Mr. found his wife face down in the pool in the backyard of their Gloucester home. Police initially said they thought Mrs. drowned. But two days later, Mr., a bar manager, was arrested and charged with second-degree murder. The forensic pathologist that conducted the autopsy, Dr. decided Mrs. had died of strangulation.

See DEATH on PAGE A2

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JAMES ORBAN, Publisher
Death: ‘A rush to judgment’

The development shocked the family, and Mr. Edelson retained another pathologist to do a second autopsy on Mrs. body. That pathologist determined the cause of death was drowning.

A month later, Mr. who had no previous criminal record, was released on bail to live with his daughter.

At a preliminary hearing, evidence showed Mrs. had been drinking heavily that night and was taking painkillers. She was outside, by the pool, speaking to a friend on the telephone, while her husband was inside eating, and a boater was in the basement.

The woman she was talking to told police Mrs. said she needed to put down the phone to fix something in the pool, and she never came back on the line. The woman said she heard no struggle and no sounds indicating what happened.

The tenant said during that time, he didn’t hear Mr. leave the house. At roughly 9 p.m., Mr. called 911 saying he’d gone into the backyard and found his wife in the pool. He started CPR and emergency crews took over when they arrived.

While trying to revive Mrs., paramedics made several attempts to insert a breathing tube in her wind pipe. Mrs. was declared dead on arrival at the Montfort Hospital a short time later.

To the media, police said they were investigating the death, and it looked like a drowning. However, there were some nagging questions. For instance, Mrs. had an injury on her head.

At the preliminary hearing, under questioning by assistant Crown attorney Donna Eastwood, Dr. testified the cause of death was neck compression. She said that although there were no injuries on the outside of Mrs. neck, the injuries on the inside of her throat showed she’d been strangled.

During cross-examination by Mr. Edelson, it was shown the injuries on the inside of her throat could have been caused by paramedics trying to insert the breathing tube.

Classic pathological signs of strangulation, such as burst blood vessels in the face and eyes, weren’t present. And there was evidence to suggest cause of death was drowning after she fell, hit her head, and ended up in the pool.

Despite being shown studies suggesting her findings could be wrong, and evidence suggesting Mrs. death was consistent with an accidental fall and drowning, Dr. refused to consider anything but strangulation as the cause of death.

Indeed, transcripts of the preliminary hearing show she became combative when it was suggested she’d made a mistake.

“It became obvious that there were significant problems with the pathologist,” Mr. Edelson said. “She became combative for her opinion in the face of the evidence.”

Dr. didn’t return a message for comment on this story yesterday.

In a statement to Ontario Court Justice Bernard Ryan yesterday, Ms. Eastwood said the new information caused her concern “about the pathology evidence as to the cause of death.” She sought a second opinion from one of Ontario’s leading forensic pathologists.

“The critical issue in this case is the cause of death,” Ms. Eastwood told the court. “The original, unequivocal opinion was that the cause of death was due to neck compression.

“The opinion of the second pathologist retained by the Crown is that the absence of petechial hemorrhages and a lack of injuries to the front of the neck do not support neck compression as the cause of death. But that the presence of wet and heavy lungs and fluid in the airway support the diagnosis of drowning.”

Ms. Eastwood said this, coupled with the defence pathologist’s opinion that Mrs. accidentally drowned, show “there is no longer a reasonable prospect of conviction in this case.”

“The Crown is not asking for a committal to trial.”

Immediately after this, Judge Ryan discharged Mr. “I would agree with Ms. Eastwood,” he said. “I had some concerns, too, after hearing the evidence on this issue.”

Afterwards, Mr. Edelson said his client’s plight was the result of a “rush to judgment.”

“If the police had done a proper investigation, they would have had a very different body of evidence to look at than when they made the decision to lay charges,” he said.

“I think Dr. work was one of the biggest problems in this case. It was also a rush to judgment.”

FRIDAY’S LOTTERIES

Last night’s winning numbers were drawn too late to make this edition of The Citizen. They will be printed tomorrow. To check your numbers, you can go online to www.olgclotteries.ca or phone the toll-free line at 1-800-387-0098.
pathologist should not work in isolation always look for second opinion and do they ever have opinions!

here is an example for illustration
In research and other studies autopsies or necropsies are performed as part of the whole study.

The pathologists works within the team to find specific answers.

The pathology report forms part of the testing of hypotheses.
other reasons for AUTOPSY / NECROPSY

versatility of veterinary pathologist

advantage of comparative / biological view of pathology

field work together with other professionals:

e.g. biologists, traditional hunters, trappers in research on wildlife diseases

sometimes on other continents
AUTOPSY

importance of recording, documentation
importance of recording, documentation

field work together with other professionals:

- e.g. biologists, traditional hunters, trappers
- in research on wildlife diseases
- sometimes on other continents
AUTOPSY

field work together with other professionals:

e.g. biologists, traditional hunters, trappers in research on wildlife diseases
AUTOPSY

field work together with other professionals:

e.g. biologists, traditional hunters, trappers
in research on wildlife diseases
role of pathologist: between organism and environment

starvation in wildlife
role of pathologist:

Interaction between organism and environment

starvation in wildlife:

(the case of the starving Lynx)

why not wolf or otter?
other reasons for AUTOPSY / NECROPSY

some times veterinary pathologists have to compete with others
ENVIRONMENTAL RESEARCH

role of pathologist:

between organism and environment

turtles get run over on road
sometimes just flipped over

how do they get up?
role of pathologist:

between organism and environment

sealed envelope, bag with formalin fixative

chain of custody important for legal
ENVIRONMENTAL RESEARCH

role of pathologist:

between organism and environment

swollen gills
role of pathologist:

between organism and environment

swollen gills with abundant mucus
role of pathologist:

between *organism* and *environment*

section of entire organism and most of its organs on one glass slide
Research with hypotheses, which we can prove or disprove.

where do such hypotheses come from?

observations: case reports
epidemiology
biological research
role of pathologist: to establish link between cellular and molecular
between cellular and organ
between organ and whole body
between organism and environment
EXPERIMENTAL RESEARCH

role of pathologist: respect the interaction between organism and environment between organism and chemicals etc. behavior intrinsic or extrinsic

animals serve as models, ultimately they serve us we think in analogies after all the living beings on this earth have basically similar building blocks at least from an anatomical point of view

typical situation in the development of pharmaceuticals:

we choose a model to test products before we use them ourselves

the biased view: if results are promising we have a good model and are confident if results are questionable? perhaps it is just that what happens in the rat is not necessarily indicative of what is going to happen to us
AUTOPSY / NECROPSY / ANALOGY

Your Inner Fish
A Journey into the 3.5-Billion-Year History of the Human Body

Neil Shubin

"Shubin shows us how to discover that long and fascinating history in the structure of our own bodies while weaving in a charming account of his own scientific journey. This is the ideal book for anyone who wants to explore beyond the usual anthropocentric account of human origins."

—Ian Tattersall, curator, American Museum of Natural History


Pantheon
In the Flesh: The Monro Dynasty

Three hundred years ago, Scottish army surgeon John Monro (1670-1740) initiated a series of events that lead to the establishment of a dynasty which, beginning with his son Alexander Monro, changed the course of medical teaching and learning. Three men (father, son and grandson), each called Alexander Monro (Primus, Secundus and Tertius), consecutively held the Chair of Anatomy at the University of Edinburgh for 126 years.
Alexander Monro (Secundus)

1733 - 1817

Anatomist. Monro succeeded his father, another Alexander (1697 - 1767), as Professor of Anatomy at the University of Edinburgh. He discovered the lymphatic systems, established the structure and function of the nervous system and noted the physiological effects of drugs.

Monro in turn was succeeded by his son, Alexander (1773 - 1859), the third to hold the Chair of Anatomy.
Comparative Pathology out of Necessity?

Studying anatomy / pathology required dissection. Dissection required bodies. A watch tower was built to guard the bodies.

there was a dark side to this discipline

The first Alexander Monro worried in 1725 that "the requirements of anatomical teaching provided unscrupulous criminals with a particularly macabre opportunity for illicit gain."

in 1828 with the notorious case of Burke and Hare. Having legally sold one dead person to the university, they went on to sell another sixteen. Unfortunately, all of those had been alive until they met the two murderers.
role of pathologist: respect the interaction between organism and environment behavior intrinsic or extrinsic

looking at dead rat pups:

why is there no milk in their stomach?
GENERAL OBSERVATIONS

Experimental PATHOGENESIS
sequence of events leading to the observations

- stimulus
- injury
- etiologic agent
- etiologic event
- toxin

the pathologist describes the pathogenesis
puts the whole story together
GENERAL OBSERVATIONS

Experimental PATHOGENESIS
sequence of events leading to the observations

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the pathologist describes the pathogenesis
puts the whole story together

TOXICOLOGIST
designs and carries out experiment
GENERAL OBSERVATIONS

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TOXICOLOGIST
designs and
carries out experiment

observation
GENERAL OBSERVATIONS

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TOXICOLOGIST

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GENERAL OBSERVATIONS

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puts the whole story together
GENERAL OBSERVATIONS

Experimental PATHOGENESIS
sequence of events leading to the observations

- stimulus
- injury
- etiologic agent
- etiologic event
- toxin

the pathologist describes the pathogenesis, puts the whole story together in a causal relationship

interpretation of cause and effect
other reasons for AUTOPSY / NECROPSY

versatility of veterinary pathologist

together with other professionals:
e.g. cardiac surgeons, mechanical engineers

development of implantable devices
e.g. devices to support the heart function:
Ventricular Assist Devices VAD’s
planned AUTOPSY

experimental studies

Collecting data *in vivo*
AUTOPSY

collecting data

ante mortem
AUTOPSY

step by step examination of targeted areas
AUTOPSY

adhesions, interaction of body tissues with material
AUTOPSY

study of interaction of body with implanted devices
adhesions

adhesions!
AUTOPSY

reporting with visual explanations

putting observation in context

attribute relevancy
AUTOPSY

documentation of observations
results of experimental surgery

RENAL INFARCT
AUTOPSY

adhesions in chest result of surgery
Observation at Autopsy

- change of size
- change of shape
- change of color
- change of smell

deviation from what is considered normal
the observations are based on the experience that causes of various origins are leading to changes in morphology

diagnosis

pathogenesis etiology

morphology

clinical significance

task of

PATHOLOGIST

diagnosis

synthesis

STORY
organism in its normal environment
organism at necropsy
GENERAL PATHOLOGY OBSERVATIONS

in “life” observation
GENERAL PATHOLOGY OBSERVATIONS

change over time
observation, analysis at time of “necropsy”
GENERAL PATHOLOGY OBSERVATIONS

70 % of body is water
75 % of muscle is water
50 % of fat is water
50 % of bone is water

Respiratory
Digestive continuous new elements exchange etc.
ETIOLOGY  cause

finding the culprit (i.e. germ)
finding the primary cause  →  therapy
prevention

factors to consider

intrinsic  (i.e. genetic)
extrinsic  (i.e. acquired)

discovery and knowledge of primary disease  →  diagnosis
GENERAL PATHOLOGY OBSERVATIONS

PATHOGENESIS
sequence of events leading to the observations

- stimulus
- injury
- etiologic agent
- etiologic event

response

expression of disease

the pathologist describes the pathogenesis
puts the whole story together
the study of **pathogenesis** today is more exciting than ever as new **tools** become available

the new tools allow for increased **scientific relevance**
in exercising the craft of medicine

**medicine** is the **art of combining science and intuition**
with patient care thus really helping the patient
morphologic changes are the basis of diagnostic pathology

changes can be structural physical

cells, tissues, organs show characteristics to etiologic processes

often pathologic observations infer causality

similar observations variety of causes!
diagnostic pathology
based on observation, defined by the nature
and progression of disease

limitation of the traditional morphology
leads to inclusion of additional investigative methods
molecular biology
immunology
immunohistochemistry
 genetics
Immuno Histochemistry

demonstration of prions in neurons

mad cow disease
Immuno Histochemistry

demonstration of prions in neurons  
*mad cow disease*

demonstration of plaques  
*Alzheimer’s disease*

causal relationship?

if we find scars in the skin (our largest organ)
do we conclude the patient has a skin disease with the scars being the cause?
removal of specific structures or cells for further analysis

using laser dissection to cut out structure and flipping it into a small container
diagnostic pathology
based on observation, defined by the nature and progression of disease

most important in biopsy pathology – clinical pathology

_in vivo_ sampling of tissues:
- bone marrow
- tumor biopsies (during and after surgery)

establish _prospective behavior of disease_ (i.e. tumor)
there is a future in pathology
morphology alone is not enough

future sequence of events:

1) **DIAGNOSIS of DISEASE**
2) **DIAGNOSIS of ETIOLOGY** including new techniques that apply genetic factors

3) **SPECIFIC THERAPY** etiology / individual / family

4) **Designer THERAPY** drug metabolism / genetic profile
UNDERLYING MECHANISMS

the function is deranged
clinical manifestations
morphologic changes
distribution, degree

the principal changes occur at the level of the cell
molecular
structural

while the body reacts to injury the changes are happening at the cellular level
CELLULAR RESPONSE TO STIMULI

- Normal cell (homeostasis)
  - Adaptation
  - Increased demand stress
  - Injurious stimulus
    - Cell injury
      - Cell death
    - Inability to adapt
CELLULAR ADAPTATION

heart

adaptation to increased workload

hypertrophy

normal myocyte

increased protein degradation

atrophy

reversible injury

cell death

irreversible scar

cell injury
normal

marginal nutrition

atrophy of fat reserves around kidney
CELLULAR ADAPTATION

hyperplasia

increase in growth factors leading to cellular proliferation

thyroid hyperplasia

as a result of hormonal stimuli
abnormal hyperplasia

leading to abnormal function
hyperplasia without control

could lead to tumors, cancer
abnormal hyperplasia - beyond adaptation
leading to abnormal function - cells active in function measurable output with secondary systemic changes
hyperplasia without control - growth of cells, organs at variable accelerated speed cells with / without function space occupying
could lead to tumors, cancer - secondary effects of cancer abnormal chemicals produced space occupying
GENE EXPRESSION IN HYPERTROPHY

heart, myocardium

\(\alpha\)-adrenergic hormones

angiotensin II

donothelin

growth factors

mechanical stretch

\{ agonists \}

receptors

transcription factors

induction of contractile protein genes

myosin light chain

Cardiac \(\alpha\)-actin

\(\beta\)-myosin heavy chain

Skeletal \(\alpha\)-actin

Atrial natriuretic factor

increased muscle activity

decreased workload
METAPLASIA

SQUAMOUS METAPLASIA OF EPITHELIUM

columnar → chronic irritation → squamous

basement membrane

normal columnar epithelium

reserve cells

metaplastic cells
EVOLUTION OF CELL INJURY, DEATH

injurious stimulus

transition to irreversibility

1. REVERSIBLE CELL INJURY
2. NECROSIS
3. APOPTOPSIS

reversible stage?
CELL INJURY

level of reversible cell injury

level of irreversible cell injury

necrosis

normal cells

swelling of endoplasmatic reticulum

swelling of mitochondria

chromatin clumping

accumulation of lysosomes

swelling of endoplasmatic reticulum and loss of ribosomes

condensation of nucleus

fragmentation of cell membrane

lysosome rupture

membrane blebs

myelin figures

fragmentation of nucleus
NECROSIS vs APOPTOSIS

- NECROSIS:
  - Enzymatic digestion
  - Leakage of cell contents

- APOPTOSIS:
  - Apoptotic bodies
  - Phagocytosis of apoptotic cells and fragments
**NECROSIS vs APOPTOSIS**

- **Cell**: Enlarged, swelling vs. cell size reduced, shrinkage
- **Nucleus**: Pyknosis, kariorrhexis, kariolysis vs. fragmentation nucleosome sized fragments
- **Plasma Membrane**: Disrupted vs. intact plasma membrane with altered structure
- **Enzymatic Digestion**: Enzymatic digestion of cellular contents vs. intact cellular contents, apoptotic bodies
- **Inflammation**: Inflammation, pathologic, related to disease vs. no infl., physiologic, often

**Pathologic**: NECROSIS, related to disease
**Physiologic**: APOPTOSIS, often
CELLULAR ADAPTATION

histology of apoptosis
CELLULAR ADAPTATION

apoptosis electron microscopy
MECHANISMS OF APOPTOSIS

**intrinsic**
(mitochondrial)
- withdrawal of growth factors, hormones

**extrinsic**
(death receptor-initiated)
- receptor-ligand interaction: TNF, Fas receptors

- injury
  - radiation
  - toxins
  - free radicals

- cytotoxic T-lymphocytes
- ligands for phagocytic cells

- cytoplastic bud
- apoptotic body
REVERSIBLE - IRREVERSIBLE

EFFECT

DURATION of INJURY

Reversible cell injury → Cell function
Irreversible cell injury → Cell death
Ultrastructural changes
Light microscopic changes
Gross morphologic changes
CELLULAR RESPONSE TO INJURY

HETEROPHAGY
- Phagocytosis
- Endocytosis
- Phagolysosome
- Residual body

AUTOPTHAGY
- Primary lysosome
- Autophagic vacuole
- Residual body
- Lipofuscin pigment granule

EXOCYTOSIS
INTRACELLULAR ACCUMULATION

Normal cell
- Abnormal metabolism
- Toxins, drugs

Fatty liver

Alteration in protein folding
- Protein mutation
- Protein folding transport

Aggregation of abnormal proteins
FATTY LIVER

UPTAKE

free fatty acids

CATABOLISM

Acetate
Fatty acids
α-Glycerophosphate
Oxidation to ketone bodies, CO₂
Phospholipids
Cholesterol esters
Triglycerides
Apoprotein
Lipoproteins

SECRETION

lipid transport in circulation
**INTRACELLULAR ACCUMULATIONS**

- **Enzyme deficiency**
- **Lack of enzyme**
- **Inhibition of enzyme**
- **Storage, accumulation of endogenous materials**
- **Phagocytosis of particles**
- **Incorporation of indigestible materials**
- **Accumulation of exogenous materials**
PHOSPHOLIPIDOSIS

resulting from interference with lysosomal enzymes

intracellular accumulation of phospholipids, membrane remnants
PHOSPHOLIPIDOSIS

expulsion of phospholipids from hepatocytes
CELLULAR RESPONSE TO STIMULUS

- altered physiology
  - increased demand
  - decreased nutrients
  - chronic irritation
- reduced oxygen supply
- chemical injury
- microbial infection
- metabolic alteration
  - genetic / acquired
- prolonged lifespan
  - cumulative, sub-lethal injury

- cellular adaptation
  - hyperplasia hypertrophy
  - atrophy
  - metaplasia
- cell injury
  - reversible
  - irreversible: (necrosis)
  - subcellular (organelles)
- intracellular accumulation
  - calcification
- cellular aging
**CELLULAR AGING**

**GENETIC FACTORS**
- DNA repair defects
- cumulative mutations
- Genetic abnormalities
  - abnormal Cellular signaling
  - replicative senescence
  - reduced ability to produce new cells

**ENVIRONMENTAL FACTORS**
- environmental insults
  - Free radical Mediated damage
  - reduced proteasomal activity
  - accumulation of damaged cellular proteins / organelles

**CELLULAR AGING**
INFLAMMATION

inflammation interacts with repair regenerative processes

stimulation of inflammation by
• tissue necrosis
• foreign bodies
• immune reactions
ACUTE and CHRONIC INFLAMMATION

- Mastcell
- Fibroblast
- Macrophage
- Connective tissue
- Blood vessel
- Smooth muscle
- Endothelium
- Basement membrane
- Elastic fibers
- Collagen fibers
- Proteoglycans
TISSUE RESPONSE TO INJURY

- regeneration
  - renewal tissues
    - epidermis
    - GI tract
    - hemopoietic
  - stable tissues
    - compensatory growth
- healing
  - wound
    - wound healing
  - chronic inflammation
  - scar formation
  - fibrosis
ACUTE INFLAMMATION

normal

inflamed

occasional lymphocyte or macrophage

extracellular matrix

dilated arteriole

venule

neutrophil emigration

expanded matrix

edema, deposition of fibrin, other plasma proteins

dilated venule

dilated arteriole

expansion of capillary bed

increased blood flow

occasional lymphocyte or macrophage
INFLAMMATION in MICROCIRCULATION

normal

acetate inflammation

net flow out

net flow in

no net flow

net flow out

net flow out

net flow out

hydrostatic pressure

colloid osmotic pressure

arteriole

venule

capillaries
SEQUENCE IN ACUTE INJURY

edema

neutrophils

monocytes, macrophages

ACTIVITY

DAYS

1

2

3
LEUKOCYTE MIGRATION THROUGH BLOOD VESSEL WALL

- Cytokines (TNF, IL-1)
- Macrophage (with microbes)
- Chemokines
- Fibrin

**Diagram Description:**
- Leukocyte
- Sialyl-Lewis X-modified glycoprotein
- Integrin (low affinity state)
- Integron (high-affinity state)
- PECAM-1 (CD31)
FLUID BALANCE

hydrostatic pressure

capillary bed

increased interstitial fluid pressure

Plasma colloid osmotic pressure

to thoracic duct

drainage
Increased Hydrostatic Pressure

- Impaired venous return
- Congestive heart failure
- Constrictive pericarditis
- Ascites (liver cirrhosis)
- Venous obstruction or compression
- Thrombosis
- External pressure (e.g., mass)
- Lower extremity inactivity with prolonged dependency
- Arteriolar dilation
- Heat
- Neurohumoral dysregulation
Reduced Plasma Osmotic Pressure (Hypoproteinemia)

- Protein-losing glomerulopathies (nephrotic syndrome)
- Liver cirrhosis (ascites)
- Malnutrition
- Protein-losing gastroenteropathy
FLUID BALANCE

Lymphatic Obstruction

Inflammatory
Neoplastic
Postsurgical
Postirradiation
**Sodium Retention**

- Excessive salt intake with renal insufficiency
- Increased tubular reabsorption of sodium
- Renal hypoperfusion
- Increased renin-angiotensin-aldosterone secretion
HEMODYNAMIC DISORDERS

hyperemia
edema
hemorrhage
thrombosis
BLEEDING HEMORRHAGE

petechia

hemorrhage
HEMOSTASIS THROMBOSIS

PRIMARY HEMOSTASIS

Endothelin release

extracellular matrix exposed

vasoconstriction

AGGREGATION HEMOSTATIC PLUG

Site of injury
HEMOSTASIS THROMBOSIS

SECONDARY HEMOSTASIS

1. Tissue factor
2. Phospholipid complex expression
3. Thrombin activation
4. Fibrin polymerization

Release of:
- t-PA (fibrinolysis)
- thrombomodulin (blocks coagulation cascade)

Trapped neutrophil
Trapped red blood cells
Polymers fibrin

fibrin
HEMOSTASIS THROMBOSIS

ENDOTHELIAL INJURY

THROMBOSIS

ABNORMAL BLOOD FLOW

HYPERCOAGULABILITY
TISSUE REGENERATION

skin

[Diagram showing skin anatomy with labels: Dermis, Epidermis, Sebaceous gland, Hair follicle bulge, Epidermal stem cell]
TISSUE REGENERATION

intestine
THERAPEUTIC CLONING

- enucleated oocyte
- patient's cell
- nuclear transfer embryo
- blastocyst
- embryonic stem cells
- neuron
- muscle
- ec
TISSUE REGENERATION

eye cornea

conjunctiva

limbus

corneal stem cells

cornea
TISSUE REGENERATION

eye cornea

corneal stem cells
TISSUE REGENERATION

eye cornea

inflammation

metaplasia

Squamous cell carcinoma
TISSUE REGENERATION

- growth factors, cytokines, matrix
- in bone marrow
- pluripotent stromal cells
- muscle
- fibroblasts
- chondroblasts
- fat cell
- osteoblasts
TISSUE REGENERATION

liver regeneration

regeneration

<table>
<thead>
<tr>
<th>Transcript Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA replication</td>
</tr>
<tr>
<td>10x</td>
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<tr>
<td>6x</td>
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</tbody>
</table>

mitosis

hours
TISSUE REGENERATION

tomography
donor liver sample
regeneration
TISSUE REPAIR

- Inflammation
- Granulation tissue
- Wound contraction
- Collagen accumulation
- Remodeling

Days: 0.1, 0.3, 1, 3, 10, 30, 100
TISSUE REGENERATION REPAIR

granulation tissue

fibrosis, scar
TISSUE REPAIR

first intention

second intention

scab

neutrophils

mitoses

new capillaries

fibrous union

wound contraction
TISSUE ULCERATION

healing by second intention

skin ulcer

ulcer
TISSUE REGENERATION

- granulation tissue
- reepithelialization
## TISSUE REGENERATION
### Factors That Retard Wound Healing

<table>
<thead>
<tr>
<th>Local Factors</th>
<th>Systemic Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood supply</td>
<td>Age</td>
</tr>
<tr>
<td>Denervation</td>
<td>Malnutrition</td>
</tr>
<tr>
<td>Local infection</td>
<td>Anemia</td>
</tr>
<tr>
<td>Foreign body</td>
<td>Drugs (steroids, cytotoxic medications, intensive antibiotic therapy)</td>
</tr>
<tr>
<td>Hematoma</td>
<td>Systemic infection</td>
</tr>
<tr>
<td></td>
<td>Temperature</td>
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<tr>
<td></td>
<td>Trauma, hypovolemia, and hypoxia</td>
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<tr>
<td></td>
<td>Genetic disorders (osteog. imp., Ehlers-Danlos syndromes, Marfan syndrome)</td>
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<tr>
<td></td>
<td>Uremia vitamin deficiency (vitamin C)</td>
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<tr>
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<td>Hormones</td>
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<td>Trace metal deficiency (zinc, copper)</td>
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<td>Diabetes</td>
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<tr>
<td></td>
<td>Malignant disease</td>
</tr>
</tbody>
</table>
TISSUE REPAIR

abnormal tissue reaction with excessive fibroplasia
collagen deposition

keloid
Growth Factors and Cytokines Affecting Various Steps in Wound Healing

<table>
<thead>
<tr>
<th>Function</th>
<th>Growth Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monocyte chemotaxis</td>
<td>PDGF, FGF, TGF-β</td>
</tr>
<tr>
<td>Fibroblast migration</td>
<td>PDGF, EGF, FGF, TGF-β, TNF, IL-1</td>
</tr>
<tr>
<td>Fibroblast proliferation</td>
<td>PDGF, EGF, FGF, TNF</td>
</tr>
<tr>
<td>Angiogenesis</td>
<td>VEGF, Ang, FGF</td>
</tr>
<tr>
<td>Collagen synthesis</td>
<td>TGF-β, PDGF</td>
</tr>
<tr>
<td>Collagenase secretion</td>
<td>PDGF, FGF, EGF, TNF, TGF-β inhibits</td>
</tr>
</tbody>
</table>