INTRODUCTION TO GENERAL PATHOLOGY

AUTOPSY

INVESTIGATIVE PATHOLOGY

Biopsies
Surgical Pathology

MANIFESTATION OF DISEASE

Macroscopic
Microscopic
Ultrastructure
AUTOPSY or NECROPSY

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
AUTOPSY
the two-handed pathologist
according to Bernhard Wagner, MD New York

On one hand we have a clear example of ........
on the other hand.......
Leads to discussion

Eustachi Bartolomeo 1574
PATHOLOGY and LABORATORY MEDICINE

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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PATHOLOGY and LABORATORY MEDICINE

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.
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.
PATHOLOGIST ... STORY TELLER

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...........

Pathologists 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.

can describe diseases in mummies and skeletons

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
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“hic locus est ubi mors gaudet succurrere vitae"

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

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
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.
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AUTOPSY

The chest organs, including the heart and lungs, and chest fluid are inspected.
AUTOPSY

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
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.
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.
AUTOPSY

These sketches do not show all the steps of an autopsy, but will give you the general idea.

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.
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.
The lungs are almost never normal at autopsy. The pathologist will inspect and feel them for areas of pneumonia and other abnormalities.
AUTOPSY
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
ANTE MORTEM X-RAY

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
Death: ‘A rush to judgment’

Continued from PAGE A1

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. 2, who had no previous criminal record, was released on bail to live with his daughter. At a preliminary hearing, evidence showed Mrs. 2 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 boar was in the basement.

The woman she was talking to told police Mrs. 2 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. 2 leave the house. At roughly 9 p.m., Mr. 2 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. 2, paramedics made several attempts to insert a breathing tube in her windpipe. Mrs. 2 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. 2 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.

Dr. under 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 showed 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 advocate 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. 2. “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.olgclottoon.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
other reasons for AUTOPSY

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
AUTOPSY

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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.
ENVIROMENTAL 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
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
EXPERIMENTAL RESEARCH

role of pathologist: to establish link between cellular and molecular

between cellular and organ

between organ and whole body

between organism and environment
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

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.
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.
EXPERIMENTAL RESEARCH

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
Experimental PATHOGENESIS
sequence of events leading to the observations

-the pathologist describes the pathogenesis
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TOXICOLOGIST
designs and
carries out experiment
GENERAL OBSERVATIONS

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GENERAL OBSERVATIONS

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GENERAL OBSERVATIONS

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- toxin

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

PATHOS - suffering

LOGOS - study
the observations are based on the experience that causes of various origins are leading to changes in morphology.

**Pathogenesis** --- **Morphology** --- **Clinical Significance**

Task of **PATHOLOGIST**

**Diagnosis** --- **Synthesis** --- **Story**
organism in its normal environment
GENERAL PATHOLOGY OBSERVATIONS

organism at necropsy
GENERAL PATHOLOGY OBSERVATIONS

in “life” observation
GENERAL PATHOLOGY OBSERVATIONS

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

increased protein degradation

irreversible scar

cell injury

reversible injury

cell death

CELLULAR ADAPTATION

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
<table>
<thead>
<tr>
<th>Abnormal Hyperplasia</th>
<th>Leading to Abnormal Function</th>
<th>Hyperplasia Without Control</th>
<th>Could Lead to Tumors, Cancer</th>
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</thead>
<tbody>
<tr>
<td>- beyond adaptation</td>
<td>- cells active in function</td>
<td>- growth of cells, organs</td>
<td>- secondary effects of cancer</td>
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<tr>
<td></td>
<td>measurable output</td>
<td>at variable accelerated speed</td>
<td>abnormal chemicals produced</td>
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<td></td>
<td>with secondary systemic changes</td>
<td>cells with / without function</td>
<td>space occupying</td>
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<td></td>
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<td>space occupying</td>
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</table>
GENE EXPRESSION IN HYPERTROPHY

heart, myocardium

α-adrenergic hormones  angiotensin II  endothelin  growth factors  mechanical stretch  \{ agonists \}

receptors

TRANSCRIPTION FACTORS

c-Jun  c-Fos  Egr-1

INDUCTION OF CONTRACTILE PROTEIN GENES

Myosin light chain  Cardiac α-actin

INDUCTION OF EMBRYONIC GENES

β-myosin heavy chain  Skeletal α-actin  Atrial natriuretic factor

Increased muscle activity  Decreased workload
METAPLASIA

SQUAMOUS METAPLASIA OF EPITHELIUM

columnar → chronic irritation → squamous

basement membrane

reserve cells

metaplastic cells

normal columnar epithelium
EVOLUTION OF CELL INJURY, DEATH

- Injurious stimulus
- Reversible stage?
- Transition to irreversibility

- Reversible cell injury
- Necrosis
- Apoptosis
CELL INJURY

level of reversible cell injury
- swelling of endoplasmatic reticulum
- chromatin clumping
- swelling of mitochondria

level of irreversible cell injury
- lysosome rupture
- membrane blebs
- myelin figures
- condensation of nucleus

necrosis
- accumulation of lysosomes
- fragmentation of nucleus
- fragmentation of cell membrane
NECROSIS vs APOPTOSIS

NECROSIS
- Enzymatic digestion
- Leakage of cell contents

APOPTOSIS
- Apoptotic bodies
- Phagocytosis of apoptotic cells and fragments

Phagocyte
**NECROSIS vs APOPTOSIS**

- Cell enlarged, swelling
- Nucleus: pyknosis, kariorrhexis, kariolysis
- Disrupted plasma membrane
- Enzymatic digestion of cellular contents
- Inflammation: pathologic, related to disease

- Cell size reduced shrinkage
- Fragmentation: nucleosome sized fragments
- Intact plasma membrane with altered structure
- Intact cellular contents: apoptotic bodies
- No infl.: physiologic, often

Pathologic, often related to disease.
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

**cytoplasmic bud**

**apoptotic body**

**ligands for phagocytic cells**

**cytotoxic T-lymphocytes**
REVERSIBLE - IRREVERSIBLE

EFFECT

DURATION of INJURY
CELLULAR RESPONSE TO INJURY

HETEROPHAGY
- phagocytosis
- endocytosis
- phagolysosome

AUTOPHAGY
- primary lysosome
- autophagic vacuole
- residual body
- lipofuscin pigment granule

EXOCYTOSIS
INTRACELLULAR ACCUMULATIONS

normal cell → abnormal metabolism → fatty liver

alteration in protein folding → protein folding transport → aggregation of abnormal proteins
FATTY LIVER

UPTAKE
free fatty acids

CATABOLISM
Fatty acids
- Oxidation to ketone bodies, CO₂
- Phospholipids
- Cholesterol esters

Triglycerides
- Apoprotein
- Lipoproteins

SECRETION
lipid transport in circulation
INTRACELLULAR ACCUMULATIONS

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

intracellular accumulation of phospholipids, membrane remnants

resulting from interference with lysosomal enzymes
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
• acute self limited
• progressive, severe
• mild chronic

metabolic alteration
 genetic / acquired

prolonged lifespan
 cumulative, sub-lethal injury

cellular adaptation
• hyperplasia hypertrophy
• atrophy
• metaplasia

cell injury
• reversible
• irreversible: (necrosis)
• subcellular (organelles)

intracell. 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 → accumulation of damaged cellular proteins / organelles

reduced proteasomal activity

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
- Smooth muscle
- Blood vessel
- Endothelium
- Basement membrane
- Elastic fibers
- Collagen fibers
- Proteoglycans
TISSUE RESPONSE TO INJURY

Injury

Regeneration
- Stable tissues
  - Renewing tissues
    - Epidermis
    - GI tract
    - Hemopoietic

Healing
- Wound
  - Wound healing
- Chronic inflammation
  - Scar formation
  - Fibrosis
ACUTE INFLAMMATION

- Dilated arteriole
- Dilated venule
- Expansion of capillary bed
- Increased blood flow
- Neutrophil emigration
- Edema, deposition of fibrin, other plasma proteins
- Occasional lymphocyte or macrophage
- Expanded extracellular matrix
INFLAMMATION in MICROCIRCULATION

normal

net flow out

no net flow

arteriole

capillaries

net flow in

venule

capillaries

hydrostatic pressure

colloid osmotic pressure

acute inflammation

net flow out

net flow out

net flow out

venule

capillaries

net flow out
SEQUENCE IN ACUTE INJURY

Days: 1, 2, 3

Monocytes, macrophages, neutrophils, edema

Activity vs. Days

1 2 3
LEUKOCYTE MIGRATION THROUGH BLOOD VESSEL WALL

- Rolling
- Integrin activation by chemokines
- Stable adhesion
- Migration through endothelium

Leukocyte: Sialyl-Lewis X-modified glycoprotein
Integrin (low affinity state)
Integrin (high-affinity state)
PECAM-1 (CD31)

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

normal

hyperemia

congestion
FLUID BALANCE

hydrostatic pressure

increased interstitial fluid pressure

capillary bed

to thoracic duct

drainage

Plasma colloid osmotic pressure
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

Site of injury

AGGREGATION
HEMOSTATIC PLUG

1. Platelet adhesion (ADP, TXA₂)
2. Shape change
3. Granule release
4. vWF
5.
HEMOSTASIS THROMBOSIS

ENDOTHELIAL INJURY

THROMBOSIS

ABNORMAL BLOOD FLOW

HYPERCOAGULABILITY
TISSUE REGENERATION

skin

Epidermis

Sebaceous gland

Hair follicle bulge

Epidermal stem cell

Dermis
TISSUE REGENERATION

intestine

Goblet cell
Absorptive enterocyte
Enteroendocrine cell
Crypt cells (stem cells)
Paneth cells
THERAPEUTIC CLONING

enucleated oocyte

patient's cell

nuclear transfer

embryo

blastocyst

embryonic stem cells

muscle

neuron

ec

u Ottawa
Dr. R. Mueller
TISSUE REGENERATION

eye cornea

limbus

corneal stem cells

cornea

conjunctiva
TISSUE REGENERATION

eye cornea

corneal stem cells
Tissue regeneration

eye cornea

inflammation

metaplasia
TISSUE REGENERATION

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

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TISSUE REGENERATION

liver regeneration

regeneration

transcript levels

DNA replication

mitosis

hours

10x

6x
TISSUE REGENERATION

tomography

donor liver sample

regeneration
TISSUE REPAIR

Inflammation
Granulation tissue
Wound contraction
Collagen accumulation
Remodeling

Days
TISSUE REGENERATION REPAIR

granulation tissue

fibrosis, scar
TISSUE REPAIR

first intention

scab

neutrophils

mitoses

new capillaries

fibrous union

wound contraction

second intention
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>
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<tbody>
<tr>
<td>Blood supply</td>
<td>Age</td>
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<tr>
<td>Denervation</td>
<td>Anemia</td>
</tr>
<tr>
<td>Local infection</td>
<td>Drugs (steroids, cytotoxic medications, intensive antibiotic therapy)</td>
</tr>
<tr>
<td>Foreign body</td>
<td>Genetic disorders (osteog. imp., Ehlers-Danlos syndromes, Marfan syndrome)</td>
</tr>
<tr>
<td>Hematoma</td>
<td>Hormones</td>
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<tr>
<td></td>
<td>Diabetes</td>
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<td></td>
<td>Malignant disease</td>
</tr>
<tr>
<td>Mechanical stress</td>
<td>Uremia vitamin deficiency (vitamin C)</td>
</tr>
<tr>
<td>Necrotic tissue</td>
<td>Temperature</td>
</tr>
<tr>
<td>Protection (dressings)</td>
<td>Trauma, hypovolemia, and hypoxia</td>
</tr>
<tr>
<td>Surgical techniques</td>
<td></td>
</tr>
<tr>
<td>Type of tissue</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trace metal deficiency (zinc, copper)</td>
</tr>
</tbody>
</table>
TISSUE REPAIR

abnormal tissue reaction with excessive fibroplasia
collagen deposition

keloid
dense collagen
Growth Factors and Cytokines Affecting Various Steps in Wound Healing

<table>
<thead>
<tr>
<th>Process</th>
<th>Growth Factors</th>
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<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>