General tutorial session # 1

08/07/2006

Introduction to infectious diseases

Jeffrey Drazen

- The body is a great environment for bacteria and viruses to proliferate.
  Bacteria need water, warmth and nutrients to live "alone" and thrive.
  Higher-order organisms function much the same.
  Viruses are parasites by nature : they need another organism to replicate their DNA.
  Most pathogens are bacteria or viruses

- Asia, Nov. 2002, pneumonia = infection of the lungs, outbreak in Guangdong province
  lungs have a large surface area (~ tennis court)
  SARS : severe acute respiratory syndrome, new infection (February - March 2003)
  rapid and "contact-less" contagion
  The New England Journal of Medicine : a novel coronavirus discovered in April 2003
  by electron microscopy (EM)
  immune response observed, virus sequenced
  Koch's postulates : you have to be able to identify the virus in every case of the disease
  culture bacteria (infected) autonomously
  infect other organisms
  culture the ensuing infected bodies independently
  from civet cats and raccoon dogs, reservoirs of SARS-associated virus, on sale ?
  viruses can mutate : RNA viroses have no checkpoint for validity of replication

- many specific treatments have been developed for identified infectious diseases (syndromes clear
  syndromic recognition is key
  epidemiology : history of the disease, track communicable diseases, maps of endemic d.

- the body has built inflammatory responses / immune responses } to fight infectious diseases
  they also can be dangerous to human health.
  innate and adaptive immunity against inoculum.

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Human tuberculosis and malaria

Geneviève Milon

- key initial process of human infectious diseases :
  - . invasive live microbes
  - . production of transmissible progeny

  e.g. avian influenza virus ; size or number of mutations of progeny matter

- malaria mostly in tropical areas

  some historial elements : 2700 BC in a Chinese medical document } before any
  6th century B.C in India } etiology
  Hypocrates ... : swampy areas & mosquitos
  1860s and next : Pasteur, Koch (tried to attenuate)

  transmission of a vector, or etiological agent, not disease ! { 1880 Laveran within red blood cells
  1897 Ross observed sporozoites in blood-feeding mosquitos
  1898 Grassi : Anopheles mosquitos only

  eradication of A. mosquito habitats and niches does not always eradicate disease
  malaria is a parasite that lives in two hosts : . blood-feeding A. mosquitoes
  . humans

- high morbidity and mortality
  mono-prophylaxic treatment ⇒ resistance ↗

- malaria describes intra-erythrocytic asexual development of Plasmodium in human red blood cells (h RBC)

  parasite delivered through dermis, then vascular bed, in hepatocytes (25 in liver-) without any symptoms, then 1-second-long invasion of RBC, deploy quickly escape and reinvasion (symptoms from anemia, inflammation).
  Plasmodium falsiparum in human hosts : ring form, trophozoite and schizont stages
  . systemic inflammatory process → fever
  seen in vitro, not in RBC !

- severe malaria : cerebral m.•, severe anemia, acute respiratory distress
  or mere febrile episodes (93 out 100 cases in sub-Saharia African children)
  • accumulation of platelets in brain microvessels (→ haemorrage)
  RBCs adhere (via " knobs ") to endothelial cells (Grau & Schofield 2005)
  in a pro-inflammatory manner (cytokine & chemokine casc

during intra-erythrocytic development, plasma membrane asymmetry disrupted
flip-flop enzymes dysfunctional.

- tuberculosis : pulmonary disease
historical notes : Koch (1885 - 1890) cultured microorganisms in agar for colonies
lung parenchyma disrupted by bacteria
symptoms & signs : cough, sputum, haemoptysis, weight loss, fever, malaise

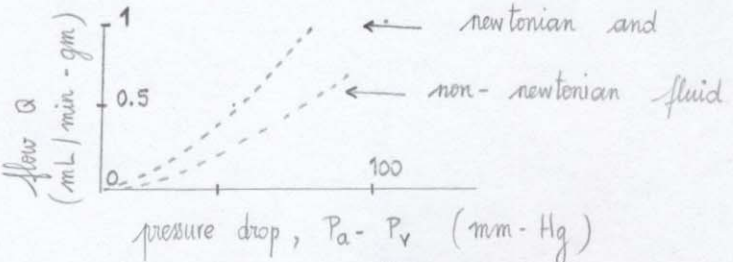
- Mycobacterium tuberculosis inhaled by 100 individuals
progress to cavitary TB only in 5 to 10 cases (phagocytosis)
extracellular progeny AND intracellular quiescent bacteria

balancing protective immunity (IFN γ, NO, TNF α, IL12, IL23)
and immunopathology

The inflammatory cascade : shock and multi-organ failure — Geert Schmid-Schönbein

- the inflammatory process plays out in the microcirculation : 10^{11} capillaries
in muscle, networks * fed by a range of arterioles (arcade) (vs. 10^4 veins)
in human lungs, tree-like structure of blood vessels
* terminal arterioles → capillaries → collecting venuoles
very low Reynold's numbers Re (honey-, not water-like)
the network of lymphatic vessels surrounds the arterioles

- pressure-flow relationship
in skeletal muscle microcirculation



- many diseases have cell activation & inflammation as hallmarks :
cardiovascular disease, stroke, diabetes, hypertension, myocardial ischemia, cancer, ...
physiological shock and multi-organ foulure

cascade : • cell response = ion exchange, pseudopods from actin poly/depolymerization,
degranulation, inflammatory mediators, endothelial permeability
upregulation of membrane adhesion molecules

cascade (c'ed) : • <u>tissue</u> degradation : neutrophil entrapment in microvessels, transmigration, platelet attachment, aggregation, thrombosis, red cell aggregation protease release, oxygen free radical formation, apoptosis organ dysfunction

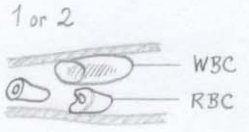
• initial repair : downregulation of anti-inflammatory genes upregulation of pro-inflammatory genes (cytokines ...) monocyte & T-lymphocyte infiltration

• <u>repair</u> : release of growth factors, growth of connective tissue revascularization, "resolution of inflammation"

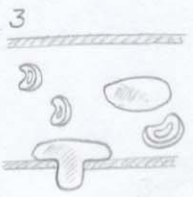
sometimes, no healing, no resolution of the inflammation ; why ?

(pictures of actin depolymerization, pore formation, neutrophil infiltration, apoptosis)
(pictures of the attachment of platelets and white blood cells to post-capillary venuoles)

capillaries (low Re) venule



WBC adhere to the endothelium only if RBC push them against walls



infiltration later, once adhesion has occurred

- trigger mechanisms for cardiovascular cell activation :
inflammatory mediators[1], depletion of anti-i. mediators[2], fluid stress, transients of gas pressure or temperature, juxtacrine activation, bio-implant interfaces.

(1) bacterial sources, endotoxins, oxidized products, LTB_4, PAF

(2) NO for instance

in shock [1] are "leukotaxin peptide", "clastogenic factor", ... : plasma-transported
what organ shows neutrophil activation ? pancreas ! (insulin + digestion)
actually, inflammatory mediator produced if pancreatic enzyme trypsin present or another digestive protease ↵

intestinal mucus normally protects you from <u>inflammatory mediators = digestive enzymes</u>
both the lipid and the proteinated fractions can kill you ⇒ several fragments act (800 - 1500 Da)

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Biosafety and laboratory preparedness

Rhonda O'Keefe

- routes of exposure : injection, ingestion, inhalation, mucous membranes
  attire : closed shoes, long pants, goggles, coats, gloves
  x 100 in case of emergencies
  wash well if exposed to hazardous materials, MIT medical
  evacuate if asked to.
- have a safe experience !