The point of this lecture is to get you to see that, while this course focuses on what happens in individual cell types or tissues, disease effects something bigger, the body as a whole, sometimes in surprising or unexpected ways. An epidemiologist might argue that its real effect is on a population, since – from a population standpoint – loss of one animal’s genes due to a sporadic disease is irrelevant. It is also a memo to myself. I am sometimes critical of molecular biologists who are so focused on one protein in one cell type they lose sight of the larger picture. Pathologists focusing on the cellular basis of injury, who utter the fatal phrase: “Man what a great lesion!” are equally guilty of forgetting these lesions originate in a patient, with biological significance for the animal and its owner. Nevertheless, the patient of pathologists is the sick cell. A corollary of Virchow’s popularization of the above Latin phrase is that the cell is the seat of all disease.

**Location of disease at the level of molecules, organelles and cell types**

In a previous lecture Dr. Montgomery underscored that disease may primarily target subcellular compartments of the cell. So the nucleus and its DNA is the basis for most genetic and for all neoplastic disease. The organelle-based location of some of these diseases has been helpful in some classifications. So, some disorders associated with mutations in mitochondrial DNA are **mitochondriopathies**: this classification clarified the peculiar nature and distribution of lesions, primarily in brain and skeletal muscle for obvious reasons. Almost all of the storage **diseases** are due to defective lysosomal enzymes. The substrate for the enzymes accumulates in abnormal lysosomes and so the diseases are classified based on which enzyme is affected. Clinical signs determined by which tissues or organs that most need those specific missing enzymes. **Peroxisomal diseases** are disorders in which peroxisomes fail due either to single peroxisomal enzyme deficiencies or to disorders of peroxisomal biogenesis. Dr. Montgomery briefly noted defects in other cellular components, such as intercellular junctions and cell membranes. I find it helpful for many viral diseases to remember that some groups of viruses some have specific cellular or tissue tropisms. Once you have a good understanding of the tropism of one member of the family, you may be able extend it to others you are less familiar with. So some viral families are **neurontropic**, targeting neurons in the central or peripheral nervous system (example: rabies virus and related rhabdoviruses). Others are **lymphotropic** (example: many of the retroviruses). Still others are **epitheliotropic**, (example: alphaherpesviruses causing similar epithelial blisters and ulcers in humans and domestic animals).

**Determinants of clinical disease**

Many factors are at play when a specific tissue or organ is damaged by in disease. Major ones are listed in the PPT slides. These include the vital nature of the tissue affected. As a result, a cardiotropic virus is more likely to be clinically significant than one infecting fat cells. Other factors that determine the clinical outcome are a tissue’s spare capacity and ability to undertake parenchymal repair; the extent, intensity and duration of injury; host-specific factors such as nutritional status, species, age, sex and genetic susceptibility, and integrity of tissue following injury such as the degree to which basement
membrane, connective tissue matrix and blood supply survive. Death due to an insult is easy to understand in some organs and circumstances. Three factors operating in concert are responsible for cardiac arrest and sudden death in young athletes after non-disruptive blunt cardiac trauma (commotio cordis). First, ventricular arrhythmia is induced when mechanical energy from a blow is confined to a small area of the chest directly over the heart. Second, this only occurs when the heart is in a specific stage of electrical activity (10 - 20 msec on the upstroke of the T wave before its peak; this represents 1% of the cardiac electrical cycle). And third, the thin, underdeveloped, compliant chest cage of adolescents and their participation in specific sports makes them vulnerable.

An example of the importance of a viable stroma for survival, repair and eventual recovery is acute tubular nephrosis following exposure to particular nephrotoxins such as ethylene glycol (in antifreeze) and aminoglycosides antimicrobials (e.g., gentamicin), and to endogenous ones such as myoglobin from damaged muscle. If a patient, dog or human, can be medically managed through acute renal failure due to tubular nephrosis, and no residual toxin remain lodged in the kidney to perpetuate injury, surprisingly good renal function and histology can be regained. This is due to the maintenance of an intact connective tissue framework to support and organize regenerating tubular epithelial cells.

**Fatal disease to localized tissue injury versus multi-organ failure due to failure of one organ**

I want to give you two examples of a fatal disease: one in which the cause of death is relatively straightforward and localized, and another in which injury occurs in one organ, but effects are systemic affecting multiple organ systems. Unfortunately for clinicians, many chronic diseases are like the latter. It can and does confound the clinician when the presenting problem is due to secondary complications. The two example diseases are blackleg and chronic renal failure.

*a. Localized fatal tissue injury: Blackleg*

Blackleg is an important common form of bacterial myositis in ruminants. It induces necrotizing emphysematous myositis (a form of gas gangrene). It is due to the bacterial anaerobe *Clostridium chauvoei*. Like many clostridial organisms, a range of potent exotoxins are formed by bacterium and damage both cellular and extracellular components (see PPT slide). Animals developing blackleg generally die acutely. Histologically these are disappointing lesions to look at. In spite of what appears to be a spectacular gross lesion, all the pathologist may see is muscle necrosis with some edema, gas formation and hemorrhage. Inflammation may be minimal. One of the PPT slides outlines the pathogenesis: it is presumed that macrophages acquire spores and carry in their cytoplasm them to various tissues, including muscle. Here they lie dormant until some event establishes an anoxic environment. An anaerobic milieu is required for *C. chauvoei* to proliferate. This may occur secondary to vigorous exercise, which may be why blackleg is a disease of younger stock, or after intramuscular injection with a vaccine or antibiotic. Death is a result of extensive tissue damage, leading to a systemic inflammatory reaction (septic shock)

*b. Systemic multi-organ injury due to failure of one organ: end-stage renal disease*

The lecture covers, maybe on more detail than is wise for an introductory course in pathology, the organs and systems impacted by renal failure. This is one reason why treating chronic renal failure is a
challenge – an important one, since it is a common renal disease of dogs and cats, particularly when elderly. This weekend I heard that the close friend of a friend is in renal failure. Because the underlying cause is diabetes mellitus, it is unlikely she will receive a renal transplant. She is 36 years old. Other major forms of organ failure, such as of the lung, liver or pancreas, can have complications far afield of the primary diseased organ.

Tissues which can be affected in chronic renal failure include:

a) **Gastrointestinal**: These are common and prominent. Typically renal failure patients display vomiting and malaise. They develop uremic gastropathy due in part to elevated gastrin levels. Gastin is normally metabolized in the kidney, reduced renal mass causes hypergastrinemia. This in turn leads to hyperacidity, with damage to the lining of the stomach. Further problems are induced by uremic enterocolitic, but these are less evident than in people, and metastatic calcification of the gastric mucosa (see image; see below)

b) **Hypertension**: This is persistently elevated systolic or diastolic pressure. It occurs due to salt and water retention from the failing kidneys. One consequence is damage to vessels, particularly arteries. This results in hypertrophied arteries with damage to the muscular wall and elastin.

c) **Hematological**: Patients in renal failure have a range of important changes in blood. They are anemic, and this correlates with the severity of renal failure. Many factors play into the anemia: short life span of RBCs; poor nutrition in a patient that cannot hold down its food; blood loss, among other. But the most important is failure of production of erythropoietin. This is normally produced by capillary endothelial cells in the kidney. As renal mass is lost, there is a relative erythropoietin deficiency. This results in less stimulation to the bone marrow, and reduced production of RBCs.

d) **Calcium and phosphorus imbalance**: Kidneys regulate phosphorus excretion. As they fail, hyperphosphatemia develops since it cannot be excreted efficiently. This causes an increased parathormone (PTH) secretion from the parathyroid glands. This leads to increased withdrawal of calcium from its major reservoir: bone. As this is secondary to a disease occurring elsewhere, and not intrinsic to the parathyroid glands, this is called **secondary hyperparathyroidism**. Excess calcium from bone is deposited in tissues, particularly those with proton pumps. The end result is hypocalcemic bones, and metastatic calcification in stomach, kidney, heart and lung. The bone disease is called **renal osteodystrophy**. It is most commonly seen clinically in young, growing dogs. For reasons we don’t fully understand, this is most readily recognized in bones of the face of dogs. There is increased deposition of new unmineralized bone matrix, so skull and mandibles are paradoxically thicker and more pliable.

e) **Uremic encephalopathy**: A proportion of animals in renal failure have neurological signs – as do people. These include altered mentation, tremor and seizures. Terminally, patients develop coma. A combination of low blood calcium, accumulation of uremic waste products and hypertension are thought to be responsible.

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1 February 2011