Clinical findings of inflammatory breast cancer (IBC)
The diagnosis of IBC is made based on three clinical findings, 1) *eythema*, 2) *edema* or peau d’orange, and 3) *wheals* or ridging of the skin. A *clinical history of rapid onset of tumor growth within 3 months* is often used to distinguish IBC patients from those with a more indolent form of breast cancer that has also infiltrated the dermis and caused skin changes or ulceration (these patients have a better prognosis than those with IBC). Diagnosis is delayed frequently because IBC can be confused with a local infection of the breast (in IBC, there should be no fever, leukocytosis, or localized tenderness).

On PE: The breast will appear warm, swollen, and tender, with a discrete mass in 70% of cases. Axillary adenopathy is palpated in 50%-60%, and supraclavicular involvement occurs in 25% or patients with IBC.

**Differential diagnosis (other than IBC)**
1. leukemia
2. lymphoma
3. sarcoma
4. post-radiation dermatitis

N.B. Tissue evidence of dermal invasion is useful but not essential for diagnosis of IBC, the significance of this finding is controversial.

**FYI:**
1. median age of diagnosis is 52
2. median survival is 1.5 years
3. 17%-36% of patients with IBC have distant mets at time of diagnosis
4. Therapy includes neoadjuvant chemotherapy, “toilet” mastectomy, and XRT and chemotherapy

**Indications for sentinel lymph node biopsy in invasive ductal breast cancer.**
Sentinal lymph node mapping (SLN) has emerged as a treatment option for patients with clinically negative axilla and an early-stage breast cancer. There are, however, those that hold an equally strong opinion that axillary lymphadenectomy provides excellent local control of the disease providing a modest improvement in survival and, when performed by an experienced surgeon, rarely is associated with any long-term morbidity. With T1a, b, and c tumors, the incidence of axillary metastasis is 10 to 15 percent, 15 percent and about 30 percent. SLN can be performed on an outpatient basis and under local anesthesia. Therefore, at this writing, the indications for SLN include a clinically negative axilla, high-grade or extensive DCIS, a solitary T1 or small T2 primary tumor, the absence of a large hematoma or seroma from prior biopsy, and no neoadjuvant chemotherapy. In T1c and T2 carcinoma it is important to ensure that SLN biopsy is done in a clinical trial setting because this technique is still not considered the standard of care. If the SLN cannot be identified or if the SLN is positive, the patient should have a formal axillary dissection.

Abeloff, Clinical Oncology 2nd edition
Discuss the diagnosis of lymphedema

Lymphedema is the collection of fluid and proteins in the soft tissue resulting from the inadequate function of the lymphatic system. Early onset presents with pitting edema, with more chronic lymphedema fibrosis of the soft tissue occurring resulting in non-pitting edema. Skin changes also occur over time resulting in hyperkeratosis, lichenification, and peau d’orange.

The differential diagnosis for lymphedema includes all of the causes of edema. The work up at initial presentation begins with a duplex scan to evaluate if the vascular system is functioning correctly. Venous disease can be an underlying cause of edema. Malignancy must also be ruled out at some point because that can also be a frequent cause of lymphedema. This can be accomplished by CT scan. Lymphoscintigraphy is the appropriate test to confirm the diagnosis of lymphedema. In this test technetium 99 labeled antimony sulfur colloid is injected into the interdigital space of the affected extremity.

Management of Papillary Thyroid Cancer w/ Lymph Node Metastases

Papillary thyroid cancer accounts for 80-85% of all thyroid cancers in the US and has the best prognosis. It is associated with h/o low-dose radiation to the neck, and peak incidence is in 3rd and 4th decades of life, with 3:1 female: male predilection. Diagnosis can be made by FNA or frozen section of papillary structures with “orphan annie” nuclei and psammoma bodies (calcium deposits). Papillary cancers are often multifocal and bilobar. However, for “minimal disease” (localized, nonmetastatic tumors < 1cm), lobectomy or near-total lobectomy is adequate. For all other papillary cancers, total or near-total thyroidectomy is required along with central compartment lymphadenectomy. Only when enlarged lymph nodes are detected in the lateral triangle should modified radical neck dissection (with preservation of the spinal accessory nerve and jugular vein) be performed. Following surgery, high-dose radioactive iodine ablation (>150 mCi) should be performed (can only be performed after all normal thyroid tissue has been removed). Patients should also be maintained on enough thyroid hormone replacement to suppress TSH production and followed semiannual with neck examination and monitoring of serum thyroglobulin levels. Overall mortality for papillary cancer w/ LN metastases only is 3.5% vs. <1% for pts. w/ uninvolved nodes and 70% for pts. with distant metastases.

Describe MALT lymphoma

Mucosa-Associated Lymphoid Tissue (MALT) refers to unencapsulated secondary lymphoid tissue lining the respiratory, gastrointestinal, and genitourinary tracts.

MALT lymphoma is a collection of lymphoid tissue that resembles the mucosa-associated lymphoid tissue rather than lymph node lymphoid tissue.

In the stomach, MALT lymphoma is felt to be a precursor to gastric lymphoma and is associated with H. pylori infection. Infection triggers a proliferation of malignant, monoclonal B-cells. In cases of low-grade MALT lymphoma, antibiotics alone can be effective therapy. Surgical resection and possibly chemotherapy is required in those patients who fail antibiotic therapy.

Discuss the management of hypercalcemic crisis

Pathophysiology of Hypercalcemia

The skeleton contains 98% of total body calcium; the remaining 2% circulates throughout the body; one half of circulating calcium is free (ionized) and is the only form with physiologic effects; the remainder of circulating calcium is bound to albumin. Low albumin levels can affect the total serum calcium level which should be corrected with the following formula: \[4.0 – (\text{plasma albumin})\] x 0.8 + (serum calcium)

There are three hormones involved in calcium homeostasis:

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Effect on Calcium</th>
<th>Effect on Phosphorus</th>
<th>Effect on bones</th>
<th>Effect on gut</th>
<th>Effect on kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parathyroid hormone</td>
<td>Increases</td>
<td>Decreases</td>
<td>Supports osteoclast resorption</td>
<td>Indirect effects via increase in calcitriol from 1-hydroxylation</td>
<td>Supports Ca resorption and PO₄ excretion; activates 1-hydroxylation</td>
</tr>
<tr>
<td>Calcitriol (Vitamin D)</td>
<td>Increases</td>
<td>Increases</td>
<td>No direct effects</td>
<td>Increases Ca and PO₄ absorption</td>
<td>No direct effects</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Decreases</td>
<td>Decreases</td>
<td>Inhibits osteoclast resorption</td>
<td>No direct effects</td>
<td>Promotes Ca and PO₄ excretion</td>
</tr>
</tbody>
</table>

Clinical Manifestations of Hypercalcemia

Renal “stones” \(\Rightarrow\) nephrolithiasis, nephrogenic diabetes insipidus, nephrocalcinosis

Skeleton “bones” \(\Rightarrow\) bone pain, arthritis, osteoporosis

GI “abdominal moans” \(\Rightarrow\) nausea, vomiting, anorexia, weight loss, constipation, abdominal pain, pancreatitis, peptic ulcer disease

Neuromuscular “psychic groans” \(\Rightarrow\) impaired concentration/memory, confusion, stupor/coma, lethargy/fatigue, muscle weakness

Cardiovascular \(\Rightarrow\) hypertension, short QT interval on EKG, cardiac arrhythmias, vascular calcification

Differential Diagnosis of Hypercalcemia

Primary hyperparathyroidism and malignancy account for more than 90% of hypercalcemia cases

Parathyroid hormone related \(\Rightarrow\) primary hyperparathyroid, sporadic or familial associated with MEN I or II, secondary hyperparathyroid (see with chronic renal failure) and tertiary hyperparathyroid (autonomous parathyroid glands due to longstanding secondary hyperparathyroidism)

Vitamin D related \(\Rightarrow\) vitamin D intoxication; granulomatous diseases cause increased extra-renal conversion of 25-hydroxyvitamin D3 to calcitriol (sarcoid, Tb, Hodgkin’s lymphoma)

Malignancy \(\Rightarrow\) mediated by parathyroid hormone related protein (PTHrP); solid tumors—lung, head and neck squamous cancers, renal cell tumors; local osteolysis—multiple myeloma, breast cancer

Medications \(\Rightarrow\) thiazides, lithium, calcium antacids, Vitamin A intoxication

Endocrine disorders \(\Rightarrow\) hyperthyroidism, adrenal insufficiency, acromegaly, pheo

Genetic disorders \(\Rightarrow\) familial hypocalciuric hypercalcemia (due to mutated calcium sensing receptor)

Other \(\Rightarrow\) immobilization, high bone turnover (Paget’s disease), recovery phase of rhabdomyolysis

Treatment of Hypercalcemic Crisis

Patients with Ca level >14 mg/dL or symptomatic patients with level > 12 mg/dL should be treated

Safest and most effective: saline rehydration (2-4 liters/day for 1-3 days) which enhances filtration and excretion of calcium; followed by furosemide (lasix) diuresis which inhibits calcium reabsorption in the distal tubule

Other medications: bisphosphonates (i.e. pamidronate (aredia): 60-90mg IV over 4 hours \(\Rightarrow\) inhibits osteoclast action and bone resorption (use in hypercalcemia of malignancy but beware of nephrotoxicity); calcitonin (4-8 IU IM/SQ q 6 hours x 24 hours) \(\Rightarrow\) inhibits bone resorption and augments calcium excretion (has rapid onset but short duration; patients develop tolerance to effect)

If diuresis is not effective or there is impaired renal function \(\Rightarrow\) hemodialysis should be performed with low-calcium dialysate

References:

Describe the diagnostic test for stage 4 lymphoma

The diagnosis of non-Hodgkin's lymphoma rests entirely on biopsy of a lymph node or an affected extranodal site. This should be performed by an experienced surgeon, at a time of day when full attention may be paid to it in the laboratory. The choice of site to biopsy when more than one node is involved should depend on the clinical circumstances. Usually the largest or most rapidly enlarging node is chosen because it is thought most likely to reveal the most aggressive histology (thereby influencing therapy) and because it will provide the most tissue. Multiple node biopsies may on occasion be indicated. Biopsy of nodes within the mediastinum and abdomen requires special caution. Thoracotomy may be required but should never be performed without particular attention to the patency of the airways and recognition of the risks of extubation. While excision biopsy is to be preferred, Trucut needle biopsy under computed tomographic (CT) or ultrasonographic guidance in the hands of an experienced radiologist may provide enough tissue to avoid open surgery, either in the chest or the abdomen. The pathologic diagnosis of lymphomas is difficult, and it is a mistake to handicap one's pathologist with inadequate tissue. Fine-needle aspiration, for cytology only, should be used only when biopsy is impossible or when confirmation of previously established lymphoma is required. It does not allow the morphologic distinction between different types of lymphoma and may be misleading.

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Management of incidental lobular carcinoma in situ (LCIS)

Lobular carcinoma in situ (LCIS) usually occurs in premenopausal women in their fourth decade of life. LCIS is typically invisible to mammography and rarely produces palpable breast abnormalities; as a result, its diagnosis is usually incidental. It is discovered in 0.8 – 8% of breast biopsies performed for other palpable or mammographic abnormalities. In contrast to ductal carcinoma in situ (DCIS), LCIS is not a precursor to a malignant lesion. Rather, it is a risk factor for the development of invasive breast cancer in both the ipsilateral and contralateral breasts. LCIS confers approximately a 13% relative risk of developing breast cancer within 10 years of LCIS-diagnosis, 26% within 20 years, and 35% in 35 years. Although the risk of developing invasive lobular carcinoma is greater in patients with LCIS, it is important to remember that the vast majority of women with LCIS who subsequently develop invasive breast cancer have infiltrating ductal carcinomas. As 80-85% of women with LCIS will remain cancer free up to 15 years after diagnosis, the treatment of incidentally discovered LCIS consists of close interval follow up (monthly breast self-exams, examination by a physician every 6 months, and annual mammography). Any suspicious lesions noted should undergo tissue biopsy and pathologic examination. The follow-up course for LCIS should be applied to both breasts, as both are at increased risk of developing invasive cancer. Bilateral simple mastectomy, once a recommended treatment, is no longer routinely advocated, and is only utilized for those patients with strong family history of breast or ovarian cancer (BRCA1-2), and in those patients who are mentally tormented by their newly-discovered increased risk for breast cancer and desire surgical therapy.

References: Cameron JL. Current Surgical Therapy, 7th Ed. pp 725-727.
Discuss the treatment of hypotension after GSW to the abdomen

Treatment should begin, as with any trauma, with assessment of Airway, Breathing and Circulation. Once the airway and breathing are secured then the circulatory condition of the patient must be evaluated and fluid resuscitation initiated. All trauma patients should have two large bore IV’s and resuscitation should be started with Lactated Ringers or normal saline. If the need for transfusion is emergent, type O negative blood can safely be administered while the patient’s blood is typed and crossed.

Some patients clearly require emergency laparotomy. Indicators of intra-abdominal injury following penetrating abdominal trauma include vital sign abnormalities, pain pattern, abdominal contour derangement, evisceration, and differential vascular examination. Gunshot wounds, in particular, have a higher propensity to cause injury secondary to the high kinetic energy involved. They may even result in intra-abdominal injury without penetrating the abdominal cavity. Therefore, hypotension in the setting of a gunshot wound to the abdomen warrants exploration in the OR. A chest film is routine prior to going to the operating room to diagnose hemothorax or pneumothorax. Treatment of these injuries is essential before exploratory laparotomy to avoid possible life threatening cardiopulmonary complications.

When the patient is taken to the OR venous access should be established in two or more locations if that has not already been done. Many surgeons prefer subclavian or internal jugular access because access to the groin may be needed if IVC or iliac injuries are found. The patient should be properly positioned and prepped; this is accomplished with the patient in the supine position with the arms abducted to be available to the anesthesiologist. The patient should be prepped and draped to include the chest and groin in the operative field. Before making an incision in a distended abdomen the surgeon should be prepared for decompression of the hemoperitoneum and heavy bleeding. This includes communication with the anesthesiologist and waiting, if necessary, for their preparation for massive resuscitation.
Discuss the primary site of sporadic gastrinoma

Zollinger-Ellison Syndrome (ZES) consists of ulcer disease of the upper GI tract, marked increase in gastric acid secretion, and non-beta islet cell tumors. Gastrinomas are most common in the head of the pancreas and duodenum and may vary in size from 1mm to more than 20 cm in diameter.

Approximately 90 percent of sporadic gastrinomas are found within the anatomic “gastrinoma triangle” defined by:
- the junction of CBD and cystic duct superiorly,
- the junction of D2/D3 inferiorly,
- and the junction of the pancreatic neck/body medially.

In unusual circumstances, ZES has resulted from gastrinomas originating in remote organs, such as the parathyroids or ovaries.

Sporadic gastrinoma is to be distinguished from the MEN 1 (multiple endocrine neoplasia - type 1) syndrome – an autosomal dominant disorder with a high degree of penetrance and highly variable expressivity. Patients with MEN 1 usually present with multiple gastrinomas, which generally are smaller than sporadic gastrinomas. Gastrinomas with MEN 1 are located more frequently in the wall of the duodenum than in the pancreas.

Currently Somatostatin Receptor Scintigraphy (SRS) [aka Octreotide uptake scan] is the initial imaging modality of choice once diagnosis of ZES established. This nuclear medicine study is limited only by the size of the tumor, and not by location. Assistance in detecting duodenal wall gastrinomas may be achieved with the additional modality of endoscopic ultrasound. SRS is equivalent to the combined modalities of angiography, MRI, CT and transabdominal US.

Reference: Cameron: Current Surgical Therapy, 7th edition, pp85-8
Mastery of Surgery, 3rd edition, pp544-6
Discuss the management of thyroid storm

**Definition:**
Fulminant increase in the signs and symptoms of thyrotoxicosis

**Timing:**
Postop in patients poorly prepared for surgery
Untreated or inadequately treated patients

**Precipitating factors:**
Surgical Emergencies or complicating illnesses, usually sepsis

**Signs/Sx:**
- Extreme irritability, restlessness
- Delirium/Coma
- Fever to 41 degrees Celsius
- Tachycardia, hypotension
- Vomiting, diarrhea

**Pathophys:**
Largely unknown, might represent a shift from protein bound to free hormone secondary to circulating inhibitors binding

**Supportive Care to Consider:**
- Cooling blanket, acetaminophen, abx for known infections
- Treatment of dehydration - Fluid replacement w/ glucose and saline
- Vitamin B complex/Glucocorticoids – indicated because of the increased glucocorticoid requirements in thyrotoxicosis and b/c adrenal reserve may be reduced
- Digoxin treatment afib

**Medical Therapy:**
- Antithyroid Medications – blockade of hormone synthesis
  - Propylthiouracil
  - Methimazole
- Radioiodine Therapy – blockade of hormone release
  - 131I
  - Iopanoic Acid (Ipodate) – also blocks peripheral conversion of T4 to T3
- B-adrenergic Blockade – blockade of signs/sx
  - Propranolol
  - Atenolol
- Dexamethasone
  - Inhibits hormone release, impairs the peripheral conversion of T4 to T3, provides adrenal support

**Thyroidectomy –** Rarely necessary emergently w/ adequate pharmacologic therapy
  - Subtotal
  - Total
Management of Blunt Splenic Injury

The spleen is the most commonly injured organ in blunt trauma, particularly when left lower rib fractures are present (uncommon in kids). The therapeutic goal is splenic preservation because of the immune function of the spleen in clearing poorly opsonized bacteria from the blood—the spleen produces the opsonin Tuftsin, which enhances antibody-mediated cytotoxicity, and Properdin, which plays a key role in alternative complement activation pathway.

Signs/symptoms of splenic injury are non-specific and may include: left lower rib fractures, contusions/abrasions to left chest wall/abdomen/flank, localized or diffuse abdominal pain/tenderness/rigidity, left scapular/shoulder pain, clinical shock/hypotension.

Majority of patients with splenic injury are stable/can be stabilized with fluid resuscitation, but if they are unstable they should undergo diagnostic peritoneal lavage (DPL) or four-quadrant abdominal sonogram for trauma (FAST). DPL is highly sensitive for detecting gross hemoperitoneum, however it cannot identify the source of bleeding as being the spleen or other organs. FAST scan is being used more frequently and can be highly sensitive in identifying free fluid in experienced hands. Signs of splenic injury on FAST scan include: enlarged spleen, irregular splenic contour, progressive enlargement of spleen, and double contour. Unstable patients with positive DPL or FAST scan should undergo emergent laparotomy.

Stable victims of blunt trauma usually undergo abdominal/pelvis CT scan, which is highly sensitive and specific for splenic injury—lacerations are seen as dense bands across the splenic parenchyma, subcapsular/intraparenchymal hematomas are seen as low-density perisplenic masses or intrasplenic accumulations of contrast. The AAST scale grades splenic injury from I (subcapsular, nonexpanding hematoma <10% surface area or nonbleeding capsular tea < 1cm deep) to V (shattered spleen or complete devascularization)—CT scan is estimated to overcall severity of splenic injury in 4% to 8% cases. In general, hemodynamically stable patients with grades I & II (non-expanding 10-50% hematoma or capsular tear 1-3 cm deep) splenic injury can be managed non-operatively. Non-operative management entails: bedrest, monitoring of patient in ICU/telemetry, and serial physical examination/Hgb/Hct Q4-6hours for 1st 24 hours, which may be done less frequently thereafter if patient and Hct remains stable. Follow-up CT scan should be done 3-5days after injury and should demonstrate improvement. On discharge, patients should have activity restrictions for 6 weeks to 3 months, depending on the severity of splenic injury, and follow-up CT scan. Studies have shown that non-operative management in hemodynamically stable children with splenic injury is successful 98% of the time, and anywhere from 30% to 100% in adults. Deterioration in patient’s hemodynamic status, ongoing blood transfusion requirement, or worsening of pain/tenderness should prompt surgical exploration. Velmahos, et al. found that risk factors for failure of non-operative management include: positive abdominal ultrasound findings, ≥ grade III injury, > 300 ml free fluid on CT, and need for blood transfusion.2

Patients with grade III (>50% subcapsular/expanding/actively bleeding hematoma or laceration >3cm deep) injuries often will require surgery. Grade IV (actively bleeding ruptured hematoma or laceration producing major devascularization) and grade V injuries require surgery.

At operation, grades I-III splenic injuries can usually be managed by hemostatic agents/splenorrhaphy, while splenectomy is often needed for grade IV and V injury. Splenectomy is also indicated if the patient remains in shock, has strong contraindications to prolonged operation, or has other potentially life-threatening injuries—severe head trauma, pelvic fractures, etc. Post-operative complications occur 8% of the time and include: atelectasis, pneumonia, left pleural effusion, subphrenic abscess (3%-13%), recurrent bleeding, pancreatitis, thrombocytosis (do not treat unless platelet count > 1million)and leukocytosis following splenectomy, and overwhelming post-splenectomy sepsis. Overwhelming post-splenectomy sepsis is caused by inability to opsonize (Tuftsin deficiency) encapsulated bacterium—primarily strep. pneumoniae, meningococcus, and H. influenzae. Patients should receive immunizations against these organisms after splenectomy and may need booster vaccines in 8-10 years.


Discuss the diagnosis of diabetes insipidus

Diabetes Insipidus (DI) is characterized by an absence of the function of antidiuretce hormone (ADH). In the case of nephrogenic DI this absence of ADH function is due to renal resistance to ADH, secondary to genetic defects, lithium, or hypercalcemia. In central DI, there is decreased secretion of ADH, usually secondary to trauma, surgery, ischemia, or idiopathic. Both result in increased urine output and production of dilute urine, in the presence of normal or elevated plasma sodium.

The diagnosis should be considered in cases of polyuria in which osmotic diuresis and primary polydipsia have been excluded. Diagnosis is suggested by history (e.g. head trauma, lithium use, etc.) and plasma sodium concentration. A low plasma sodium concentration supports a diagnosis of primary polydipsia.

The diagnosis of DI can be confirmed by the water deprivation test. The patient stops drinking (usually for at least 2-3 hours), then urine volume and osmolality are measured every hour and plasma osmolality every two hours. In the normal individual water restriction should lead to increasing plasma osmolality, subsequent ADH release and increased urine osmolality. The test is continued until either urine osmolality rises normally (primary polydipsia), the urine osmolality remains constant on three consecutive measurements, or the plasma osmolality exceeds 295 mosm/kg. In the latter two cases dDAVP can be administered. In the case of central DI the urine osmolality will increase in response to dDAVP. In nephrogenic DI the urine osmolality may rise with dDAVP administration, depending on whether there is partial or complete DI. Nephrogenic DI can usually be distinguished by historical information.

Sources
Discuss the preop management of adrenal pheochromocytoma

Preoperative management of patients with pheochromocytoma centers on (1) control of hypertension, (2) alpha-adrenergic blockade to prevent intraoperative hypertensive crisis resulting from tumor manipulation and release of catecholamines, and (3) fluid resuscitation to prevent circulatory collapse after removal of the catecholamine-secreting tumor. Alpha-adrenergic blockade is achieved with phenoxybenzamine, starting at 10 mg twice a day and increasing the dosage by 10 to 20 mg per day until the patient demonstrates postural hypotension. The drug is usually administered for at least 1 week before operation, and the patient should be hospitalized for several days before operation when postural hypotension is present, for observation and administration of intravenous fluid. Alpha-adrenergic blockade can also be accomplished with intravenous phentolamine, although response to this drug is less satisfactory than with phenoxybenzamine. Side effects of alpha-adrenergic blockade include reflex tachycardia, nasal congestion, and an inability to ejaculate.

Beta-adrenergic blockade with propranolol is indicated in patients who develop tachycardia. Propranolol may enhance pressor response to endogenous norepinephrine and thus should not be given until adequate alpha-adrenergic blockade has been established. Propranolol can also produce profound bradycardia, myocardial depression, and congestive heart failure. Cardiac asystole and death after propranolol administration have been reported in patients with pheochromocytoma. Newer drug regimens to manage hypertension in pheochromocytoma include selective alpha₁-adrenergic antagonists (terazosin and doxazosin) and calcium channel blockers (nifedipine and nicardipine).

Patients with pheochromocytoma can be expected to have blood pressure volatility and high intravascular volume requirements during and immediately after surgical procedures. An arterial pressure monitoring line and a Swan-Ganz catheter are commonly used in the intraoperative monitoring of hemodynamic changes.

Anesthetic agents may trigger the release of catecholamines from pheochromocytomas. The anesthetic plane is now considered more important than the choice of agent, and both enflurane and isoflurane have been used successfully. Intraoperative hypertension is best treated with a sodium nitroprusside infusion, and cardiac arrhythmias are best managed with short-acting beta-blockers (esmolol) or lidocaine. Morphine and phenothiazines may precipitate hypertensive crisis and should be avoided preoperatively.

Townsend: Sabiston Textbook of Surgery, 16th ed., Copyright © 2001 W. B. Saunders Company
Discuss the chemistry abnormalities with adrenal insufficiency

Hypofunction of the adrenal cortex results in mineralocorticoid deficiency. This process may demonstrate laboratory abnormalities in the advanced stage of adrenal destruction. Serum sodium, chloride, and bicarbonate levels are reduced, and the serum potassium level is elevated. It is also associated with metabolic acidosis and hypoglycemia.

*Hyponatremia* is due to both loss of sodium into the urine (due to aldosterone insufficiency) and to movement into the intracellular compartment. This intravascular sodium loss depletes extracellular fluid and accentuates hypotension. Elevated plasma vasopressin and angiotensin II levels contribute to hyponatremia by impairing free water clearance.

*Hypokalemia* is due to a combination of aldosterone insufficiency, impaired glomerular filtration, and acidosis.

Mild to moderate hypercalcemia occurs in 10 to 20 percent of patients for unclear reasons.

Reference: *Harrison’s Principles of Internal Medicine*. Williams, Dluhy, 14th edition; Chapter 332
*Cameron: Current Surgical Therapy*, 7th edition, pp1338-9
Condition associated with ZE syndrome and pituitary adenoma

Anterior pituitary tumor occurs in about one third of MEN1 cases. The frequency of MEN1 in cases of apparently sporadic pituitary tumor is probably below 5%, although estimates vary widely to as high as 15% with prolactinoma. The overall frequency of hormones hypersecreted is similar to those in non–MEN1 pituitary tumors. Pituitary mass effects can be the principal problem. In fact, pituitary tumors in MEN1 have been larger and less responsive to treatment than those without MEN1. Pituitary tumor can occur early in MEN1 and is occasionally the first recognized feature.

Prolactinoma is the most common pituitary tumor in MEN1 and the third most frequent endocrine tumor in MEN1 after parathyroid tumors and gastrinomas. MEN1 prolactinoma may be large. Dopamine agonists (e.g., cabergoline, bromocriptine, pergolide, quinagolide) are the preferred treatment. In patients who escape from the growth inhibitory effects of these dopamine agonists or who are noncompliant, transsphenoidal surgery combined with radiation therapy is usually effective. [170]

The second most frequent component of MEN1 is the development of neuroendocrine tumors of the duodenum or pancreas. Depending on the method of study, 30 to 80% of patients with MEN1 develop these tumors. The most common functional neuroendocrine tumor in patients with MEN1 is gastrinoma. The presenting signs and symptoms in patients with hypergastrinemia, or the Zollinger-Ellison syndrome (ZES), may include epigastric pain, reflux esophagitis, secretory diarrhea, and weight loss. Active peptic ulcer disease is present in approximately 70 to 80% of patients at the time of diagnosis. Gastrinomas associated with MEN1 account for approximately 20% of all cases of ZES. Gastrinoma is diagnosed by the documentation of gastric acid hypersecretion (>15 mEq per liter in patients without surgery or >5 mEq per liter in patients with prior ulcer surgery) associated with elevated fasting levels of serum gastrin (>100 pg per ml). The diagnosis can be confirmed by an abnormal secretin test. A test result is positive when serum levels of gastrin rise more than 200 pg per ml after the intravenous administration of secretin (2 U per kg).

Gastrinomas that develop in patients with MEN1 are usually malignant, as indicated by the presence of regional lymph node or distant metastases. The value of surgical resection for intended cure of gastrinoma in patients with MEN1 is controversial. Although most evidence indicates that patients with ZES and MEN1 are rarely cured by surgery, wide local resection of a potentially malignant neuroendocrine tumor may be indicated in an attempt to control the tumoral process and to prevent subsequent malignant dissemination. Total gastrectomy is no longer indicated for patients with gastrinoma, because medical management with high-dose H2-receptor antagonists or proton-pump inhibitors effectively prevents most of the symptoms or complications resulting from the acid hypersecretion. Patients with primary HPT should undergo parathyroidectomy, because normalization of the serum calcium level improves the ZES. [47]
BRCA2

BRCA2 is a gene, which, when damaged or mutated, places a woman at a much higher risk for development of breast cancer and/or ovarian cancer than the general population. BRCA1 and BRCA2 are both tumor suppressor genes on chromosomes 17q21 and 13q12, respectively. In families with high rate of breast cancer, i.e. at least four cases per family, approximately 50% of the affected individuals have mutations in BRCA1 and 30% in BRCA2. In families with higher rates of both breast and ovarian cancers, 75% are attributable to BRCA1 and 23% to BRCA2. BRCA2 is most often associated with male breast cancer. Families with germline mutations in BRCA2 are also at increased risk for prostatic malignancy.

While BRCA2 was already known to be a tumor suppressor gene, only recently, structural biologists at Memorial Sloan-Kettering Cancer Center have discovered the function of the protein. It interacts directly with DNA and help to repair genetic damage. Inability to correct the genetic damage leads to unstable chromosomes and often to cancer. BRCA-2 is an unusually large molecule, which has made it difficult to study. By crystallizing the protein, then bombarding them with high-energy X-rays (X-ray Crystallography), the diffraction patterns created by the X-rays were used to calculate the 3-D picture of the protein. This picture revealed that BRCA2 is similar in structure to other proteins known to bind DNA. BRCA2 was shown to bind DNA in special regions that are commonly found around broken DNA strands. It participates in the repair of “double-strand” breaks. Such breaks are particularly lethal type of damage because if both strands of the DNA double helix break at the same time, cells can permanently lose genetic information. BRCA2 binds broken strands and enable the recovery of lost information via homologous recombination, in which the missing DNA is copied from another part of the cell.

Reference:
2. Science. 2002 Sep 13; 297(5588):1837-48 Pavletich NP et el. BRCA2 function in DNA binding and recombination from a BRCA2-DSS1-ssDNA structure
GENE ABNORMALITY ASSOCIATED WITH MEDULLARY THYROID CANCER

Thyroid cancer represents approximately 1% of malignancies occurring in the United States, accounting for an estimated 18,400 cancer diagnoses and 1200 cancer deaths per year. Of these cancers, 3% to 4% are medullary thyroid cancer (MTC). Average survival for MTC is lower than that for more common thyroid cancers, e.g., 86% 5-year survival for MTC compared to 98% 5-year survival for papillary and follicular thyroid cancer. Survival is correlated with stage at diagnosis, and decreased survival in MTC can be accounted for in part by a high proportion of late-stage diagnoses.

MTC arises from the parafollicular calcitonin-secreting cells of the thyroid gland. MTC occurs in sporadic and familial forms, and may be preceded by C-cell hyperplasia (CCH), although CCH is a relatively common abnormality in middle-aged adults. In a population-based study in Sweden, 26% of patients with MTC were familial. A French national registry and a US clinical series both reported a higher proportion of familial cases (43% and 44% respectively). Familial cases represent Multiple Endocrine Neoplasia Type 2 (MEN2), a group of autosomal dominant genetic disorders caused by inherited mutations in the RET oncogene.

In addition to early stage at diagnosis, other factors associated with improved survival in MTC include smaller tumor size, younger age at diagnosis, familial vs sporadic, and diagnosis by biochemical screening (that is, screening for calcitonin elevation) vs symptoms.

MEN 2 syndromes are due to inherited mutations in the RET gene, located on chromosome locus 10q11. RET produces a receptor tyrosine kinase with extracellular, transmembrane, and intracellular domains. The extracellular domain consists of a calcium-binding cadherin-like region and a cysteine-rich region. The extracellular domain interacts with at least 1 ligand identified to date, glial-derived neurotropic factor (GDNF), which promotes dimerization of the protein after interacting with a second protein called GDNFRa. The tyrosine kinase catalytic core is located in the intracellular domain, which causes downstream signaling events with unidentified second messenger molecules. Normal tissues contain transcripts of several lengths.

Approximately 95% of families with MEN 2A have a RET mutation in exon 10 or 11. Mutations of codon 634 Cys occur in about 85% of families; mutation of cysteine residues at codons 609, 611, 618, and 620 together account for the remainder of identifiable mutations in exons 10 and 11.

Approximately 85% of families with FMTC have an identifiable RET mutation. These mutations occur at 1 of the 5 cysteine residues (codons 609, 611, 618, 620, and 634).

Approximately 95% of individuals with the MEN 2B phenotype have a single point mutation in the tyrosine kinase domain of the RET gene at codon 918 in exon 16, which substitutes a threonine for methionine (M918T).
Discuss the effects of glucocorticoids in injury

The integrity of the hypothalamic-pituitary-adrenal (HPA) axis is a major determinant of the host response to stress. Activation of the HPA axis during critical illness culminates in increased cortisol synthesis and secretion, typically resulting in plasma cortisol levels greater than 25 to 30 ìg/dL. Glucocorticoids, ie. hydrocortisone and dexamethasone, are potent anti-inflammatory agents. Corticosteroids inhibit the release of TNF and IL-1 from activated monocytes and other cell types. Glucocorticoids act as natural inhibitors of proinflammatory cytokine production, such as tumor necrosis factor (TNF)-á, interleukin (IL)-1á, interferon-ã, IL-2, IL-3, IL-5, IL-6, IL-8, IL-12, and granulocyte-macrophage colony-stimulating factor. Glucocorticoids act in synergy with some anti-inflammatory cytokines, including IL-4, IL-10, and IL-13, and increase transcription of IL-1. Glucocorticoids also inhibit fibroblast proliferation and collagen deposition; stimulate T-cell, eosinophil, and monocyte apoptosis; and inhibit neutrophil activation. Cortisol suppresses the synthesis of phospholipase A2, cyclooxygenase, and inducible nitric oxide synthase. During stress, hypothalamus releases corticotropin-releasing hormone (CRH) in response to activation by norepinephrine and serotoninergic/cholinergic neurons, resulting in stimulation of pituitary ACTH release. During systemic inflammation, circulating cytokines, principally TNF-á, IL-1, and IL-6, also stimulate hypothalamic CRH release, which is further amplified by prostanoids and platelet activating factor. ACTH acts on the adrenal cortex to release up to 225-440 mg/day of cortisol, which, feeds back to inhibit immune-mediated hypothalamic activation. During immune activation of the HPA axis, diurnal variation appears to be lost. Interestingly, TNF-á also has been reported to inhibit pituitary release of ACTH in response to CRH, suggesting a dual role for HPA modulation by this cytokine. During critical illness, cortisol concentrations are roughly four to five times those seen in normal subjects.


The production of glucocorticoids by the adrenal cortex is regulated predominantly by adrenocorticotropic hormone (ACTH) secreted by the anterior pituitary under the influence of hypothalamic corticotropin-releasing hormone (CRH). ACTH and CRH are under direct negative feedback from cortisol. Normal daily production of cortisol is approximately 15 to 20 mg/d.[28] Glucocorticoids play an important role in the metabolism of carbohydrates, lipids, and proteins and have profound regulatory effects on immune and circulatory function.[40] Glucocorticoids increase glucose production through gluconeogenesis and antagonism of insulin action. Lipolysis is stimulated as well as proteolysis, making amino acid substrates available for gluconeogenesis. Glucocorticoids have a positive inotropic influence on the heart and a permissive effect on the actions of epinephrine and norepinephrine