1. **Which of the following best describes neuroendocrine tumors (NETs):**
   A. Result in functional symptoms related to the overproduction of insulin
   B. Most commonly occurs as a result of genetic syndromes such as von Hippel-Lindau disease, tuberous sclerosis complex, and neurofibromatosis
   C. Arise from neuroendocrine cells and can affect the secretion of various regulatory hormones or vasoactive peptides throughout the body
   D. The most common types arise from the parathyroid, adrenal, pituitary, and thyroid glands

   **Correct Answer C:** NETs arise from neuroendocrine cells and can affect the secretion of various regulatory hormones or vasoactive peptides throughout the body. These include hormones causing functional symptoms related to hyperinsulinemia, hypergastrinemia, elevated glucagon, vasoactive intestinal peptide, and serotonin, or those such as pancreatic polypeptide (PPomas), chromogranin-A, neurotensin, α/β subunits of human chorionic gonadotropin (HCG), ghrelin, and neuron-specific enolase, which do not produce any functional symptoms.

   Incorrect answer A; Result in functional symptoms related to the overproduction of insulin is incorrect because although this does describe insulinomas, this statement does not account for the various other hormones and vasoactive peptides that are released in various other types of NETs.

   Incorrect answer B: Most commonly occurs as a result of genetic syndromes, such as von Hippel-Lindau disease, tuberous sclerosis complex, and neurofibromatosis is incorrect because NETs tend to be sporadic, but some can be hereditary and are typically associated with mutations in the *menin* gene or *RET* proto-oncogene.

   Incorrect answer D: The most common types arise from the parathyroid, adrenal, pituitary, and thyroid glands is incorrect because the most common types of NETs include pancreatic neuroendocrine tumors (PNETs) and carcinoid tumors, which most commonly arise in the gastrointestinal tract.

2. **Which of the following classification systems best allocates patients into different risk categories:**
   A. World Health Organization (WHO) 2000 classification system
   B. European Neuroendocrine Tumor Society (ENETS) classification system
   C. WHO 2010 classification system
   D. B and C

   **Correct Answer D:** Both the ENETS classification system and the WHO 2010 classification system provide information about tumor location and size and take into account tumor differentiation.
and proliferation. Although these classification systems are slightly different, both have been validated in clinical trials and are currently used in practice.

Incorrect answer A: WHO 2000 classification system is incorrect because it classifies all tumors into one of the following 3 main groups: well-differentiated tumors showing benign behavior, versus well-differentiated carcinomas distinguished by low-grade malignancy, versus poorly differentiated carcinomas of high-grade malignancy, and may inadequately allocate patients into risk categories.

Incorrect answer B: The ENETs classification system is only 1 of the 2 systems that have been developed to account for tumor location, size, differentiation, and proliferation.

Incorrect answer C: The WHO 2010 classification system is only 1 of the 2 systems that have been developed to account for tumor location, size, differentiation, and proliferation.

3. A patient presents with a dermatitis located on the perineum, thighs, and distal extremities. The provider suspects that this is a classic necrolytic migratory erythema caused by a glucagonoma. Which of the following biochemical analyses should be performed to confirm a diagnosis of glucagonoma:
   A. Glucose, plasma insulin, C-peptide, and proinsulin levels
   B. Gastrin level after the use of antacids, histamine (H2) receptor blockers, and proton pump inhibitors (PPIs) are discontinued for 1 week
   C. Vasoactive intestinal peptide (VIP) level
   D. Glucagon level

   Correct Answer D. Glucagon levels between 500 and 1000 pg/mL in a setting in which other causes, such as cirrhosis, pancreatitis, diabetes mellitus, myocardial infarction, celiac disease, and renal failure, among others, have been ruled out would be highly suggestive of a glucagonoma. Whereas, levels greater than 10,000 pg/mL are practically diagnostic for a glucagonoma.

Incorrect answer A: Glucose, plasma insulin, C-peptide, and proinsulin levels are used to diagnose insulinomas.
Incorrect answer B: Gastrin level after the use of antacids, histamine (H2) receptor blockers, and proton pump inhibitors (PPIs) are discontinued for 1 week as a method to diagnose gastrinomas.
Incorrect answer C: Vasoactive intestinal peptide levels are used to diagnose VIPomas.

4. A patient with an insulinoma complains about mild symptoms of hypoglycemia. She will be undergoing surgery in 2 weeks. In the meantime, which of the following should be tried to help manage these symptoms:
A. Octreotide LAR 20 mg intramuscular (IM) monthly
B. Streptozocin 400 mg/m² intravenous (IV) D1 - 5 every 4 weeks
C. Eating frequent small meals***
D. Diazoxide 3 mg/kg/day orally in divided doses every 8 hours

Correct Answer C: Eating frequent small meals would be the best solution since this patient’s symptoms are mild. This should allow the patient to maintain blood glucose levels throughout the day without introducing additive toxicities. Additionally, this method should provide an immediate relief since titration or tumor response is not needed to induce the response.

Incorrect answer A: Octreotide LAR 20 mg IM monthly is incorrect. Long-acting forms of octreotide should be given concurrently with short-acting octreotide for at least 2 weeks to minimize symptom exacerbation. This patient is going to surgery in 2 weeks and needs a more immediate way to manage her symptoms.

Incorrect answer B: Streptozocin 400 mg/m² IV D1 - 5 every 4 weeks is incorrect because this patient is going to surgery in 2 weeks and needs a more immediate way to manage symptoms. Additionally, in this short period of time, chemotherapy would introduce unnecessary toxicity.

Incorrect answer D: Diazoxide 3 mg/kg/day in divided doses every 8 hours. Diazoxide introduces toxicity and takes time to titrate the dose to achieve the desired response. The patient’s symptoms are mild and they are headed to surgery soon.

5. Which of the following should be used to predict the utility of a somatostatin analog:
   A. Metaiodobenzylguanidine (MIBG) scintigraphy
   B. Magnetic resonance imaging (MRI)
   C. Somatostatin receptor scintigraphy (SRS)***
   D. Endoscopic ultrasound (EUS)

Correct Answer C: Somatostatin receptor scintigraphy (SRS) is a technique that uses the ¹¹¹In-labelled somatostatin analog pentetreotide, which, similar to octreotide, concentrates in NETs containing somatostatin receptor subtypes 2 and 5. This allows the radio-imaging of tumors containing these receptors and, therefore, the ability to assess the extent of tumors with receptor positivity. Since somatostatin analogs bind with high affinity to these somatostatin receptors and mediate the release of peptides from tumor lesions, this imaging test allows a way to anticipate response to somatostatin analog therapy.

Incorrect answer A: Metaiodobenzylguanidine scintigraphy (MIBG) is incorrect because it is not a first-line tool to assess somatostatin receptor expression. It may be useful in cases where the somatostatin receptor scintigraphy is negative or nondefinitive, since it concentrates in carcinoid tumors and can be taken up by the tumor instead of octreotide.
Incorrect answer B: Magnetic resonance imaging (MRI) is incorrect because it is an imaging tool that determines anatomic location and extent of tumor involvement. It is unable to assess receptor status. It is also used only as an adjunct to computed tomography (CT) to characterize tumor localization.

Incorrect answer D: Endoscopic ultrasound (EUS) is incorrect because it is used primarily to characterize tumor size, location, and extent. This tool is used primarily for small tumors, such as insulinomas, which are usually < 2cm in size. It is particularly useful for smaller tumors.

6. What constellation of symptoms best describes the clinical presentation of carcinoid syndrome?

A. Confusion, visual disturbances, diaphoresis
B. Flushing, diarrhea, bronchial constriction, carcinoid heart disease***
C. Large volume watery diarrhea, dehydration, and hypokalemia
D. Glucose intolerance, weight loss, anemia

Correct Answer B: Flushing, diarrhea, bronchial constriction, and carcinoid heart disease typically occur in patients with small-bowel carcinoid tumors and result from the release of serotonin, tachykinins, and histamine from these tumors.

Incorrect answer A: Confusion, visual disturbances, diaphoresis are symptoms of hypoglycemia that are typically seen in patients with an insulinoma.
Incorrect answer C: Large volume watery diarrhea, dehydration, and hypokalemia are characteristic symptoms of a gastrinoma.
Incorrect answer D: Glucose intolerance, weight loss, anemia are symptoms of a glucagonoma.

7. Which of the following patients with carcinoid of the small intestine would be most likely to experience carcinoid syndrome:

A. Elevated chromogranin A (CgA) level, lymph nodes metastases, and a 2.4 cm tumor
B. Elevated 5-hydroxyindoleacetic acid (5-HIAA) level, liver metastases, and a 2 cm tumor***
C. Elevated CgA level, lymph nodes metastases, and a 1.5 cm tumor
D. Elevated 5-HIAA level, no metastases, and a 2.6 cm tumor

Correct Answer B: Elevated 5-HIAA level, liver metastases, and a 2 cm tumor is correct. First, carcinoid tumors can produce serotonin, which is metabolized by monoamine oxidases in the liver to 5-HIAA. Therefore, elevated 5-HIAA levels are reflective of tumors secreting excess serotonin, which can produce symptoms of carcinoid tumors. Secondly, rapid degradation of the active amine occurs in the liver, therefore patients become symptomatic only after liver metastases are present.
Incorrect answer A: Elevated CgA level, lymph nodes metastases, and a 2.4 cm tumor is incorrect. Several studies indicate that CgA levels may correlate with disease burden and patients with metastatic disease, but in this case it is noted that the patient has lymph node
metastasis and not liver metastases. Therefore, excess 5-HIAA should be metabolized by the liver circumventing symptoms.
Incorrect answer C: Elevated CgA level, lymph nodes metastases and a 1.5 cm tumor is incorrect because the liver should be able to metabolize excess 5-HIAA levels and prevent subsequent symptoms of carcinoid syndrome.
Incorrect answer D: Elevated 5-HIAA level, no metastases and a 2.6 cm tumor is incorrect because the liver should be able to metabolize excess 5-HIAA levels and prevent subsequent symptoms of carcinoid syndrome.

8. **AH is a woman, 50 years of age, with a past medical history significant for hypertension and gastroesophageal reflux disease who was recently diagnosed with metastatic carcinoid tumor.**
She presents to the clinic with complaints of severe diarrhea and flushing. Which of the following is the best option to control her symptoms:
A. Loperamide 2 mg orally every 2 to 4 hours
B. Octreotide LAR 20 mg IM every month
C. Octreotide 100 mcg subcutaneous (SQ) 3 times daily***
D. Lansoprazole 120 mg by mouth daily

**Correct Answer C;** Octreotide 100 mcg SQ 3 times daily is the best option to block the release of the substances causing diarrhea and flushing caused by carcinoid tumors. Initiating a short-acting somatostatin analog, such as octreotide, at the lowest dose and then titrating upwards to symptomatic control is a good first-line approach.

Incorrect answer A: Loperamide 2 mg orally every 2 to 4 hours is incorrect because it does not target the underlying cause of the diarrhea or flushing.
Incorrect answer B: Octreotide LAR 20 mg IM every month is incorrect because the long-acting formulation has a pharmacokinetic profile that does not allow for immediate symptomatic relief. This product takes time to achieve steady state concentrations and patients should first be initiated on a short-acting formulation that should be continued for at least 2 weeks after the first long-acting injection.
Incorrect answer D: Lansoprazole 120 mg by mouth daily is incorrect because this agent will not target the biochemical substances causing the symptoms. Proton-pump inhibitors are typically used for the management of symptoms for patients with gastrinomas and serve as a cornerstone of therapy for those patients and not patients with carcinoid tumors.

9. **AH has been receiving Octreotide LAR 20 mg IM monthly for the treatment of her diarrhea for the last 9 months. Today she presents to the clinic with complaints that her diarrhea is significantly worse at the end of each month. Which of the following would you recommend:**
   A. Increase the dose to octreotide LAR 30 mg IM monthly
   B. Add short acting octreotide 100 mcg SQ 3 times daily
   C. Add loperamide 2 mg orally every 4 hours as needed
   D. Administer octreotide LAR 20 mg IM every 3 weeks***
Correct answer D: Administer Octreotide LAR 20 mg IM every 3 weeks is correct because the dose that the patient is receiving seems to control her symptoms for the majority of the month. It appears that the effects are “wearing-off”; therefore, decreasing the intervals between doses may be an effective way to eliminate breakthroughs.

Incorrect answer A: Increase the dose to Octreotide LAR 30 mg IM monthly is incorrect because the dose may not last the entire month because it seems the patient is experiencing a “wearing-off” effect versus inadequate dose. This may be the case when symptoms are occurring throughout the month.

Incorrect answer B: Add short acting Octreotide 100 mcg SQ 3 times daily is incorrect because an additional medication for the entire month is not needed when her symptoms are relatively controlled for most of the month. A short-acting octreotide could be used during the last week of the month to control breakthrough symptoms, but most patients would want to avoid 3 times a day injections if possible.

Incorrect answer C: Add loperamide 2 mg orally every 4 hours as needed is incorrect because this medication will not target the underlying cause of the issue. It may be an option after others have failed. In this case, AH should try titrating the dose and interval of the octreotide LAR first.

10. H0 is a man, 65 years of age, who was recently diagnosed with malignant gastrinomas after presenting with a past medical history of severe peptic ulcer disease, chronic diarrhea, and most recently, abdominal pain. H0 arrives in clinic today to inquire about available options to help relieve his excessive gastric production symptoms. Which of the following is the best treatment option for these symptoms:
   
   A. Ranitidine 150 mg by mouth twice daily
   B. Octreotide 100 mg SQ 3 times daily
   C. Everolimus 10 mg by mouth daily
   D. Lansoprazole 120 mg by mouth daily***

Correct Answer D: Lansoprazole 120 mg by mouth daily is correct because these agents can effectively control the symptoms of acid hypersecretion. They also have a longer half-life compared with other acid suppressors, which minimizes breakthrough symptoms.

Incorrect answer A: Ranitidine 150 mg by mouth twice daily is incorrect. Although these agents can be used, they typically need to be dosed every 4 to 6 hours to maintain efficacy.

Incorrect answer B: Octreotide 100 mg SQ 3 times daily should not be chosen because this agent is typically used in the second-line setting.

Incorrect answer C: Everolimus 10 mg po daily is incorrect because the patient has not tried therapy with a proton-pump inhibitor yet. Everolimus has been investigated in the setting of failed therapies.

11. RS is a man, 60 years of age, who was diagnosed with a poorly differentiated, malignant VIPoma about 1 year ago. Since then, his treatment has consisted of octreotide LAR 30 mg IM
every month, then octreotide LAR 30 mg IM every 3 weeks, and most recently octreotide LAR 30 mg IM every 3 weeks, plus octreotide 200 mcg SQ 3 times daily. Despite the therapeutic changes, RS continues to present to the clinic with diffuse diarrhea, dehydration, and electrolyte disturbances. Which of the following is the best treatment option for RS at this time:

A. Streptozocin 400 mg/m$^2$ IV D1 - 5 every 10 weeks, fluorouracil 400 mg/m$^2$ IV D1 - 5, D36 - 40 every 10 weeks***
B. Sunitinib 37.5 mg by mouth daily
C. Octreotide LAR 30 mg every 2 weeks plus octreotide 200 mcg SQ 4 times a day
D. Everolimus 10 mg by mouth daily

**Correct Answer A:** Streptozocin 400 mg/m$^2$ IV D1 - 5 every 10 weeks, Fluorouracil 400 mg/m$^2$ IV D1 - 5, D36 - 40 every 10 weeks is correct because the patient has failed prior therapy with multiple titrations, has poorly differentiated metastatic disease, and still presents with significant symptoms. In this setting, cytotoxic chemotherapy has been evaluated with documented response.

Incorrect answer B: Sunitinib 37.5 mg by mouth daily is incorrect because this targeted agent has been investigated in patients with well-differentiated tumors. Its effect in a more aggressive setting is unknown.

Incorrect answer C: Octreotide LAR 30 mg every 2 weeks plus Octreotide 200 mcg SQ 4 times a day is incorrect because the highest recommended dose of short-acting octreotide is 600 mcg/day and it seems that the patient has developed tachyphylaxis in the setting of maximum titration. Trying an alternative agent at this time is warranted.

Incorrect answer D: Everolimus 10 mg by mouth daily is incorrect because this agent has been investigated in patients with well or intermediate grade tumors.

12. TR is a woman, 58 years of age, diagnosed with a well-differentiated, low-grade PNET, who presents to the clinic for treatment options after treatment failure with octreotide. It is determined that TR will begin therapy with sunitinib 37.5 mg by mouth daily. Which of the following should TR be counseled about:

A. Diarrhea, nausea, fatigue, hand-foot syndrome, hypothyroidism***
B. Hyperglycemia, hyperlipidemia, diarrhea, and rash
C. Hyperthyroidism, hand-foot syndrome, diarrhea
D. Hypoglycemia, diarrhea, rash

**Correct Answer A:** Diarrhea, nausea, fatigue, hand-foot syndrome, and hypothyroidism are all adverse effects seen with sunitinib therapy. Patients should be counseled about these effects and how best to monitor and manage them.
Incorrect answer B: Hyperglycemia, hyperlipidemia, diarrhea, and rash is incorrect because sunitinib does not cause hyperglycemia or hyperlipidemia.
Incorrect answer C: Hyperthyroidism, hand-foot syndrome, and diarrhea is incorrect because sunitinib causes hypothyroidism and not hyperthyroidism. Thyroid function levels should be monitored and replacement therapy should occur as appropriate.
Incorrect answer D: Hypoglycemia, rash, and diarrhea is incorrect because hypoglycemia is not caused by sunitinib therapy.

13. PM presents to the pharmacy to pick up her prescription refill for everolimus for the treatment of her gastrinoma. During the encounter, the pharmacist reviews her medication profile which includes the following: Tylenol 500 mg orally as needed, metoprolol XL 50 mg by mouth daily, lisinopril 20 mg by mouth daily, and a new prescription for clarithromycin 500 mg orally twice a day for a sinus infection. Which of the following should the pharmacist recommend:
   A. Change metoprolol extended release to diltiazem extended release 120 mg by mouth daily
   B. Change clarithromycin to levofloxacin 500 mg by mouth daily
   C. Change lisinopril to enalapril 10 mg by mouth daily
   D. Change clarithromycin to bactrim double strength (DS) 1 tablet by mouth daily***

Correct Answer D: Change clarithromycin to bactrim DS 1 tablet by mouth daily is correct.
Everolimus is metabolized through the cytochrome P450 (CYP) 3A4 pathway. Consequently agents that inhibit this pathway should be avoided because they may impair the breakdown of everolimus and cause toxicity. Clarithromycin is a CYP3A4 inhibitor and should be avoided if possible. Since bactrim does not inhibit this metabolic pathway and can effectively treat sinus infections, it can be recommended as an option for this patient.
Incorrect answer A: Change metoprolol XL to diltiazem SR 120 mg by mouth daily is incorrect because metoprolol does not inhibit the CYP3A4 metabolic pathway.
Incorrect answer B: Change clarithromycin to levofloxacin 500 mg po daily is incorrect because levofloxacin also inhibits the CYP3A4 pathway and therefore does not provide minimize the risk of drug interaction.
Incorrect answer C: Change lisinopril to enalapril 10 mg by mouth daily is incorrect because this agent is excreted through the kidneys as an unchanged drug. Therefore, there is no risk of a drug interaction via the CYP3A4 system.