Topics/subtopics

1. Understanding the nature of science
   a. Future research can upset current knowledge yet future findings are more likely to refine than upset well established science
      ➢ Identify the current limits of medical knowledge.
      ➢ Distinguish among medical unknowns speculation, tentative knowledge based on limited evidence, and well-established knowledge based on concordant evidence.
      ➢ Describe how basic scientific knowledge can inform interpretations of clinical evidence.
      ➢ Describe established biomedical scientific knowledge that was upset and that was modified/refined
      ➢ Describe established biomedical scientific biomedical knowledge that was challenged but ultimately vindicated
   b. Recognize that scientific judgment requires a balance of skepticism and openness
      ➢ Identify a medical scientific controversy and form a scientific judgment
      ➢ Describe limitations in scientific evidence for a standard medical intervention
      ➢ Identify a medical intervention that holds great promise, despite limited current evidence.
   c. Understand the need for controls, and evaluate the validity of the controls
      ➢ Describe experimental controls and their usefulness.
      ➢ Explain the value of uncontrolled clinical studies for specific biomedical situations (e.g. establishing safety of a population).
   d. Recognize the frontiers of knowledge
      ➢ Identify unknowns in medicine and biomedical science.

2. Awareness of the power and limitations of observation
   a. What you can learn from experience/anecdote
      ➢ Describe how clinical observations and anecdotes are useful for making observations and developing hypotheses about medicine and identify a medical historical event in which clinical experience/anecdote lead to a scientific medical breakthrough
   b. Limitations of experience/anecdote
      ➢ Identify the inherent limitations of clinical experience, such as the difficulty of ascribing causes to antecedents.
      ➢ Identify a clinical situation in which experience could lead to a misleading conclusion
      ➢ Describe a historical medical event in which physicians erroneously pursued an ineffective treatment based on experience/anecdote.
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3. Awareness of bias and misconceptions
   a. Correlation versus causation
      ➢ Describe the Hill criteria of causation and how they are applied
      ➢ Apply the Hill criteria in one or more examples to establish the degree of confidence in causation
   b. Biases in biomedical science, including confirmation bias, ascertainment bias, selection bias, observer bias, publication bias.
      ➢ Explain the source of each type of bias
      ➢ Define the consequences of the bias
      ➢ Identify methods to overcome/eliminate each type of bias
   c. Experimental design overcoming bias and misconceptions
      ➢ Describe appropriate and inappropriate controls
      ➢ Identify methods of research design to overcome bias

4. Endpoints in clinical research
   a. Selecting the appropriate endpoint
      ➢ Describe the difference between objective and subjective endpoints
      ➢ Explain the strengths and limitations of surrogate endpoints why surrogate endpoints can be misleading indicators of an ultimate endpoint
      ➢ Describe the difference between primary endpoint and secondary endpoints in clinical research
      ➢ Explain why secondary endpoints have elevated false positive rate
   b. When surrogate endpoints are valid
      ➢ Explain how surrogate endpoints are validated
      ➢ Identify one or more well validated surrogate endpoints
   c. Prespecified versus post-hoc endpoints/subsets (and researcher degrees of freedom)
      ➢ Describe how publication bias leads researchers to search for positive findings.
      ➢ Explain how endpoints or subsets that are not predefined lead to an elevated likelihood of false positive findings.

5. The placebo and nocebo effects
   a. Understanding that placebo (broadly defined) operates in subjective endpoints
      ➢ Describe the placebo effect
      ➢ Describe clinical endpoints in which placebo effect is most likely to operate.
      ➢ Describe how the placebo (broadly defined) is impacted by bias of the observer (requiring double blinding).
      ➢ Identify controls that can eliminate the placebo effect to identify the specific intervention that caused the medical outcome.
   b. Understanding sources of nonspecific/contextual effects that are conflated with placebo (broadly defined).
      ➢ Identify how natural healing/regression to mean could impact placebo
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➢ Describe the Hawthorne effect (behavioral change/reporting in context of research)
➢ Explain how true clinically-useful placebo effect is smaller in magnitude than the broadly defined placebo.
➢ Provide an example of apparent placebo observed in a research study, and identify the components.

c. Understanding nocebo (apparent toxicity from placebo)
➢ Describe the nocebo effect
➢ Identify a clinical study in which the nocebo effect operates.

6. Understanding the value and limitations of statistics
a. Clinical significance versus statistical significance
➢ Distinguish statistical and clinical significance including recognizing when statistically significant results may not be clinically significant.
b. Multiple-hypothesis testing
➢ Describe how multiple hypothesis testing affects likelihood of false positives.
c. Testing implausible hypotheses
➢ Explain the limitation of purely clinical evidence to validate implausible hypotheses.
➢ Demonstrate the ability to incorporate preclinical evidence to evaluate the plausibility of a hypothesis of a clinical trial.
➢ Use preclinical evidence to weigh the likelihood of true- versus false-positives among clinical trials that meet p<0.05 on the primary endpoint.
d. Testing non-inferiority versus establishing superiority
➢ Describe the difference between a superiority study and a non-inferiority trial
➢ Explain the elevated rate of type II error (falsely accepting no difference) when interpreting a superiority study as non-inferior.

7. Weighing evidence
a. Understand the value of concordant lines of evidence
➢ Identify medical knowledge that is based on strong lines of concordant evidence
➢ Evaluate current medical knowledge by synthesis of multiple concordant types of evidence spanning 3 or more of basic, translational clinical, observational, epidemiological evidence
➢ Identify clinical evidence that lacks concordance

b. The value and limitations of RCT
➢ Describe the strength of RCT in eliminating biases in establishing biomedical knowledge
➢ Describe and interpret a CONSORT diagram to identify limitations and biases of a completed RCT.
➢ Explain how RCT may not reflect utility of an intervention in clinical practice (e.g. efficacy versus effectiveness)
c. Value and limitations of observational clinical evidence (cohort studies, case-controls)
   - Describe the strengths and limitations of observational evidence.
   - Identify historical discrepancies between observational and RCT evidence.
   - Identify observational evidence that is concordant with RCT, and describe how the observational evidence lends credence to in the interpretation of the RCT

d. The value of preclinical evidence
   - Demonstrate the ability to weigh evidence across scientific domains including basic/preclinical evidence

8. Clinical application of scientific information
   a. How to create a model of pathophysiology and disease management informed by scientific research
      - Build a model of pathophysiology and disease management through synthesized evidence spanning basic, preclinical, observational and RCT evidence
      - Explain which types of evidence could be provided by a single research study that could modify this model, considering both (a) a study that entirely refutes the established model; and (b) a study that fits with the model but modestly adjusts the clinical application.
   b. Using the model to optimize care for patients who do not fit RCT
      - Explain whether patients who do not meet specific criteria of RCT should be given a therapy defined as effective
      - Apply scientific knowledge to patients who do not fall within an RCT
      - Demonstrate how to apply the best understood model of pathophysiology constructed with concordant evidence to individuals who may not fall strictly within the bounds of RCT.
   c. Weighing personal comfort in how to extrapolate/apply limited evidence
      - Identify a situation in which a particular clinical practice may be wrong by virtue of an incorrect model, too many assumptions, or weak evidence
      - Identify a situation in which you judge it appropriate to deviate or extrapolate your model despite limited/weak evidence.
   d. Appropriately weigh preliminary/preclinical evidence.
      - Describe the relative breadth and value of knowledge established by research that is purely empiric (e.g. cause-effect without mechanism), and conceptual (e.g. mechanistic knowledge that establishes broadly applicable concepts such as immune suppressants for autoimmune disease).
      - Express and justify personal philosophy on how clinical, preclinical, and basic evidence can be synthesized to inform scientifically-informed clinical practice.
      - Illustrate a situation in which preclinical evidence might change clinical practice.
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- Identify how a basic science research discovery has informed/changed current clinical practice.