WHAT IS THE QUESTION?

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Consider a medical student, early in her training, seeing a patient with newly diagnosed diabetes mellitus. She will ask questions such as the following: What is type 2 diabetes mellitus? Why does this patient have polyuria? Why does this patient have numbness and pain in his legs? What treatment options are available? These questions address normal human physiology and the pathophysiology associated with a medical condition.

Traditional medical textbooks that describe underlying physiology, pathology, epidemiology, and general treatment approaches provide an excellent resource for addressing these background questions. The sorts of questions that seasoned clinicians usually ask require different resources.

Browsing

A general internist scanning the September/October 2005 ACP Journal Club (http://www.acponline.org/journals/acpjc/jcmenu.htm) comes across the following articles: “Intensive Insulin-Glucose Infusion Regimens With Long-Term or Standard Glucose Control Did Not Differ for Reducing Mortality in Type 2 Diabetes Mellitus and MI,”¹ and “Review: Mixed Signals From Trials Concerning Pharmacologic Prevention of Type 2 Diabetes Mellitus.”²

This internist is in the process of asking a general question—what important new information should I know to optimally treat my patients? Traditionally, clinicians address this question by subscribing to a number of target medical journals in which articles relevant to their practice appear. They keep up to date by skimming the table of contents and reading relevant articles. This traditional approach to what we might call the browsing mode of using the medical literature has major limitations of inefficiency and resulting frustration. Evidence-based medicine offers solutions to this problem.

The most efficient strategy is to restrict your browsing to secondary journals. For internal and general medicine, ACP Journal Club publishes synopses of articles that meet criteria of both clinical relevance and methodologic quality. We describe such secondary journals in more detail in Chapter 4, Finding the Evidence.

Some specialties (primary care, mental health) and subspecialties (cardiology, gastroenterology) already have their own devoted secondary journals; others do not. The New York Academy of Medicine keeps a current list of available secondary journals in many health care disciplines (http://www.ebmny.org/journal.html). If you are not yet fortunate enough to have your own, you can apply your own relevance and methodologic screen to articles in your target specialty or subspecialty journals. When you have learned the skills, you will be surprised at the small proportion of studies to which you need attend and at the efficiency with which you can identify them.

Problem Solving

Experienced clinicians confronting a patient with diabetes mellitus will ask questions such as, In patients with new-onset type 2 diabetes mellitus, which clinical features or test results predict the development of diabetic complications? In patients with type 2
diabetes mellitus requiring drug therapy, does starting with metformin treatment yield improved diabetes control and reduce long-term complications better than other initial treatments? Here, clinicians are defining specific questions raised in caring for patients and then consulting the literature to resolve these questions.

Background and Foreground Questions

One can think of the first set of questions, those of the medical student, as background questions and of the browsing and problem-solving sets as foreground questions. In most situations, you need to understand the background thoroughly before it makes sense to address foreground issues.

A seasoned clinician may occasionally require background information, which is most likely when a new condition or medical syndrome appears (“What is SARS?”) or when a new diagnostic test (“How does PCR work?”) or treatment modality (“What are atypical antipsychotic agents?”) appears in the clinical arena.

Figure 3-1 represents the evolution of the questions we ask as we progress from being novices posing background questions to experts posing foreground questions. This book explores how clinicians can use the medical literature to solve their foreground questions.

Clarifying Your Question

The Structure: Patients, Exposure, Outcome

Clinical questions often spring to mind in a form that makes finding answers in the medical literature a challenge. Dissecting the question into its component parts to facilitate finding the best evidence is a fundamental skill. One can divide most
TABLE 3-1

Framing Clinical Questions

1. The population. Who are the relevant patients?

2. The interventions or exposures (diagnostic tests, foods, drugs, surgical procedures, time, risk factors, etc). What are the management strategies we are interested in comparing or the potentially harmful exposures about which we are concerned? For issues of therapy, prevention, or harm, there will always be both an experimental intervention or putative harmful exposure and a control, alternative, or comparison intervention or state to which it is compared.

3. The outcome. What are the patient-relevant consequences of the exposures in which we are interested? We may also be interested in the consequences to society, including cost or resource use. It may also be important to specify the period of interest.

questions into 3 parts: the patients, the intervention or exposure, and the outcome (Table 3-1).

Five Types of Clinical Questions

In addition to clarifying the population, intervention or exposures, and outcome, it is productive to label the nature of the question that you are asking. There are 5 fundamental types of clinical questions:

1. Therapy: determining the effect of interventions on patient-important outcomes (symptoms, function, morbidity, mortality, costs)

2. Harm: ascertaining the effects of potentially harmful agents (including therapies from the first type of question) on patient-important outcomes

3. Differential diagnosis: in patients with a particular clinical presentation, establishing the frequency of the underlying disorders

4. Diagnosis: establishing the power of a test to differentiate between those with and without a target condition or disease

5. Prognosis: estimating a patient’s future course

Finding a Suitably Designed Study for Your Question Type

You need to correctly identify the category of study because, to answer your question, you must find an appropriately designed study. If you look for a randomized trial to inform you of the properties of a diagnostic test, you are unlikely to find the answer you seek. We will now review the study designs associated with the 5 major types of questions.

To answer questions about a therapeutic issue, we identify studies in which a process analogous to flipping a coin determines participants’ receipt of an experimental treatment or a control or standard treatment, a randomized controlled trial (RCT) (see Chapter 6, Therapy [Randomized Trials]). Once investigators allocate participants to treatment or control groups, they follow them forward in time to
determine whether they have, for instance, a stroke or heart attack—what we call
the outcome of interest (Figure 3-2).

Ideally, we would also look to randomized trials to address issues of harm. For
many potentially harmful exposures, however, randomly allocating patients is
neither practical nor ethical. For instance, one cannot suggest to potential study
participants that an investigator will decide by the flip of a coin whether or not they
smoke during the next 20 years. For exposures like smoking, the best one can do is
identify studies in which personal choice, or happenstance, determines whether
people are exposed or not exposed. These observational studies (often subclassified
as cohort or case-control studies) provide weaker evidence than randomized trials
(see Chapter 12, Harm [Observational Studies]).

Figure 3-3 depicts a common observational study design in which patients with
and without the exposures of interest are followed forward in time to determine
whether they experience the outcome of interest. For smoking, one important
outcome would likely be the development of cancer.
For sorting out *differential diagnosis*, we need a different study design (Figure 3-4). Here, investigators collect a group of patients with a similar presentation (painless jaundice, syncope, headache), conduct an extensive battery of tests, and, if necessary, follow patients forward in time. Ultimately, for each patient they hope to establish the underlying cause of the *symptoms* and *signs* with which the patient presented.

Establishing the value of a particular diagnostic test (what we call its properties or operating characteristics) requires a slightly different design (Figure 3-5). In diagnostic test studies, investigators identify a group of patients in whom they suspect a disease or condition of interest exists (such as tuberculosis, lung cancer, or iron-deficiency anemia), which we call the target condition. These patients undergo the new diagnostic test and a *reference standard*, *gold standard*, or *criterion standard*. Investigators evaluate the diagnostic test by comparing its classification of patients with that of the reference standard (Figure 3-5).

A final type of study examines a patient’s *prognosis* and may identify factors that modify that prognosis. Here, investigators identify patients who belong to a particular group (such as pregnant women, patients undergoing surgery, or...
patients with cancer) with or without factors that may modify their prognosis (such as age or comorbidity). The exposure here is time, and investigators follow patients to determine whether they experience the target outcome, such as a problem birth at the end of a pregnancy, a myocardial infarction after surgery, or survival in cancer (Figure 3-6).

Three Examples of Question Clarification

We will now provide examples of the transformation of unstructured clinical questions into the structured questions that facilitate the use of the medical literature.

Example 1: Diabetes and Target Blood Pressure

A 55-year-old white woman presents with type 2 diabetes mellitus and hypertension. Her glycemic control is excellent with metformin, and she has no history of complications. To manage her hypertension, she takes a small daily dose of a thiazide diuretic. During a 6-month period, her blood pressure is near 155/88 mm Hg.

Initial Question: When treating hypertension, at what target blood pressure should we aim?

Digging Deeper: One limitation of this formulation of the question is that it fails to specify the population in adequate detail. The benefits of tight control of blood pressure may differ in diabetic patients vs nondiabetic patients, in type 1 vs type 2 diabetes, and in patients with and without diabetic complications.
The detail in which we specify the patient population is a double-edged sword. On the one hand, being very specific (middle-aged women with uncomplicated type 2 diabetes) will ensure that the answer we get is applicable to our patients. We may, however, fail to find any studies that restrict themselves to this population. The solution is to start with a specific patient population but be ready to drop specifications to find a relevant article. In this case, we may be ready to drop the “female,” “middle-aged,” “uncomplicated,” and “type 2,” in that order. If we suspect that optimal target blood pressure may be similar in diabetic and nondiabetic patients, and it proves absolutely necessary, we might drop the “diabetes.”

We may wish to specify that we are interested in the addition of a specific antihypertensive agent. Alternatively, the intervention of interest may be any antihypertensive treatment. Furthermore, a key part of the intervention will be the target for blood pressure control. For instance, we might be interested in knowing whether it makes any difference if our target diastolic blood pressure is less than 80 mm Hg vs less than 90 mm Hg. Another limitation of the initial question formulation is that it fails to specify the criteria by which we will judge the appropriate target for our hypertensive treatment.

**Improved (Searchable) Question: A question of THERAPY**

- **Patients:** Hypertensive type 2 diabetic patients without diabetic complications.
- **Intervention:** Any antihypertensive agent aiming at a target diastolic blood pressure of 90 mm Hg vs a comparison target of 80 mm Hg.
- **Outcomes:** Stroke, myocardial infarction, cardiovascular death, total mortality.

**Example 2: Transient Loss of Consciousness**

A 55-year-old man, previously well, although a heavy drinker, presents to the emergency department with an episode of transient loss of consciousness. On the evening of presentation, he had his usual 5 beers and started to climb the stairs at bedtime. The next thing he remembers is being woken by his son, who found him lying near the bottom of the stairs. The patient took about a minute to regain consciousness and remained confused for another 2 minutes. His son did not witness any shaking, and there had not been any incontinence. Physical examination result was unremarkable; the electrocardiogram showed a sinus rhythm with a rate of 80/min and no abnormalities. Glucose, sodium, and other laboratory results were normal.

**Initial Question:** How extensively should I investigate this patient?
Digging Deeper: The initial question gives us little idea of where to look in the literature for an answer. As it turns out, there is a host of questions that could be helpful in choosing an optimal investigational strategy. We could, for instance, pose a question of differential diagnosis: If we knew the distribution of ultimate diagnoses in such patients, we could choose to investigate the more common and omit investigations targeted at remote possibilities.

Other information that would help us would be the properties of individual diagnostic tests. If an electroencephalogram were extremely accurate for diagnosing a seizure, or a 24-hour Holter monitor for diagnosing arrhythmia, we would be far more inclined to order the tests than if they missed patients with the underlying problems or falsely labeled patients without the problems.

Alternatively, we could ask a question of prognosis. If patients like ours had a benign prognosis, we might be much less eager to investigate extensively than if patients tended to do badly. Finally, the ultimate answer to how intensively we should investigate might come from a randomized trial in which patients similar to this man were allocated to more vs less intensive investigation.

Improved (Searchable) Questions: A question of DIFFERENTIAL DIAGNOSIS

• Patients: Middle-aged patients presenting with transient loss of consciousness.
• Intervention/Exposure: Thorough investigation and follow-up.
• Outcomes: Frequency of underlying disorders such as vasovagal syncope, seizure, arrhythmia, and transient ischemic attack.

A question of DIAGNOSIS

• Patients: Middle-aged patients presenting with transient loss of consciousness.
• Intervention/Exposure: Electroencephalogram.
• Outcomes: Gold standard investigation (probably long-term follow-up).

A question of PROGNOSIS

• Patients: Middle-aged patients presenting with transient loss of consciousness.
• Intervention/Exposure: Time.
• Outcomes: Morbidity (complicated arrhythmias or seizures, strokes, serious accidents) and mortality in the year after presentation.

A question of THERAPY

• Patients: Middle-aged patients presenting with loss of consciousness.
• *Intervention/Exposure*: Comprehensive investigation vs a comparator of minimal investigation.

• *Outcomes*: Morbidity and mortality in the year after presentation.

**Example 3: Squamous Cell Carcinoma**

A 60-year-old man with a 40-pack-year smoking history presents with hemoptysis. A chest radiograph shows a parenchymal mass with a normal mediastinalum, and a fine-needle aspiration of the mass shows squamous cell carcinoma. Aside from hemoptysis, the patient is asymptomatic and physical examination result is entirely normal.

**Initial Question:** What investigations should we undertake before deciding whether to offer this patient surgery?

**Digging Deeper:** The key defining features of this patient are his non–small cell carcinoma and the fact that his medical history, physical examination, and chest radiograph show no evidence of intrathoracic or extrathoracic metastatic disease. Alternative investigational strategies address 2 separate issues: Does the patient have occult mediastinal disease, and does he have occult extrathoracic metastatic disease? For this discussion, we will focus on the former issue. Investigational strategies for addressing the possibility of occult mediastinal disease include undertaking a mediastinoscopy or performing a computed tomographic (CT) scan of the chest and proceeding according to the results of this investigation.

What outcomes are we trying to influence in our choice of investigational approach? We would like to prolong the patient’s life, but the extent of his underlying tumor is likely to be the major determinant of survival, and our investigations cannot change that. We wish to detect occult mediastinal metastases if they are present because, if the cancer has spread to the mediastinum, resectional surgery is unlikely to benefit the patient. Thus, in the presence of mediastinal disease, patients will usually receive palliative approaches and avoid an unnecessary thoracotomy.

We could frame our structured clinical question in 2 ways. One would be asking about the usefulness of the CT scan for identifying mediastinal disease. More definitive would be to ask a question of therapy: what investigational strategy would yield superior clinical outcomes?

**Improved (Searchable) Questions:** A *question of DIAGNOSIS*

• *Patients*: Newly diagnosed non–small cell lung cancer with no evidence of extrapulmonary metastases.

• *Intervention*: CT scan of the chest.
• **Outcome**: Mediastinal spread at mediastinoscopy.

_A question of THERAPY_

• **Patients**: Newly diagnosed non–small cell lung cancer with no evidence of extrapulmonary metastases.

• **Intervention**: Mediastinoscopy for all or restricted to those with suspicious lesions on CT scan of the thorax.

• **Outcome**: Unnecessary thoracotomy.

**DEFINING THE QUESTION: CONCLUSION**

Constructing a searchable question that allows you to use the medical literature to solve problems is no simple matter. It requires a detailed understanding of the clinical issues involved in patient management. The 3 examples in this chapter illustrate that each patient encounter may trigger a number of clinical questions and that you must give careful thought to what you really want to know. Bearing the structure of the question in mind—patient, intervention or exposure and control, and outcome—is extremely helpful in arriving at an answerable question. Identifying the type of questions—therapy, harm, differential diagnosis, diagnosis, and prognosis—will further ensure that you are looking for a study with an appropriate design.

Careful definition of the question will provide another benefit: you will be less likely to be misled by a study that addresses a question related to the one in which you are interested, but with 1 or more important differences. For instance, making sure that the study compares experimental treatment to current optimal care may highlight the limitations of trials that use a _placebo_ control (see Chapter 11.3, Dealing With Misleading Presentations of Clinical Trial Results). Specifying that you are interested in patient-important outcomes (such as long bone fractures) makes vivid the limitations of studies that focus on _substitute_ or _surrogate endpoints_ (such as bone density) (see Chapter 11.4, Surrogate Outcomes). Specifying that you are primarily interested in avoiding progression to dialysis will make you appropriately wary of a _composite endpoint_ of progression to dialysis or doubling of serum creatinine level (see Chapter 10.4, Composite Endpoints). You will not reject such studies out of hand, but the careful definition of the question will help you to critically apply the results to your patient care.

A final crucial benefit from careful consideration of the question is that it sets the stage for efficient and effective literature searching to identify and retrieve the best evidence. Chapter 4, Finding the Evidence, uses the components of patient, intervention, and outcome for the questions in this chapter to provide you with the searching tools you will need for effective _evidence-based practice._
References
